Economic Evaluation

Serving different actors in a changing environment; some examples

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Economic Evaluation

Serving different actors in a changing environment; some examples

Economische evaluatie
Het bedienen van verschillende actoren in een veranderende omgeving;
enkele voorbeelden

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	Prof.dr. J.L. Severens
	Prof.dr. B. Löwenberg
Copromotor:	Dr. C.A. Uyl-de Groot

Taking a new step... is what people fear most.

Dostoyevski

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PUBLICATIONS

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Chapter 3

M.T. Groot, M. van Agthoven, B. Löwenberg, R. Willemze and C.A. Uyl-de Groot. The role of cost analysis in the evaluation of the development of medical technology. The case of allogeneic stem-cell transplantation (in Dutch). Nederlands Tijdschrift voor Geneeskunde, 2004, 148(10);480-484.[b]

Chapter 4

M.T. Groot, R. Baltussen, C.A. Uyl-de Groot, B.O. Anderson and G.N. Hortobágyi. Costs and Health Effects of Breast Cancer Interventions in Epidemiologically Different Regions of Africa, North America, and Asia. The Breast Journal, 2006. 12 (Suppl. 1): S81–S90.[b]

Chapter 5

M.T. Groot, M.J. Al, D. Bergqvist, L-Å. Levin, B. Kartman. Cost-effectiveness of melagatran/ximelagatran for the prevention of venous thromboembolism following major elective orthopaedic surgery. Submitted for publication

Chapter 6

M.T Groot, P.J. Lugtenburg, J. Hornberger, P.C. Huijgens and C.A. Uyl-de Groot. Cost-effectiveness of rituximab (MabThera®) in diffuse large B-cell lymphoma (DLBCL) in the Netherlands. Eur J Haematol, 2005. 74(3):194-202.[b]

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M.T. Groot, G.J. Ossenkoppele, M.H.H. Kramer, G. van den Boom, P.C. Huigens en C.A. Uyl-de Groot. Drug treatment of chronic myeloid leukemia: a cost-effectiveness analysis of first- and second-line treatment (in Dutch). Nederlands Tijdschrift voor Geneeskunde, 2003, 147(30);1460-1465.[a]

Chapter 8

M.T. Groot, G.J. Ossenkoppele, S.D. Reed, P.C. Huigens en C.A. Uyl-de Groot. Cost-effectiveness of chronic myeloid leukaemia treatment in the imatinib era (in Dutch). Nederlands Tijdschrift voor Hematologie, 2006. In press, Nederlands Tijdschrift voor Hematologie.[c]

Chapter 9

M.T. Groot, P.C. Huijgens and C.A. Uyl-de Groot. Introduction of expensive drugs in haemato-oncology in the Netherlands and throughout Europe. Submitted for publication

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Chapter 1

Introduction

BACKGROUND

In the past decades healthcare expenditures have risen significantly (Meltzer 2001). This is primarily caused by the development of costly new medical technologies and a steadily increasing age in the western world.

Particularly in the last decade, developments in healthcare have been characterized by an increasing number of treatments aimed at groups of patients for whom there were no treatment options previously. The question is raised whether these treatments provide value for money. In other words, is their added clinical value in balance with the additional costs they incur? In many countries manufacturers must provide cost-effectiveness data when applying for reimbursement of new drugs or techniques (van Oostenbruggen 2005). Cost-effectiveness information has also been included in the development of clinical practice guidelines (Niessen 2000; Antioch 2002; NICE 2004). As a consequence there is a growing need for economic evaluations. These evaluations can be performed using different data sources: on the basis of the results from clinical trials in which resource use is collected, by means of retrospective patient chart research, or by constructing a model on the basis of information from a variety of sources. One can furthermore distinguish different types of economic evaluations: cost analyses, cost-minimisation studies, cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses (Gold 1996; Drummond 1997). Despite different approaches, all economic evaluations have a common interest: to support decision makers. This can be for the reimbursement of drugs, the introduction of new medical technologies or for an optimal budget allocation. Therefore, economic evaluations must share a common basis and as a consequence guidelines have been developed in many countries (Hjelmgren 2001). These give guidance on all aspects of economic evaluations including the perspective of the study, allocation of resource use and costs, uncertainty analysis and modelling techniques.

Probably the most frequently used technique for economic evaluations is modelling. Models offer a way to structure the complex nature of clinical information and they offer the possibility to simulate strategies that can not be performed in real life. In general there are two situations in which models are typically used: 1) where the relevant clinical trials have not been conducted or did not include resource use, models are used to synthesize the best available data; 2) when the clinical trials report intermediate endpoints or have only short-term follow-up, models are used to extrapolate beyond the trial in order to estimate final outcomes (Buxton 1997). As the number of modelling studies is steadily increasing, concerns are raised regarding potential sources of bias and regarding their supposed lack of transparency that make peer review more difficult. Therefore, in addition to the general criteria for economic evaluations there are several guidelines and textbooks that are specifically aimed at providing guidance on the proper conduct of modelling exercises (Brennan 2000; Hunink 2001; Kuntz 2001; Weinstein 2003).

Economic evaluations are performed in a rapidly changing environment. Compared to 10 years ago much more new drugs, especially in the field of haematology and oncology, are introduced on the basis of phase II data or on data from preliminarily closed phase III trials as the results are so promising that it is considered unethical to withhold treatment from other patients. This has implications for the information that is available for economic evaluations. In these cases much less information is available since phase II studies are not designed to compare treatment alternatives and resource use is not collected alongside such trials. A similar reasoning is true for economic evaluations that are performed to support reimbursement decisions on the basis of phase III studies. For such analyses no real life data are available yet and the time horizon of such studies is often not long enough and only intermediate results are available. This thesis presents a number of economic evaluations that were performed under these circumstances and that dealt with the associated difficulties.

Additionally, more actors have become interested in the outcomes of economic evaluations which affects the available information and characteristics of the mathematical models used as well. Actors are interested in answering different questions; when a study is performed for a budget revision, a detailed analysis that incorporates all resources required to perform a particular medical intervention is usually required. This also counts when outcomes are used for reimbursement decisions. When analysing a range of interventions to determine an optimal resource allocation in different countries however, one is forced to take a step down in terms of detail. Data availability and resources will never be sufficient to answer this question in the level of detail that is required for budget revisions and reimbursement decisions. Economic evaluations, performed with varying resources and data, that are aimed at these different actors require certain characteristics to be of use for them. This thesis presents the results and characteristics of a number of studies performed for different actors.

As already mentioned above, economic evaluations are subject to an increased interest from different actors in healthcare as they can help in determining the added value of new technologies. However, healthcare resource allocation decisions are not performed in a vacuum. Economic evaluations can be used to highlight and understand discrepancies within health care but other aspects influence the diffusion of medical technologies as well. It is critical that these aspects are taken into consideration to understand the broader picture of the introduction of new technologies. These aspects are also explored in this thesis.

OUTLINE OF THE THESIS

This thesis deals with economic evaluations performed under different conditions and for different actors with applications in oncology and internal medicine (figure 1). It contains eight studies and is divided in three different parts (figure 1). These parts are structured around two

central topics that are discussed in the final chapter of this thesis. The next paragraphs discuss the specific aims of the individual chapters.

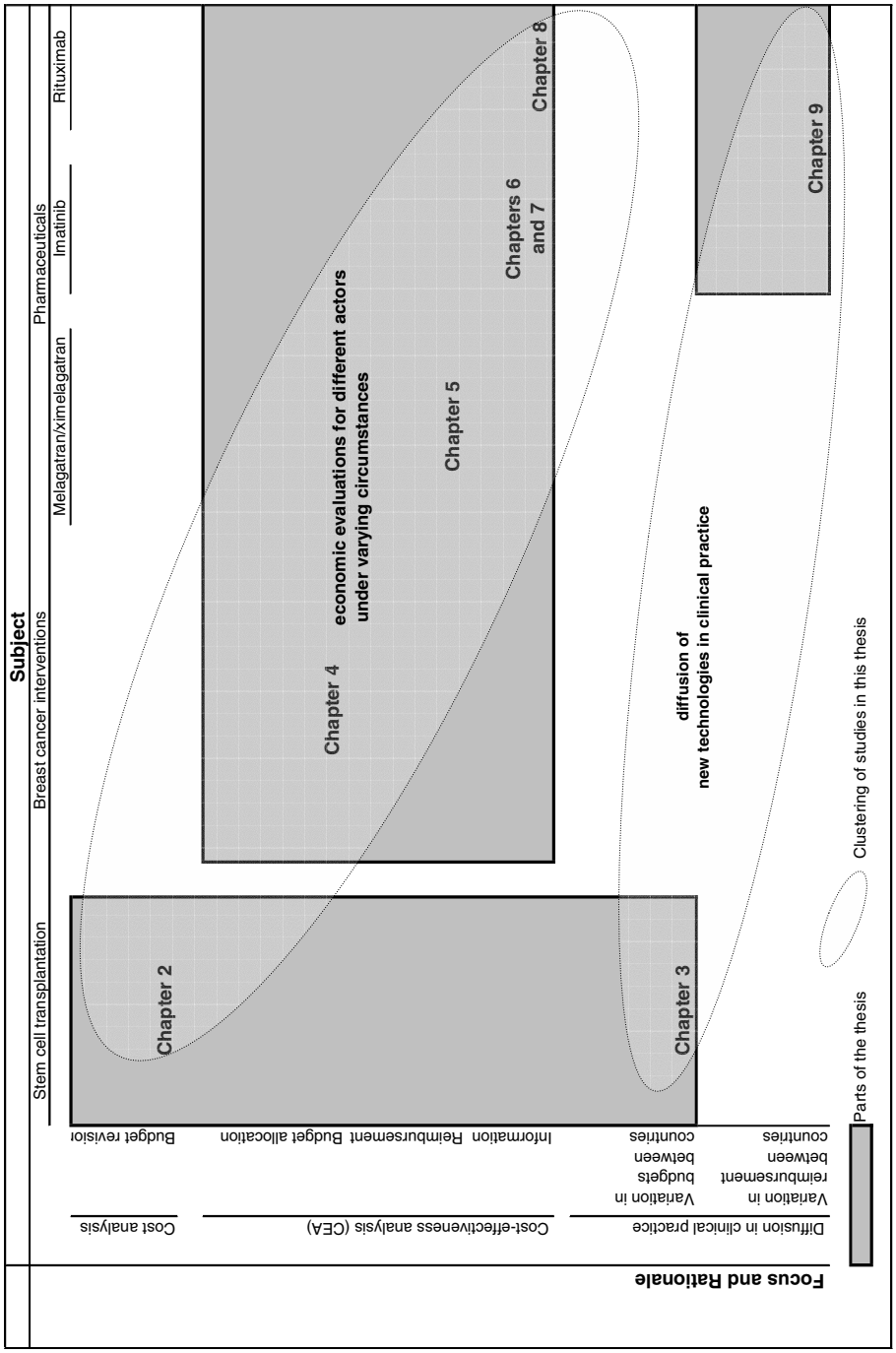

Figure 1: outline of this thesis

PART 1. COST ANALYSIS OF ALLOGENEIC STEM CELL TRANSPLANTATIONS

The first part of this thesis comprises a detailed cost analysis of allogeneic stem cell transplantations (SCT) in the Netherlands (chapter 2). Allogeneic SCT is one of the most expensive medical procedures, due to long hospital care, high-technology medical interventions and the provision of specialized facilities (Johnson 1998). Allogeneic SCTs are performed for different haematological malignancies including acute and chronic leukemia, multiple myeloma and malignant lymphoma (IGZ 1999). In the Netherlands 179 allogeneic SCTs were performed in 2002 (source: TYPHON). The budget for performing allogeneic SCT was assigned more than 10 years ago and is currently assumed to be far from sufficient. New developments such as use of grafts from unrelated voluntary donors, improved possibilities of preventing and treating graft-versus-host disease, and the use of donor lymphocyte infusions, make the intervention more costly. Therefore, an analysis was performed to determine the actual current costs of SCT. Using the results from the detailed cost analysis of allogeneic SCT the role that such an analysis can play in the evaluation of this intervention is illustrated and subsequently placed in a European perspective in chapter 3.

PART 2. COST-EFFECTIVENESS ANALYSES

Generalized cost-effectiveness of breast cancer interventions

Each year more than 1 million women worldwide are newly diagnosed with breast cancer and more than 400,000 die from it annually (Stewart 2003; Ferlay 2004). As a public health problem it is especially increasing in developing regions, where the incidence increases as much as 5% per year (2002a; Stewart and Kleihues 2003). The mortality-to-incidence ratio is much higher in developing countries than in developed countries: while half of global breast cancers are diagnosed in the developing world they represent three fourths of breast cancer related deaths (Stewart and Kleihues 2003). Several cost-effectiveness analyses in breast cancer have been performed in recent years, usually aimed at one single intervention in developed countries. Although this offers useful data for situations where proper breast cancer care is present, these data do not aid in resource allocation decisions in developing countries. The aim of the study in chapter 4 is to broadly assess the cost-effectiveness of various forms of breast cancer control in different settings. These basic interventions are aimed at different stages of disease and include both surgical treatment supplement with radiotherapy and chemotherapy. A strategy that included early detection through active case finding is also included. In this study the generalized cost-effectiveness methodology, which is developed by the World Health Organization (WHO) for the use in priority setting is used.

Cost-effectiveness of melagatran/ximelagatran

In the Netherlands the total of number of total hip replacements (THR) increased by 68% in the period 1986-1997, to 17,400 per year with a possible increase by 50% in the year 2020 (Ostendorf 2002). In the period 1990-2000 the number of total knee replacements (TKR) increased from 2727 to 7764 with an expected increase towards approximately 11,000 procedures in the year 2020 (personal communication, M. Ostendorf, November 2002). As patients are at an increased risk of getting venous thromboembolic events (VTEs) effective thromboprophylaxis is essential for patients undergoing major elective orthopaedic surgery (1998a; Geerts 2004).

Melagatran/ximelagatran, an oral direct thrombin inhibitor, has been developed to overcome the limitations of the currently used low molecular weight heparins (daily subcutaneous injection) and vitamin K antagonists (small therapeutic window which requires frequent monitoring) for VTE prophylaxis. As in many other countries, there is a trend towards a reduced length of hospital stay in the Netherlands (Prismant), with a discharge to home or a rehabilitation clinic after less than five days. The introduction of melagatran/ximelagatran makes such early discharges considerably easier. In chapter 5 a cost-effectiveness analysis of melagatran/ximelagatran is presented.

Cost-effectiveness of rituximab

In the Netherlands there are approximately 2300 new cases of non-Hodgkin's lymphoma (NHL) making it the ninth most incident cancer (Visser 2003). NHL is actually a generic name for a variety of lymphatic malignancies, with diffuse large B-cell lymphoma (DLBCL) as the largest subgroup (approximately 40%) (Krol 2003). Standard treatment is CHOP for over 30 years for patients with this disease. The addition of the monoclonal antibody 'rituximab' to this standard chemotherapy has improved the disease-free and overall survival in patients both above and under 60 years significantly (Coiffier 2002; Pfreundschuh 2004c). The aim of this study is to perform a cost-effectiveness analysis of rituximab in DLBCL in the Netherlands (chapter 6).

Cost-effectiveness of imatinib

The two studies in chapters 7 and 8 relate to the treatment of patients with chronic myeloid leukaemia (CML). With an incidence of 170 new cases in 2000, CML is one of the less significant haematological indications in the Netherlands (Visser 2000). The introduction of imatinib at the end of 2001, on the basis of a phase II study, changed the treatment of CML substantially. Almost 90% of patients with resistance or intolerance to interferon-alfa (IFN), the standard of first-line care before imatinib introduction, who were treated with imatinib reached a complete haematological response. 49% of these patients reached a complete or partial cytogenetic response. The goal of the first study (chapter 7) is to determine the average cost-effectiveness ratios in patients with CML in the chronic phase of first-line treatment with IFN or second-line imatinib following IFN failure. First-line IFN treatment is chosen as a comparator as, according to

the involved medical specialists, there were no suitable second-line treatment options available at the time.

In chapter 8 the results of the incremental cost-effectiveness analysis of interferon alpha-2a plus low-dose cytarabine (IFN+Ara-C) versus imatinib as first-line treatment option for CML in the chronic phase are presented. This study is based on the pivotal phase III registration study of imatinib in the first-line that enabled us, in contrast to the analysis in chapter 7, to perform an incremental cost-effectiveness analysis to determine the added value of imatinib in the treatment of CML patients. In additional scenario-analyses, two additional second-line treatment options for the imatinib group are included to give an impression of the possible cost-effectiveness outcomes of treatment strategies that are currently being investigated in clinical trials.

PART 3. DIFFUSION OF INNOVATIVE DRUGS

Drug expenditures as part of the overall healthcare expenditure are growing rapidly in most countries as a result of an increasing number of prescriptions and the introduction of new innovative drugs. Governmental authorities try to control this growth in drug expenditure using various techniques. Drugs that are prescribed for use outside the hospital are among the most transparently regulated parts of healthcare. This is in sharp contrast with the regulation of drugs that are used within the hospital, which is much less transparent. Dutch clinicians indicate that the prescription of new innovative drugs is limited by financial constraints and that they lag behind with other European countries. This is an increasingly important issue as most of the drugs currently under development in the field of haematology, oncology and immunology are expensive. The objective of chapter 9 is to quantify and qualify the position of the Netherlands compared to other European countries with regard to the introduction and diffusion of innovative drugs in haemato-oncology and to relate this to the variation in regulation and financing systems in these countries.

DISCUSSION

In chapter 10 the findings of the individual chapters will be discussed in relation to two central topics of this thesis. Furthermore an exploration of future developments in economic evaluations and how these can be studied will be presented.

Part 1

Cost analysis of allogeneic stem cell transplantations

Chapter 2

Cost analysis of HLA-identical sibling and voluntary unrelated allogeneic bone marrow and peripheral blood stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia

SUMMARY

Allogeneic stem cell transplantation (SCT) is one of the most expensive medical procedures. However, only a few studies to date have addressed the costs of HLA identical sibling transplantation and only one study has reported costs of unrelated transplantation. No recent cost analysis with a proper follow-up period and donor identification expenses is available on related or voluntary matched unrelated donor (MUD) SCT for adult AML or ALL. Therefore, we calculated direct medical (hospital) costs based on 97 adults who underwent HLA-identical sibling bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT), and patients who received a graft from a MUD between 1994 and 1999. The average costs per transplanted patient were € 98,334 (BMT), € 151,754 (MUD), and 98,977 (PBSCT), including donor identification expenses, 2 years follow-up and costs of patients who were not transplanted after they had been planned to receive an allograft. The majority of these costs was generated during the hospitalisation for graft infusion. For MUD transplants, nearly one-third of these costs was spent on the search for a suitable donor. For patients who were alive after 2 years, cumulative expenses were calculated to be € 103,509 (BMT), € 173,587 (MUD), and € 105,906 (PBSCT).

INTRODUCTION

Allogeneic SCT for leukaemias is known to be one of the most expensive medical procedures, due to long hospital care, high-technology medical interventions and the provision of specialised facilities (Johnson 1998). In The Netherlands, a few licensed hospitals perform allogeneic stem cell transplantations (SCT), for which they receive historically determined financial budgets. However, these budgets were assigned more than 10 years ago and are currently assumed to be far from sufficient. Due to new developments such as use of grafts from unrelated voluntary donors, improved possibilities of preventing and treating graft-versus-host disease, and use of donor lymphocyte infusions, a revision of the costs of SCT was felt to be needed to allow adequate budget allocation.

Few studies have addressed the costs of SCT (Waters 1998). To our knowledge, only one study on costs of transplantations using unrelated donor stem cells has been published, for patients with chronic phase chronic myelogenous leukaemia (Lee 1998). Published studies on the basis of real patient data estimating costs of SCT for adult leukaemia using HLA identical sibling donors show wide variations and range from approximately US$ 20,000 to US$ 225,000 (Armitage 1984; Welch 1989; Beard 1991; Dufoir 1992; Barr 1996; Faucher 1998). The differences are probably due to different costing methodologies and varying follow-up durations. These also hamper valid comparison of results. Except for the studies of Lee *et al* (Lee 1998) and Faucher *et al*, (Faucher 1998) most studies are based on data from patients treated before 1990. Unfortunately, the Lee study (Lee 1998) only considered chronic phase chronic myeloid leukaemia and the Faucher study (Faucher 1998) only considered a 100-day follow-up and did not include donor identification costs. Analysing cost data from recently treated acute leukaemia patients is recommended, because learning curve effects of this kind of highly specialised care could have reduced the costs of SCT (Waters 1998). Bennett *et al* (Bennett 1995) demonstrated such an effect on the costs of autologous SCT for Hodgkin's disease and non-Hodgkin's lymphoma.

To present recent costs of SCT for adult patients with acute leukaemia and to provide a basis for revision of hospital budgets, we calculated direct medical (hospital) costs (Horngren 2000) of both HLA-identical sibling and unrelated donor SCT in a retrospective study, in patients treated between 1994 and 1999. The cost analysis was based on data from patients with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL), which are amongst the diagnostic categories for which SCT is currently most frequently used (Gratwohl 2001).

PATIENTS AND METHODS

This cost analysis was performed by following two complementary methods. First, the usual method (multiplying the medical consumption units used by the patients by the unit costs of each of the items that can be distinguished within this consumption) was applied. However, a structural program for allogeneic transplants brings along costs that are not expressed within the registration of the medical consumption of patients. The costs of these items were identified by documents from the financial departments of the hospitals, and by expert opinion.

Patients

In four Dutch hospitals performing allogeneic stem cell transplants (University Medical Centres of Utrecht, Rotterdam, Nijmegen and Leiden), a random selection was made from patients with acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL) who had received a stem cell graft harvested from the bone marrow of an HLAidentical sibling (BMT), or a stem cell graft harvested from the peripheral blood of an HLA-identical sibling (PBSCT), or a stem cell graft from the bone marrow or peripheral blood of a voluntary matched unrelated donor (MUD). The transplants were performed between 1994 and 1999. We aimed to reach a 2-year follow-up, in which five phases were identified: (1) Pretransplantation: screening of the patient's eligibility to undergo allogeneic SCT; (2) Transplantation: starting with the first day of hospitalisation for the transplant procedure until the first discharge after the transplant procedure; (3) Follow-up phase 1: from the first discharge after the transplant procedure until 6 months after transplant date; (4) Follow-up phase 2: 6–12 months after transplantation date; (5) Follow-up phase 3: 12–24 months after transplantation date.

Irrespective of disease state, the aim was to follow all patients until 24 months after the transplant date or until the day they died, if earlier. One phase was identified for the HLA-identical sibling donors: (1) Harvesting: from the first hospital visit preceding the harvesting to the final visit thereafter. Within these phases, medical consumption items used by the patients and HLA-identical sibling donors were recorded, by using data from the hospital information systems and patient charts. The institutional perspective was taken, as this analysis was designed to be a basis for determining a hospital budget.

Unit costs

In contrast to charges, unit costs are the best estimators of the theoretically exact opportunity costs (Drummond 1997). Therefore, we determined average unit costs (Table 1) for the most important cost items that appeared from an inventory of medical consumption, reflecting real resource use, including an increase for overhead costs (Horngren and Foster 2000; Oostenbrink 2000). Valuation of resources and overhead costs was based on financial data from two of the four hospitals (1998 level, 1 € = 2.20371 Dutch Guilders).

All unit costs excluded costs of the haematologists, because their costs were determined separately. The unit cost of an isolation hospital day (Table 1) reflected the high nursing intensity for patients who have just received an allograft. Within the 'transplantation phase', all hospital days were multiplied by this unit cost. The hospital days in all other phases were multiplied by the unit cost of a regular hospital day, reflecting normal nursing intensity. Costs of parenteral nutrition were calculated separately. The unit cost of day care treatment was particularly based on the staff (excluding haematologist) and resources required for administrating blood components or performing phereses. The unit cost of an outpatient visit was based on the staff and resources required for a regular follow-up visit. Diagnostic tests and other procedures were multiplied by Dutch tariffs, as these are proper approximations of the actual unit costs (Oostenbrink 2000). Costs of medication were based on Dutch 1998 wholesale prices (van der Kuy 1998).

Table 1: Unit costs (€) of hospital days, day care treatments and outpatient visits

Unit cost component	**Hospital days**			**Other**	
	Haematology 'regular'	Haematology 'isolation'	Intensive care unit	Day care treatment	Outpatient visit
Nursing staff	133	230	500	11	24
Administration staff	9	9	12	5	15
Materials	21	21	95	19	2
Debits and interest	7	7	48	4	1
Regular nutrition	11	11	11	3	0
Launddry	10	10	10	10	0
Cleaning	5	5	6	5	0
Accomodation	57	57	75	54	8
Overheads	59	59	183	26	13
Total (excluding haematologist	312	409	941	137	64

Pretransplantation screening

The transplantation process started with patient screening. Its costs were calculated on the basis of protocol schedules (Table 2). The HLA was typed twice: one full test and one confirmatory test. Full HLA-typing included typing for HLA-ABC and HLA-DR(DQ) by serological and molecular methods. Confirmatory HLA-typing included determination of HLA-ABC and HLA-DR(DQ) by molecular methods.

Family HLA-typing (HLA-identical sibling transplant only)

Before an HLA-identical sibling transplant was performed (BMT or PBSCT), an average of four family members had been fully HLA typed, of whom one was finally selected as the stem cell

donor. In Results, the HLA typing costs of the three rejected family members will be accounted for in the 'donor table' (Table 5). Typing costs of the selected donor (including a confirmatory HLA test) will be reflected in the 'donor table' (Table 5).

Table 2: Pretransplantation screening (unit costs in €)

Screening components	Costs
Two patient information sessions	128
HLA (A, B, C, DR) typing + confirmation	1,010
Hemogram	12
Chemistry (Na, K, Cl, Ca, P, HCO3, Creat, Bili, AF, gGT, SGOT, SGPT, LDH)	37
Blood group + Rh factor, antibody screening	2
Virus serology (HBsAg, HBcAg, CMV, EBV, VZV, HSV, HIV, Toxoplasmosis)	85
Leucocytes antibodies	11
Chimerism	209
X-thorax, X-sinus, X-OPG	174
Spirometry, CT-lung	1,774
ECG	18
Ejection fraction	191
BM morphology, immunology	204
Dental consultation	84
Total (excluding haematologist)	2,342

Stem cell harvesting from HLA-identical siblings

In cases of an HLA-identical sibling transplant, the choice for harvesting stem cells from either the bone marrow (BM) or the peripheral blood (PB) is made by the donor.

BM stem cell harvesting*:* Harvesting stem cells from BM was performed in one session in the operating theatre under general or local anaesthesia. Costs of the 2.5-h use of the theatre (including theatre personnel, equipment, cleaning, housing, and overheads) were € 840 (including € 274 overhead costs). It further required 2 h from two nurses, 0.5 h from an anaesthetist, and 2.5 h from an anaesthetic assistant. Their cumulative costs were € 260. Material costs were € 76. The total costs of BM stem cell harvesting were therefore € 1,176. Costs of two haematologists involved have not been calculated here, because their costs were calculated separately.

PB stem cell harvesting*:* Harvesting stem cells from PB was performed at the day care centre in two sessions. The unit cost of day care treatment was therefore calculated twice (€ 274). Nursing costs (5.5 h per harvesting) were € 315. In total, the costs of PB stem cell harvesting added to € 1,209 (of which € 371 was material costs, € 56 equipment costs, and € 193 overhead costs).

Donor costs for unrelated transplants

The costs for searching for an unrelated allograft consisted of five parts: Family HLA-typing, Requesting donor blood samples, Sample typing, Requesting the donor graft, Europdonor costs. In the results section, the costs of these parts are presented in Table 5.

About 45% of all patients for whom an unrelated allograft had been searched finally underwent transplantation. Sometimes no donor could be found (20%) or the donor was found when the patient's condition had deteriorated too much for transplantation (35%). However, for these 55% of all patients, search activities were also undertaken. To give account for their costs, an increase of 122% (55/45) was applied to the costs of patients who underwent transplantation.

Family HLA typing

Although no HLA-identical sibling was found, the search for an HLA identical graft had been started initially on four family members (on average) of the patient. They were fully HLA typed. Also, in 15% of all cases, an average of six cousins were fully HLA typed. The costs added up to € 3,082. Account was given for the 55% of all MUD patients who did not undergo transplantation. This resulted in an increase of € 3,760 (122% of € 3,082) per transplanted patient. The total costs of family HLA typing therefore added up to € 6,842.

Requesting blood samples

The search for an unrelated HLA identical donor was started in the Bone Marrow Donors Worldwide system. On average, blood samples of six potential donors were requested, but only four requests were fulfilled (generally due to withdrawals of formerly potential donors). The charges for these samples are highly dependent on the country delivering the samples. We determined an average weighted charge of € 620 per sample, based on the national registry specific charges and the percentage of samples originating from these countries. The costs of the four samples were therefore € 2,480. Applying the 122% rise for the patients who did not undergo transplantation led to total costs of € 5,506 per transplanted patient.

Sample typing

HLA retyping of each of the four samples was performed in the Dutch hospitals, consisting of a medium/low resolution HLA class I test and a high resolution test for DRB1/DQB, costing € 390 per sample (€ 1,561). Within each palette of four samples, an HLA high resolution HLA-I test (€ 681) was performed on 2.43 samples, an HLA-DPB1 test (€ 79) on 3.31 samples, a MLC-test (€ 908) on 0.78 samples, and a CTLp-test (€ 1,361) on 0.89 samples, resulting in additional costs of € 3,836. Virology tests (€ 113) were performed on the finally selected sample, resulting in total sample typing costs of € 5,510. Per transplant, the costs were € 12,232, which includes the 122% rise for patients who did not undergo transplant.

Requesting donor graft

Again, the costs of the selected donor graft were highly dependent on country of origin. We determined an average weighted charge of € 15,971 per graft (which generally contained stem cells harvested from bone marrow) on the basis of the country-specific charges and the percentage of grafts originating from these countries.

Europdonor intermediation

The average charges of the Europdonor Foundation, which coordinates the logistic procedures of requesting the samples and grafts for all Dutch transplant centres amounted to € 1,929 per transplanted patient.

CD34 selection or T cell depletion

When the stem cells had been collected (regardless of origin, i.e. related or unrelated), they all underwent CD34 selection or T cell depletion. For this calculation, we assessed them as identical procedures, as the required materials and equipment are comparable. These costs have been based on inventories from the participating hospitals. On average, the procedure amounted to € 4,592, consisting of reagents (€ 2,042), a large tubing set (€ 1,089), EDTA (€ 100) and quality control tests (€ 1,361). The quality control tests included a FACS analysis (CD3, 4, 8, 19, 34, 56), haematopoietic progenitor tests, sterility tests and freezing/storing reference vials (see Results, Table 5).

Donor lymphocyte infusion (DLI)

Patients sometimes needed one or more additional infusions with lymphocytes from the original stem cell donor to achieve complete remission. On average, one DLI was required in 50% of the transplanted patients. The additional costs of DLI depended on the origin of the stem cells. These costs are presented in the follow-up table (Table 6) of the Results section, as a DLI was mostly required in the follow-up phase 1.

DLI following HLA-identical sibling transplant

When DLI following HLA-identical sibling transplantation was done, the original donor was requested to visit the outpatient clinic (costs of an outpatient visit: € 64). Additional tests were performed: haematological counts, white blood cell counts and differential counts (€ 12), chemistry tests (Na, K, Cl, Ca, P, HCO3, Creat, Bili, AF, gGT, SGOT, SGPT, LDH: € 37), virus serology (HBsAg, HBcAg, CMV, EBV, VZV, HSV, HIV, Toxoplasmosis: € 85). The use of materials, equipment and the staff required for the phereses was similar to that for the PB stem cell harvesting with the exception that lymphocytes pheresis was performed in one day care session only. Harvesting costs were therefore € 1,072. The harvested lymphocytes were processed at the stem cell laboratory, costing € 753. The total DLI costs therefore added up to € 2,023. As DLIs

were used in 50% of patients on average, half of this amount will be accounted for in the Results section (Table 6).

DLI following unrelated transplantation

Charges for additional lymphocytes from the original unrelated stem cell donor consisted of the request for those lymphocytes and courier costs. Lymphocytes of European origin cost € 4,538 on average, of which € 1,134 was courier costs. Lymphocytes from other parts of the world cost € 9,076 on average, of which € 2,269 was courier costs. Two out of three requested unrelated lymphocytes came from European donors, which resulted in average DLI costs of € 6,051. Lymphocytes were processed at the stem cell laboratory in the Dutch transplant centre, costing € 753. In total, the costs added up to € 6,804, of which 50% will be accounted for (€ 3402) in the Results section (Table 6), for the above-mentioned reason.

Total body irradiation (TBI)

The conditioning regimen preceding transplantation consisted of cyclophosphamide (accounted for in costs of cytostatics; Results, Table 4) and TBI. The TBI procedure started with an outpatient visit to the radiotherapy department (at € 64). The radiotherapist spent 70 min with each patient before the TBI and 35 min thereafter (costing € 135). Laboratory personnel spent 355 min and 280 min, respectively (costing € 303). Eighty minutes were required from administration staff (€ 38). Debits for the accelerator, the simulator and the radiotherapy chair were € 486, € 36 and € 69 per TBI. Exploitation costs amounted to € 233. housing and overheads were € 77 per TBI. In total, TBI costs summed up to € 1,441.

Transplantation program personnel

The personnel required to run a structured transplant (set at 35 transplants per year) program is reported in Table 3. Note that the Table does not include the following personnel: (1) Personnel performing HLA typings: their costs have been included in the unit costs of HLA typing. (2) Radiotherapists and radiotherapy laboratory personnel: since they are only involved in the transplantation program during TBI, their costs have been included in the TBI unit costs. (3) Theatre staff: as these are only involved during BM stem cell harvesting, their costs have been included in the BM harvesting unit costs. (4) Nursing staff: their costs have been included in the hospital day unit costs (see Table 1) to give account for the difference between isolation hospital days and regular hospital days.

Total costs resulting from multiplying full-time equivalents (FTEs) of personnel in Table 3 by total employer costs (including wages, bonuses for irregular working hours and social premiums) added up to € 929,001. If this amount is distributed over an average of 35 transplant patients per year, the costs would be € 26,543. In the results, these costs are presented in the final table (Table 7).

Table 3: Personnel required for an annual program for 35 allogeneic transplantations (costs in €)

Personnel	FTEs required	Employer costs per FTE
Chief of stem cell transplants (senior haematologist)	1.0 FTE	119,120
Senior haematologist	2.1 FTE	119,120
Junior haematologist	2.5 FTE	72,000
Bloodbank laboratory	0.8 FTE	32,400
Stem cell laboratory	2.0 FTE	37,350
Pheresis laboratory	1.1 FTE	37,350
Data manager	2.0 FTE	37,350
BMT coordinator	1.0 FTE	37,350
Secretary of haematology department	1.0 FTE	32,400
Outpatient clinic secretary	1.0 FTE	32,400
Dietician	0.4 FTE	37,350
Microbiologist	0.2 FTE	119,120
Social worker	0.2 FTE	37,350
Psychological nurse	0.2 FTE	37,350
Central registration	0.2 FTE	37,350
Total	15.7 FTE	929,001

RESULTS

Patients

Data from 97 patients (45 male, 52 female; 66 AML, 31 ALL) were studied, of whom 47 had undergone sibling BMT, 29 MUD transplantation, 21 sibling PBSCT between 1994 and 1999. Mean age of the patients was similar in the three groups: 35.6 years on average (median, 36.0; range, 14–61).

Costs

Transplantation phase

The average costs per patient during the transplant phase (from the start of the high-dose conditioning regimen until first discharge after transplantation) are reported in Table 4. The costs of the pretransplant screening (which had been specified in Table 2) have been accounted for in this phase. A specification of donor costs is presented in Table 5. Costs of the haematology isolation hospital days are based on the average durations of hospitalisation during this phase: 39.74 (BMT), 43.10 (MUD) and 43.33 (PBSCT). In total, costs during the transplantation phase (including pretransplantation screening costs and donor costs) were € 42,129 (BMT), € 84,948

Table 4: Average costs per patient (€) during the transplantation phase (from start of high-dose conditioning regimen up to first discharge after the transplantation)

Cost component	BMT	MUD	PBSCT
Pretransplantation screening (see Table 2)	2,342	2,342	2,342
Donor costs (see Table 5)	10,843	47,063	11,137
Haematology 'isolation' hospital days	16,248	17,622	17,716
Consultations	98	113	120
Cytostatics	94	102	124
Antibiotics	2,700	3,394	2,058
Hematopoietic growth factors	337	34	103
Immunosuppressants	510	638	720
ATG anti-thymocyte globulin	0	2,723	0
Other medication	451	473	497
Blood components	1,303	2,405	2,552
Parenteral nutrition	602	645	341
TBI	1,441	1,441	1,441
Laboratory diagnostics	2,038	2,763	2,610
Microbiology diagnostics	1,047	1,452	1,271
Pathology diagnostics	993	752	1,306
Radiology diagnostics	396	509	817
Other imaging diagnostics	290	182	300
Other procedures	396	295	279
Total costs, excluding personnel costs	42,129	84,948	45,734

(MUD), and € 45,734 (PBSCT). It should be noted that these costs do not include the costs of the transplantation personnel, as these will be reflected only in the final table (Table 7).

Follow-up phases

Table 6 presents the average costs during the follow-up phases, per patient alive (the percentage of patients alive within each of the phases is shown in Table 7). Only in the final table (Table 7), will account be given to the fact that patients die during the follow-up. Again, Table 6 does not include costs of transplantation personnel; these have only been accounted for in Table 7.

In follow-up phase 1, the patients were hospitalised for 19.43 (BMT), 28.19 (MUD) and 13.20 days (PBSCT) on average. They visited the outpatient clinic 22.45 (BMT), 19.00 (MUD) and 19.58 times (PBSCT) on average.

During follow-up phase 2 (6–12 months after transplantation), patients were hospitalised for 12.79 (BMT), 18.79 (MUD) and 9.94 days (PBSCT) on average. Average frequencies of outpatient visits were 12.58 (BMT), 10.60 (MUD) and 9.27 (PBSCT).

In the follow-up phase 3 (12–24 months after transplantation), patients had 12.53 (BMT), 18.00 (MUD) and 6.82 (PBSCT) hospital days on average. They were seen in the outpatient clinic on average 10.22 (BMT), 26.50 (MUD) and 5.71 (PBSCT) times.

Total costs

Table 5: Donor costs (in €)

Cost component	**BMT**	**MUD**	**PBSCT**
HLA-identical sibling transplantations only			
HLA rejected related donors	1,887	–	1,887
HLA selected related donor	1,010	–	1,010
Stem cell harvesting	1,176	–	1,209
Haematology 'regular' hospital days	918	–	0
Haematology outpatient visits	118	–	116
Other consultations	10	–	7
Hematopoietic growth factors	0	–	1,387
Blood components	61	–	20
Laboratory diagnostics	686	–	678
Microbiology diagnostics	7	–	3
Pathology diagnostics	139	–	136
Radiology diagnostics	43	–	45
Other imaging diagnostics	20	–	13
Other procedures	176	–	34
Unrelated transplantations only			
Family HLA typing	–	6,842	–
Requesting blood samples	–	5,506	–
Sample typing	–	12,232	–
Requesting donor graft	–	15,971	–
Europdonor intermediation	–	1,920	–
Both related/unrelated transplantations			
CD34 selection/T cell depletion	4,592	4,592	4,592
Total costs, excluding personnel costs	10,843	47,063	11,137

Table 6: Average costs (€) per (living) patient in the follow-up phases

Cost component	Follow-up phase 1			Follow-up phase 2			Follow-up phase 3		
	BMT	MUD	PBSCT	BMT	MUD	PBSCT	BMT	MUD	PBSCT
Haematology 'regular' hospital days	6,066	8,801	4,121	3,993	5,866	3,103	3,912	5,620	2,129
Intensive Care hospital days	0	543	0	0	1,143	0	0	0	0
Haematology outpatient visits	1,436	1,216	1,253	805	678	593	654	1,696	365
Other consultations	402	707	657	286	523	482	326	572	402
Antibiotics	11	1,006	109	132	166	12	0	0	0
Hematopoeitic growth factors	0	368	0	0	0	0	0	0	0
Other medication	7	116	88	9	35	4	0	6	0
Day care department	106	260	112	46	14	15	104	46	0
Radiotherapy	0	0	0	0	216	0	83	0	0
Blood components	1,317	2,740	1,127	1,006	1,735	1,027	599	1,270	210
Laboratory diagnostics	2,717	4,796	2,486	1,800	3,161	2,769	1,358	2,256	1,403
Microbiology diagnostics	732	1,180	706	359	757	766	255	202	493
Pathology diagnostics	1,692	2,413	2,201	811	1,765	1,159	411	509	706
Radiology diagnostics	525	1,119	441	394	879	1,133	163	714	293
Other imaging diagnostics	469	1,060	567	340	904	1,065	129	398	261
Other procedures	94	568	172	177	632	135	99	42	52
Donor lymphocytes infusion	1,012	3,402	1,012	0	0	0	0	0	0
Total costs, excluding personnel costs	16,587	30,292	15,051	10,157	18,473	12,265	8,093	13,331	6,313

Follow-up phase 1 = from first discharge after transplantation up to 6 months after transplantation date. Follow-up phase 2 = 6–12 months after transplantation date. Follow-up phase 3 = 12–24 months after transplantation date.

Table 7: Calculation of the average costs (€) per transplanted patient

	BMT			MUD			PBSCT		
	Average cost per living patient	* % alive	= Average costs per transplant patient	Average cost per living patient	* % alive	= Average costs per transplant patient	Average cost per living patient	* % alive	= Average costs per transplant patient
Personnel	26,543		26,543	26,543		26,543	26,543		26,543
Transplantation	42,192	100	42,129	84,948	100	84,948	45,734	100	45,734
FU1-phase	16,587	98	16,255	30,292	90	27,263	15,051	92	13,847
FU2-phase	10,157	81	8,227	18,473	48	8,867	12,265	77	9,444
FU3-phase	8,093	64	5,180	13,331	31	4,133	6,313	54	3,409
Total costs	103,509		98,334	173,587		151,754	105,906		98,977

FU = follow-up.

Tables 4 and 6 present the average costs per living patient, up to 2 years after transplantation. As this analysis was performed for an adequate budget revision, we calculated the average costs per new and transplanted patient in Table 7. This approach is based on the assumption that budget parts 'saved' by patients who died relatively early are used to cover the costs of patients who live longer. For example, each BMT patient underwent the transplantation phase, which cost € 42,129 on average. Follow-up phase 1 cost € 16,587 per living BMT patient on average, but this applied to 98% of the initial group. Therefore, 98% of € 16,587 (€ 16,255) was accounted for in the calculation of the average costs per transplanted patient. Consequently, 81% of the average costs per BMT patient during follow-up phase 2, and 64% of the average costs during follow-up phase 3 have been accounted for. Yearly costs of the transplantation personnel (€ 26,543) have been divided over all transplanted patients within a certain year. Finally, the average costs per transplanted patient were € 98,334 (BMT), 151,754 (MUD) and € 98,977 (PBSCT). Table 7 also gives an impression of the costs of patients who were alive after 2 years follow-up, these were € 103,509 (BMT), € 173,587 (MUD) and € 105,906 (PBSCT).

DISCUSSION

We analysed the costs of 97 adult patients with AML or ALL who received a bone marrow (BMT) or peripheral blood stem cell graft (PBSCT) from an HLA-identical sibling or a graft from a voluntary matched unrelated donor (MUD). The average costs per transplanted patient were € 98,334 (BMT), € 151,754 (MUD), and € 98,977 (PBSCT), including donor identification expenses, 2 years' follow-up and costs of patients who were not transplanted after they had been planned to receive an allograft. The vast majority of these costs was generated during hospitalisation for the transplant procedure. For MUD transplant, nearly one-third of these costs was spent on the search for a donor. Patients who were alive after 2 years had generated cumulative costs of € 103,509 (BMT), € 173,587 (MUD) and € 105,906 (PBSCT).

We have determined the average costs per patient and we assume we have calculated these adequately by assessing a large total number of patients. Nevertheless, it could be argued that a cost analysis should incorporate a sensitivity analysis to give account for uncertainty in the calculated average costs (Drummond 1997). The reason for its omission was the difference in sources used to calculate the medical consumption of the patients. It was not possible to invest time in merging those different sources into one statistical database. In this analysis, the uncertainty in hospitalisation costs during the transplantation phase would be most important, as variation in this cost component may exert a major influence on the calculated average costs, due to the high unit cost of a haematology isolation hospital day. Moreover, the costs of hospitalisation are almost always the most important cost component in economic evaluations of clinical treatments (Oostenbrink 2000). The availability of a database with hospital days enabled us to provide some 95% confidence intervals illustrating the possible

variation in hospital costs. During the transplantation phase, the average number of hospital days on the haematology isolation ward was 39.74 (BMT), 43.10 (MUD) and 43.33 (PBSCT). The 95% confidence intervals were 37.44–42.45 (BMT), 34.43–51.78 (MUD) and 35.50– 51.17 (PBSCT), resulting in uncertainties of, respectively, € 940 (1% of average total costs per patient), € 3,553 (2%) and € 3,205 (3%). As the sample sizes decreased due to a descending survival curve, variations in hospitalisation during the follow-up phases were somewhat wider, but these exerted less influence due to lower unit costs of the follow-up hospital days. Given these low variations, we estimate that the total uncertainty would not be higher than approximately 10%, particularly since the second major cost component (personnel costs) consists of fixed costs.

Few studies have so far reported costs of HLA-identical sibling SCT, (Armitage 1984; Welch and Larson 1989; Beard 1991; Dufoir 1992; Barr 1996; Faucher 1998) and only one study has been published on costs of unrelated voluntary SCT (Lee 1998) for a narrowly defined patient group, chronic phase CML. We have not attempted to compare the absolute costs reported, as there are too many possible biases and discrepancies. Some studies exclude certain cost items, unit costs are subject to a large variation between countries (particularly if they were based on charges), and price levels varied. Moreover, the follow-up durations assessed were not comparable between different publications, donor costs have not always been taken into account, and the 'state of technology' implicitly assessed may have been very different as most of the studies were based on patients treated in the 1980s (except studies described in Refs 3 and 9). Finally, except for one study, (Lee 1998) the sample sizes on which the calculations were based, have generally been small (<43). We refer to Johnson *et al* (Johnson 1998) and Waters *et al* (Waters 1998) for proper overviews of the costs calculated in different studies.

It is generally assumed that allogeneic PBSCT results in faster haematological recovery than allogeneic BMT, which was demonstrated by Bensinger in a retrospective analysis (Bensinger 1996). This faster recovery may lead to cost advantages of PBSCT over BMT, due to earlier discharge, fewer transfusions, and fewer antibiotics. These cost advantages have been confirmed several times in autologous transplants for lymphoma patients (Faucher 1994; Uyl-de Groot 1994; Ager 1995; Bennett 1995; Bensinger 1996; Smith 1997; Woronoff-Lemsi 1997; Faucher 1998; van Agthoven 2001b). In allogeneic transplants, such a cost advantage has been confirmed by Faucher *et al*. (Faucher 1998). Although this comparison was not the aim of our analysis, it is inconsistent that the costs of our PBSCT patients were found to be very similar to those of our BMT patients. Particularly in the transplantation phase, the former group was hospitalised somewhat longer. This difference may relate to the fact that the Dutch centres used PBSCT following T cell depletion, which had the potential advantage of reducing incidence and severity of post-transplantation graft-versus-host disease, but the disadvantage of losing some of the accelerated haematopoietic repopulation. In addition, we may coincidentally have selected a sample of PBSCT patients in a relatively poor condition.

An advantage of this analysis is that it provides an opportunity for defining the requirements for (setting up) a program for allogeneic transplants. A number of articles have already provided

recommendations for the performance of SCT (1990; 1992; Goldman 1994; Link 1995). Our analysis directly links the requirements of an infrastructural program for allogeneic transplants as drawn up by four experienced centres to their financial implications, and to numbers of full-time equivalents (FTEs).

Together with the studies of Lee *et al* (Lee 1998) and Faucher *et al*, (Faucher 1998) our study is one of the very few on the costs of recent allogeneic transplants. Just as the earlier studies, it only considered direct medical (hospital) costs, but it comprises the largest sample of adult acute leukaemia patients assessed to date within a cost analysis, in which all essential components have been taken into account, including costs of donor identification, and a 2-year follow-up. A recommendation for future research would be to investigate the non-medical indirect costs, such as costs of lost production due to absence from work, as these costs may also be considerable in this young patient group.

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Chapter 3

The role of cost analysis in the evaluation of the development of medical technology. The case of allogeneic stem-cell transplantations

SUMMARY

Objective: To estimate the real costs of allogeneic haematopoietic stem-cell transplantation and to compare these with the historically determined budget that is made available for this purpose (€ 70,038 for genetically related donors and € 76,826 for unrelated donors).

Design: Cost analysis

Methods: In the period 1994-1999, the direct medical costs (price level of 1998) of bone-marrow transplantation from related donors (BMT), stem-cell transplantation from unrelated donors (VUD-SCT) and allogeneic peripheral-blood stem-cell transplantation (PBSCT) from related donors were determined on the basis of data on adult patients with either acute myeloid leukaemia (n=66) or acute lymphocytic leukaemia (n=31). First, the medical resource use by these patients was determined and multiplied by the unit costs of each of the items. Second, a structural program for allogeneic stem-cell transplantation brings along costs that are not evident from the registration of the medical resource use (e.g. the cost of pre transplantation screening and the selection of the donor). The cost of these items were calculated by taking inventory in the hospitals and assessed by experts.

Results: The average costs per transplanted patient were € 98,334 (BMT), € 151,754 (VUD-SCT) and € 98,977 (PBSCT) during the first two years after transplantation. The greater part of the costs was incurred in the transplantation phase. In VUD-SCT, one-third of the total cost was due to the costs of finding a suitable donor.

Conclusion: The current budget for allogeneic stem-cell transplantation is insufficient to perform the transplantations adequately. Periodic evaluation of the budgets for complicated procedures based on cost analyses has added value for the evaluation of the development of these procedures over time and can thereby contribute to the quality and continuity of care.

INTRODUCTION

Medical treatments are continuously evolving. Not only are they subject to technical developments within medicine, e.g. new operating techniques and treatment protocols, but they also depend on several factors outside the hospital that make the intervention possible, like legislation and permits. The reimbursement for performing an intervention and its relation to the true costs play an additional role in the evolution of medical interventions. It is the latter relation that can be made visible by means of cost analyses. Such cost analyses can contribute to the evaluation of the evolution of these medical interventions.

We will illustrate this on the basis of a recently performed cost analysis for a budget revision of allogeneic stem-cell transplantation in the Netherlands (van Agthoven 2002b).

Allogeneic stem-cell transplantation is an accepted intervention for patients with haematological malignancies (e.g. leukaemia or lymphoma) and qualitative or quantitative bone marrow insufficiencies (e.g. a-plastic anaemia or innate immunodeficiency).

Allogeneic stem-cell transplantations are performed in all Dutch academic centres (IGZ 1999; IGZ 2001). This type of transplantation is very expensive because it is difficult to find a suitable donor and due the complexity of interactions between graft and recipient (graft-versus-host and host-versus-graft reaction). The intervention requires very specialized knowledge, a multi-disciplinary approach and high-grade laboratory facilities, as well as nursing and medical facilities. The Dutch budget for this intervention were determined approximately 10 years ago and are € 70,038 or € 76,826 depending on the donor, related or unrelated (2003). These budgets are considered far from adequate by the transplantation centres. For comparison: The budget for stem-cell transplantation in Germany is currently around € 130,000 for related donors, exclusive of the cost for selecting a compatible donor, and around € 195,000 for unrelated donors, exclusive of the cost for selecting a compatible donor. In France, the budget for allogeneic stem-cell transplantations is approximately € 130,000.

In the Netherlands, the health care council studied the costs of allogeneic stem-cell transplantations for the last time in 1987 (Engel 1987). At that time, the costs of allogeneic stem-cell transplantations for adults were € 86,218 (Fl. 190,000) with a possible spread of 20%, price level of 1985. Since this analysis is performed 15 years ago and a number of developments took place in the meantime, this amount is probably – just like the current budget – outdated and bears insufficient relation to the true costs. To come to a well-argued budget revision, we studied the true costs of allogeneic stem-cell transplantations at the request of the transplantation centres.

The current budget for allogeneic stem-cell transplantations deviates from the budget of surrounding countries and the last Dutch cost analysis is over 15 years old, despite technological improvements. This case is therefore well suited to show the added value of cost analyses for political decision-making regarding medical interventions. This case also shows the necessity to update the cost analysis regularly.

*Table 1: average costs of allogeneic stem-cell transplantation, per living patients (in Euros: price level 1998)**

Cost component	Transplantation phase[xx]			Follow-up phase 1: hospital discharge till 6 months post transplantation			Follow-up phase 2: 6 months till 1 year post transplantation			Follow-up phase 3: 2nd year post transplantation		
	BMT (100)	*VUD-SCT (100)*	*PBSCT (100)*	*BMT (98)*	*VUD-SCT (90)*	*PBSCT (92)*	*BMT (81)*	*VUD-SCT (48)*	*PBSCT (77)*	*BMT (64)*	*VUD-SCT (31)*	*PBSCT (54)*
Personnel	26,543	26,543	26,543	-	-	-	-	-	-	-	-	-
Pretransplantation screening	2,342	2,342	2,342	-	-	-	-	-	-	-	-	-
Donor costs	10,843	47,063	11,137	-	-	-	-	-	-	-	-	-
Haematology 'isolation' hospital days	16,248	17,622	17,716	-	-	-	-	-	-	-	-	-
Haematology 'regular' hospital days	-	-	-	6,066	8,801	4,121	3,993	5,866	3,103	3,912	5,620	2,129
Intensive Care hospital days	-	-	-	-	543	-	-	1,143	-	-	-	-
Haematology outpatient visits	98	113	120	1,436	1,216	1,253	805	678	593	654	1,696	365
Other consultations	-	-	-	402	707	657	286	523	482	326	572	402
Daycare treatment	-	-	-	106	260	112	46	14	15	104	46	0
Medication												
Cytostatics	94	102	124	-	-	-	-	-	-	-	-	-
Antibiotics	2,700	3,394	2,058	11	1,006	109	132	166	12	0	0	0
Haematopoietic growth factors	337	34	103	0	368	0	0	0	0	0	0	0
Other medication	961	3,834	1,217	7	116	88	9	35	4	0	6	0
Radiotherapy	-	-	-	0	0	0	0	216	0	83	0	0
Total body irradiation	1,441	1,441	1,441	-	-	-	-	-	-	-	-	-
Blood components	1,303	2,405	2,552	1,317	2,740	1,127	1,006	1,735	1,027	599	1,270	210
Parenteral nutrition	602	645	341	-	-	-	-	-	-	-	-	-
Diagnostics	4,764	5,658	6,304	6,135	10,568	6,401	3,704	7,466	6,892	2,316	4,079	3,156
Other procedures	396	295	279	93	565	171	176	631	137	99	42	51
Donor lymphocytes infusion	-	-	-	1,012	3,402	1,012	-	-	-	-	-	-
Total costs	68,672	111,491	72,277	16,587	30,292	15,051	10,157	18,473	12,265	8,093	13,331	6,313

BMT= bone marrow transplant from related donors; VUD-SCT= stem-cell transplantation from unrelated donors; PBSCT= allogeneic peripheral blood stem-cell transplantation from related donors. *Between brackets is the percentage of patients alive in the different phases. [xx] The phase that started with high dose chemotherapy and that ended with hospital discharge; the costs of personnel, pretransplantion screening and donor selection were included in this phase.

We will briefly present the cost analysis of allogeneic stem-cell transplantation for illustrational purposed. We will describe the added value cost analyses can play in the evaluation of this intervention in the discussion.

PATIENTS AND METHODS

Patients

In the academic centres of Utrecht, Rotterdam, Nijmegen and Leiden a random sample was drawn from patients with acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) who underwent allogeneic stem-cell transplantation in the period 1994-1999. Three groups of patients were distinguished; patients receiving a stem-cell transplant from the bone marrow of a compatible related donor (BMT), from the bone marrow of a voluntary unrelated donor (VUD-SCT), or with stem-cells mobilized from peripheral blood of a related donor (PBSCT).

Costs

In the cost analysis direct medical costs from the hospital perspective were included. The price level was that of 1998.

The cost analysis was performed through two complementary methods. First the medical consumption was determined and multiplied with the unit costs thereof. Additionally, the costs related to transplantations that did not show up in the patient registration were estimated. The costs of medical specialists were calculated separately. Hereto, an estimation of the medical specialists that would be required to perform a structural program of 35 transplants on a yearly basis was made. The personnel costs were subsequently converted to the costs per patient that received a transplant.

Depending on the nature of a hospitalisation, different hospitalisation prices were applied: costs of a day on a regular ward, on the intensive care and the cost of treatment on a isolation ward. These costs were respectively, € 312, € 941 and € 409 (van Agthoven 2002b). Cost of a day care visit were € 137 and an haematological outpatient visit € 64 (van Agthoven 2002b). Other costs were calculated on the basis of tariffs,(1998c) and the costs of medication were derived from the pharmacotherapeutic compass (van der Kuy 1998).

Several cost components that were inherent to the transplantation programme could not be derived from the medical consumption, e.g. the cost of pre-transplantation screening, stem cell removal from related donors and the selection of a suitable unrelated donor. These costs were calculated as separate items on the basis of hospital inventories and expert opinion. A detailed overview of these costs is published previously (van Agthoven 2002b).

Table 2: Calculation of the average costs (in €, price level 1998) per allogeneic stem-cell transplantation

	BMT			MUD			PBSCT		
	Average cost per living patient	* % alive	= Average costs per transplant patient	Average cost per living patient	* % alive	= Average costs per transplant patient	Average cost per living patient	* % alive	= Average costs per transplant patient
Personnel	26,543		26,543	26,543		26,543	26,543		26,543
Transplantation	42,192	100	42,129	84,948	100	84,948	45,734	100	45,734
FU1-phase	16,587	98	16,255	30,292	90	27,263	15,051	92	13,847
FU2-phase	10,157	81	8,227	18,473	48	8,867	12,265	77	9,444
FU3-phase	8,093	64	5,180	13,331	31	4,133	6,313	54	3,409
Total costs	103,509		98,334	173,587		151,754	105,906		98,977

FU = follow-up

RESULTS

Patients

Detailed medical consumption of 97 patients that underwent transplantation was catalogued (45 males and 52 females). 66 patients had AML and 31 ALL. The types of transplantations were as follows: 47 BMT, 29 VUD-SCT and 21 PBSCT. The average age was 35.6 year (median 36, range: 14-61).

Costs

The average costs for living patients during transplantation and the three follow-up phases are presented in table 1.

The transplantation phase is the period starting with high-dose chemotherapy and ending with hospital discharge after transplantation. Cost of personnel, pre-transplantation screening and donor selection were also included in this phase. There is a large difference in donor costs between related and unrelated donors as a result of the donor selection; this is considerably more extensive for unrelated donors.

The first follow-up phase covers the period from hospital discharge till six months post transplantation. The other follow-up phases cover the periods of six months to a year post-transplantation and the second year post-transplantation. In all follow-up phases the costs per living patient are highest after VUD-SCT.

Performing allogeneic stem-cell transplantations is associated with mortality due to complications of transplantation. Additionally, patients die because of leukaemia relapse. As a result the number of patients are smaller in follow-up phases compared to the original number that received a transplant (Table 1). This is important for determining a budget, as this is allocated per treated patient. Total costs from table one will have to be corrected for this mortality to arrive at the required budget per transplanted patient. This was done in table 2 by incorporating the probability of survival in the different phase in the calculation. In this way, the average budget, required to cover the costs of the two-year period per transplant patient, was calculated. These figures show that the budget for transplantations with a related donor (BMT and PBSCT) are very similar. For patients, receiving a transplant from an unrelated donor, the required budget is considerably higher.

DISCUSSION

In this analysis, the costs were calculated for adult patients with acute leukaemia (AML or ALL), receiving bone marrow stem-cells (BMT) or peripheral blood stem-cells (PBSCT) from an HLA-identical donor, or a transplant from an HLA-compatible unrelated donor (VUD-SCT). The average costs per patient were € 98,334 (BMT), € 98,977 (PBSCT) and € 151,754 (VUD-SCT).

These costs included the costs of screening, personnel, donor identification and 2-year follow-up. Additionally, the costs of patients who were screened but never received a transplant were also included in this figure.

The number of allogeneic stem-cell transplantations that are performed for the treatment of patients with haematological malignancies is recorded in the Dutch stem-cell transplantation registry, TYPHON, in Leiden. The shortage that results from the inadequate budget, can be easily calculated on the basis of this registration. In 2002, 179 allogeneic stem-cell transplantations were performed, 40 BMT, 83 PBSCT and 56 VUD-SCT (source: TYPHON, and the EUROPDONOR foundation, which is the national bone marrow database in the Netherlands). The budget received for these transplantations was approximately € 13 million (excluding the costs of medication) while the actual costs were almost € 20 million. Naturally, this shortage has consequences for the quality of aftercare that can be offered. Expensive laboratory tests like chimerism determination, monitoring of Epstein-Barr virus infections and determination of residual disease cannot be performed as often as deemed appropriate.

The above-mentioned calculations show that Dutch transplantation centres incurred considerable shortages as the result of the inadequate budget. These shortages might explain why the development of the number of stem-cell transplantations lags behind with our surrounding countries. This lag is described in a study from the European group for blood and bone marrow transplantations (EBMT) who analysed the development of the numbers and types of transplantations (Gratwohl 2002a). In this database the numbers and types of transplantations are registered on the basis of information from the different transplantation centres. This registration shows that the number of transplantation increases in Europe in the period 1990-2000 but that the growth per 10 million inhabitants lags behind considerably in the Netherlands. Definite statements on the causality between the budget shortage and the lag of the number of transplantations compared to other European countries must be made cautiously because of other medical developments. It is possible that the recent introduction of imatinib as a treatment option in chronic myeloid leukaemia also causes a reduction in the number of transplantations (Gratwohl 2002b). This however, is not investigated for the Dutch situation.

Although the care for patients undergoing allogeneic stem-cell transplantations is adequate on the basis of two reports from the health care inspection,(IGZ 1999; IGZ 2001) the current study shows that these transplantations are performed with a far from adequate budget. In the reports from the inspection no attention is given to the current financial pressure of the transplantation programs. The presented cost analysis offers a tool to do this. This offers the opportunity to look in a different way at the evolution of medical technologies, not only to relate these to developments in surrounding countries, but also to offer the appropriate (financial) recognition for the achievement that is delivered in our own country. This, not only to prevent that the backlog we have compared to the our surrounding countries increases, but mainly to make sure that the quality of care is guaranteed.

This example furthermore shows that the costs of performing a medical technology also evolves over time and that it is desirable for the continuum and quality of care that such an exercise is performed periodically. This approach finally offers the opportunity to make an inventory of expensive interventions. As such, this approach can also be used within the development of diagnosis-treatment combinations or other financing systems within the healthcare sector.

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Part 2

Cost-effectiveness analyses

Chapter 4

Costs and Health Effects of Breast Cancer Interventions in Epidemiologically Different Regions of Africa, North America, and Asia

SUMMARY

We estimated the costs and health effects of treating stage I, II, III, and IV breast cancer individually, of treating all stages, and of introducing an extensive cancer control program (treating all stages plus early stage diagnosis) in three epidemiologically different world regions—Africa, North America, and Asia. We developed a mathematical simulation model of breast cancer using the stage distribution and case fatality rates in the presence and absence of treatment as predictors of survival. Outcome measures were life-years adjusted for disability (DALYs), costs (in 2000 U.S. dollars) of treatment and follow-up, and cost-effectiveness ratios (CERs; in dollars per DALY averted). Sensitivity analyses were performed to determine the robustness of the results. Treating patients with stage I breast cancer resulted in 23.41, 12.25, and 19.25 DALYs averted per patient in Africa, North America, and Asia, respectively. The corresponding average CERs compared with no intervention were $78, $1960, and $62 per DALY averted. The number of DALYs averted per patient decreased with stage; the value was lowest for stage IV treatment (0.18–0.19), with average CERs of $4986 in Africa, $70,380 in North America, and $3510 per DALY averted in Asia. An extensive breast cancer program resulted in 16.14, 12.91, and 12.58 DALYs averted per patient and average CERs of $75, $915, and $75 per DALY averted. Outcomes were most sensitive to case fatality rates for untreated patients, but varying model assumptions did not change the conclusions. These findings suggest that treating stage I disease and introducing an extensive breast cancer program are the most cost-effective breast cancer interventions.

INTRODUCTION

Each year, breast cancer is newly diagnosed in more than 1 million women worldwide and more than 400,000 women die from it (Stewart and Kleihues 2003; Ferlay 2004). Breast cancer as a public health problem is growing throughout the world, but especially in developing regions, where the incidence has increased as much as 5% per year (2002a; Stewart and Kleihues 2003). The mortality: incidence ratio is much higher in developing countries than in developed countries: only half of global breast cancers are diagnosed in the developing world, but they account for three-fourths of total deaths from the disease (Stewart and Kleihues 2003). The increasing burden of breast cancer is also acknowledged in the resolution on cancer prevention and control, as adopted by the 58th World Health Assembly in May 2005. Therein, member states are urged to develop and reinforce comprehensive cancer control programs to reduce cancer mortality and improve quality of life for patients and their families.

Cost-effectiveness analyses (CEAs) can provide useful information for planning and developing a breast cancer control policy. CEAs can be used to guide budget development, justify allocation of scarce resources to national breast cancer control programs, and identify the most efficient ways of delivering diagnostic and treatment services. Nearly all studies of the costs and health effects of breast cancer control interventions have been performed in developed countries (Radice 2003), so data to guide resource allocation decisions in developing countries are scarce. Moreover, studies to date have focused on individual interventions, and interactions among interventions have been largely ignored. In addition, existing studies have focused on interventions specific to breast cancer control in situations where breast cancer care was already in place. This limitation precludes comparisons with interventions in settings where care systems have not been established or with interventions that might be more relevant to other regions of the world.

Our intention was to broadly assess the cost-effectiveness of breast cancer control that covers various interventions in different settings and to enable comparisons with recent CEAs of other health care interventions that follow the same analytic approach (Dziekan 2003; Murray 2003; Shibuya 2003; Baltussen 2004).

PATIENTS AND METHODS

Study Design

We used a simplified breast cancer model to simulate the impact of six basic interventions on the course of breast cancer in three regions of the world (Tan-Torres Edejer 2003). Each intervention was compared with no intervention (i.e., no active case finding or breast cancer treatment). All interventions were introduced starting in the year 2000 for a period of 10 years, after which no breast cancer interventions were available, and the maximum follow-up was 100 years, which

is in line with the World Health Organization (WHO) guidelines on CEA (Tan-Torres Edejer 2003). Following this standardized approach, we assumed that interventions were performed optimally. The outcomes of our analysis were life-years adjusted for disability (DALYs) and the total costs of breast cancer treatment and follow-up for each of the six interventions.

We adopted a societal perspective (Gold 1996) and included all costs and effects in our model. Future costs and effects were discounted at a rate of 3% per year (Gold 1996). The average cost-effectiveness ratio (CER) compared to the do-nothing scenario was calculated for each intervention by dividing the total intervention costs (the costs are zero in the do-nothing scenario) by the total DALYs averted (i.e., the DALYs lost when no intervention is applied minus the DALYs lost when an intervention is applied for 10 years). The interventions were also compared to arrive at the incremental CER, which we defined as the additional costs of a more effective intervention divided by the size of this additional effect in terms of DALYs averted. To calculate the incremental CERs, the interventions were ordered by increasing effectiveness and the ratio of a scenario with its adjacent, less effective scenario was determined.

Study Population and Analyzed Regions

The breast health of adolescent and adult women age 15 years and older was simulated in an open cohort. The costs, effects, and cost-effectiveness of each of the interventions were evaluated for three epidemiologic regions of Africa, North America (including Cuba), and Asia, defined by mortality strata (Appendix A) (Tan-Torres Edejer 2003).

Model Assumptions

Interventions In recent years, many developments in diagnosing and treating breast cancer have occurred, and we could analyze a large number of interventions in our model. However, we confined the model to a small set of basic interventions to allow comparability among the regions. We assessed the following six basic interventions:

- Stage I treatment: Lumpectomy with axillary dissection supplemented with external radiotherapy to the breast. Eligible patients also receive endocrine therapy.
- Stage II treatment: Lumpectomy with axillary dissection supplemented with external radiotherapy to the breast. Eligible patients also receive endocrine therapy.
- Stage III treatment: Neoadjuvant chemotherapy followed by mastectomy with axillary dissection supplemented with adjuvant chemotherapy. External radiotherapy to the breast is also administered and eligible patients receive endocrine therapy.
- Stage IV treatment: Systemic chemotherapy, supplemented with endocrine therapy for eligible patients. In this group of patients, these therapies are palliative.
- Treatment all stages: Treatment of all stages as described above.
- Extensive program: Treatment of all stages as described above, plus a breast awareness program and early case finding through biannual mammographic screening in women age 50–70 years.

Model Structure

Six mutually exclusive health states were included (Fig. 1): healthy (no breast cancer); American Joint Committee on Cancer (AJCC 2002) stages I, II, III, and IV breast cancer; and death from breast cancer. Regional age-adjusted population estimates of breast cancer incidence, breast cancer prevalence, percentage of prevalent cases treated, and background mortality rates were based on the WHO Burden of Disease study estimates for 2000 (Shibuya 2002).

Following the WHO guidelines (Tan-Torres Edejer 2003), the interventions were aimed at initial disease treatment only, but patients could experience a relapse or progression after initial diagnosis; therefore we filtered out the effect of treating patients whose disease progressed. It was assumed that patients could have a progression only to stage IV breast cancer and that cancer progressed at a constant rate (Engel 2003).

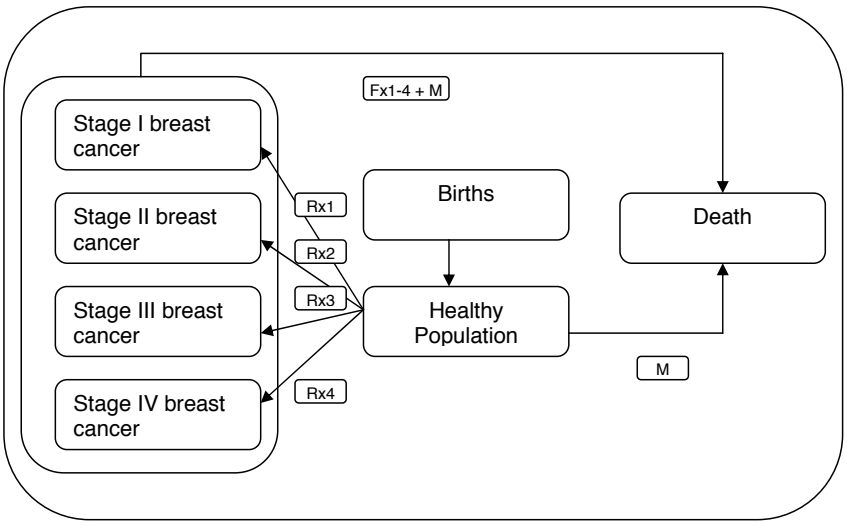

Figure 1: Graphical representation of the model showing the relationships between the six different health states through the incidence rates of breast cancer (Rx1–Rx4) and the different mortality rates for the different breast cancer stages (Fx1–4) and the background mortality (M).

Stage Distribution and Case Fatality Rates

The key elements of the model were the stage distribution of both prevalent and incident cases, and the case fatality rate for untreated and treated patients (Table 1). We distinguished between the stage distribution in the developed region (North America) and the two developing regions (Africa and Asia) to reflect the difference in levels of breast cancer care.

Stage distributions for prevalent cases were derived from registry data (Table 1). The stage distribution of prevalent cases in North America was based on the U.S. National Cancer Data Base (NCDB) (Bland 1998). The stage distribution of prevalent cases in Africa and Asia was based

Table 1: Input Data for the Disease Model by Breast Cancer Stage and WHO Region (Tan-Torres Edejer 2003)

Model element	North America	Africa and Asia	References
Stage distribution of prevalent cases, 2000 (%)			
Stage I	49.00	9.40	(Bland 1998;Sankaranarayanan 1998)
Stage II	37.40	14.20	(Bland 1998;Sankaranarayanan 1998)
Stage III	8.60	58.00	(Bland 1998;Sankaranarayanan 1998)
Stage IV	5.00	18.40	(Bland 1998;Sankaranarayanan 1998)
Stage distribution of incident cases in absence of an extensive program, 2000–2010 and the whole population thereafter (%)			
Stage I	9.40	9.40	(Sankaranarayanan 1998)
Stage II	14.20	14.20	(Sankaranarayanan 1998)
Stage III	58.00	58.00	(Sankaranarayanan 1998)
Stage IV	18.40	18.40	(Sankaranarayanan 1998)
Stage distribution of incident cases in presence of an extensive program, 2000–2010 (%)			
Stage I	49.00	49.00	(Bland 1998)
Stage II	37.40	37.40	(Bland 1998)
Stage III	8.60	8.60	(Bland 1998)
Stage IV	5.00	5.00	(Bland 1998)
Case fatality rate of untreated patients, 2000–2100			
Stage I	0.020	0.020	(Sankaranarayanan 1998)
Stage II	0.063	0.063	(Sankaranarayanan 1998)
Stage III	0.150	0.150	(Sankaranarayanan 1998)
Stage IV	0.300	0.300	(Sankaranarayanan 1998)
Case fatality rate of treated patients, 2000–2100[a]			
Stage I	0.006	0.006	(Bland 1998)
Stage II	0.042	0.042	(Bland 1998)
Stage III	0.093	0.093	(Bland 1998)
Stage IV	0.275	0.275	(Bland 1998)
Quality of life[b]			
Stage I	0.9325	0.9325	(de Koning 1991; Launois 1996; Murray and Lopez 1996; Norum 1999)
Stage II	0.9301	0.9301	(de Koning 1991; Launois 1996; Murray and Lopez 1996; Norum 1999)
Stage III	0.9284	0.9284	(de Koning 1991; Launois 1996; Murray and Lopez 1996; Norum 1999)
Stage IV untreated	0.9097	0.9097	(de Koning 1991; Launois 1996; Murray and Lopez 1996; Norum 1999)
Stage IV treated	0.9275	0.9275	(de Koning 1991; Launois 1996; Murray and Lopez 1996; Norum 1999)

a) Includes the 100% of prevalent cases in North America, 10% in Africa, and 25% in Asia that were treated in 2000 (Shibuya 2002).
b) On a scale from 0 (dead) to 1 (perfect health).

on registry data from Southeast Asia (Sankaranarayanan 1998).

In the no-intervention scenario, the stage distribution of incident cases and stage-specific case fatality rates were based on registry data from Southeast Asia (Sankaranarayanan 1998) and applied to all regions. The case fatality rates for treated patients were derived from the NCDB (Bland 1998). In the extensive breast cancer program scenario, the stage distribution of incident cases and stage-specific case fatality rates were based on data from the NCDB for all regions (Bland 1998).

Quality of Life

The quality of life of patients with breast cancer (Table 1) was based on the WHO Global Burden of Disease study (Murray 1996). Using NCDB data on stage distribution (Bland 1998) and quality of life data from several sources (de Koning 1991; Launois 1996; Norum 1999), we arrived at stage-specific quality of life estimates. The quality of life of the susceptible population was also included (Murray and Lopez 1996).

Costs

All costs were calculated and are presented in 2000 U.S. dollars. Two types of costs for health services were distinguished: patient-level costs, which were those incurred for individual patients, and program-level costs, which were those incurred at a level above that of the patient (Tan-Torres Edejer 2003).

Patient-Level Costs: In all regions patient-level patterns of resource use (i.e., initial evaluation, local treatment, and follow-up) were based on clinical practice guidelines (Table 2). These costs included evaluation of women without breast cancer; it was assumed that breast cancer was diagnosed in only 6% of all presenting women (Flobbe 2001).

Screening in the extensive cancer program included costs of mammographic screening in women age 50–70 years and further diagnostic tests on referral (Table 2). Detailed lists of all tests and procedures, including housing, personnel, and medical devices, were retrieved from a South African database and were validated for western countries by a team of oncologists.

Unit costs were retrieved from the WHO-CHOICE database on prices of traded and nontraded goods (http://www.who.int/choice). Unit costs of health center visits and hospital inpatient days were based on a report by Adam et al. (Adam 2003). We combined unit costs with resource use patterns to estimate the total costs per patient treated. All unit costs are presented for the regions of Africa, North America, and Asia in Appendix B.

Program-Level Costs: We based estimated quantities of resources required to start up and maintain each intervention for 10 years (e.g., personnel, materials and supplies, media, transport, maintenance, utilities, and capital) at national, provincial, and district levels on a series of evaluations made by regional costing teams in the different WHO regions and validated against the literature (Johns 2004). We obtained unit cost estimates of program-level resources (e.g.,

Table 2: Patient-Level Resource Use Patterns for Breast Cancer Interventions

	Resource[a]	No. of outpatient visits	Length of hospitalization (days)
Diagnosis		1	NA
	Bilateral mammography		
	Complete blood count		
	Total bilirubin assay		
	Alkaline phosphatase assay		
	Fine needle aspiration or core needle biopsy		
	Liver function tests		
	ECG in 50%		
	Bone scan in 25%		
	Ultrasonography of the liver in 25%		
Non–breast cancer examination[b]		1	NA
	Bilateral mammography		
	Ultrasonography of the liver in 28%		
	Fine needle aspiration or core needle biopsy in 0.27%		
Stage I treatment		1	2
	Lumpectomy with axillary dissection		
	Radiotherapy[c]		
	Endocrine therapy in 50%[d]		
Stage II treatment		1	2
	Lumpectomy with axillary dissection		
	Radiotherapy[c]		
	Endocrine therapy in 50%[d]		
Stage III treatment		1	2
	(Neo)adjuvant chemotherapy[e]		
	Mastectomy with axillary dissection		
	Radiotherapy[c]		
	Endocrine therapy in 50%[d]		
Stage IV treatment		1	2
	(Neo)adjuvant chemotherapy[le]		
	Endocrine therapy in 50%[§]		
Follow-up year 1–5 (per year)		2	NA
	2 Bilateral mammographies		
	Pelvic examination in 50%		
Follow-up year 6–10 (per year)		1	NA
	Bilateral mammography		
	Pelvic examination in 50%		
Screening		1	NA
	Bilateral mammography		
	Ultrasonography of the liver in 28%[b]		
	Fine needle aspiration or core needle biopsy in 0.27%[b]		

a) Based on clinical practice guidelines.
b) Includes resource use of initial evaluation of women without breast cancer who were initially suspected of having breast cancer (Flobbe 2001).
c) Radiotherapy includes a standard dose of 50 Gy given in 25 fractions of 2 Gy on an outpatient basis in all stages of breast cancer (Blamey 1998).
d) Endocrine therapy consists of 20 mg tamoxifen per day for 5 years.
e) The (neo)adjuvant chemotherapy combination regimen consists of 4, 21-day cycles of doxorubicin (60 mg/m2) and cyclophosphamide (830 mg/m2) supplemented with 4 mg dexamethasone, given on an outpatient basis.
ECG, electrocardiography; NA, not applicable.

the salaries of central administrators, capital costs of vehicles, storage, offices, and furniture) from a review of the literature, which was supplemented by primary data from several countries (the full list of unit cost estimates is available at http://www.who.int/choice). The process and methodology for estimating program costs are described in detail elsewhere (Johns 2003; Johns and Baltussen 2004).

Sensitivity Analyses

To address uncertainty and determine the robustness of the model, we conducted both univariate and multivariate sensitivity analyses on key parameters. Specifically we assessed the effects of varying the stage distribution of prevalent cases, the stage distribution of incident cases, and the case fatality rate of treated patients, individually and then collectively.

RESULTS

Intervention Effectiveness

In Africa, the smallest group treated in the 10-year period was women who had stage I breast cancer (Table 3); of these 37,277 cases, 9604 were previously untreated prevalent cases and 27,673 were new cases of breast cancer. Most of the treated women were those with stage III breast cancer (228,914; 58,978 prevalent and 169,936 incident cases). In North America and Asia, the trends were the same, although the absolute numbers of treated patients were higher. The female population in North America was four times smaller than the female population in Asia, but the number of treated breast cancer patients was one-third higher in North America. The population sizes in North America and Africa were similar, but the number of treated patients was four times larger in North America.

Because of these differences between regions, the number of DALYs averted for the total population or per treated patient in the 10-year period also varied considerably (Table 3). For example, in Africa, treatment of stage I patients resulted in a total of 873,000 DALYs averted for the total population and 23.41 DALYs averted per treated patient. Despite the greater number of treated patients with stage II, III, or IV breast cancer, the total number of DALYs averted was considerably less for each of these stages. When all diagnosed cases were treated, 1,490,000 DALYs were averted for the total population (3.77 per treated patient). When an extensive breast cancer program was assumed to exist in Africa, 6,374,000 DALYs were averted for the total population (16.14 per treated patient).

Costs and Cost-Effectiveness

The range in total costs per intervention over the 10-year period was considerable. For example, the total costs for introducing stage I treatment was $68 million in Africa, $3879 million in North America, and $143 million in Asia (Table 3).

Table 3: Number of Patients Treated, DALYs Averted, Costs, and CERs at an 80% Coverage Level, Over a 10-Year Period (2000–2010) by WHO Region

Region and intervention	No. of patients treated	Total DALYs averted (in thousands)	DALYs averted per patient	Population-level costs (millions of 2000 U.S.$)								Costs per treated patient 2000 U.S.$	CER (2000 U.S.$ per DALY averted)	
				Diagnosis	Non–breast cancer examination	Treatment	Follow-up	Screening	Total per patient	Total per program	Total overall		Average[a]	Incremental[b]
Africa														
Stage I treatment	37,277	873	23.41	11	31	13	2		56	12	68	1829	78	NA
Stage II treatment	55,955	231	4.13	11	31	19	3		63	12	75	1342	324	NA
Stage III treatment	228,914	399	1.74	11	31	93	9		143	12	155	679	389	NA
Stage IV treatment	72,738	14	0.19	11	31	14	2		58	12	70	959	4986	NA
Treatment all stages	394,884	1490	3.77	11	31	138	15		195	42	238	602	159	NA
Extensive program	394,884	6374	16.14	11	20	134	17	180	362	115	477	1208	75	75
North America														
Stage I treatment	161,558	1979	12.25	500	2171	1040	108		3820	59	3879	24,008	1960	NA
Stage II treatment	242,507	542	2.24	500	2171	1562	147		4380	59	4439	18,304	8187	NA
Stage III treatment	992,107	1587	1.60	500	2171	7136	526		10,334	59	10,392	10,475	6549	NA
Stage IV treatment	315,214	56	0.18	500	2171	1074	110		3857	59	3915	12,421	70,380	NA
Treatment all stages	1,711,414	4282	2.50	500	2171	10,812	892		14,375	223	14,598	8530	3409	NA
Extensive program	1,711,414	22,098	12.91	500	1626	10,874	1057	5299	19,356	856	20,213	11,811	915	915
Asia														
Stage I treatment	120,738	2325	19.25	27	64	23	5		120	24	143	1188	62	62
Stage II treatment	181,235	663	3.66	27	64	34	7		133	24	156	863	236	NA
Stage III treatment	741,439	1205	1.63	27	64	178	23		292	24	316	426	262	NA
Stage IV treatment	235,593	42	0.18	27	64	29	4		125	24	149	630	3510	NA
Treatment all stages	1,279,005	4155	3.25	27	64	264	38		393	62	455	356	110	NA
Extensive program	1,279,005	16,086	12.58	27	38	251	42	703	1061	145	1206	943	75	77

a) Average CER compared to the do-nothing scenario. In the do-nothing scenario costs were zero.
b) Incremental CER versus less effective alternative. To calculate the incremental CER, the interventions were ordered by increasing effectiveness and the ratio of a scenario with its adjacent, less effective scenario was determined.
CER, cost-effectiveness ratio; DALY, disability-adjusted life-year; WHO, World Health Organization; NA, not applicable, because the intervention is less cost-effective than others.

The costs of diagnosis were a fixed component in all intervention scenarios because cases must be diagnosed correctly before treatment can be initiated. This category also accounted for the exclusion of women presenting without breast cancer. As a result, costs per treated patient were lowest when all diagnosed cases were treated (Table 3). In all three regions, the diagnostic costs for patients with stage I breast cancer constituted 62–68% of the total costs, whereas the diagnostic costs for all patients made up 17–20% of the total costs.

The costs per treated patient with stage I disease were $1829 in Africa, $24,008 in North America, and $1188 in Asia (Table 3). The costs of treatment represented 16–27% of the total costs in each region.

In the extensive program, different cost items accounted for widely varying proportions of the total costs (Table 3). In Africa, the patient-level costs of screening and associated diagnostic examination of false-positive screens ($180 million) were 38% of the total costs; in North America, these costs ($5299 million) constituted only 26% of the total costs; and in Asia, these costs ($703 million) made up 58% of the total costs.

In each of the six intervention scenarios, the total program costs accounted for 8–24% of the total costs in Africa and Asia, but only 1–4% of the total costs in North America (Table 3).

When we compared the intervention scenarios with the no-intervention scenario, treatment of stage I patients and the extensive breast cancer program were the most cost-effective interventions, with average CERs for stage I treatment and extensive programs, respectively, of $78 and $75 per DALY averted in Africa, $1960 and $915 per DALY averted in North America, and $62 and $75 per DALY averted in Asia (Table 3). The least cost-effective option was stage IV treatment (average CERs of $4986, $70,380, and $3510 per DALY averted in Africa, North America, and Asia, respectively).

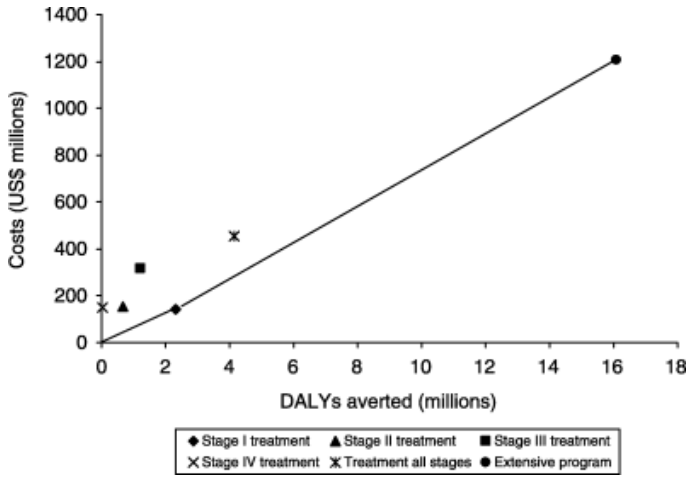

Figure 2: Expansion path for the Asian region.

Incremental CERs revealed that in Africa and North America, the optimal breast cancer program was the most cost-effective intervention scenario ($75 and $915 per DALY averted, respectively) (Table 3). In Asia, the most cost-effective options were stage I treatment ($62 per DALY averted) and then the optimal breast cancer program ($77 per DALY averted).

The order in which interventions should be introduced according to the cost-effectiveness results (i.e., the "expansion path;" for more details on expansion paths, see Tan-Torres Edejer et al. (Tan-Torres Edejer 2003)) is illustrated for Asia in Figure 2. Stage I treatment would be introduced first. With more resources, an optimal breast cancer program would be established.

SENSITIVITY ANALYSES

In the first two univariate sensitivity analyses, it was assumed that cancers were diagnosed earlier compared with the base case analysis (i.e., more stage I and II cancers and fewer stage III and IV cancers). This assumption produces a more favorable distribution, with the sole exception of the prevalent cases in North America, where the distribution becomes less favorable. Applying these alternative stage distributions for prevalent and incident breast cancer cases resulted in lower average CERs for stage I treatment and for treatment of all stages in Africa, North America, and Asia because more stage I patients received treatment, which was associated with lower case fatality rates (Table 4 shows results for Asia as an example). For stage III and IV treatment, the average CERs increased because fewer cases were diagnosed at these stages. Because the shift in distribution of incident cases of stage II breast cancer decreased the overall mortality in the no-intervention scenario, the average CERs for stage II treatment and the extensive program also increased.

In a third univariate analysis, the assumption of a 50% reduction in treatment effect on case fatality rates (i.e., higher case fatality rates of treated cases than those used in the base case analysis) increased the average CERs of each of the six interventions in Africa, North America, and Asia (Table 4 shows results for Asia as an example).

Combining all three univariate sensitivity analyses in a multivariate analysis resulted in a further increase in the average CERs for stage II, III, and IV treatment and the extensive program (Table 4). The average CERs for stage I treatment and treatment of all stages were between the CERs calculated in the individual sensitivity analyses.

DISCUSSION

Our analyses showed that treating early stage breast cancer is more cost-effective than treating late-stage disease. In Africa and Asia, treatment of stage I, II, or III disease costs less than $390 per DALY averted, whereas treatment of stage IV disease costs more than $3500 per DALY averted;

Table 4: Results of Univariate and Multivariate Sensitivity Analyses for Asia[a]

Intervention	Univariate analyses							
	Alternative stage distribution of prevalent cases[b]		Alternative stage distribution of incident cases[b,c]		Alternative case fatality rates[d]		Multivariate analysis[e]	
	Average	Incremental[f]	Average	Incremental[f]	Average	Incremental[f]	Average	Incremental[f]
Stage I treatment	45	45	48	48	162	NA	107	107
Stage II treatment	224	NA	261	NA	609	NA	618	NA
Stage III treatment	283	NA	390	NA	642	NA	1186	NA
Stage IV treatment	4103	NA	4888	NA	5175	NA	8875	NA
Treatment all stages	79	NA	84	NA	255	NA	178	NA
Extensive program	73	82	127	182	113	113	216	274

a) Data are presented as cost-effectiveness ratios, calculated as cost (in 2000 U.S.$) per DALY (disability-adjusted life-year) averted.
b) Stage distribution: stage I, 29%; stage II, 26%; stage III, 33%; and stage IV, 12%.
c) In the absence of an extensive breast cancer program.
d) Case fatality rates of treated patients: stage I, 0.013; stage II, 0.053; stage III, 0.122; and stage IV, 0.288.
e) All adjustments in the three univariate sensitivity analyses were implemented simultaneously.
f) Incremental cost-effectiveness ratio versus lesser effective alternative.
NA, not applicable, because the intervention is less cost-effective than others.

in North America, the respective values were $6550 and $70,400. For comparison, we can use benchmarks suggested by other researchers to assess whether a health intervention is cost-effective: cost per DALY averted or life-year gained equal to the per capita income (Murray 1998), twice per capita income (Garber 1997), or three times per capita income (2002b) (low-income countries are defined as having per capita incomes of $765 or less per year, and high-income countries are defined as having per capita incomes of more than $9386 per year). According to these benchmarks, all interventions except treatment of stage IV disease were cost effective in all three regions.

The incremental CERs indicated that priorities in national breast cancer control programs would be treatment of stage I disease or implementation of an extensive cancer control program (including breast cancer awareness campaigns and active mammographic screening).

Although the extensive cancer control program reflects the economic attractiveness of diagnosing breast cancer at an earlier stage, many developing countries may not be able to meet the total costs of such a program (including the required infrastructure, logistics, and expertise). Given the limited available resources, priorities are probably best directed at treatment of early stage disease and at developing a less expensive means of early diagnosis. We did not evaluate clinical breast examination or breast self-examination because currently there is no consensus on their value alone or in addition to mammography. Nevertheless, together with other ways of raising awareness, clinical breast examination and breast self-examination could be a cost-effective means by which to diagnose breast cancer earlier in resource-poor settings.

A number of our study limitations have to be addressed. We used data on stage distribution and case fatality rates from a sample of developing countries to reflect the absence of breast cancer control interventions. For the same variables, we used data from U.S. cancer registries to reflect intervention effectiveness. Whether these data are accurate can be assessed only when studies on the effectiveness of breast cancer interventions in developing countries become available.

We did not include stage 0 disease (i.e., ductal carcinoma in situ) in our model because very little information is available on this type of breast cancer in developing regions. Furthermore, the WHO Global Burden of Disease study provides information only on the prevalence and incidence of palpable breast cancer. From the NCDB, it is clear that through screening, the proportion of disease diagnosed at stage 0 increased substantially in the United States (Bland 1998). Although not all stage 0 breast cancer will result in breast cancer-related death if not treated, and overtreatment (with its associated costs) will likely be introduced, including stage 0 disease in the model will probably reinforce our conclusion that treating earlier stages of breast cancer is the most cost-effective intervention.

We estimated program costs for breast cancer interventions that are not yet in place on this scale in developing countries and therefore cannot be validated. However, an extensive cancer control program was estimated to cost $50 million for 95% geographic coverage in The

Netherlands; this value compares well with the costs of breast cancer screening in that country, which were $49 million in 2003.

Our simplified cost-effectiveness model is appropriate to use for broadly assessing the relative economic attractiveness of breast cancer interventions and for comparing interventions among regions. Our analysis shows that there is a broad variation in epidemiology between regions and that there are large differences in cost structure as well. In contrast to North America, where personnel is the major cost component, the costs of personnel are only a small part of the total costs in developing regions (Africa and Asia). Therefore, while the pattern of most cost-effective interventions is the same, there are substantial differences between interventions across regions and likely within a region. A more detailed country-level analysis, using local cost and resource estimates and epidemiologic information, could be useful for testing whether our model assumptions hold and for obtaining more specific information on the impact of interventions on budgets, especially when there is competition for scarce resources with interventions that are more intensive with respect to either personnel time or resource use. We developed the cost-effectiveness model in such a way that these country-specific adaptations can be performed easily.

For reasons of comparability, we were unable to include many of the elements of breast cancer care that are considered standard in developed countries. A few examples are sentinel lymph node biopsy, breast reconstruction after surgery, and variations in surgical treatment of breast cancer within the same stage. Furthermore, we assumed the use of only one type of chemotherapy and one type of hormonal therapy. These issues can be addressed in a more tailor-made country-level analysis using the model's framework.

Finally, we are aware of the current debate surrounding the relative effect of breast cancer screening on reducing mortality rates. This debate focuses on the overtreatment and overdiagnosis that are said to be underappreciated harms of screening (Schwartz 2004). In our analysis, we assumed that the introduction of an extensive breast cancer program would cause a shift in stage distribution that would result in reduced mortality rates for all patients, and this assumption probably led to an overestimation of the impact of such a program. Sensitivity analyses showed that varying model assumptions did affect the cost-effectiveness of the interventions, but not our principal study conclusion.

We conclude that both treatment of early stage breast cancer and interventions for down-staging disease at diagnosis are among the most valuable interventions in breast cancer control.

Appendix A: Epidemiologic Regions as Applied in WHO Generalized CEA (Tan-Torres Edejer 2003)

WHO region	Mortality stratuma	WHO member states
Africa	E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
North America	A	Canada, Cuba, United States of America
Asia	D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal

a) A, have very low rates of adult and child mortality; D, have high adult and child mortality; E, have very high adult and high child mortality.
WHO, World Health Organization; CEA, cost-effectiveness analysis.

Appendix B: Unit Costs and Total Costs per Patient (in 2000 U.S. Dollars) by WHO Region[a]

Resource or intervention	Africa	North America	Asia
Unit costs			
Outpatient visit	0.82	24.05	0.53
Hospitalization	4.65	203.35	3.75
Lumpectomy	34.00	414.72	23.54
Mastectomy	34.56	417.01	24.01
Radiotherapy	323.43	6465.55	173.2
(Neo)adjuvant chemotherapy	75.96	852.72	54.87
Endocrine therapy	0.01	0.04	0.01
Bilateral mammography	3.57	48.36	2.60
Fine needle aspiration biopsy	8.22	51.42	6.47
Chest radiograph	3.05	31.76	2.26
Bone scan	15.96	107.79	13.06
Electrocardiography	1.58	28.47	0.91
Pelvic examination	1.22	20.44	0.70
Ultrasonography of the liver	3.61	66.10	2.12
Complete blood count	2.68	35.10	1.97
Total bilirubin assay	2.23	36.83	1.51
Alkaline phosphatase assay	4.70	46.76	3.59
Total costs per patient			
Diagnosis	30.96	300.23	17.32
Non-breast cancer examination	5.57	91.94	3.85
Stage I treatment	367.54	7311.01	204.77
Stage II treatment	367.54	7311.01	204.77
Stage III treatment	444.06	8166.03	260.11
Stage IV treatment	86.08	1283.47	62.89
Follow-up year 1–5	31.95	547.31	22.75
Follow-up year 6–10	24.26	378.69	17.51
Screening	4.46	62.60	3.15

a) All unit costs are derived from a South African database. WHO, World Health Organization.

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Chapter 5

Cost-effectiveness of melagatran/ximelagatran for the prevention of venous thromboembolism following major elective orthopaedic surgery

SUMMARY

Introduction. The efficacy of the oral direct thrombin inhibitor ximelagatran, whose active form is melagatran, for the prevention of venous thromboembolism (VTE) following major elective orthopaedic surgery (OS) has been investigated in several clinical studies. The objective was to evaluate the cost-effectiveness of melagatran/ximelagatran compared with enoxaparin for the prevention of VTE following major elective OS.

Patients and Methods. Based on results from the METHRO III study, costs (drugs, diagnosis/treatment of VTE, blood transfusions, long-term complications of DVT) and effects (symptomatic VTE) were estimated for cohorts receiving melagatran/ximelagatran initiated 4 – <8 hours after surgery or enoxaparin for 11 days. Dutch unit costs were used. Costs are presented in euros (€), 2004 prices.

Results. The cost per 1000 patients was € 23,000 lower in the melagatran/ximelagatran group than in the enoxaparin group (€ 337,000 vs € 360,000). The number of symptomatic VTE events was comparable in the two groups, but there was a significantly lower need for blood transfusion in the melagatran/ximelagatran group. Probabilistic sensitivity analysis showed that the cost was lower in the melagatran/ximelagatran group (95% uncertainty interval for cost difference: -€ 5,104 to -€ 44,454). In almost 50% of simulations melagatran/ximelagatran reduced both costs and symptomatic VTE.

Conclusion. Thromboprophylaxis with melagatran/ximelagatran initiated 4 – <8 hours after surgery provides comparable efficacy and safety to enoxaparin but is associated with lower costs. With the advantage of oral administration, melagatran/ximelagatran offers a cost-effective alternative to enoxaparin for the prevention of VTE following major elective OS.

INTRODUCTION

Patients undergoing major elective orthopaedic surgery are at increased risk of venous thromboembolism (VTE) manifested as deep vein thrombosis (DVT) and/or pulmonary embolism (PE) (Geerts 2004). DVT episodes predispose patients to future episodes of recurrent DVT, increase the risk of PE, reduce survival, and may lead to the chronic complication of post-thrombotic syndrome (Geerts 2004). The economic consequences of VTE and associated long-term complications are substantial (Bergqvist 1997; Ollendorf 2002; Caprini 2003; Sullivan 2003; Oster 2004).

Effective thromboprophylaxis is essential for patients undergoing major elective orthopaedic surgery if the risk of VTE and its complications are to be reduced (1998a; Geerts 2004). Currently, low-molecular-weight heparins (LMWHs), the factor Xa inhibitor fondaparinux, or dose-adjusted vitamin K antagonists (VKAs), such as warfarin, are recommended for routine use (Geerts 2004). However, these thromboprophylactic agents are not without limitations. LMWHs and fondaparinux are only available as a daily subcutaneous injection, which is uncomfortable for patients and requires training for self-injection or dependency on outpatient facilities and community nurse visits in order to continue prophylaxis outside the hospital. VKAs have a narrow therapeutic window and require frequent monitoring and, often, dose adjustment for anticoagulation to be effective and safe. VKAs are also associated with numerous food and drug interactions.

Ximelagatran is a novel, oral direct thrombin inhibitor that was developed to overcome limitations of currently available thromboprophylactic agents (Eriksson 2003b). Following oral administration, ximelagatran is rapidly biotransformed to its active form melagatran (Eriksson 2003c). Melagatran itself can be administered subcutaneously (Johansson 2003).

The efficacy of ximelagatran for the prevention of VTE in major elective orthopaedic surgery patients has been investigated in studies in Europe (Eriksson 2002; Eriksson 2003a; Eriksson 2003b) and North America (Colwell; Heit 2001; Francis 2002; Colwell 2003; Francis 2003). The METHRO III study investigated the efficacy and safety of subcutaneous melagatran (3 mg) started 4–12 hours post-operatively and followed by oral ximelagatran (24 mg twice daily) compared with enoxaparin started pre-operatively as used in Europe (Dahl 2005). In the original METHRO III study protocol the primary and secondary efficacy endpoints were total VTE (DVT, fatal/non-fatal PE, or unexplained death) and major VTE (proximal DVT, fatal/non-fatal PE, or unexplained death) respectively. During the course of the study an amendment to the study protocol was made to match the requirements of the new Committee for Proprietary Medicinal Products (CPMP) guidelines ; total VTE was defined as DVT, fatal/non-fatal PE, or death from any cause; major VTE was defined as proximal DVT, fatal/non-fatal PE, or VTE-related death; major VTE also became a primary endpoint. Furthermore, the amendment also allowed assessment of non-inferiority using endpoints as defined by the CPMP criteria. The primary analysis of the METHRO III data showed no statistically significant differences in the risks of total VTE or

major VTE between the treatments (Dahl 2005). A post hoc analysis suggested that the risks of total VTE and major VTE were significantly lower in patients who received their first dose of melagatran 4 – <8 hours after surgery than in those who received their first dose later, with no statistically significant difference from the risk in patients who received enoxaparin (Dahl 2005). These results have formed the basis for the approved Summary of Product Characteristics, which states that melagatran 3 mg should be administered by subcutaneous injection not earlier than 4 hours and not later than 8 hours after the completion of surgery. This dose should be continued twice daily during 1-2 days until the patient is able to use oral route.

The number of total hip replacements (THRs) and total knee replacements (TKRs) has increased substantially in the last decade and is expected to rise a further 40-50% over the next decades (Birrell 1999; Ostendorf 2002; Dixon 2004). This development will increase pressure on constrained health care budgets and calls for the importance of evaluating the health economic properties of currently available thromboprophylactic agents. The objective of this study was to evaluate the cost-effectiveness of the approved melagatran/ximelagatran regimen compared with enoxaparin for the prevention of venous thromboembolism following major elective orthopaedic surgery, based on results from patients in the METHRO III study who received their first dose of melagatran 4 – <8 hours after surgery and Dutch costs.

PATIENTS AND METHODS

The cost-effectiveness analysis was carried out using a decision analytic model developed in Microsoft Excel. The model estimated costs and effects for cohorts of THR and TKR patients receiving prophylaxis with melagatran/ximelagatran or enoxaparin for 11 days. The clinical outcome measure was symptomatic VTE events, which included symptomatic DVT and fatal or non-fatal PE. The analysis was performed from the perspective of the Dutch health care system and included costs for drugs, diagnosis and treatment of VTE, blood transfusions, and long-term complications of DVT.

Decision analytic model

The model structure and the VTE probabilities are shown in Figure 1. The model departed from risks of total DVT (distal or proximal DVT) verified by mandatory venography at the end of the treatment period in the melagatran/ximelagatran (initiated 4 – <8 hours after surgery) and enoxaparin groups in METHRO III (p1). Since venography is not carried out routinely in clinical practice the risks of total DVT were transformed into pre-discharge DVT events that would have been symptomatic as compared to asymptomatic in clinical practice (p2). Patients with symptomatic DVT were assumed to be treated, while patients with asymptomatic and hence undetected DVT were not treated. Patients with asymptomatic pre-discharge DVT had a risk of developing post-discharge symptomatic DVT, fatal PE, or non-fatal symptomatic PE (p3, p4, p5).

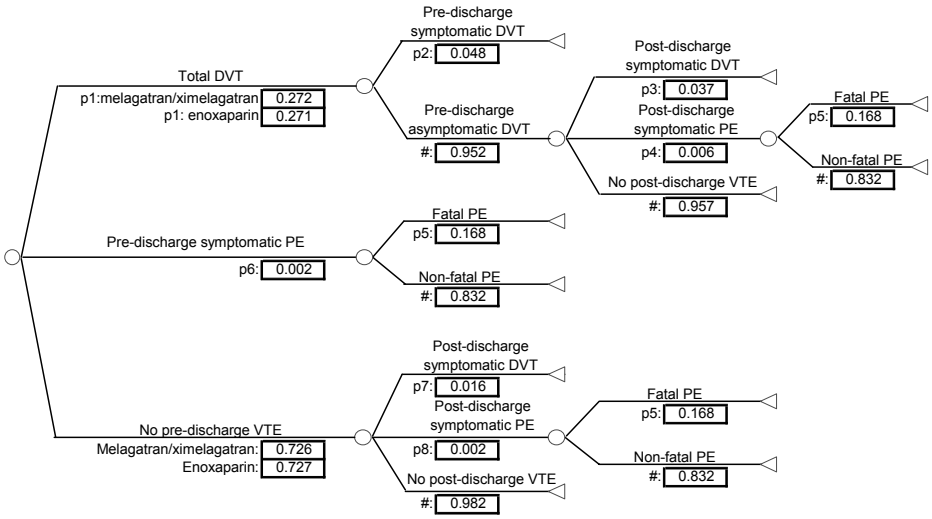

Figure 1: The decision analytic model. Circles represent chance nodes for events that can occur. Probabilities of these events are shown in the boxes and described in the text. # refers to 1 minus the sum of the probabilities at the other branches. 'Melagatran/ximelagatran' refers to melagatran/ximelagatran initiated 4 – <8 hours after surgery.

Patients without pre-discharge DVT had a risk of developing pre-discharge symptomatic PE (p6) or post-discharge symptomatic DVT, fatal PE, or non-fatal symptomatic PE (p7, p8). The p1 figure was specific to melagatran/ximelagatran and enoxaparin, while the other probabilities in the model were the same for both treatments. Details on the probabilities are given in the next section. The model predicted symptomatic VTE events over a period of approximately three months. Expected costs for long-term complications of DVT were also included, as described in the costs section below.

Model probabilities

p1: This treatment specific probability was derived from the proportion of patients with venographically verified total DVT in METHRO III (Data on file). Melagatran/ximelagatran initiated 4 – <8 hours after surgery was non-inferior to enoxaparin with respect to the risks of total VTE (absolute risk reduction [ARR] 0%; 95% confidence interval [CI] –4.4, 4.4) and major VTE (ARR –0.63%; 95% CI –2.94, 1.67) (Dahl 2005). A formal test of non-inferiority with regard to the risk of total DVT has not been performed. However, the number of events in the total VTE and total DVT endpoints differed with respect to 'only' two PE events, both of which occurred in the enoxaparin group. Thus, the non-inferiority conclusion should hold also for the total DVT endpoint.

p2: This probability was derived from a pooled analysis of the proportion of patients with symptomatic DVT in patients with venographically verified DVT in clinical studies of melagatran/ximelagatran or enoxaparin in THR or TKR (Bauer 2001; Turpie 2001; Eriksson 2002; Lassen 2002; Turpie 2002; Colwell 2003; Eriksson 2003a; Eriksson 2003b).

p3-4: To find accurate estimates of these probabilities is one of the key issues in health economic modelling of VTE prophylaxis. This is because patients with verified asymptomatic DVT in studies usually receive treatment, hence, data on which p3 and p4 could be based were not readily available. These probabilities were instead derived from results in placebo group patients in clinical studies of long-term prophylaxis (approximately 4 weeks), where venography was not performed after the initial short-term prophylaxis period (Bergqvist 1996; Lassen 1998; Heit 2000; Comp 2001). Placebo group patients were used as they received only short-term prophylaxis and thus matched the patient population in the current analysis in terms of treatment duration.

p5: This probability was derived from a pooled analysis of the proportion of fatal PE events of all PE events in the clinical studies on which p1-p4 were based (Bergqvist 1996; Heit 2000; Bauer 2001; Comp 2001; Turpie 2001; Eriksson 2002; Lassen 2002; Turpie 2002; Colwell 2003; Eriksson 2003a; Eriksson 2003b).

p6: This probability was derived from a pooled analysis of the proportion of patients with PE in patients with evaluable venogram in clinical studies of melagatran/ximelagatran or enoxaparin in THR or TKR (Bauer 2001; Lassen 2002; Turpie 2002; Colwell 2003; Eriksson 2003a; Eriksson 2003b).

p7-8: These probabilities were derived from a pooled analysis of the proportion of patients with post-discharge symptomatic DVT or PE in patients with negative venography at discharge from hospital (Ricotta 1996).

Bleeding events

In METHRO III, there was no significant difference in the rate of severe bleeding between the melagatran/ximelagatran and enoxaparin groups (Dahl 2005). It was assumed in the cost-effectiveness analysis that resource implications of these events were covered by the need for blood transfusion, which was significantly lower with ximelagatran/melagatran initiated 4 – <8 hours after surgery than with enoxaparin (ARR –4.6%; 95% CI –8.9, –0.3) (Dahl 2005). Expected cost per patient for blood transfusion was calculated using the transfusion probabilities and number of blood units shown in Table 1.

Table 1: Probability of blood transfusion and average number of blood units

	Enoxaparin	Melagatran/ Ximelagatrana
Probability of blood transfusion	0.662	0.616
Average number of blood units:		
In patients requiring blood transfusion	2.2[b]	2.1[b]
In total patient population	1.5[c]	1.3[c]

a) initiated 4 – <8 hours after surgery, b) Calculated using volumes of transfused blood in METHRO III and a volume per blood unit of 300 mL, c) Calculated by multiplying the probability of blood transfusion by the average number of blood units in patients requiring blood transfusion.

Costs

Prices and unit costs used in the analysis were derived from the Dutch costing manual, the Z-taxe, the National Health Tariffs Authority (CTG) and from the Dutch consensus guideline (1998a; Oostenbrink 2000; 2004a; march 2004). Costs are presented in euros (€€ in 2004 prices. Unit costs from earlier years were adjusted using Dutch price indices (CBS). Costs for diagnosis and treatment of symptomatic VTE were not discounted as they occurred within 1 year after surgery. Expected costs for long-term complications of DVT were discounted at an annual rate of 5%.

The price per enoxaparin injection (40 mg) was € 4.10 (march 2004). As of April 2005 there were no official prices for melagatran or ximelagatran in the Netherlands. The prices used in the analysis were the proposed price per 3 mg melagatran injection (€ 4.35) and per 24 mg ximelagatran tablet (€ 2.18). The average price per day for melagatran/ximelagatran was € 4.60, assuming two doses of melagatran/ximelagatran per day for 11 days (22 doses) and using METHRO III data on the number of injections per patient (1.23) and the implied number of oral doses (20.77).

Costs for symptomatic VTE events included costs for diagnosis and treatment and were estimated by determining resource use and multiplying by associated unit costs (Tables 2-3). Resource use was derived from the Dutch consensus guidelines on DVT and PE (1998a). These guidelines were judged, adjusted and subsequently approved by an expert review board consisting of 4 Dutch specialists (see Acknowledgement for expert review board participants). Cost for fatal PE was assumed to be 50% of the costs for non-fatal PE [expert review board judgement]. Patients with DVT were also assigned the expected discounted cost for treatment of long-term complications over 15 years, which was assumed to be 70% of the costs of treating primary DVT (Bergqvist 1997).

The price charged by the blood banks in the Netherlands per unit of 300 mL filtered erythrocytes (€ 179) was used as the cost per unit of blood.

Table 2: Cost for diagnosis of DVT and PE (€)

		Unit cost	Percentage of patients	Number of units	Cost
DVT:					
	Hospitalisation (days)	288[a]	100[c]	1[c]	288
	LMWH (120 mg day)	12.3[b]	100[d]	1[d]	12
	Ultrasound	56[e]	100[d]	1[d]	56
	Flebography	165[e]	10[d]	1[d]	17
	Total cost				373
PE:					
	Hospitalisation (days)	288[a]	85[d]	1[d]	245
	LMWH (120 mg day)	12.3[b]	85[d]	1[d]	10
	Hospitalisation (days)	288[a]	15[d]	2[d]	86
	LMWH (120 mg day)	12.3[b]	15[d]	2[c]	4
	Perfusion scan	145[e]	100[d]	1[d]	145
	Ventilation scan	193[e]	15[d]	1[d]	29
	Spiral CT	219[e]	15[d]	1[d]	33
	Total cost				552

a) Reference (Oostenbrink 2000), b) Reference (march 2004), c) Reference (1998a), d) Expert review board judgement, e) Reference (2004a).

Table 3: Cost for treatment of DVT and PE (€)

		Unit cost	Percentage of patients	Number of units	Cost
DVT:					
	Hospitalisation (days)	288[a]	20[d]	3[c]	173
	LMWH (120 mg day)	12.3[b]	100[d]	6[c]	74
	Extended treatment (months)	42[c]	90[d]	3[d]	113
	Extended treatment (months)	42[c]	10[d]	6[d]	25
	Long-term complications	533[e]	100[e]	1	533
	Total cost				918
PE:					
	Hospitalisation	288[a]	100[c]	6[c]	1,728
	LMWH (120 mg day)	12.3[b]	100[c]	6[c]	74
	Extended treatment (months)	42[c]	40[d]	3[d]	50
	Extended treatment (months)	42[c]	60[d]	6[d]	151
	Total cost				2,003

a) Reference (Oostenbrink 2000), b) Reference (march 2004), c) VKA+monitoring (1998a), d) Expert review board judgement, e) 70% of the cost of primary DVT (Bergqvist 1997).

Sensitivity analysis

The uncertainty surrounding costs and effects was assessed using probabilistic and univariate sensitivity analysis. In the probabilistic sensitivity analysis the parameters shown in Table 4 were varied simultaneously in 5,000 simulations using Monte Carlo simulation. In each simulation, a value of the parameter was drawn from its distribution (Briggs 2002). Table 4 also shows 95% confidence intervals for the average of the proportions that were used in the probabilistic sensitivity analysis. A range of +/- 30% around the average costs was used to represent the relatively large variation in resource use estimates (Buijt 2003). In the univariate sensitivity analysis, lower and upper limits of the 95% confidence intervals were used.

Table 4: Parameters, figures and distributions used in the probabilistic sensitivity analysis

				95% CI	
	Average	Range	Distribution	Lower limit	Upper limit
Costs (€):					
DVT[a]	1,290	+/- 30%	Normal	692	1,286
Non fatal PE[a]	2,552	+/- 30%	Normal	1,786	3,318
Fatal PE	1,276	+/- 30%	Normal	893	1,659
One unit of blood	179	+/- 30%	Normal	125	232
Model probabilities:[b]		SE			
p1 (enoxaparin)	0.271	0.0133	Beta	0.245	0.297
p1 (melagatran/ximelagatran[c])	0.272	0.0180	Beta	0.238	0.308
p2	0.048	0.0080	Beta	0.034	0.065
p3	0.037	0.0120	Beta	0.018	0.064
p4	0.006	0.0020	Beta	0.003	0.011
p5	0.168	0.0600	Beta	0.069	0.301
p6	0.002	0.0004	Beta	0.001	0.003
p7	0.016	0.0055	Beta	0.007	0.028
p8	0.002	0.0006	Beta	0.001	0.003
Probability of blood transfusion:[d]					
Enoxaparin	0.662	0.0127	Beta	0.637	0.687
Melagatran/ximelagatran[c]	0.616	0.0196	Beta	0.577	0.654

a) Includes the costs for diagnosis and treatment shown in Tables 2-3, b) p1 was treatment specific while p2-p8 were the same for both treatments, CI=confidence interval, SE=standard error, c) Initiated 4 – <8 hours after surgery, d) Note that while the treatment specific confidence intervals overlap, the difference between the groups was statistically significant (Dahl 2005).

RESULTS

Costs and symptomatic VTE events per 1,000 patients in the enoxaparin and melagatran/ximelagatran groups are shown in Table 5. The drug cost was € 5,500 higher in the melagatran/ximelagatran group, while costs for diagnosis and treatment of VTE were comparable in the two groups. Blood transfusions were the main driver of costs. The significantly lower need for transfusion in the melagatran/ximelagatran group resulted in 46 fewer patients requiring transfusion and an associated cost reduction of € 29,076. The total cost was € 23,479 lower in the melagatran/ximelagatran group. The number of symptomatic VTE events was comparable in the two groups.

Table 5: Breakdown of costs (€) and effects (per 1000 patients)

		Melagatran/ximelagatrana	Enoxaparin	Difference
Costs:				
	Drug costs	50,600	45,100	5,500
	Symptomatic DVT	44,313	44,226	87
	Fatal PE	1,003	1,002	1
	Non-fatal PE	9,926	9,917	9
	Blood transfusion	231,037	260,113	-29,076
	Total	336,879	360,358	-23,479
Effects:				
	Symptomatic DVT	34.35	34.28	0.07
	Fatal PE	0.79	0.79	0
	Non fatal PE	3.89	3.89	0
	Total	39.03	38.96	0.07

a) Initiated 4 – <8 hours after surgery.

Results from the probabilistic sensitivity analysis are shown in Figure 2. The scatter plot illustrates the variation in the cost and effect differences in a random sample of 1,000 from the 5,000 simulations. The cost was lower in the melagatran/ximelagatran group (95% uncertainty interval -€ 5,104 to -€ 44,454). Furthermore, in almost 50% of simulations melagatran/ximelagatran was the dominant strategy with a reduction in both costs and symptomatic VTE events.

Results from the univariate sensitivity analyses are presented in Table 6. In all analyses melagatran/ximelagatran was cost saving. The probability of blood transfusion and the cost per unit of blood had the largest impact on the difference in costs between the two groups. Of the model probabilities, only p1 had an impact on symptomatic VTE events. Results from sensitivity analyses of p2-p8 are therefore not presented here.

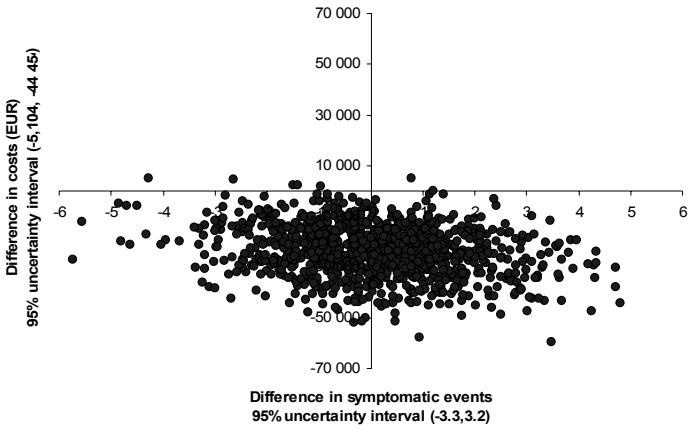

Figure 2: Scatter plot of results from the probabilistic sensitivity analysis. The figure shows a random sample of 1,000 from the 5,000 simulations. Differences refer to melagatran/ximelagatran -enoxaparin.

DISCUSSION

This paper presents a cost-effectiveness analysis of melagatran/ximelagatran initiated 4 – <8 hours after surgery compared to enoxaparin for the prevention venous thromboembolism following major elective orthopaedic surgery.The results suggest that moving from prophylaxis with enoxaparin to melagatran/ximelagatran results in lower costs and a comparable number of symptomatic VTE events. In the Netherlands, the number of THR procedures increased by 68% in the period 1986-1997, to 17,400 per year (Ostendorf 2002). Assuming no further change in the age- and sex-specific arthroplasty rate, the predicted annual rate of THR procedures will have increased by 50% in the year 2020 (Ostendorf 2002). In the period 1990-2000 the number of TKR procedures increased from 2,727 to 7,764 with an expected increase towards approximately 11,000 procedures in the year 2020 [personal communication, M. Ostendorf, November 2002]. Against this background the cost savings following the introduction of melagatran/ximelagatran may be considerable.

As in many other countries there is a trend towards reduced length of hospital stay in the Netherlands (Prismant), with specialized centres aiming at discharge to home or rehabilitation clinics after less than five days [expert review board judgement]. The ease of administration of oral ximelagatran in an outpatient or community setting may increase the likelihood of patients receiving treatment for the prescribed duration, thereby reducing the risk of VTE and associated costs. Furthermore, LMWHs are only available as a daily subcutaneous injection, which requires training for self-injection or dependency on outpatient facilities and community nurse visits in order to continue prophylaxis outside the hospital. Oral ximelagatran is quicker and safer to administer and patients do not require training on usage or do not become dependent on

Table 6: Results from the univariate sensitivity analysis (per 1000 patients)

	Difference in costs[a]			Difference in symptomatic events[a]			
	Drugs	Efficay, safety[b]	Total	DVT	Fatal PE	Non-fatal PE	Total
Base Case	5,500	-28,979	-23,479	0.07	0.00	0.00	0.07
p1:							
Enoxaparin (0.297)	5,500	-31,542	-26,042	-1.72	-0.02	-0.09	-1.83
Enoxaparin (0.245)	5,500	-26,492	-20,992	1.80	0.02	0.09	1.91
Melagatran/ximelagatran[c] (0.308)	5,500	-25,494	-19,994	2.50	0.03	0.13	2.66
Melagatran/ximelagatran[c] (0.238)	5,500	-32,327	-26,827	-2.27	-0.02	-0.12	-2.41
Probability of blood transfusion:							
Enoxaparin (0.687)	5,500	-38,668	-33,168	0.07	0.00	0.00	0.07
Enoxaparin (0.637)	5,500	-19,116	-13,616	0.07	0.00	0.00	0.07
Melagatran/ximelagatran[c] (0.654)	5,500	-14,679	-9,179	0.07	0.00	0.00	0.07
Melagatran/ximelagatran[c] (0.577)	5,500	-43,548	-38,048	0.07	0.00	0.00	0.07
Cost per unit of blood ( ):							
232	5,500	-37,702	-32,202	0.07	0.00	0.00	0.07
125	5,500	-20,256	-14,756	0.07	0.00	0.00	0.07

a) Melagatran/ximelagatran-enoxaparin, b) Includes costs for diagnosis and treatment of VTE, blood transfusions, and long-term complications of DVT, c) Initiated 4 – <8 hours after surger

outpatient facilities, thereby saving on nursing time both in the hospital and the community. In addition, thromboprophylaxis with LMWHs with pre-operative start requires contact with hospital 12 hours or more before the surgery is scheduled, to allow dosing to be initiated at the appropriate time to achieve full therapeutic protection. Melagatran/ximelagatran has a convenient dosage schedule that allows initiation of the treatment closely after surgery, providing the opportunity for day-of-surgery admission and an associated reduction in hospital costs. The approved Summary of Product Characteristics states that an alanine aminotransferase (ALAT) value should be obtained before administration of melagatran. This ALAT value may be obtained from the routine pre-operative assessment (at little or no additional resource utilisation), which allows pre-operatively started LMWH in patients in whom melagatran/ximelagatran is contraindicated (hepatic impairment and/or ALAT >2 x the upper limit of normal).

A limitation of our analysis is that the clinical outcome measure in the model was defined as symptomatic VTE events. Ideally, economic evaluations should use quality-adjusted life expectancy as an outcome measure to ensure comparability with evaluations in other clinical areas. However, as the difference in total DVT between the enoxaparin and melagatran/ximelagatran groups was very small, we decided not to estimate quality-adjusted life expectancy but to keep the model as simple as possible by using symptomatic VTE events as the outcome measure. For the same reason we also decided to incorporate costs for long-term complications costs by assigning DVT patients an expected cost for long-term complications, rather than incorporating these explicitly in the decision model as has been done in other cost-effectiveness analyses in the field (Levin 1998; Gordois 2003; Honorato 2004; Sullivan 2004). Unlike other analyses we also decided not to include false-positive cases of DVT or PE (Levin 1998; Gordois 2003; Honorato 2004; Sullivan 2004). With the small difference in total DVT, inclusion of these cases would have had a marginal effect on the difference in costs. Finally, the results may not be generalizable across countries as prices and unit costs used in the analysis may differ.

In conclusion, thromboprophylaxis with melagatran/ximelagatran initiated 4 – <8 hours after surgery provides comparable efficacy and safety to enoxaparin but is associated with lower costs. With the advantage of oral administration, melagatran/ximelagatran offers a cost-effective alternative to enoxaparin for the prevention of VTE following major elective orthopaedic surgery.

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Chapter 6

Cost-effectiveness of rituximab(MabThera®) in diffuse large B-cell lymphoma in the Netherlands

SUMMARY

Objective: To determine the incremental cost-effectiveness ratio (ICER) of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) vs. CHOP plus rituximab (R-CHOP) in diffuse large B-cell lymphoma (DLBCL) patients in the Netherlands.

Methods: A state transition model was developed to estimate the clinical course, costs and quality of life of patients with stage II, III or IV DLBCL receiving initial treatment with CHOP or R-CHOP to arrive at the ICER. The base year for the cost analysis was 2002 and was performed from the societal perspective. Only direct medical costs were included. The time horizon of the model was 15 years and both costs and effects were discounted at 4%. Sensitivity analyses were performed to determine the effect of varying base-line assumptions of the model.

Results: The incremental gain in quality adjusted life years (QALYs) was 0.88 in both the younger and the older patient groups. The costs were € 12,343 higher in the younger group of patients and € 15,860 in the older patients. This resulted in an ICER of € 13,983 for the younger and € 17,933 for the older patients per QALY gained. These results were sensitive to the time horizon of the model, other variations had a marginal impact on the outcome.

Conclusion: The addition of rituximab to standard therapy for DLBCL results in a gain of 0.88 QALYs. The ICER of € 13,983 for younger and € 17,933 for older patients per QALY gained should, seen in the light of disease severity, be considered acceptable by most policy makers in priority setting for budget allocation.

INTRODUCTION

In the Netherlands there are approximately 2300 new cases of non-Hodgkin's lymphoma (NHL), making it the ninth most frequent cancer (Visser 2003). Dutch cancer registry data suggest that approximately 40% of newly diagnosed NHL patients have diffuse large B-cell lymphoma (DLBCL) and 64% of these patients are over 60 yr of age (Krol 2003). This age limit is the age cut-off point in the international prognostic index (1993).

Since the mid-1970s cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) given every 3 wk has been shown to be the best chemotherapy for aggressive lymphomas with regard to response and survival rates. However, only 40–45% of patients are cured with CHOP. The recent addition of Rituximab to CHOP, so called R-CHOP, has improved the disease-free and overall survival in patients both above and under 60 yr (Coiffier 2002; Pfreundschuh 2004c). Rituximab is a monoclonal antibody targeted against CD-20, which is present on the tumor cells in approximately 80% of patients with DLBCL. The R-CHOP is approved as first-line treatment of patients with CD-20 positive DLBCL, for Ann-Arbor stages II, III or IV in Europe. Partly based on economic evaluations it is endorsed as a treatment option that should be used systematically in this setting for all adult patients by the National Institute for Clinical Excellence (NICE) in the UK (NICE 2003). These outcomes cannot be translated directly to the Dutch situation because of differences in clinical approach of these patients, overall costing approaches and differences in unit costs.

In the Netherlands, rituximab has been placed on the list of expensive medicines that is issued by the National Health Tariffs Authority (CTG). Hospitals can negotiate a budget compensation of up to 75% of the net cost price of the medicines that are on this list with individual insurance companies (CTG 2004b). There is a growing pressure on hospital drug budgets. In the period 1996–2000 the contribution of new and expensive medicines to the overall hospital drug budget almost doubled (Pharmo 2002). Together with the overall shortage in the cure sector and the introduction of more innovative new and expensive medications there is a need for insight in the additional costs in combination with its clinical effectiveness. Such an analysis provides possibilities to weigh costs and benefits of therapeutic strategies in cancer treatment by clinicians and more importantly policymakers and healthcare insurers.

The aim of this study is therefore to perform a cost-effectiveness analysis of rituximab in DLBCL in the Netherlands to aid decision-making.

PATIENTS AND METHODS

Model description

Previously, a state transition model was developed in Microsoft Excel. The clinical course, costs and quality of life (QoL) of patients with stage II, III or IV DLBCL receiving initial treatment with

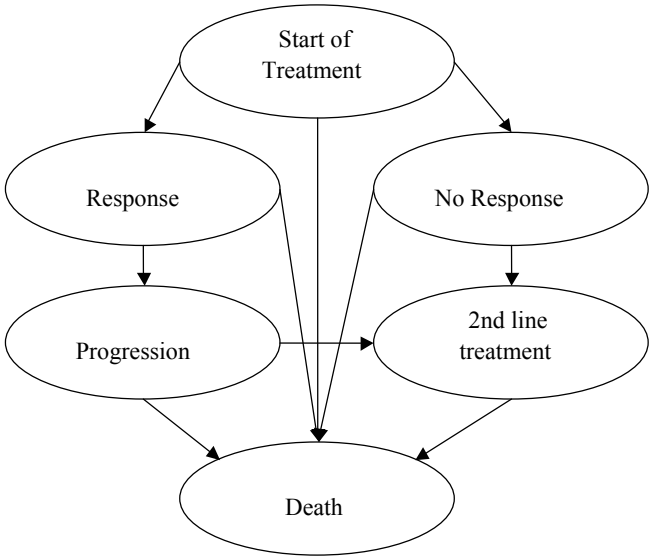


Figure 1: treatment path of DLBCL patients

CHOP or R-CHOP were incorporated to arrive at the incremental cost-effectiveness per life year and quality adjusted life year (QALY) gained by these treatments. This model was evaluated in the NICE appraisal and the outcomes were confirmed by an independent analysis conducted by the School for Health and Related Research (ScHARR) of the university of Sheffield (Knight 2003; NICE 2003). This model was adapted to fit the Dutch situation. In the model the transition from one state to another is based on hazard rates. The Scottish Newcastle Lymphoma Group (SNLG) database was used to compute the disease-free and overall survival of DLBCL-patients treated with conventional CHOP. This database was established in 1979 and since 1994 population-based capturing on treatment and outcomes on more than 95% of the lymphomas in a catchment population of 8.5 million. Also, data from the Group d'Etude des Lymphomes de l'Adulte Non-Hodgkin's Lymphoma 98.5 (GELALNH 98.5) randomized controlled trial were used to calculate the relative increase in complete response rate and relative risk reduction in disease- free and overall survival associated with RCHOP over CHOP (Coiffier 2002).

In the model two outcomes after initial treatment are defined, 'complete response' and 'no complete response' (Figure 1). The complete response arm comprises complete responders (CR) and unconfirmed complete responders (CRu) according to international criteria (Cheson 1999). In our analysis, we made a distinction between patients under and over 60 yr of age as younger patients with DLBCL have a better prognosis as a result of a higher initial response rate and a better survival. Furthermore, they are more frequently given high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation in combination with induction chemotherapy in case of resistance to or relapse after CHOP (van Agthoven 2002a). In line with

Dutch clinical practice, we assumed that after initial treatment with CHOP and R-CHOP palliative treatment or salvage chemotherapy was given to patients older than 60 yr of age not reaching complete response. Younger patients were eligible for second induction chemotherapy with or without high-dose chemotherapy and autologous stem cell rescue.

The cost analysis was performed from the societal perspective, but only direct medical costs were included. The base-year for our cost-analysis was 2002. The time horizon of the model was 15 yr and continuous discounting at a rate of 4% per year for both costs and effects in accordance with the Dutch recommendations was applied (Oostenbrink 2000).

Response rates and survival

The initial complete response rates for the CHOP arm in the younger and older group of patients were derived from the SNLG data. Because the GELA-study so far has no follow-up data beyond year 4, we also used data from the SNLG to compute the long-term disease-free and overall survival of patients treated with CHOP. As the database did not report coherent overall survival data after year 8 we fitted a continuous survival curve alongside the SNLG overall survival data in both the younger and the older patients. For this fit SPSS (version 11.5) was used, a Weibull distribution was assumed for the original data on which subsequently a non-linear regression was performed as described by Kalbfleisch and Prentice (Kalbfleisch 1980). This resulted in estimated overall survival curves with a fit of 94% and 99% compared with the original survival curves for the younger and the older patient groups, respectively.

The mean disease-free survival among patients who reached CR or CRu and the mean overall survival for all patients were calculated by summing the area-under-the-curve of the Kaplan–Meier estimates of disease-free and overall survival.

Data from the GELA-LNH 98.5 trial were analyzed to estimate the effect of rituximab on mean disease-free and overall survival. R-CHOP demonstrated a relative increase in CR of 22.1%, which we applied to estimate the increase in CR for patients receiving R-CHOP. Additionally, the GELA-study showed a relative risk reduction for disease-free and overall survival in the 4 yr of followup. As the GELA-study only had a median follow-up of 4 yr we assumed that this relative risk reduction only lasted for this period. We assumed that the relative increase in CR and CRu and the relative risk reductions for disease-free and overall survival were comparable for the younger and the older patients. Table 1 presents the initial complete response rates and other efficacy assumptions used in the model. Mean disease-free and overall survival was calculated in the same way as in the CHOP-group.

Quality of life

Utility estimates for QALY calculations were derived from a previous study, performed in older patients with aggressive NHL (Doorduijn 2003a). The utility weights in the CR and the no CR or progression group were a weighted average of utilities found on different time points after initial treatment in this study (Doorduijn 2003a). In the absence of specific estimates we used

Table 1: Model assumptions and sources

	CHOP	R-CHOP	Source
Complete response rates			
Older patients	62.1%	75.9%	SNLG/ GELA CSR
Younger patients	71.3%	87.0%	SNLG/ GELA CSR
% Second-line treatment			
Older patients	37.9%	24.1%	Expert opinion
Younger patients	28.8%	13.0%	Expert opinion
Efficacy assumptions			
Relative increase in CR, %		22.1%	GELA CSR
Relative risk reduction			
Overall survival		31.0%	GELA CSR
Disease-free survival		43.9%	GELA CSR
Duration of risk reduction, yrs		4	Expert opinion
Mean number of initial courses			
CHOP	7.1	7.5	GELA CSR
Rituximab		7.4	GELA CSR
Utilities			
Initial treatment	0.60	0.60	(Doorduijn 2003a)
Progression-free	0.81	0.81	(Doorduijn 2003a)
No CR or progression	0.60	0.60	(Doorduijn 2003a)
Death	0.00	0.00	Expert opinion
Discount rates			
Health outcomes	4.0%	4.0%	(Oostenbrink 2000)
Costs	4.0%	4.0%	(Oostenbrink 2000)
Time horizon, yrs	15	15	Expert opinion
Costs assumptions (Euro)			
Costs per cycle of CHOP, older patients	2,091	2,091	(Doorduijn 2003b; Doorduijn 2004)
Costs per cycle of CHOP, younger patients	1,640	1,640	(van Agthoven 2002a)
Drug Cost per infusion of rituximab		2,088	(van Loenen 2003)
Follow-up costs per year, older patients	3,732	3,732	(Doorduijn 2003b; Doorduijn 2004)
Follow-up costs per year, younger patients	3,025	3,025	(van Agthoven 2002a)
Surveillance costs per year after year four, both patient groups	166	166	Expert opinion / treatment protocols
Second-line treatment for younger patients	% of patients	Weighted cost	(van Agthoven 2001a)
Induction only	50%	10,395	
Induction and PBSCT	50%	23,888	
Weighted average		34,283	
Second-line treatment for older patients	% of patients	Weighted cost	(van Agthoven 2001a)
Palliation	50%	4,805	
Induction only	50%	10,395	
Weighted average		15,200	

CR: complete response, SNLG: Scottish Newcastle Lymphoma group, GELA: Groupe d'etude des lymphomas de l'adulte, CSR: clinical study report, PBSCT: peripheral blood stem cell transplantation

the same utility estimates for the younger patients. In our analysis we valued the utility of initial treatment with CHOP or R-CHOP at 0.6 during the first 5 months in our model. Subsequently, we assigned different utility weights to the different disease states in our model. The utility weights are described in Table 1.

Resource use

Data on mean number of courses of CHOP and R-CHOP were derived from the GELA-study. Information on resource use during initial treatment, follow-up during the first 4 yr after treatment and second-line treatment costs were derived from detailed cost-effectiveness studies previously performed in patients with aggressive NHL in the Netherlands (van Agthoven 2002a; Doorduijn 2004). In these studies patient records were studied to determine the resource use in detail. Surveillance after year 4 consisted of two specialist visits with laboratory testing (complete blood count and LDH testing) per year, which is in line with practice patterns in the Netherlands. Costs were calculated by multiplying the units of resource use by the unit costs. For the most important resource use items detailed unit costs were calculated using the micro-costing method (Gold 1996). For the other resource use, Dutch tariffs were used (van Loenen 2003). Wholesale drug prices were used for the costs of rituximab and other drugs used during hospitalization or chemotherapy (CTG 2004a). Table 1 presents the mean total treatment costs for initial, follow-up and second-line treatment used in the model.

Incremental cost-effectiveness

The incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total costs of the R-CHOP and the CHOP treatment arm by the difference in quality adjusted survival between both treatment arms. Both discounted and undiscounted results are presented.

Sensitivity analysis

We performed several one-way sensitivity analyses to determine the effect of varying base-line assumptions chosen for variables used in the model. An overview of the different assumptions tested and the ranges we investigated are presented in Table 2. We also performed a probabilistic sensitivity analysis of selected variables that was performed using Monte–Carlo simulation. In the probabilistic sensitivity analysis 1000 simulations are run. For the relative increase in CR and the relative risk reductions for disease-free and overall survival we assumed a lognormal distribution. A uniform distribution was assumed for the utilities while we assumed a normal distribution for the follow-up costs. The variables and their assumptions are described in Table 3. As it is perceived that there is a relation between response and survival we assumed a correlation of 0.7 between CR and survival in our Monte–Carlo simulation, this figure was based on the opinion of four experts in the Dutch Organization for Hemato-oncology in Adults (HOVON) cooperative study group.

Table 2: Variables tested in one-way sensitivity analysis

Variables	Assumptions
Relative increase in CR rate	
Low	Lower by 10%
High	Higher by 10%
Relative risk reduction (DF and overall survival)	
Low	Lower by 15%
High	Higher by 15%
Duration of treatment effect, yrs.	
Low	2
High	5
Costs of initial treatment	
CHOP	
Low	Lower by 15%
High	Higher by 15%
Costs of rituximab	
Low	Lower by 15%
High	Higher by 15%
Percentage/costs of second-line treatment	
Low	Lower by 15%
High	Higher by 15%
Costs of follow-up	
Low	Lower by 15%
High	Higher by 15%
Utilities (Progression free and with progression)	
Low	Lower by 15%
High	Higher by 15%
Discount Rate (costs and effects)	
Low	0%
High	6%
Time Horizon, yrs	
Low	5
High	20

Table 3: variables for Monte-Carlo analysis

Variable	Distribution	Parameters
Relative increase in CR rate	Log-Normal	μ=ln(1,195), =0.08
Relative risk reduction of disease-free survival	Log-Normal	μ=ln(.52), =0.23
Relative risk reduction of overall survival	Log-Normal	μ=ln(.47), =0.21
Utilities	Uniform	
Progression free		(0.66-0.99)
Progression		(0.71-0.49)
Follow-up costs	Normal	μ=3732 or 3025, =10% of μ

RESULTS

Survival

Figure 2 shows the Kaplan–Meier estimates of the disease free survival in both age groups derived from the SNLG database. The maximum duration of disease-free survival follow-up was 11.6 yr in the group of older patients and 12.5 yr in the younger patients. Estimates for the R-CHOP disease-free survival were based on the CHOP estimates, adjusted for the 4 yr of relative risk reduction shown in Table 1. In the older patients there was a 1.81 yr increase in the mean undiscounted disease-free survival of the R-CHOP over the CHOP patients, 4.51 yr vs. 2.70 yr, respectively. In the younger group this difference was larger; 2.34, a mean disease-free survival in patients with complete response of 8.57 yr in the R-CHOP patients vs. 6.22 in the CHOP patients. Figure 3 shows the Kaplan–Meier estimates of the overall survival in both age groups. The undiscounted mean overall survival in the older patients was 5.05 yr in the CHOP group and 6.28 yr in the R-CHOP group. For the younger patients these figures were 8.79 yr in the CHOP group and 9.89 in the R-CHOP group. Table 4 presents the undiscounted survival estimates of both age groups as well as the discounted survival figures and the number of

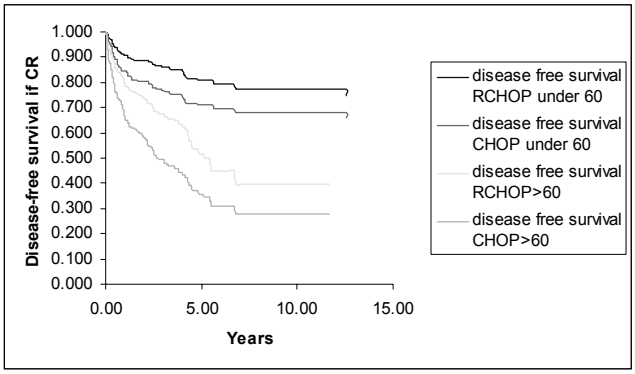


Figure 2: Kaplan Meier curves of disease-free survival in the different treatment groups

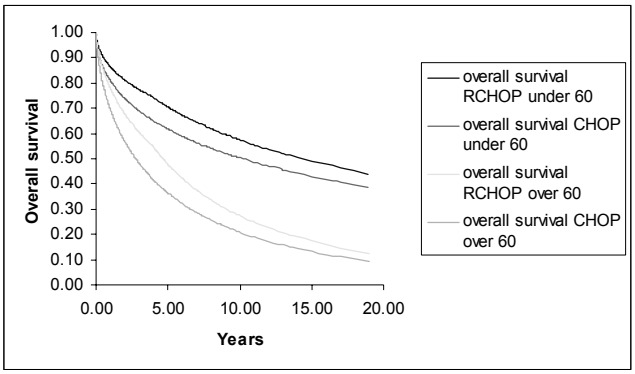


Figure 3: Kaplan Meier curves of the overall survival in the different treatment groups

QALYs. These figures show that the addition of rituximab to the standard treatment of patients with DLBCL leads to an increase in discounted QALYs of 0.88 for both age groups.

Costs

The discounted and undiscounted estimated costs of treatment are presented in Table 4. The addition of rituximab resulted in a discounted cost increase of € 15,350 to the initial treatment. Additionally, costs of CHOP were higher in the R-CHOP group as on average more cycles of treatment were received. Furthermore, it showed that despite the differences in costs per cycle of CHOP the differences in overall CHOP costs were similar in both age groups. The difference in follow-up costs in the younger patient group was smaller because of the lower difference in overall survival compared with the older patients. In the younger patient group there was a small reduction in second-line treatment costs caused by the higher initial complete response rate despite the higher costs of second-line treatment in this group.

Cost-effectiveness

Taking into account the increased costs of initial treatment and the small incremental costs associated with the increased survival there was an overall increase in discounted costs of treatment for the older patients of € 15,860 and of € 12,343 for the younger patients. CE-ratios are obtained by taking these added costs for the both age groups and dividing them by the increase in discounted overall and quality adjusted survival. In older patients the cost per discounted life year gained was € 16,493 and € 17,933 per discounted QALY. In the younger patients the costs per discounted life year gained were lower, € 14,865, the costs per discounted QALY gained were € 13,983.

Sensitivity analysis

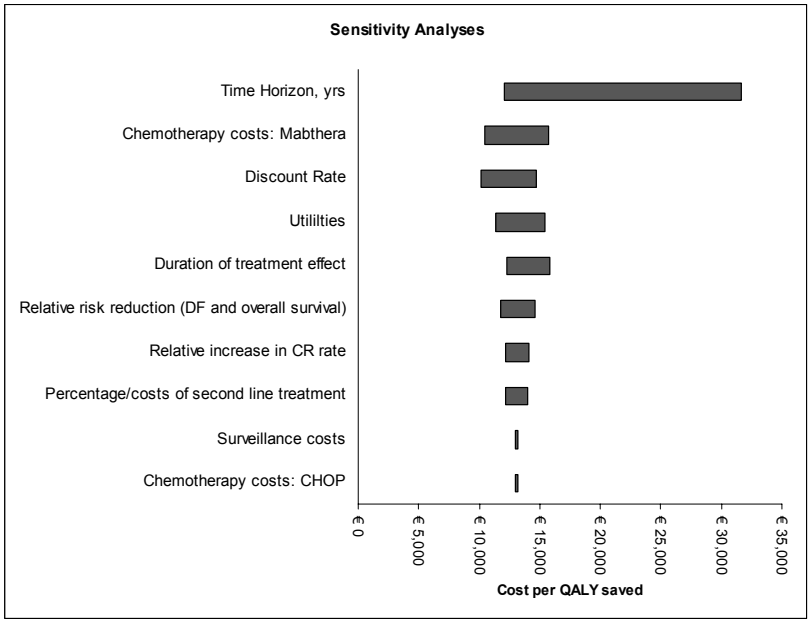
We performed one-way sensitivity analyses to test the impact of varying the baseline assumptions used in this cost-effectiveness model (Fig. 4A and B). These analyses show that in all except one

Table 4: Results of the model-based analysis for both younger and older patients

Undiscounted	**Younger**			**Older**		
	CHOP	R-CHOP	Difference	CHOP	R-CHOP	Difference
Survival						
Disease-free	6.22	8.57	2.34	2.70	4.51	1.81
Post-progression	2.57	1.32	-1.25	2.36	1.77	-0.58
Total	8.79	9.89	1.09	5.05	6.28	1.22
QALYs	6.59	7.74	1.14	3.61	4.72	1.11
Costs (Euros)						
Chemotherapy						
Mabthera		15,448	15,448		15,448	15,448
CHOP	11,644	12,300	656	14,846	15,683	836
Follow-up	8,938	9,896	958	8,015	9,601	1,586
Second-line treatment	8,372	3,781	-4,591	4,893	3,118	-1,774
Total	28,954	41,425	12,471	27,754	43,850	16,096
Incremental cost effectivenes						
Per LY gained			11,410			13,177
Per QALY gained			10,906			14,499

Discounted	**Younger**			**Older**		
	CHOP	R-CHOP	Difference	CHOP	R-CHOP	Difference
Survival						
Disease-free	4.94	6.79	1.85	2.24	3.72	1.47
Post-progression	1.96	0.95	-1.02	1.93	1.42	-0.51
Total	6.91	7.74	0.83	4.17	5.14	0.96
QALYs	5.19	6.07	0.88	2.98	3.87	0.88
Costs (Euros)						
Chemotherapy						
Mabthera		15,350	15,350		15,350	15,350
CHOP	11,566	12,222	656	14,747	15,584	836
Follow-up	8,021	8,877	856	7,328	8,748	1,420
Second-line treatment	8,241	3,722	-4,519	4,816	3,069	-1,747
Total	27,828	40,171	12,343	26,891	42,751	15,860
Incremental cost effectiveness						
Per LY gained			14,865			16,493
Per QALY gained			13,983			17,933

LY: life years, QALY: quality adjusted life years



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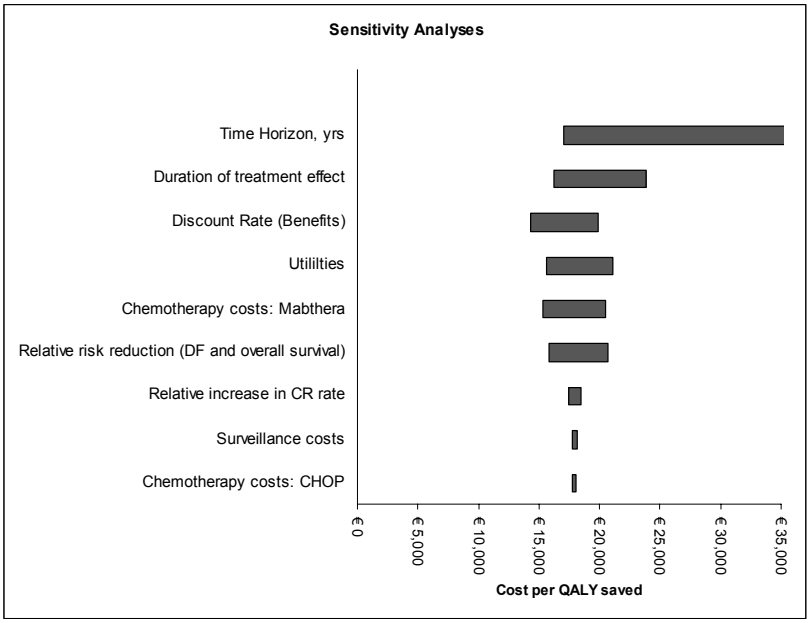

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Figure 4A and 4B: Results of the one-way sensitivity analysis. The bars represent the variation in cost effectiveness ratios caused by the changes of input parameters as described in Table 2. (A) Patients over 60 yr. (B) Patients under 60 yr.

analysis, variations in base line assumptions did not lead to large changes in cost-effectiveness ratios. Only in the case of limiting the model's time horizon to 5 yr there was a large shift in cost-effectiveness ratio to approximately € 35,355 per QALY gained in the older patient group and € 31,676 in the younger group of patients (all discounted). This is caused by the fact that, as in many treatment strategies, the costs are especially made in the beginning while the gain in effects (i.e. increase in life years) occurs later. Based on the 4-yr follow-up data of the GELA study this scenario is however very unrealistic. The cumulative distribution functions of the results of the probabilistic sensitivity analysis are presented in Fig. 5. This type of presentation of results represents the probability that a treatment is considered cost-effective given a specific budget (R or ceiling ratio). In this simulation the 5th and 95th percentile were 11 044 and € 30,139 for the older group of patients and € 6282 and € 27,601 for the younger patient group, implying that 90% of simulation results lay between these limits.

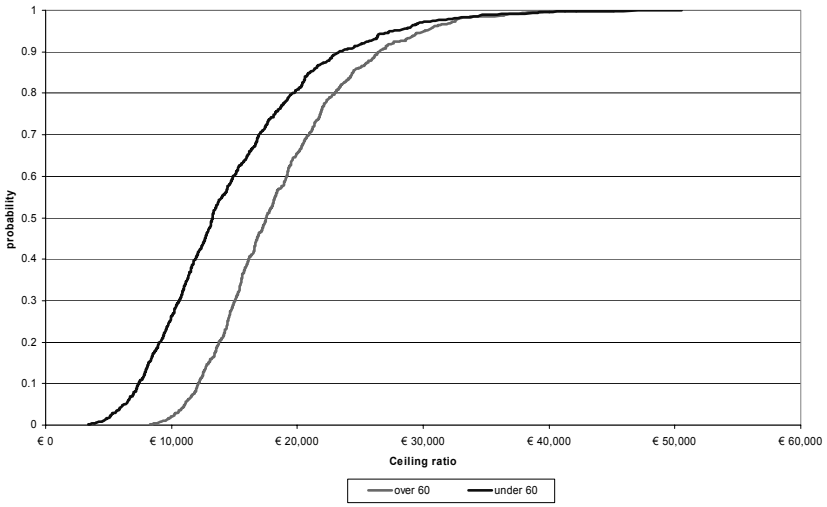


Figure 5: Cumulative distribution functions for the Monte Carlo simulation. This graph represents the probability (on the y-axis) that the outcome of the probabilistic sensitivity analysis is equal to or lower than the ceiling ratio (on the x-axis).

DISCUSSION

In this analysis the addition of rituximab to CHOP for the first-line treatment of advanced phase DLBCL resulted in an incremental discounted cost per QALY gained of € 13,983 for the younger patients and € 17,933 for the older patients. Sensitivity analyses showed that this ratio was relatively insensitive to changes in the input parameters and assumptions underlying the current analysis, only the reduction of the model's time horizon to 5 yr resulted in ratios per QALY gained above € 30,000.

As the SNLG database was used to model the long-term survival we also used the initial response rates reported in this database. This rate was slightly lower for the older patients than reported in the GELA-study. However, the 4-yr survival rates were almost equal, 47% and 48% respectively. In our analysis we assumed that the increase in response rate observed in the Coiffier study (Coiffier 2002) for patients over 60 yr of age was also applicable to the patients younger than 60 yr. Recently presented data from a trial in young, low risk patients with DLBCL indicate this to be a reasonable assumption (Pfreundschuh 2004c). In this trial previously untreated patients with low-risk DLBCL were randomized to receive 6, 3-weekly, cycles of a CHOP-like regimen (CHEMO) or the same chemotherapy plus rituximab 375 mg/mg (R-CHEMO) with additional radiotherapy for initial bulky disease. In this trial a complete responserate of 84.7% was found in the R-CHEMO group and 66% in the CHEMO group (Pfreundschuh 2004c).

We assumed that the survival data from the SNLG also account for the survival gain accomplished by second-line treatment in both groups of patients. Second-line treatment is offered to all patients not reaching complete response after initial therapy. Being an assumption based on expert opinion, it was shown in sensitivity analysis that the percentage of patients receiving second-line treatment did not influence the cost-effectiveness ratio significantly.

The treatment effect in the R-CHOP patients group is included for the first 4 yr of follow-up as there are no follow-up data beyond this period available. This is likely to be an underestimation of the treatment effect, future follow-up data should be awaited to confirm this.

When comparing the results of the cost-effectiveness analysis that was performed in the UK the Dutch cost-effectiveness ratios are slightly less favorable despite the use of the same clinical data (Knight 2003). There are a number of reasons for these differences that do not disqualify one of the two approaches. For the Dutch analysis we were able to use detailed information describing the costs associated with disease and associated quality of life in more detail. Additionally we assigned second-line treatment to the older patient group as well. Furthermore we chose to extend the overall survival data from the SNLG as this database gives no information for the last 4 yr of the follow-up period used in the analysis. Together with the different discounting levels applied, in accordance with differences in country recommendations, these account for the variations in cost-effectiveness ratios.

The prognosis of DLBCL patients improved significantly with the introduction of rituximab. Promising results of the NHL-B1 and NHL-B2 trials of the German High Grade Non-Hodgkin's

Lymphoma Group that studied CHOP with or without etoposide given every 2 wk were reported (Pfreundschuh 2004a; Pfreundschuh 2004b). These studies led to the initiation of new clinical trials that currently investigate the possibilities of improving treatment outcomes in these patients further by combining the addition of rituximab to CHOP-like regimens with decreasing dose intervals. These studies aim to both optimize CHOP treatment and autologous transplantation strategies and are likely to have an influence on future ICERs calculated for these patients.

In the clinical studies addition of rituximab to standard therapy for DLBCL significantly increased the complete response rates, reduced the rate of treatment failure and relapse and increased both overall and event free survival. These gains were established without a significant increase in toxic effects. Nevertheless, additional costs will be made with the addition of rituximab. Although there are no well defined cost-effectiveness threshold ratios, the ratio for both groups are lower than the often quoted limit of € 18,000 for cholesterol lowering medicines in the Netherlands (CBO 1998). According to a recently conducted analysis investigating the relationship between disease severity and willingness to pay, the maximum acceptable cost per QALY for NHL would be € 45,378 (Poley 2002). This is considerably higher than the present outcomes. Given the severity of the disease for which rituximab is indicated the presented cost-effectiveness ratios should be considered acceptable by policy makers in priority setting for budget allocation.

ACKNOWLEDGEMENT

We would like to thank Prof. Stephen Proctor and Dr Jo White of the Scottish Newcastle Lymphoma Group for providing the CHOP response rates and the overall and disease-free survival data of DLBCL patients from the SNLG database.

Chapter 7

Drug treatment of chronic myeloid leukaemia: a cost-effectiveness analysis of first- and second-line treatment.

SUMMARY

Objective. To determine the average cost-effectiveness ratio of treatment of patients with chronic myeloid leukaemia (CML): with first-line interferon alpha-2a (IFN) or second-line imatinib following IFN failure.

Design. Cost-effectiveness analysis

Patients and Methods. A general cost-effectiveness analysis was performed using a model. This model consists of two phases: an induction phase of eight months, in which patients are treated with IFN or imatinib, and a chronic treatment phase wherein patients are treated according the result of the induction phase. Input for this model was derived from literature and expert opinion. Costs were based on real prices and tariffs.

Results. Treatment with imatinib resulted in 6.67 quality adjusted life years (QALYs) and treatment with IFN in 4.98 QALYs. Average costs of treatment with 5 million IU/day of IFN were € 76,969 and € 53,257 with 3 million IU/day. For imatinib at 400mg/day the costs were € 140,765 per patient. Costs per QALY were € 15,445, € 10,687 and € 21,082 respectively.

Conclusion. The addition of imatinib to the treatment options in CML resulted in increased quality-adjusted survival, but also in higher costs of treatment.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a malignant myelo-proliferative disease, which is characterised by a clonal expansion of myeloid progenitors in bone marrow and blood. The disease evolution usually has three phases. After an initial 3-4 year chronic phase, an acute phase, the blastic crisis, develops via an accelerated phase, which leads to death in a limited number of months (Sawyers 1999; Kantarjian 2000).

Hydroxycarbamid is the initial treatment of choice for CML. After that, a difficult choice has to be made between different treatment options. Currently, curation is only possible with an allogeneic stem-cell transplantation, this option, however, is associated with high morbidity and mortality (Reiter 1999; Hehlmann 2000). Additionally, due to age criteria and limited availability of donors, only 20-30% of all CML patients are eligible for this treatment (Sawyers 1999; Mughal 2001) For the remaining group of CML patients, the treatment of choice is interferon alfa-2a (IFN), sometimes combined with low-dose cytarabin (Sawyers 1999; Kantarjian 2000). However, IFN has many side-effects that lower quality of life considerably. As a result 20-40% of patients stops treatment (Guilhot 1997; Baccarani 2002).

Much has changed with the introduction of imatinib, an inhibitor of the tyrosine kinase bcr-abl. The drug was registered in Europe at the end of 2001 for the treatment of CML in the chronic phase after failure of treatment with IFN. Imatinib has proven to be very effective in clinical trials initiated in 1998. Almost 90% of patients with IFN-resistance or intolerance that were treated with imatinib reached a complete haematological response, while 49% reached complete or partial cytogenetic response. Even in patients in accelerated phase or blastic crisis haematological and cytogenetic responses are reached (Druker 2001; Kantarjian 2002a).

Because of the considerable costs of IFN and imatinib, and the differences in cytogenetic response, it is relevant to compare the cost-effectiveness of these different treatments with each other.

PATIENTS AND METHOD

Patients

The study population consists of 2 groups of patients with CML in the chronic phase. The first group received first-line treatment with chemotherapy treatment with IFN. The second group consisted of patients that had a relapse after IFN treatment, who were IFN resistant or intolerable. These patients were treated with imatinib.

The model

The model was constructed in DataPro (Treeage Software Inc, Williamstown, MA, USA) and consisted of 2 phases: (a) an induction phase; the first 8 months of treatment, (b) a chronic or follow-up phase; treatment and clinical evolution from 8 months till death.

The most important outcome parameters in the induction phase were initial response and the percentage of patients that were intolerant to treatment with IFN or imatinib. When a patient became intolerant to initial treatment they were treated with hydroxycarbamid thereafter. The different disease stages of the induction phase are presented in figure 1.

The clinical evolution after month 8 – the chronic treatment phase – was modelled using a so-called Markov-model (Sonnenberg 1993). Stage transitions were calculated with transition probabilities (table 2). The model had a cycle length of 6 months in the chronic treatment phase;

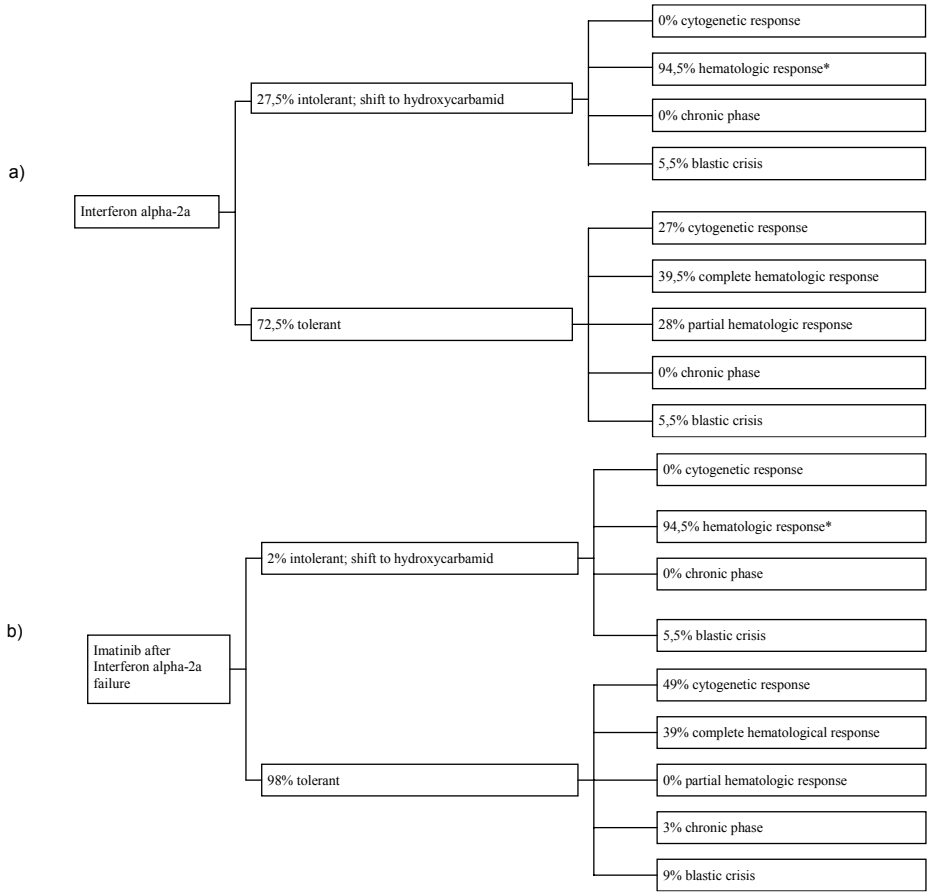


*Figure 1: Probabilities of response for patients with chronic phase chronic myeloid leukemia per stage in the first 8 months of treatment. On Interferon alfa-2a (a) or – when resistant or intolerant therefore – on Imatinib (b) (Liberato, 1997; Pharma, 2001). * Partial or complete hematologic response.*

after each cycle, costs were calculated on the basis of distribution over the different disease stages and added to the total costs. When patients went into blastic crisis it was assumed that they lived for an additional 6 months and subsequently died. Costs and effects were calculated for a total of 25 years.

Probabilities

Response percentages and the percentage of patients with intolerance after 8 months of treatment were derived from a previous study for IFN (Liberato 1997) and from the registration study for imatinib (Pharma 2001). The transition probabilities of the clinical evolution after 8 months was based on a previous study (Liberato 1997) It was assumed that clinical evolution in patients with a cytogenetic response was the same, irrespective of treatment patients were receiving to reach and maintain this response. Initial response percentages and transition probabilities are presented in figure 1 and 2.

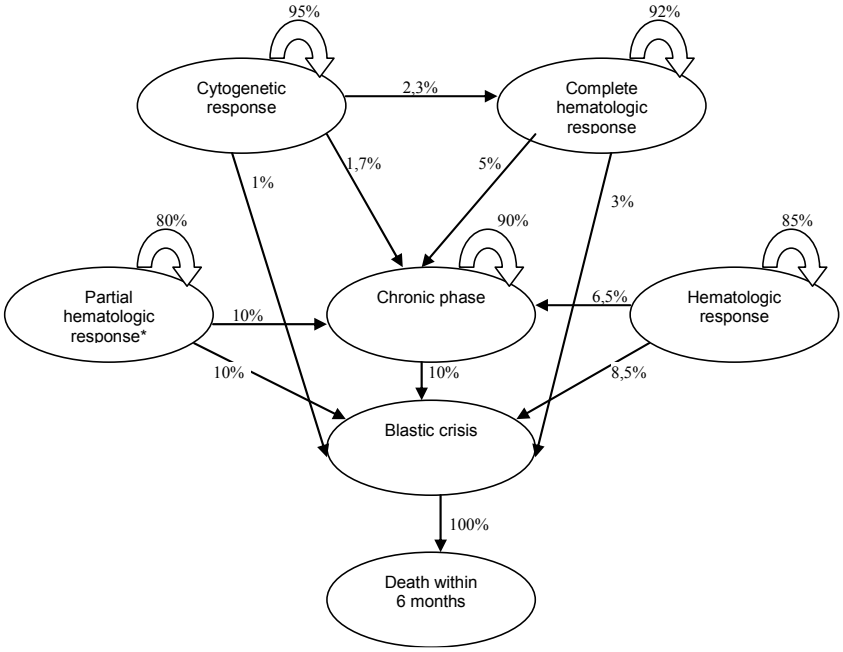


Figure 2: Kaplan Meier curves of disease-free survival in the different treatment groups

Cost analysis

The costs of medication were derived from the pharmaceutical compass (van der Kuy 2000). IFN costs were calculated for 2 different dosages; 3 million IE and 5 million IE per patient per day. The former dosage was the maximum dosage that could be sustained for longer periods of time in studies aiming at a maximum dose of 5 million IE per square meter of body surface per day

(Guilhot 1997; Shepherd 2001; Baccarani 2002). The latter dosage proved to be equally effective as the higher dosage (Shepherd 2001). In the base case analysis costs of imatinib were based on a dosage of 400mg per day, the costs of hydroxycarbamid on 2g per day. Costs of follow-up were based on monthly outpatient visits and 2 bone marrow tests per year. Treatment for blastic crisis was based on expert opinion, assuming treatment with induction chemotherapy in 5% of patients; costs of induction chemotherapy were based on a previous cost analysis in patients with acute myeloid leukaemia (Uyl-de Groot 2001). The costs of blood transfusions and were also included. These were based on the costs of 36 units of erythrocytes in 12 day care visits and 7 units of thrombocytes in 1 day care visit per 3 months. The costs of terminal care during blastic crisis were based on a previous study (Smeenk 1998). The basis for the cost analysis is presented in table 1. The base year for the cost analysis was 2000.

Quality of life

To correct life years for quality of life, utilities, varying between 0 (worst possible situation) and 1 (full health), are used in health economics. These utilities were based on estimations from 7 haematologists/internists with a broad experience in treating CML patients. The valuation of the different health states was measured with a visual analogue scale (table 2).

Table 1: Costs of treatment of patients with chronic myeloid leukaemia (van der Kuy 1998; Oostenbrink 2000; Uyl-de Groot 2001)*

	Average total costs per cycle (€)
Induction phase	
Interferon alfa-2a	
5 million IE/day	14,970
3 million IE/day	7,876
Imatinib	20,781
Chronic treatment phase	
In case of cytogenetic response on:	
Interferon alpha-2a 5 million IE/day	11,176
Interferon alpha-2a 3 million IE/day	5,856
Imatinib	15,535
In case of complete or partial hematologic response after or chronic phase on hydroxycarbamid	769
In case of blastic crisis	27,744

The induction phase last 8 months. Subsequently, there is a switch to 6 months cycles in which patients are treated with Interferon alpha-2a, imatinib or hydroxycarbamid depending on their health state. Patients in blastic crisis are treated divergent.

*Table 2: Quality of life during treatment for chronic myeloid leukaemia, expressed as utilities**

Treatment and disease stage	Utility
Interferon alpha-2a	
- Cytogenetic response	0.72
- No cytogenetic response (induction phase)	0.68
Imatinib	
- Cytogenetic response	0.83
- No cytogenetic response (induction phase)	0.81
Hydroxycarbamid	
- Complete or partial hematologic response	0.77
- Chronic phase	0.80
- Blastic crise	0.33

* A utility is a weighing factor that is assigned to life years for correction of loss of quality; its value varies between 0 (worst possible health state) and 1 (perfect health).

Cost effectiveness

Costs of treatment were related to the effects using average cost-effectiveness ratios. In addition to the costs per QALY, the average costs per cytogenetic response after the 8-month induction period was also calculated. A discount rate for costs and effects of 4% was used (Oostenbrink 2000).

Sensitivity analysis. To test the robustness of the model, the effect of varying a number of variables was studied. Upper and lower limits of ±10% than base case estimates were tested. The effect of increasing the imatinib dosage to 600mg per day was also studied. Finally, a Monte Carlo analysis was performed to estimate the range of costs and effects (Sonnenberg and Beck 1993).

RESULTS

Survival

The average number of life years was 6.82 in the IFN group irrespective of dosage and 8.54 in the imatinib group (table 3). Treatment with imatinib also resulted in more QALYs: 6.67 versus 4.98. Despite previous failure on IFN treatment and initiation of treatment later in time, the average survival was higher for imatinib, 1.72 life years and 1.69 QALYs respectively. This is not the same as life years gained as IFN and imatinib are currently mutually exclusive due to the treatment restriction of imatinib.

Table 3: costs of treatment of patients with chronic myeloid leukaemia: interferon alpha-2a as first-line treatment or imatinib as second-line treatment

	Treatment		
	interferon alpha-2a; daily dose		imatinib
	5 million IE	3 million IE	
Assumptions			
Average survival			
In years	6.82	6.82	8.54
In QALYs	4.98	4.98	6.67
Average percentage with cytogenetic response after 1 year	20	20	48
Costs of induction treatment (€)	15,780	9,796	22,705
Total costs per patient (€)	76,969	53,257	140,765
Outcomes			
Costs (€)			
Per cytogenetic response*	78,900	48,980	47,302
Per QALY†	15,445	10,687	21,082

QALY= quality adjusted life year.
* Calculated as the costs of induction treatment divided by the average percentage of respons after 1 year.
† Calculated als the total costs per patient divided by the average number of QALYs.

Costs

Average costs of treatment with IFN were € 76,969 or € 53,257,depending on IFN dosage. 76 and 60% of these costs were attributable to IFN. The costs in the imatinib group were higher: € 140,765 per patient. 86.5% of these costs were for imatinib. Despite these higher costs of treatment the average costs per cytogenetic response were considerably lower in the imatinib compared to the 5 million IE IFN and slightly lower compared to the 3 million IE IFN group, € 47,302, € 78,900 and € 48,980.

Cost effectiveness

The costs per QALY in the group receiving treatment with 5 million IE per day were € 15,445 and € 10,687 in the 3 million IE group. Costs per QALY in the imatinib group were € 21,082.

Sensitivity analysis

The results of the sensitivity analysis are presented in table 4. Varying the percentage of cytogenetic response did not result in large changes (3-5%) of outcomes.

Varying the costs of treatment with imatinib, assuming 600mg per day, resulted in total costs of treatment of € 196,930 (€ 29,511 per QALY). Costs of treatment influenced cost-effectiveness

in the IFN group considerably as well. The Monte Carlo analysis showed that extremities that were possible in the model determined the spread in survival; this is in line with real life. Patients can die in the induction phase, but can also survive till the model's maximum of 25 years after start of treatment. The costs of treatment showed a large spread as well Costs of treatment in the IFN groups varied between € 31,556 - € 479,634 and € 28,009 - € 257,156 respectively. Costs in the imatinib group varied between € 34,462 and € 506,519.

Table 4: Results of the sensitivity analysis: costs of treatment of patients with chronic myeloid leukaemia: interferon alpha-2a (IFN) as first-line treatment or imatinib as second-line treatment, with variation in the underlying assumptions

Assumptions	**Costs per QALY (€)**			**Difference compared to base case**		
	interferon alpha-2a; daily dose		imatinib	interferon alpha-2a; daily dose		imatinib
	5 million IE	3 million IE		5 million IE	3 million IE	
base case*	15,445	10,687	21,082			
variation 1: higher or lower cytogenetic response for both treatments			29,511			
+10%	16,044	10,965	22,067	+4%	+3%	+5%
-10%	14,838	10,405	20,085	-4%	-3%	-5%
variation 2: higher or lower quality of life for both treatments						
+10%	15,001	11,013	20,092	-3%	-3%	-5%
-10%	15,916	10,379	22,201	+3%	+3%	+5%

* imatinib dosage: 400mg/day; cytogenetic response: 27% with IFN and 47 with imatinib; quality of life: 0.70 with IFN and 0.82 with imatinib

DISCUSSION

Treatment with imatinib after IFN failure results in a considerable higher percentage of cytogenetic response in CML patients in the chronic phase compared to first-line IFN treatment (Kantarjian 2002a). An other advantage is the oral administration. In this study we studied the difference in costs and effects of primary treatment with IFN in newly diagnosed CML patients on the one side and secondary treatment with imatinib after IFN failure, being a recurrence or intolerability, on the other.

Compared to treatment with IFN, treating patients with imatinib gave better results with a difference in quality adjusted life years of 1.7. This difference was insensitive to uncertainties surrounding quality of life estimates. The percentage of cytogenetic response did not influence outcomes as well. New long-term follow-up data show that at 26 months the percentage

of cytogenetic response increased to 64% in the imatinib group (Kantarjian 2002a). This indicates an underestimation of treatment effect in the current analysis. It should be taken into consideration that with first-line IFN treatment a response can take place after the induction period (Liberato 1997), which was not taken into consideration as well.

The dose of imatinib was increased to 600mg per day in 30% of patients in the course of the study (Kantarjian 2002a). Therefore, the dose of 600mg will occur in daily practice. The exact consequence on total costs and effects cannot be derived from the current study. Treatment of patients with imatinib is initiated at a later point in time, as a result is likely that the percentage of cytogenetic response is higher when imatinib treatment is given in first-line. The comparison of first-line imatinib and IFN treatment has recently been finished and the initial results from this study support this assumption. The difference in cytogenetic response increases further to 63%; 83% in the imatinib group (400mg per day) against 20% in case of treatment with IFN (5MIU/m^2 per day) with low dose cytarabine (Druker 2002).

Since the current study was aimed at a comparison of costs and effects of IFN and imatinib treatment, the possibility of an allogeneic stem-cell transplantation with bone marrow or peripheral blood stem-cells from a related or unrelated donor was not included in this analysis. It is known that the costs of allogeneic stem-cell transplantations are considerable (van Agthoven 2002b) as is the treatment related morbidity and mortality (Hehlmann 2000). A possible consequence of the introduction of imatinib might be a reduction in the number of stem-cell transplantations.

We conclude that the introduction of imatinib to the treatment armamentarium in CML patients will lead to both an increase in costs of treatment and average survival and quality of life. The costs per QALY are about € 21,000, which is an acceptable cost-effectiveness ratio in our view, especially when the severity of disease is taken into consideration. This is supported by reimbursement of other healthcare interventions that have a considerably higher cost per QALY ratio like lung transplantations (€ 82,462) and treatment of end stage renal disease (€ 43,709) (Toenders 2001). reimbursement remains, a political issue and other aspects like budget, budget impact and societal support play a role as well. The structure of the presented model can be used for cost-effectiveness calculations of other expensive medication in the haematology. The Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) is currently initiating such studies.

Chapter 8

Cost-effectiveness of chronic myeloid leukaemia treatment in the imatinib era

SUMMARY

Objective: To determine the incremental cost-effectiveness ratio (ICER) of imatinib versus IFN- +Ara-C in newly diagnosed, chronic phase CML patients.

Patients and Methods: An economic simulation model was developed in Microsoft Excel to estimate expected total cost, survival and quality-adjusted survival for patients treated with imatinib or IFN- +Ara-C. This model is based on data collected in the International Interferon versus StI571 Study (IRIS) supplemented with data from international literature and clinical experts. The analysis incorporated first-order and second-order uncertainty. Sensitivity analyses were also performed to evaluate the influence of individual parameters. In an additional scenario analysis an alternative second-line treatment was assessed. The base year for the cost analysis was 2002 and only direct medical costs were considered.

Results: Mean survival for patients receiving imatinib was estimated at 15.20 years, for the IFN- +Ara-C patients this was 9.11 years. When both costs and effects were discounted at 4%, the incremental gain in quality adjusted life years (QALYs) was 3.35. Incremental discounted lifetime costs were € 164,389 higher for patients receiving imatinib. This resulted in an ICER of € 49,021 per QALY (95% confidence interval; € 44,587, € 54,758). These results were most sensitive to assumptions that affected relative duration and costs of IFN- or imatinib. The scenario analysis showed that another second-line treatment option might proof valuable.

Conclusion: The introduction of imatinib as first-line treatment option results in a gain of 3.35 QALYs. However, this occurred at a considerable cost resulting in an ICER of € 49,021 per QALY. However, in the process of reimbursement other aspects like budget impact and disease severity also play an important role.

INTRODUCTION

Chronic myeloid leukaemia (CML) is a malignant myeloproliferative disease that is characterised by a clonal expansion of myeloid progenitors in bone marrow and blood. The incidence has remained stable in the Netherlands in the last 10 years. The incidence was 1.1 per 100,000 men and 0.6 per 100,000 women (Visser 2003). The disease evolution usually has three phases. After an initial 3-4 year chronic phase, an acute phase, the blastic crisis, develops via an accelerated phase, which leads to death in a limited number of months (Sawyers 1999; Kantarjian 2000).

Most patients, approximately 85%, are diagnosed in the chronic phase (Garcia-Manero 2003). The aim of treating CML patients is to reach cytogenetic response with the hope that acceleration is delayed or does not occur at all (Schiffer 2003). This concept has evolved from the finding that reaching complete and continuing cytogenetic response after stem cell transplantation is the most important factor for attaining prolonged survival (van Rhee 1997). This is also the case in Interferon alpha (IFN) treated patients who reach an important cytogenetic response (Kantarjian 1995; Guilhot 1997). Allogeneic stem cell transplantation is currently the only curative treatment. This treatment is only available in a small group of patient as a result of donor availability and age of the patient (Maziarz 2003; Schiffer 2003).

The introduction of imatinib (Glivec®) changed the treatment strategy of CML considerably. Imatinib has an added value in the treatment of the progressive stages of CML and also gives a high percentage of cytogenetic response in patient in the chronic phase that are resistant or intolerant to treatment with IFN (Kantarjian 2002a; Kantarjian 2002b; Talpaz 2002; Kantarjian 2004). In an open-label phase III trial first-line treatment with imatinib is compared with IFN plus low dose cytarabin (Ara-C). Clinical response was substantially better in the imatinib arm: 76.2% complete cytogenetic response (CCR) versus 14.5% in the IFN+Ara-C arm. The estimated transition to the progressive stages was 3.3% in the imatinib arm and 8.5% in the IFN+Ara-C arm (O'Brien 2003).

Despite the absence of long term follow-up, imatinib has become the new standard of first-line treatment of CML patients in the chronic phase (Maziarz and Mauro 2003; Schiffer 2003). Generally, patients are only selected for allogeneic stem cell transplantation after imatinib failure, unless they are very young. However, in contrast the above-mentioned phase III study, stem cell transplantation is currently the preferred second-line treatment option in most patients due to improvements in stem cell transplantation techniques. With the introduction of stem cell transplantation with less severe pre-treatment, so-called reduced intensity conditioning stem cell transplantation (RIST) it is also possible to treat patient who are not eligible for standard myelo-ablative stem cell transplantation (Garcia-Manero 2003; Maziarz and Mauro 2003; Stone

2004). Because of this, and through further optimisation of stem cell transplantation with related and unrelated donors, the transplantation age is increased and currently 80% of patients can be transplanted (Gratwohl 2004).

Earlier, we calculated the average cost of quality adjusted life years (QALY) of first-line treatment of CML with IFN and second-line treatment with imatinib after IFN failure (Groot 2003). These were € 10,687 to € 15,445 per QALY for IFN and € 21,082 in the imatinib arm. In that analysis it was not possible to calculate an incremental cost-effectiveness ratio, with which the difference in costs and QALYs, of the new versus the old treatment is expressed, since both treatments are mutually exclusive.

Based on the results from the IRIS trial we present the incremental cost-effectiveness ratio of imatinib versus IFN+Ara-C as first-line treatment in CML in the chronic phase.

PATIENTS AND METHODS

Patients

The study population consists of untreated patients with newly diagnosed CML in the chronic phase.

The model

For the primary analysis a simulation model is used that is developed to evaluate the cost-effectiveness of imatinib versus IFN+Ara-C as first-line treatment in CML (Anstrom 2004; Reed 2004). This model is applied to the Dutch situation and where required adjusted. The model is based on the results of the open label phase III study, (O'Brien 2003) supplemented with data on survival and treatment by progressive disease (Cervantes 1996; Guilhot 1997; 1998b; Bonifazi 2001; Kantarjian 2001; Baccarani 2002; Groot 2003). Subsequently, the expected costs, survival and quality adjusted survival of patients with newly diagnosed CML in the chronic phase are determined.

The analysis is structured around reaching complete cytogenetic response (CCR) after 2 years. It is assumed that patient with a CCR will have the same survival as patients who reached CCR with IFN-Ara-C treatment in a previous study (Anstrom 2004). Patients that reach CCR will be treated with imatinib or IFN+Ara-C till intolerance or disease progression. Patients in the imatinib that do not reach CCR within 2 years will change to IFN+Ara-C treatment. Patients in the IFN+Ara-c arm will be treated with hydroxyurea after discontinuation of IFN+Ara-C treatment. When patients reach the acceleration of acute phase, 5% will be treated with induction chemotherapy (table 1).

Table 1. Parameters and costs included in the base case analysis

Parameter	Estimate	Source
Complete cytogenetic response at year 2, proportion (SE)		
Imatinib	0.738 (0.019)	(O'Brien 2003)
IFN+LDAC	0.142 (0.021)	(Baccarani 2002)
Discontinuing first-line treatment at year 2, proportion (SE)		
Imatinib	0.132 (0.014)	(O'Brien 2003)
IFN+LDAC	0.225 (0.028)	(1998b)
Median duration of second-line treatment with interferon- and LDAC, months	34	(Guilhot 1997)
Months in accelerated phase, mean (SE)	9.64 (0.69)	(Cervantes 1996)
Months in blast crisis, mean (SE)	13.12 (0.94)	(Kantarjian 2001)
Utility weight in chronic phase, mean (SE)		
Imatinib	0.854 (0.004)	IRIS*
IFN+LDAC	0.710 (0.008)	IRIS*
Utility weight in accelerated phase or blast crisis, mean (SE)	0.595 (0.077)	IRIS*
Inpatient days per month in chronic phase, mean (SE)		
Imatinib	0.131 (0.041)	IRIS*
IFN+LDAC	0.245 (0.058)	IRIS*
Specialist visits per month in chronic phase, mean (SE)		
Imatinib	0.632 (0.035)	IRIS*
IFN+LDAC	1.054 (0.094)	IRIS*
Generalist visits per month in chronic phase, mean (SE)		
Imatinib	0.177 (0.015)	IRIS*
IFN+LDAC	0.231 (0.025)	IRIS*
Contacts with oncology nurse per month in the chronic phase, mean (SE)		
Imatinib	0.079 (0.015)	IRIS*
IFN+LDAC	0.465 (0.108)	IRIS*
Inpatient days per month in accelerated phase and blast crisis, mean (SE)	0.738 (0.297)	IRIS*
Specialist visits per month in accelerated phase and blast crisis, mean (SE)	1.048 (0.341)	IRIS*
Generalist visits per month in accelerated phase and blast crisis, mean (SE)	0.167 (0.102)	IRIS*
Nurse visits per month in accelerated phase and blast crisis, mean (SE)	0.309 (0.167)	IRIS*
Percent receiving treatment in advanced phases of CML (SE) ‡	0.05 (0.012)	(Kantarjian 2001; Groot 2003)
Medication costs, €		
Imatinib (per 100 mg)	20.18	
IFN (per 1 MU)	9.42	
Cytarabine (per 100 mg)	5.07	
Hydroxyurea (per 500 mg)	0.32	
Chemotherapy ‡	16,622	(Groot 2003)
Costs of outpatient visits		
Hematology	71	(Groot 2004)
Other specialities	71	(Groot 2004)
Oncology nurse	52.03	(Oostenbrink 2000)
Inpatient cost per day		
Chronic phase	341	(Groot 2004)
Accelerated phase	899	(Groot 2003)
Blast crisis	899	(Groot 2003)

*IRIS: 'international randomised study of interferon and STI571 clinical study report' ‡ patients receive 1 course of induction chemotherapy.

The specific medical consumption is assigned to each individual patient for each disease stage and applied treatment. Furthermore, disease stage and treatment specific quality of life weights and survival probability are assigned. In the base case analysis the uncertainty surrounding the various parameters is included. The results of the base case analysis is based on 1,000 simulations.

Cost analysis

The base year for the cost analysis is 2002. The costs represent the healthcare perspective and only direct medical costs are included. Both costs and effects (survival and quality adjusted survival) are discounted at 4% per year (Oostenbrink 2000). Costs of medication are derived from the pharmaceutical compass, costs of hospitalisation and induction chemotherapy are base on earlier studies (table 1) (Oostenbrink 2000; Uyl-de Groot 2001; van Agthoven 2002b; Groot 2003; van Loenen 2003; Groot 2004).

Cost-effectiveness

The difference in costs, survival and quality adjusted survival between the patients in the imatinib and the IFN+Ara-C arms are expressed in incremental cost-effectiveness ratios (ICERs) using the following formula: (total costs imatinib – total costs IFN+Ara-C)/(total effects imatinib – total effects IFN+Ara-C).

Sensitivity analysis

Several sensitivity analyses have been conducted to investigate the impact of applied assumptions. Among others, the variation in costs of imatinib and IFN+Ara-C, continuation of treatment after 2 years and discontinuation of IFN+Ara-C in patients not reaching CCR. Furthermore, the effect of increasing the percentage CCR in the IFN+Ara-C arm (Bonifazi 2001) and using other survival estimates (Guilhot 1997) has been investigated.

Scenario analysis

Despite the good response on imatinib, approximately 25% of patients is intolerant of will not reach complete response within 2 years (O'Brien 2003). In the base case analysis these patients are switched to IFN+Ara-C treatment. In the scenario analysis, costs and effects are calculated assuming that after imatinib failure patients are not treated with IFN+Ara-C, but will undergo a stem cell transplantation or receive treatment with 800mg imatinib when stem cell transplantation is not an option (SCT/imatinib 800), see figure 1. The treatment options from the base case analysis and continuation of imatinib treatment until disease progression are included as comparative scenarios. This results in 4 scenarios that will be analysed. These scenarios are represented by the combination of the abbreviations of first-line treatment and second-line treatment for non responders. These are IFN-IFN (comparative arm in the base case analysis), imatinib_IFN (original study arm), imatinib-imatinib (continuation of imatinib despite

Table 2: scenario analysis second-line treatment

input	current model analysis	base line analysis	SCT/imatinib 800	
Second-line treatment	IFN	imatinib 400mg/day	allogeneic stem cell transplantation	imatinib 800mg/day
Percentage	100%	100%	64%	36%
Transplantation related mortality	na	na	25%	na
Complete remission	0%	0%	75%	45%
Relapse after response	100%	100%	19%	100%
Time to relapse / progression after complete response (years)	16.8	16.8	2.0	16.8
Time to progression without complete response (years)	7.4	7.4	na	7.4
Survival without relapse (years)	na	na	16.8	na
Survival after relapse / progression (years)	1.5	1.5	9.1	1.5
Distribution of stem cell transplantations				
Allogeneic related	na	na	15%	na
Allogeneic unrelated	na	na	70%	na
Reduced intensity, related	na	na	15%	na
Costs (€)				
Stem cell transplantations				
Allogeneic related	na	na	112,200	na
Allogeneic unrelated	na	na	172,028	na
Reduced intensity, related	na	na	112,200	na
Imatinib 800 mg till progression / year	na	na	na	59,740
Imatinib 400 mg till progression / year	na	30,684	na	na
IFN till progression / year	19,524	na	na	na
Quality of Life				
First year after stem cell transplantation	0.6			
Subsequent years after stem cell transplantation	0.7			
Relapse after stem cell transplantation	0.6			
Imatinib 800mg/day	0.8			
Imatinib 400mg/day	0.8			
Interferon 4.8 MU/day	0.7			
Progression after imatinib 800mg/day	0.5			

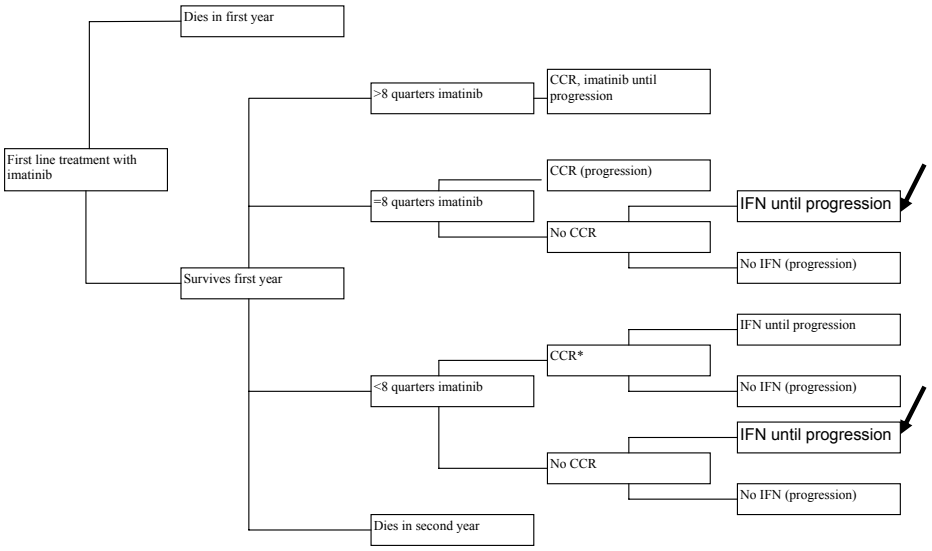


Figure 1: clinical course and treatment options in the imatinib arm of the model

Note: the scenario analysis applies for the patients that enter the "IFN until progression " cell depicted in bold.

absence of response) and the imatinib-SCT/imatinib 800 arm.

The assumptions for this scenario analysis are derived from the base line model and the literature,(van Rhee 1997; van Agthoven 2002b; Garcia-Manero 2003; Kantarjian 2003b; Maziarz and Mauro 2003; Stone 2004) supplemented with expert opinion (table 2). When patients progress they are not eligible for second-line chemotherapy. Patients undergoing stem cell transplantation are assigned a quality of life value of 0.6 for 1 year and for the rest of the follow-up they are assigned the same value as the IFN treated patients.

The results of the different second-line treatment option are subsequently combined with the results of the 75% of the patients in the imatinib arm that did reach a CCR to enable an incremental analysis between this and the comparative arm from the base line analysis possible.

RESULTS

Base case analysis

In the base case analysis, patients that are treated with imatinib have an average survival of 15.2 years (table 3). In the IFN+Ara-C arm this is 9.1 years: a difference of 6.1 years. When this survival is corrected for quality of life this difference becomes 5.7 QALYs to the advantage of imatinib.

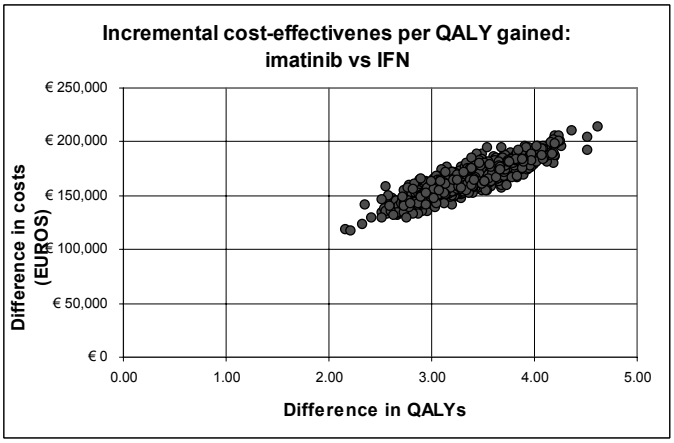


Figure 2: results of the 1,000 population level simulation on the cost-effectiveness matrix

The undiscounted total costs in the imatinib arm are € 337,055. In the IFN+Ara-C arm this is € 124,510 an absolute difference of € 252.540 per patient.

When the survival is discounted, the increase in survival is 3.34 years. The difference in survival adjusted for quality of life is slightly larger, 3.35 QALYs. The discounted total costs are € 164,398 higher in the imatinib arm. When costs and effects are combined this results in ICERs of € 49,146 per life year saved and € 49,021 per QALY gained. The results of the simulation show a strong correlation between difference in costs and effects, see figure 2.

Table 3: results of the base case analysis, average per patient

	Imatinib	IFN+LDAC	Difference	Incremental cost-effectiveness ratio (CI)
Undiscounted				
Life years	15.2	9.11	6.09	€ 41,450/LYS (37,053 tot 47,489)
QALY	11.9	6.21	5.69	€ 44,373/QALY (40,697 tot 49,164)
Costs	€ 377,050	€ 124,510	€ 252,540	
Discounted				
Life years	10.43	7.09	3.34	€ 49,146LYS (43,414 tot 57,519)
QALY	8.19	4.84	3.35	€ 49,021/QALY (44,587 tot 54,758)
Costs	€ 262,754	€ 98,365	€ 164,389	

Confidence interval is based on the 25th and 975th observation of the ordered results of the simulation
IFN+LDAC: IFN alfa plus low dose cytarabin; CI, confidence interval
LYS, life years save; QALY, quality adjusted life year

Sensitivity analysis

In each sensitivity analysis 100 populations are simulated. The results are presented in figure 3. These analyses show that the ICER is particularly sensitive to the costs of imatinib and IFN but that the choice of discontinuation at 2 years also has a considerable impact. Using Guilhot et al. (Guilhot 1997) as a source for the survival estimates in absence of a complete response and when the response rate is increased the ICER is hardly affected.

When all patients remain on treatment with IFN+Ara-C or imatinib the ICER becomes € 51,700. In case of termination of treatment with IFN+Ara-C or imatinib when no response is reached after 2 years this mainly affects the costs of treatment in the IFN+Ara-C group as the percentage of non-responders is much larger in this group. As a consequence the ICER becomes € 58,215. The impact of changing the costs of imatinib and IFN is considerable. Lowering the costs of imatinib with 25% results in an ICER of € 32,459 per QALY, raising the costs of imatinib with 25% results in an ICER of € 65,186. The impact of change the costs of IFN are less pronounced. A decrease with 25% results in an ICER of € 53,368 while raising the costs with 25% results in an ICER of € 44,465.

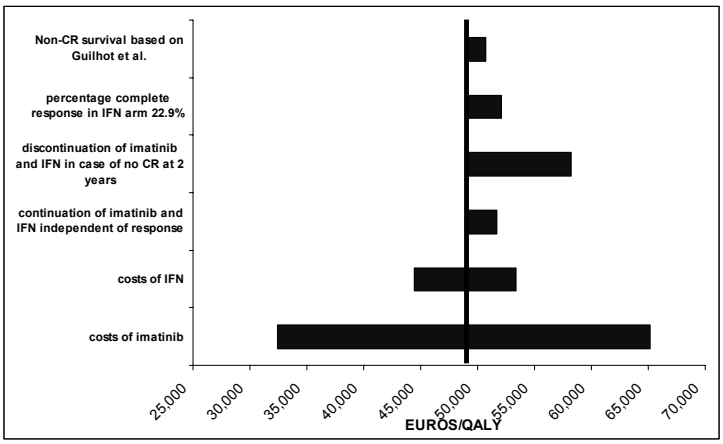


Figure 3: Results of the sensitivity analysis

Scenario analysis

The results of the different second-line treatment options are presented in table 4. These show that offering SCT/imatinib 800 to these patients results in an average survival of 12.3 years after imatinib failure. This is 3.4 years more than in the other second-line treatment options. Correction of this survival for quality of life results in an increase of 2.9 and 2.1 QALYs versus second-line treatment with IFN and imatinib respectively. This additional survival is accompanied with an increase in the average costs of second-line treatment of € 207,000 compared to IFN and € 108,000 compared to imatinib per patient.

As explained in the method section, the results presented in table 4 apply to approximately 25% of patients treated in the imatinib arm. To judge the ICERs the results from table 4 must be combined with the results (in terms of costs and effects) of the remaining 75% of the patients

Table 4: results of the second-line treatment scenario analysis in the imatinib arm, average per patient

	IFN	**imatinib 400mg/day**	**SCT/imatinib 800**
Life years	8.87	8.87	12.26
QALY	5.91	6.65	8.76
Costs	€ 173,221	€ 272,235	€ 380,419

Table 5: results of the second-line treatment scenario analysis in the imatinib arm combined with the first-line treatment results compared to the comparator from the base line analysis (IFN-IFN)

	IFN-IFN	**imatinib-IFN**	**imatinib-imatinib**	**imatinib-SCT/imatinib 800 analyse**
Life Years	10.04	15.76	15.76	17
QALY	6.73	11.96	12.15	12.99
Costs	€ 166,699	€ 449,012	€ 471,061	€ 488,374
	QALY	Costs	Incremental cost-effectiveness ratio	
IFN-IFN	6.73	€ 166,699		
imatinib-IFN	11.96	€ 449,012	€ 53,982	Excluded
imatinib-imatinib	12.15	€ 471,061	€ 111,600	Excluded
imatinib-SCT/imatinib 800	12.99	€ 488,374	€ 51,328*	

*In this ration the imatinib-scenario analysis is compared to the IFN-IFN analysis because both other analyses were excluded.

treated with imatinib. To stay in line with the base case analysis, these results are related to the comparative arm from that analysis, the IFN+Ara-C arm (table 5). Under the current assumptions SCT/imatinib 800 as second-line treatment option results in more favourable outcomes than second-line treatment with IFN after imatinib failure. When comparing more than two alternatives these must be ordered by increasing effectiveness (Gold 1996; Drummond 1997). Subsequently, the ICER is calculated between treatment options with increasing effectiveness. The options with second-line treatment with imatinib and IFn are excluded. These are not cost-effective, the ICER is higher compared to the ICER of the more effective treatment option with SCT/imatinib 800. This results in an ICER of SCT/imatinib 800 compared to the base case analysis (IFN-IFN) of € 51,328. Several univariate sensitivity analyses have been performed to investigate the impact of variation in assumptions on the outcomes. Although these analyses had an effect of on the ICER the imatinib-IFN and imatinib-imatinib options remained excluded within the explored ranges.

DISCUSSION

The addition of imatinib to the first-line treatment options of patients with CML improved the prognosis considerably. In this study the added value of imatinib over IFN+Ara0C in terms of survival, QALYs and costs has been investigated. This study shows that treatment with imatinib results in an increase of discounted survival of 3.34 years, or 3.35 QALYs. This increase in survival is accompanied by an increase in costs of treatment with € 154,389. The ICERs of this difference in costs and effects are € 49,146 and € 49,021 per life year and QALY gained respectively.

The costs of treatment and survival are strongly correlated in this study, as a consequence changes that effect survival have little effect on the outcomes. The sensitivity analysis shows that the ICER is mainly sensitive to changes that affect the costs of treatment in one of the treatment arms.

The most important assumption is the structure of the model in which reaching a complete cytogenetic response after 2 years determines the subsequent survival. Patients in both the imatinib and the IFN+Ara-C arm have the same survival on the basis of reaching this response, i.e. irrespective of the treatment they receive. This approach is taken on the basis of experiences with allogeneic stem cell transplantations in which reaching complete cytogenetic response is the determining factor for prolonged survival (Schiffer 2003). This relation has been found in CML patients that were treated with IFN (Kantarjian 1995; Guilhot 1997). Considering the fact that long term survival data are not available for patients treated with imatinib it cannot be said with complete certainty that this will count here as well. However, in patients that reach complete cytogenetic response when treated with imatinib after IFN failure this relation appears to count as well (Kantarjian 2004).

In a subanalysis by Kantarjian et al. a group of 187 imatinib treated patients from the IRIS study compared with a historical cohort of 650 comparable patients who were treated with IFN (Kantarjian 2003a). The imatinib treated patients were older and had significantly more bone marrow basophils and less leukocytosis, nevertheless these patients had a better cytogenetic respons and a significantly longer surivaval at 30 months. A multivariate analysis furthermore showed that treatment with imatinib is an independant prognostic factor for a prolonged survival. The current model is not capable of capturing such a survival gain but it is likely that the ICER will be lower when this positive effect is incorporated in the analysis. The current model can be considered conservative in this respect. Because of the high correlation between costs of treatment and survival it is not likely that this effect will be large however.

Because of the large success of imatinib the optimal treatment protocol for CML has not been established yet. Partly because of the recent development in the field of stem cell transplantations a number of new treatment options are in place that were not possible when the IRIS trial was initiated (Garcia-Manero 2003; Kantarjian 2003b; Stone 2004). As a consequence these options are not included in the base case analysis. In order to quantify these developments and the

mimic the current treatment in the Netherlands as closely as possible an additional scenario analysis was performed. This analysis shows that second-line treatment with SCT/imatinib 800 in patients that do not reach complete cytogenetic response on initial imatinib treatment is more cost-effective than the second-line treatment with IFN+Ara-C or imatinib. Due to a lack of study results this scenario analysis is based on expert opinion, in all cases conservative estimates are chosen.

The literature concerning the effectiveness of imatinib is still growing. An increased understanding of CML offers the possibility to diagnose and monitor patients very specifically. Combined with the development of new drugs for the treatment of CML this results in different treatment strategies for both first- and second-line treatment, that are currently under investigation (Cortes 2004; Crossman 2004; Tauchi 2004). The scenario analysis shows that by using cost-effectiveness modelling the impact of new drugs in a changing environment can be analysed, which can aid in determining the place in the treatment approach.

The introduction of imatinib as first-line treatment option in CML Is very effective but also very costly, resulting in an ICER of € 49,021 per QALY. This ratio is high but considering the nature of the disease this would, most likely, be considered acceptable by policy makers, when they had to decide on the reimbursement of imatinib on the basis of these findings. In a recently performed study on the relation of severity of disease and acceptable cost-effectiveness ratios it was calculated that this would be € 45,378 for non-Hodgkin lymphoma (Poley 2002).

Part 3

Diffusion of innovative drugs

Chapter 9

Introduction of expensive drugs in haemato-oncology in the Netherlands and throughout Europe.

SUMMARY

Objective: The objective of this study was to analyse the introduction and diffusion of innovative drugs in the Netherlands and other European countries in relation to healthcare system characteristics.

Methods: Characteristics of the healthcare system in Austria, Belgium, Denmark, France, Germany, Sweden, England and the Netherlands were collected through literature research. Information on drug consumption of three innovative drugs, rituximab (MabThera®), imatinib (Glivec®), and bortezomib (Velcade®) was based on IMS data. Drug consumption was re-calculated to standard units per quarter and expressed per 1,000 inhabitants since introduction. Differences in consumption patterns were analysed against the background of healthcare system characteristics.

Results: IMS data showed that the relative diffusion of inpatient drugs in the Netherlands was slower, up to a factor four, compared to other European countries, while this was not seen for the outpatient drug imatinib. Other European countries have mechanisms in place that improve the introduction and diffusion of innovative drugs. These are, among others, the provision of earmarked budgets for innovative drugs, flexibility in financial responsibility and the application of reimbursement for both in- and outpatient drugs (i.e. no financing of expensive inpatient drugs within the hospital budget).

Conclusion: In contrast to the introduction of the outpatient drug imatinib, the introduction of the innovative inpatient drugs rituximab and bortezomib lag behind in the Netherlands. Healthcare policies in other European countries might offer an approach to increase the diffusion of innovative inpatient drugs in the Netherlands. Besides the relationship between regulatory, organisational characteristics and the diffusion of drugs there is a possible relation with other aspects of society, like prescribing culture and regional variation, as well. It would be worthwhile to study these various aspects in combination and relate these to the introduction and diffusion of innovative drugs.

INTRODUCTION

In many countries, drug expenditure is rising at rates greater than gross domestic product and usually faster than other health care budgets as well (Mossialos 2004). Health authorities, including the Dutch government, try to control this growth in drug expenditure using various techniques that act on the supply and demand side (e.g. direct price or quantity controls, reference pricing, rate-of-return regulation and co-payment (Mossialos 2004). As a result the drug market is one of the most regulated parts of the healthcare sector.

In the Netherlands there is a clear separation between drugs that are prescribed for use outside the hospital (outpatient drugs) and the drugs that are used within the hospital (inpatient drugs). Outpatient drugs are part of an open-ended financing system while inpatient drugs are part of the hospital budget, which is fixed (Pronk 2005). Regulation of outpatient drugs is transparent, the health insurance fund provision of drug regulation ('regeling farmaceutische hulp 1996' (RFH)), describes the drugs that are covered under the health insurance act in the Netherlands. Only for drugs that are covered under this act, the RFH executes a reimbursement policy. To be included in the benefit package a pharmaceutical company must apply for reimbursement to the Minister of Health. Evidence on therapeutic value, effectiveness, and relevance to the public health as well as pharmacoeconomic and budget-impact information must be provided. On the basis of this information the pharmaceutical care committee (CFH) from the Health Care Insurance Board (CVZ) advises the Minister to accept or reject of the new product. Similar regulation processes are in place in other European countries (Mossialos 2004).

In the Netherlands, regulation of inpatient drugs is not as transparent as the regulation of outpatient drugs (Pronk 2005). Inpatient drugs are the responsibility of the hospital itself and can be included in the local hospital formulary when the drug is considered standard of care by the relevant specialists and published as such. The budget for these inpatient medications is part of the total, fixed, hospital budget. The relative contribution of drug costs in the total hospital budget has doubled and as a consequence these budgets are continuously under pressure (Breekveldt-Postma 2002). This increase in drug costs is mainly caused by the introduction of new expensive drugs in the field of oncology and haematology (Breekveldt-Postma and Zwart-van Rijkom 2002).

Two additional budget categories for inpatient drugs were introduced in the Netherlands: First, drugs that are grouped under the Act of Special Medical Treatment ('wet bijzondere medische verrichtingen, WBMV'), like haemophilia and HIV medications which use is restricted to a small number of specialised centres and which are reimbursed separately on top of the hospital budget (Pronk 2005). Secondly, there is an 'Expensive Medication List' (CTG 2004b; Pronk 2005). To be included on this list, the total drug costs must constitute at least 0.5% of the total drug expenses of the Dutch hospitals and the treatment must represent rational pharmacotherapy (CTG 2004b). For these drugs, additional budget (30-75%) may be negotiated

with the local health insurance company. However, the total hospital budget remains fixed. Recently, the Minister of Health proposed a change, as of 2006 all drugs that are included on this list will be reimbursed for 80% and the 0.5% threshold will be based on a forecast and not on a retrospective analysis anymore. Because of the fixed total hospital budget, hospitals have to consider if and to what extent, these expensive drugs may be exploited, regardless of the height of the reimbursement. Reimbursement, in fact means specific allocation of money within the total fixed budget!

As a result of local formulary decisions and differences in budget constraints, variation between hospitals may arise resulting in a reduced introduction of new innovative drugs and sub optimal care for specific groups of patients. This is increasingly becoming an issue as many of the inpatient drugs currently under development are expensive which will increase the budget constraints further (Breekveldt-Postma and Zwart-van Rijkom 2002). It is felt within the specialist community that because of the difficulties they have in finding the appropriate funds for these new drugs they are unable to offer the most appropriate care to their patients.

The objective of this study was to analyse the introduction and diffusion of innovative drugs in the Netherlands compared to other European countries in relation to healthcare system characteristics.

METHODS

Countries of interest

After an initial scan of different healthcare systems in Europe a set of 8 countries, including the Netherlands, were selected for further research on the basis of their differences and similarities within their healthcare delivery and financing system. The other countries were: Austria, Belgium, Denmark, France, Germany, Sweden and the UK (England). These countries represented both tax funded National Health Systems (NHS) and Social Health Insurance (SHI) systems.

Medication included in the country comparison

Three innovative drugs were included in the comparison, rituximab (MabThera®), bortezomib (Velcade®) and imatinib (Glivec®). These drugs represent innovative drugs in the field of haematology. Rituximab is indicated for the treatment of different types of lymphoma (CTG 2004b; HOVON 2004b; HOVON 2004a; CVZ 2005; 2005b).

Bortezomib is indicated for the treatment of patients with multiple myeloma who have received at least two other therapies and have demonstrated disease progression on the last therapy (2005c).

Imatinib is indicated for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) and for the treatment of adult patients

with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST) (2005a).

Data collection

Drug consumption was based on IMS data from the different countries, reported in single units. These single units were re-calculated to standard units per quarter since introduction. For imatinib and rituximab the standard unit used was 100mg and for bortezomib this was 3.5mg. Data was expressed in standard units per 1,000 inhabitants per quarter since introduction. For all countries except Denmark and Sweden a division between numbers of units distributed within the hospital and by the retail pharmacist was made as well. In Denmark and Sweden, no distinction is made between hospital and retail pharmacists as the distribution of all drugs is done by the state.

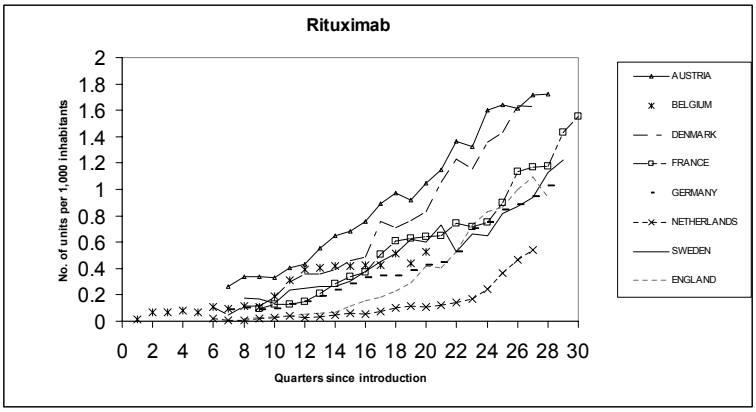
Country characteristics

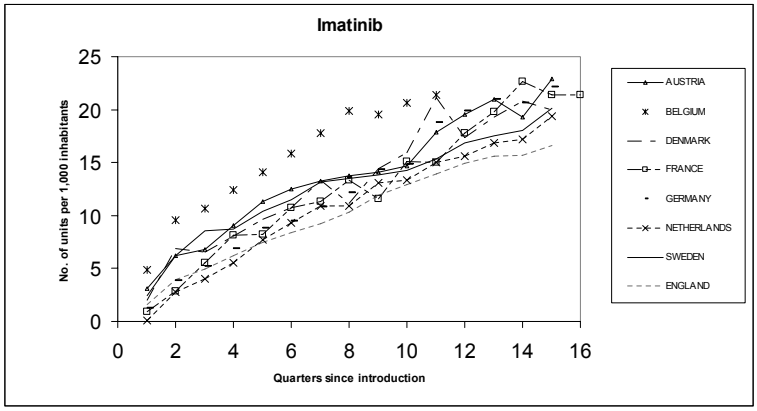
The country specific publications on Health Care Systems in Transitions (HiTs) from the European Observatory on Health Systems and Policies were used as a basis for a description of the country characteristics. These publications were supplemented with information from the European Health basket project (http://www.wm.tu-berlin.de), additional literature data and information from local authorities on the regulation of inpatient drugs.

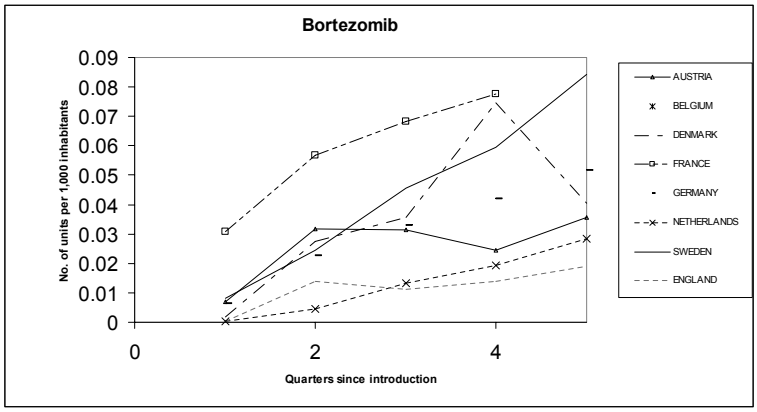
RESULTS

Consumption of rituximab, imatinib and bortezomib since introduction

Figure 1a-c present the IMS figures expressed as number of standard units sold each quarter per 1,000 inhabitants since introduction of rituximab, imatinib and bortezomib until the second quarter of 2005.







Figures 1a-c: Diffusion of Rituximab, Imatinib and Bortezomib per quarter since introduction.

Figure 1a-c show the relative differences in diffusion and the absolute difference in introduction time. The average number of standard units per 1,000 inhabitants is set out on the y-axis. This relative value represents the degree of variation in diffusion between countries since introduction of the respective drugs. On the x-axis the number of quarters since introduction are set out. When a drug is introduced later in time there are fewer observations and the line is shorter. For example, Rituximab has been on the market for 20 quarters since introduction in Belgium while in France it is on the market for 30 quarters.

Rituximab has been introduced in most countries in 1998 or early 1999, however, information on the absolute number of units was only available to us since 2000. As a consequence information on the first quarters since introduction could not be presented for all countries except Belgium. However, information on number of units and total sales expressed in standardised dollars rounded to the nearest 1,000 were available for rituximab since introduction, these show a similar trend as is seen in the quarters after 1999 (data not shown).

Figure 1 provides important information on the differences in introduction and diffusion in the different European countries. The first is the introduction time for the different drugs, which is not the same as time of approval. The European Medicines Agency (EMEA) approved Rituximab in June 1998 but sales are reported for France in the quarter prior to this approval. The opposite is the case for Belgium where rituximab was not on the market until the third quarter of 2000. Secondly, the figures on rituximab and bortezomib show a great level of variation in diffusion which is not seen for imatinib

The numerical difference in relative diffusion at the end of the second quarter of 2005 is illustrated for the 3 drugs in table 1. Both rituximab and bortezomib show a large variation in number of units per 1,000 inhabitants compared to the Netherlands. The increased diffusion in other countries compared to the Netherlands is clearly visible. This diffusion factor increased to 3, indicating that the diffusion is three times higher in Sweden as compared to the Netherlands. For imatinib this variation is much smaller, and the maximum difference in diffusion factor is much smaller as well (1.18 in Austria).

*Table 1: relative difference in diffusion of rituximab, imatinib and bortezomib compared to the Netherlands**

	rituximab	**imatinib**	**bortezomib**
AUSTRIA	3.20	1.18	1.26
BELGIUM	0.97[†]	1.10	na
DENMARK	3.03	1.03	1.43
FRANCE	2.88	1.10	2.75
GERMANY	1.90	1.14	1.83
NETHERLANDS	1.00	1.00	1.00
SWEDEN	2.27	1.04	2.98
UK	1.71	0.86	0.68

* at the end of q2 2005 [†]when taking time of introduction into account this figure is 4.85
na= not available

Regulation of innovative drugs in Europe:
Relation between healthcare systems and the introduction of innovative drugs

An overview of the most important characteristics of the healthcare systems of the different countries is presented in table 2. It presents the basic characteristics that are related to the introduction and diffusion of innovative drugs. Three basic groups of characteristics are included and will be discussed below: the healthcare organization and budget responsibility, regulation of drugs and finally other mechanisms that might influence the introduction and diffusion of innovative drugs.

Table 2: overview of healthcare systems

	Austria	**Belgium**	**Denmark**	**England**	**France**	**Germany**	**Netherlands**	**Sweden**
healthcare system	SHI	SHI	NHS	NHS	SHI	SHI	SHI	NHS
healthcare financing	central	central	de-central*	central	central	central	central	de-central*
budget responsibility								
primary care	insurers	insurers	regions	health authority (regional)	central government	insurers	insurers	regions
secondary care	regions	insurers	regions	primary care trusts (subregional)	central government	regions	insurers	regions
regulation of outpatient drugs (central government)								
authorization	XX	XX	XX	XX	XX	XX	XX	XX
reimbursement	XX	XX	XX		XX	XX	XX	XX
price-setting	XX	XX	XX		XX		XX	XX
regulation of inpatient drugs (central government)								
authorization	XX	XX	XX	XX	XX	XX	XX	XX
reimbursement		XX			XX†	XX‡		
price-setting		XX			XX†			

Table 2 (continued)

	Austria	Belgium	Denmark	England	France	Germany	Netherlands	Sweden
Financial responsibility for: general outpatient drugs	insurer	insurer	regions	primary care trust	insurer	insurer	insurer	regions
general inpatient drugs	hospital	insurer	hospital	hospital	hospital	hospital	hospital	hospital
rituximab	hospital	insurer	hospital	hospital	insurer¶	hospital/insurer	hospital**	hospital
bortezomib	hospital	insurer	hospital	hospital	insurer¶	hospital/insurer	hospital	hospital
imatinib§	insurer	insurer	hospital	primary care trust	insurer	insurer	insurer	hospital
Additional funding for expensive medications	no	no	yes (block grants provided by central government)	no	yes (expensive medication list)	no	yes (expensive medication list)	yes (additional funding by regional government)
Additional mechanisms	no	no	no	NICE††	no	Praxisbesonderheiten and extra fees‡‡	no	no

*community taxes
† when included on the expensive medication list
‡ when given in specialized centers outside the hospital
§ unless it is given to inpatients, then hospital
¶ included on French expensive medication list
** included on Dutch expensive medication list
†† NICE appraisal means that drugs must be provided to patients
‡‡ praxisbesonderheit: these drugs are not included when determining regional budget exceedings. Extra fees: addditional DRG codes for expensive drugs when used in the hospital

Organization of the healthcare system and budget allocation

In Europe two general healthcare financing systems can be defined, the tax-based systems on the one side (Denmark, England and Sweden) and the Social Health Insurance (SHI) systems (Austria, Belgium, France, Germany and the Netherlands) on the other side. In all countries except in the Netherlands, additional funds are collected through patient's co-payments (this does not count for the Netherlands), private health insurance and taxes.

On a central level there is a similar role for all governments. They issue healthcare legislation and safeguard global objectives. Additionally, the central government provides advice through committees or national institutes on the delivery and planning of healthcare by lower authorities or other regulatory bodies in the different countries. The responsibilities towards budget allocation in the healthcare system vary considerably between countries. In Belgium, France, the Netherlands and England the overall healthcare budget is set annually by the central government. In Belgium and the Netherlands this healthcare budget is subsequently distributed over the different health insurance funds. These funds are responsible for local budget negotiations. In England and France the global budget is distributed over health authorities that distribute the budget over regional groups who are responsible for the provision of primary and secondary care. In Denmark the overall healthcare budget is negotiated annually with the central government by the counties while in Sweden a greater autonomy with regard to budget setting exists on the county level. In both Denmark and Sweden the counties collect taxes that are also used for the healthcare financing. In Austria there is a separation between primary and secondary care. Primary care is financed on the basis of general contracts between specialist's organizations and the sickness funds. For secondary care (which is also financed by the sickness funds) the overall budget is updated periodically after negotiations between the regions and the central government. In Germany this separation does not exists and although the regions are responsible for the structure and adequate funding of the hospital, budgets for primary and secondary care are negotiated by the sickness funds.

When compared, the IMS figures did not show a clear pattern between the different healthcare systems and the forms of budget allocation in the different countries. Not all tax based systems perform equally well and there are also differences in diffusion between countries that allocate their budgets in the same way. It is clear though that because of the de-centralised allocation of budgets variation in the benefit package can emerge within countries and as a consequence inequalities within countries arise that can result in "postcode prescribing" often referred to in the UK.

Regulation of drugs and relation between place of administration, distribution and financing

In all European countries drugs must obtain market authorization before introduction. Institutes or organizations that work under the responsibility of the central government regulate market authorization in all European countries. Market authorization may be obtained through three

different procedures in EU member countries: via the centralized procedure with the European Medicines Agency (EMEA), a decentralized procedure for mutual recognition or by national procedure in which the authorization can be given by a local regulatory institute.

The most important difference lies in the regulation of reimbursed drugs (outpatient drugs) and drugs that are not separately reimbursed (inpatient drugs). Drugs that are used in the outpatient setting (including expensive drugs like imatinib) are subject to strict regulation by the central government. They must go through country specific procedures in which the price and reimbursement status is determined on the basis of safety, necessity, added value and clinical evidence from clinical trials. England and Germany are the only countries where prices of outpatient drugs are negotiated between manufacturers and purchasers or groups of purchasers without government involvement.

Additional ways of control that are aimed at reducing drug expenses are reference pricing and, depending on the indication, patient's co-payment. The Netherlands is the only country that does not use co-payment. Because of the severity of the disease for which imatinib is indicated, it is exempt from co-payment in most countries as well.

Drugs that are used in the hospital, like rituximab and bortezomib, are not reimbursed separately in most countries. These drugs have to be funded out of the overall hospital budget. These inpatient drugs do not have to go through the, sometimes lengthy, pricing and reimbursement procedures and can be introduced directly after market authorization. An exception to this is Belgium; here all drugs are evaluated in a price-setting and reimbursement trajectory. When a price and reimbursement status is granted, Belgian health insurers reimburse inpatient drugs separately and they are not part of the fixed hospital budget. In all other countries where inpatient drugs are part of the hospital budget, budget must be freed to provide new expensive drugs to patients. As most countries have a de-centralized organization of hospitals, wherein inclusion on local formularies remains a local decision, different priorities can be set with the consequence that these drugs are not equally available in the country.

The consequence of the split between outpatient and inpatient drugs is seen in the diffusion of rituximab, imatinib and bortezomib in the Netherlands. This diffusion is in line with other countries for imatinib while diffusion of rituximab and bortezomib lags behind. Only exceptions with regard to the financial responsibility for imatinib are Denmark and Sweden. In Denmark and Sweden imatinib, like all chemotherapeutic drugs, is included in the hospital budget irrespective of their place of administration and distribution.

There are some country specific exceptions and additional regulation mechanism that can account for the difference in introduction and diffusion of drugs. In Belgium all drugs must go through the reimbursement and pricing trajectory. This procedure that can take 120-270 days

and causes a later introduction of new drugs on the market. When reimbursement is granted however, there is no real financial impediment as drugs are reimbursed separately and fall under the open-end financing by the health insurers. As a result diffusion after reimbursement is generally high in Belgium as is shown for rituximab and imatinib as well.

Germany is the only country where chemotherapy can be delivered outside the hospital in specialised centres. Historically, Germany has an important ambulatory sector in which medical specialists offer care that in other countries is only provided in hospitals. The consequence is that chemotherapeutic drugs are reimbursed separately when they are administered in these so-called "praxes". Furthermore, chemotherapeutic drugs given here are subjected to the 'Praxisbesonderheiten', which means that they do not weigh on the ambulatory drug budget which protects specialists against financial penalties for overspending. This does not mean that unlimited additional funds are granted, but it offers specialists the possibility to plan more freely. Looking at the German IMS figures, it could well be that the possibility of delivering chemotherapy outside the hospital increased the diffusion as it gives specialists, who often work in both the hospital and in a "praxis", the opportunity to distribute their patients over both systems more evenly.

In England, where there is no financial incentive to distribute imatinib outside the hospital, this drug is almost completely distributed by the hospital, which is in sharp contrast to all other countries. Interesting to see is the time prior to reimbursement of imatinib in France. In this period only distribution by the hospital pharmacists is seen while thereafter there was a complete turnaround in two quarters. These examples furthermore highlight the relation between financial responsibility and the diffusion of innovative drugs.

Additional mechanisms

In France rituximab and bortezomib fall under a separate class of so-called expensive drugs. In order to be included in this class, drugs must be expensive, i.e. costing over 150 EURO per day, and its use must vary among patients in the same diagnosis related group (DRGs called Groupe Homogène de Sejour (GHS) in France) resulting in cost heterogeneity. These are reimbursed by the French social security at a price that is set by the economic committee for medical products. Companies are free to introduce a drug after market approval without applying for inclusion on this expensive medication list to avoid the compulsory price setting.

In Denmark and Sweden hospitals have the possibility to apply for additional funding for expensive drugs by the counties. It is not known to what extent this route is used. When looking at the IMS data it is interesting to see that in Denmark, Sweden and France, i.e. countries with additional funding, the diffusion of both rituximab and bortezomib is high compared to other countries. For the Netherlands the diffusion of rituximab lags far behind to other countries despite its place on the 'Expensive Medications List'.

Germany introduced its version of the DRG-system, the German-DRG (G-DRG, in 2004. Drugs administered in the hospital are part of these G-DRGs. However, G-DRGs do not take costly

drugs into account. Hospitals can fund their expensive treatments by applying a so-called extra fee or 'Zusatzentgelte' which is placed on top of the standard G-DRG. This is not "extra" for the hospitals, as it remains part of the fixed budget for hospitals. The division of the hospital budget into G-DRGs and extra fees allows the hospital to work with the same G-DRG price as other hospitals while creating room for more effective planning like with the 'Praxisbesonderheiten' described above.

The effect of the impact of NICE appraisals in England is seen as well in the IMS figures. After market access the diffusion of both rituximab and imatinib was low compared to other countries while during and after the NICE appraisals for these drugs the diffusion increased and returned to average values compared to other European countries. A NICE appraisal for bortezomib is not expected before 2007 and as a consequence this drug is likely to stay behind with other countries.

In France, drugs can receive a temporary authorization prior to central approval by EMEA or local authorities. Drugs that receive this status are reimbursed by regional hospital agencies from a fund for innovation and/or education within healthcare. Rituximab was introduced on the market prior to EMEA approval with a temporary authorization that was separately funded which had a positive effect on diffusion after formal approval of the drug.

DISCUSSION

In this study we present the differences in introduction and diffusion of three innovative drugs in the field of haemato-oncology in 8 different European countries. The variation in diffusion was much larger for inpatient drugs than for outpatient drugs. The regulation of inpatient drugs in the different European countries is much less transparent and subject to other restrictions as compared to outpatient drugs. The data furthermore confirm the feeling of Dutch clinical specialists that they lag behind with their European colleagues with regard to the introduction of innovative drugs. Using the different healthcare characteristics, a number of possible explanations for these differences are given. However, these cannot account for these differences alone and there are some limitations to our study that have to be addressed.

Variation in diffusion caused by other than financial or regulatory reasons, like prescribing habit were not included as an explanatory element in this study. It may be possible that the Dutch specialists could be more cautious when introducing new drugs and that as a consequence diffusion is slower. Because of the diseases for which these drugs are indicated and their life-saving properties we do not think this was a factor of importance. This was underscored by the observation that for imatinib the variation between countries is much smaller which indicates that the differences in diffusion are caused by financial and regulatory reasons.

In this study, the IMS data enabled us to illustrate inequalities between countries. They however did not give us the opportunity to study inequalities within countries. The variation in diffusion at a local level leading to inequalities in care is also a negative consequence of the current way of financing expensive drugs in several countries. This is often called 'postcode prescribing', and is referred to by clinical specialists from different countries and described in various press releases. In a recent report from the Dutch breast cancer association these inequalities were reported for trastuzamab (Herceptin®), which is also on the 'Expensive Medication List'. This report indicated that only 40% of patients who were eligible for treatment with trastuzamab received this drug in 2004 and that this percentage varied considerably between regions (2005). Studying these inequalities was not an aim of this study but these can be studied in detail on a local level using more detailed IMS data or information from other local registries.

No detailed information on the epidemiology of the diseases for which rituximab, imatinib and bortezomib was available for the included countries. Overall figures from Globocan indicate that there are some differences in incidence and prevalence but these differences alone cannot explain the large variation in diffusion seen in this study (Ferlay 2004).

Finally, many countries are currently implementing or developing a per-case payment system that follows the Diagnosis Related Group (DRG) system. These developments unfortunately could not be included in the description of most countries as little information is reported on the progress of these developments. Due to the recent introduction of these systems in most countries and the associated problems associated, the impact of these changes is most probably not expressed in the IMS data for countries other than Germany. These developments will likely have an effect on the allocation of financial resources and thereby impact on the diffusion of innovative drugs as well.

Despite its limitations this study underlines and quantifies the problems with the introduction of innovative drugs for inpatient use in the Netherlands and other countries and shows that the current 'Expensive Medication List' does not have a stimulatory effect. The presented characteristics healthcare systems in surrounding countries cannot be translated directly to the Netherlands but they possibilities that might decrease the current inequality. The current study furthermore creates a number of relevant questions, on impact of cultural variations and variation between regions within countries. It would be worthwhile to study these in combination with the regulatory and financial aspects related to the introduction and diffusion of innovative drugs. For such a study expertise from different sources should be combined to make such an integrated analysis a success.

In 2002 it was already observed that the continuing development of more and more innovative drugs would have an impact on the current hospital budget and that the financing structure

would not be up to this task (Breekveldt-Postma and Zwart-van Rijkom 2002; Timmerman 2002). In the Netherlands the necessity to anticipate on the recent developments with regard to the development and introduction of more and more expensive drugs aimed at small groups of patients is urgent and with the recent changes in healthcare financing it is time to study possible solutions. Shall we choose for a "quick and dirty" or for a "slow and thorough" solution with the possibility that in the latter case lives may be lost unnecessarily. It is probably best to use the best of both worlds. It is clear though that either way should be transparent and resolve the current inequalities.

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Chapter 10

General discussion

Economic evaluations are intended to support healthcare decision making in the broadest sense of the word. Not only can they support reimbursement decisions and budget revisions, but they can also aid in the allocation of limited resources in general. They can also highlight the added value of medical treatments and aid the understanding thereof by patients, specialists and politicians. In this thesis a number of different economic evaluations in healthcare were presented.

This chapter begins with a discussion of the elements derived from the economic evaluations performed for different actors in the context of a changing environment. Thereafter, other aspects associated with the introduction and diffusion of medical technologies are discussed.

SERVING DIFFERENT ACTORS IN A CHANGING ENVIRONMENT

In the last decade, more and more actors in healthcare have become interested in the outcomes of economic evaluations and these actors have different questions. These questions are for example related to research and development decisions, pricing and reimbursement decisions and allocation of (hospital) budgets. As a consequence there is variation in the approach used in economic evaluations. These differences in approach are encountered in the studies presented in this thesis. Each study has its own specific research question, largely depending on the demanding actor. Some elements are of increased importance in today's continuously changing environment and these will have consequences for future economic evaluations. These elements relate to the timeliness and the level of anticipation/flexibility included in economic evaluations.

TIMELINESS OF ECONOMIC EVALUATIONS

Compared to a decade ago, there are several changes in the development of new drugs, especially due to the progress in biomedical science. Despite this progress, the Food and Drug Administration (FDA) observed a slowdown in new medical products reaching patients in recent years, despite a growing public and private investment in research and development (FDA 2004). The FDA white paper indicated that current research methods are not equipped to capitalize on the progress of basic science and that there is a need to develop new methods, resulting in reliable, safe, and effective treatments at affordable prices to patients more quickly.

Recently, in cancer several new drugs have been developed with promising benefits. In the effort to develop more specific and effective therapies, several molecular targets of potential importance have been identified. A number of novel agents have been developed that act specifically against these selected targets, like bortezomib (Velcade®), bevacizumab (Avastin®) and trastuzumab (Herceptin®). As a result, these drugs are increasingly targeted towards

specific groups of patients and some efficacious drugs are introduced onto the market earlier. In fact, introduction of some drugs may take place simply on the basis of phase II trial results, especially in the fields of haematology and oncology, where these new drugs often form last resort treatments when all other treatment options have failed. These drugs are subsequently positioned earlier in the treatment strategy and can eventually replace first-line treatment, as was the case with imatinib. This however has consequences for economic evaluations, which are performed when these drugs are initially introduced on the market. At the time of introduction, little information is available on long-term outcomes, the ultimate place in the treatment approach and the outcomes in relation to the standard treatment (since phase II studies often have no comparator arm). By using a modelling approach we could adequately deal with some of these issues. However, we noticed that the best clinical evidence, i.e. results from an RCT, will never be available. As an example, this thesis reports on the difficulties that were associated with the economic evaluation of imatinib (see chapters 7 and 8).

With the increased understanding of disease processes and the currently available technical possibilities it is very well possible that such issues will occur more often in the coming years. Recently bortezomib, a new proteasome inhibitor for the treatment of multiple myeloma, was also approved for third line treatment on the basis of phase II data (2005c). For the economic evaluation of bortezomib a cost-effectiveness model was constructed which had problems similar to those seen with the second-line imatinib cost-effectiveness model, since there was no active comparator included in the phase II study (Richardson 2003).

The understanding of multiple myeloma has furthermore improved greatly as well in the last years. Nowadays it is seen more as a chronic disease, where many forms of treatments can be given in sequence. In the bortezomib phase II trial patients received up to 15 treatments prior to bortezomib treatment,(Richardson 2003) This makes the definition of the comparator, best supportive care, very difficult. However, there was a requirement to inform decision-makers about the ratio between costs and effects and, as a consequence, one had to use incomplete effectiveness data for the economic evaluation (Bagust 2004; Mujica-Mota 2004). It is likely that an incremental cost-effectiveness analysis, performed on the basis of the recently published phase III trial of bortezomib, will face similar problems as the study presented in chapter 8. Just like the imatinib phase III trial, the bortezomib phase III trial was also closed early and a crossover to the experimental treatment arm was allowed (Richardson 2005). As a result, no clear distinction can be made between treatment alternatives, i.e. new treatment compared to the old (conventional) treatment. It is therefore necessary to include data from other databases in the model in order to deal adequately with these problems.

ANTICIPATION AND FLEXIBILITY

Anticipation

For some diseases, new treatments continue to emerge, and this steady shift in treatment alternatives can affect the outcomes of cost-effectiveness analyses. This was for example the case in the imatinib cost-effectiveness analysis. In that instance it was solved through the inclusion of a scenario analysis (see chapter 8). However, changes in care can also be through developments in other elements of healthcare, as was the case in the melagatran/ximelagatran analysis.

Since the cost-effectiveness analysis of melagatran/ximelagatran was part of a reimbursement dossier, we adhered to the pharmacoeconomic guidelines set up by the Dutch College of Health Insurances (CVZ) (Riteco 1999). In these guidelines it is stated that only the registered indication of a drug should be analysed. As a consequence we could only present an analysis in which melagatran/ximelagatran treated patients switched to Vitamin K antagonists after 11 days, which is standard care for prolonged prophylaxis in the Netherlands (1998a). In anticipation of current developments, the model also included the option to prolong treatment with melagatran/ximelegatran or enoxaparin which could be used when new data would become available. Furthermore, as a consequence of the continuing reduction in length of stay, patients treated with enoxaparin might have to continue the subcutaneous administration outside the hospital as well. These possibilities were also included in the model to make it easily adaptable to changing circumstances.

Another element of anticipation of future developments is the possibility to include additional follow-up data in the model when these data become available. This enables the user to make the most up-to-date and relevant calculations of costs and health effects. This was exemplified in the rituximab cost-effectiveness analysis (chapter 6). Although nobody can look into the future, these examples make clear that it would be worthwhile to pay more attention to this when constructing cost-effectiveness models.

Flexibility

An extension of anticipation is the flexibility of a cost-effectiveness model. A cost-effectiveness model should be adjustable to changing circumstances without the need to make fundamental changes to the structural framework or, even worse, to construct a new model. Especially in a rapidly changing field where there is little certainty on future directions, this is a crucial element. The increasing numbers of actors who are interested in the outcomes of economic evaluations also require this flexibility; insurers and reimbursement agencies will have different demands than medical specialists and pharmaceutical companies. A model should be capable of adhering to these different perspectives.

In the generalised cost-effectiveness analysis (GCEA) of breast cancer interventions, the study question specifically included the element of flexibility, since the purpose of the study was to construct a model that was applicable in a variety of settings and that could easily be adapted when required. We sought a format that could be used for country adaptations by local researchers. Since this model had to adhere to the guidelines developed by the WHO, (Murray 2000; Tan-Torres Edejer 2003) all interventions were compared to the so-called counterfactual. This counterfactual represents a hypothetical situation where no interventions are possible whatsoever. In this way the results are more easily transferable to other populations and could be compared to interventions that were analysed following the same approach. The difficulty with this type of analysis is that the counterfactual is often difficult to define. Moreover, the limited availability of resources and information means that a balance must be found between detail of included interventions and practicality.

In developing countries there is a growing need to gain an understanding of the relationships between costs and effects. Unfortunately, the competition for scarce resources is much greater there than in the western world. In those situations where it is not possible to perform individual cost-effectiveness analyses because of budget constraints, generalised cost-effectiveness analyses offer a good "second best" option since it allows one to compare a large number of basic interventions in different areas of the healthcare sector in a transparent and logical way (Dziekan 2003; Murray 2003; Shibuya 2003; Baltussen 2004; Adam 2005; Baltussen 2005b; Edejer 2005; Hogan 2005; Morel 2005). Currently over 500 different interventions have been analysed for the WHO following this methodology and currently a database is under development that enables individual countries to perform country adaptations. Initial adaptations in Estonia and Ghana showed that this methodology can indeed aid local governments in healthcare prioritization and resource allocation (Baltussen 2005a; WHO 2005a).

DIFFUSION IN CLINICAL PRACTICE

This thesis furthermore shows that there are other important aspects that influence the diffusion of new technologies. There are various forms of healthcare evaluation that, in addition to economic evaluations, can aid medical specialists, insurers, and decision makers in the understanding of the diffusion of medical technologies in clinical practice. These various aspects are all included in health technology assessment (HTA) (figure 1). HTA is a policy-oriented form of research designed to inform decision-makers about medical technologies. In principle, it includes a broad set of many elements, including not only epidemiology and effectiveness but also regulatory and organisational aspects.

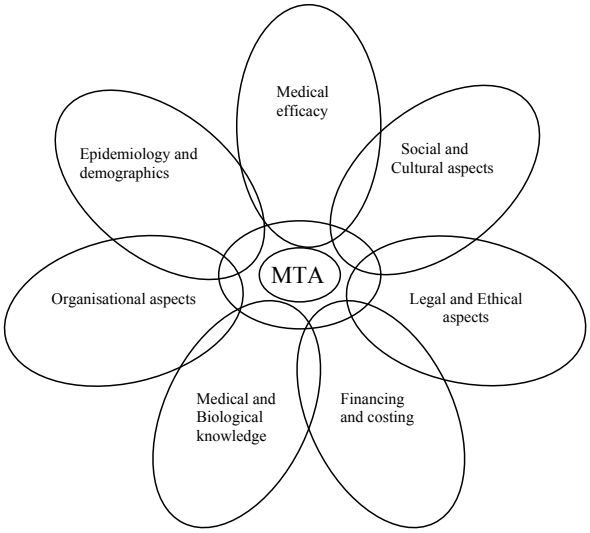

Figure 1: Graphical illustration of MTA, the involved aspects and research disciplines and their overlap.

This thesis contains two chapters that touch upon the issues of use and dissemination of medical technology. These make clear that a more integrated approach to health care evaluation, e.g. not only focussing on effectiveness but also on regulatory requirements and costs, is required to gain a better understanding of the dissemination processes.

In chapter 3 the results of the cost analysis of allogeneic stem cell transplantations from chapter 2 were used to calculate the shortages that arise as a result of inadequate budgets for this technology in the Netherlands. These calculations showed that there are substantial shortages due to the gap between assigned and required budgets for these transplantations. These inadequate budgets could well be an explanatory variable in the observed differences in numbers of allogeneic stem cell transplantations throughout Europe as the budgets in our surrounding countries are considerably higher. However, this budgetary issue is only one reason. As is described in chapters 7 and 8 there have been large shifts in the treatment approach of chronic myeloid leukaemia due to the introduction of imatinib, which replaced allogeneic stem cell transplantation as a first-line treatment in many chronic myeloid leukaemia cases. Therefore, including the substitution of stem cell transplantation in chronic myeloid leukaemia, possible variation in treatment approaches for other malignancies between countries and a possible variation in donor availability in this study would have resulted in a more complete picture.

The diffusion and financing topic was also studied in chapter 9, where the differences in introduction and diffusion of three innovative drugs (rituximab, imatinib and bortezomib) in 8 different European countries were described. This comparison quantified the differences in introduction and diffusion of innovative drugs and showed a possible relation between this diffusion and financing of these drugs. It described a number of healthcare characteristics that might lead to an increased diffusion in other countries compared to the Netherlands; such

healthcare characteristics include the allocation of earmarked funds for innovative drugs or the introduction of flexibility in the application of different budgets. As in chapter 3, this study made clear however that there is a subtle relationship between different healthcare characteristics, notably funding, epidemiology, treatment preferences, infrastructure and technological developments, and that one cannot say *a priori* what the effect of a single aspect will be on the 'success' of a new technology. It is therefore suggested that other aspects like prescribing culture, the role of central government (like the National Institute of Clinical Excellence (NICE) in the UK) and inclusion in clinical guidelines might play a role here as well. These elements should be included in an integrated manner to be able to cover more elements of HTA.

These chapters indicate that the various aspects that influence the diffusion of medical techniques and drugs cannot be studied in a mono-disciplinary fashion. It is therefore recommended to study the different aspects of healthcare simultaneously when trying to answer such questions.

EPILOGUE

Much is changing in the Dutch healthcare system with the upcoming healthcare reforms and the introduction of diagnosis-treatment combinations (DBCs) as the new form to claim expenses in the hospital. The large numbers of letters to the editor and position papers that have appeared in Dutch journals indicate that there are many difficulties associated with the introduction of DBCs and it is likely that the 2006 health care reforms will cause similar discussions. Since the introduction of competition in the healthcare sector is one of the reasons for the healthcare reforms, the relationship between costs and quality of care becomes more important. As a result, the number of economic evaluations will likely increase in the future. The DBCs offer insight into the costs of care and these might be used to streamline economic evaluations and make their results more comparable with other economic evaluations.

There are a number of other developments that indicate an increased interest in economic evaluations and which are in line with the timeliness of economic evaluations touched upon earlier in this chapter. The results of the cost-effectiveness analyses for imatinib showed that there is much uncertainty when such highly innovative drugs are introduced on the market and that little information is available to perform economic evaluations at that time. This is underscored by the recent introduction of bortezomib. Consequently, in addition to the 'fourth hurdle' that is already in place for outpatient drugs with an added value beyond currently available treatment options (the so called 'lijst 1B geneesmiddelen'), it is likely that additional requirements (the "four-b hurdle") will be introduced through a temporary reimbursement with the obligation to show the added value of a new technology in clinical practice through outcome research. In

the recent proposal of the Dutch Minister of Health regarding the 'Expensive Medications List' ("lijst dure geneesmiddelen") such a requirement is already included for drugs that are included on this list. A similar requirement is put in place in the United States for drugs considered for national coverage by Medicare Medicaid (Medicare 2005). It is good to pose these questions and determine what society is willing to pay for these new drugs. However, the height of the cost-effectiveness ratio should not only depend on economic considerations, but other factors such as available alternatives and severity of the disease should also be taken into account.

Finally, the Minister of Health of the Netherlands announced that a total sum of € 130 million will be made available to establish the Top Institute Pharma (TIP) which has the goal to improve the landscape of innovative drug research in cooperation with innovative pharmaceutical companies and academia in the Netherlands. Although the TIP will mainly focus on facilitating drug discovery and pre-clinical research, cost-effectiveness and outcomes research will also have a place in theme 6 on "Efficiency Analysis of the Process of Drugs Discovery, Development and Utilization". For this final aspect it is proposed to use the available structure of highly qualified researchers from different disciplines together with the large body of information that is available from population cohorts, patient registries, registration authorities and health insurers. This is in line with the findings from chapter 9 that there are other elements associated with the introduction of drugs that can only be studied in a multidisciplinary way which in effect goes back to the holistic approach of Health Technology Assessment of which economic evaluations form only one part.

In conclusion, this thesis presented a number of different economic evaluations that were performed from the perspective of different actors. Apart from the increased interest it is good to see that economic evaluations, like the recent budget revision of stem cell transplantations based on the results from chapter 2 and the country adaptations of the global generalized cost-effectiveness analyses in Ghana and Estonia have an impact on policy decisions. It however has to be acknowledged that other aspects impact decision making as well and that the role of economic evaluations, and the way these are judged, is sometime rather unclear. It is therefore laudable that the Dutch Health Care insurance board (CVZ) is applying for ISO-certification since one of the key elements thereof is transparency. It would be even better when the Minister of Health would adopt a similar approach as this will enhance the understanding for his decisions considerably.

Economic evaluations are still gaining ground in health policy decision-making and transitions are currently taking place, including an increased interest in outcomes research and a multidisciplinary approach. Taken together, these developments indicate that economic evaluations are adapting to the changing environment and are up to resolving the challenges that will emerge in the future.

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ABBREVIATIONS

ALL	Acute Lymphoblastic Leukaemia
AML	Acute Myeloid Leukaemia
ALAT	Alanine Aminotransferase
BM	Bone Marrow
BMT	Bone Marrow Transplantation
CHEMO	CHOP-like regimen
R-CHEMO	CHOP-like regimen plus rituximab
CML	Chronic Myeloid Leukaemia
CPMP	Committee for Proprietary Medicinal Products
CCR	Complete Cytogenetic Response
CR	Complete Responders
CEAs	Cost-effectiveness Analyses
CER	Cost-effectiveness Ratio
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
R-CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone plus Rituximab
DVT	Deep Vein Thrombosis
DRG	Diagnosis Related Group
DBCs	Diagnosis-Treatment Combinations
DLBCL	Diffuse Large B-Cell Lymphoma
DALY	Disability Adjusted Life-Year
DLI	Donor Lymphocyte Infusion
EBMT	European group for Blood and bone Marrow Transplantations
EUR	Euro
FDA	Food and Drug Administration
FTEs	Full-Time Equivalents
GCEA	Generalised Cost-Effectiveness Analysis
GELA LNH	Group d'Etude des Lymphomes de l'Adulte Non-Hodgkin's Lymphoma
GHS	Groupe Homogène de Sejour
CVZ	Health Care Insurance Board
HiTs	Health Care Systems in Transitions
HTA	Health Technology Assessment
HLA	Human Leukocyte antigen
ICER	Incremental Cost-Effectiveness Ratio
IFN+Ara-C	Interferon alpha-2a plus low-dose cytarabine
IFN	Interferon-alfa
IRIS	International Interferon versus STI571 Study

LMWHs	Low-Molecular-Weight Heparins
MUD	Matched Unrelated Donor
NCDB	National Cancer Data Base
NHS	National Health Systems
CTG	National Health Tariffs Authority
NICE	National Institute of Clinical Excellence
NHL	non-Hodgkin's Lymphoma
OS	Orthopaedic Surgery
PB	Peripheral Blood
PBSCT	Peripheral Blood Stem Cell Transplantation
CFH	Pharmaceutical Care Committee
PE	Pulmonary Embolism
QALYs	Quality Adjusted Life Years
RIST	Reduced Intensity conditioning Stem cell Transplantation
RFH	Regeling Farmaceutische Hulp 1996'
ScHARR	School for Health and Related Research
SNLG	Scottish Newcastle Lymphoma Group
SHI	Social Health Insurance
SCT	Stem Cell Transplantations
HOVON	The Dutch-Belgian Hemato-Oncology Cooperative Group
EMEA	The European Medicines Agency
TIP	Top Institute Pharma
TBI	Total body irradiation
THR	Total Hip Replacement
TKR	Total Knee Replacement
Cru	Unconfirmed Complete Responder
VTE	Venous Thromboembolism
VUD	Voluntary Unrelated Donor
WBMV	Wet Bijzondere Medische Verrichtingen
WHO	World Health Organization

SUMMARY

This thesis is based on a number of studies that address different economic evaluations in healthcare. In this summary the main findings of these studies will be summarised.

Chapter 2 describes the detailed cost analysis of HLA-identical sibling and voluntary unrelated allogeneic stem cell transplantation in adults with acute myelocytic leukaemia or acute lymphoblastic leukaemia. This analysis was performed to estimate the real costs of allogeneic haematopoietic stem-cell transplantation and to compare these with the historically determined budget that is made available for this purpose. The average costs per transplanted patient were € 98,334 (BMT), € 151,754 (VUD-SCT) and € 98,977 (PBSCT) during the first two years after transplantation. The largest part of the costs was incurred for finding a suitable donor and hospitalisation in the transplantation phase. In VUD-SCT, one-third of the total cost was due to the costs of finding a suitable donor. This study confirmed that the current budget for allogeneic stem-cell transplantation (€ 70,038 for genetically related donors and € 76,826 for unrelated donors) is insufficient to cover all the costs associated with such transplantations.

Chapter 3 extends on the cost analysis presented in chapter 2, it illustrates the role that cost analyses can play in the evaluation of the development of medical technologies. On the basis of the funds required to adequately perform stem cell transplantations and by using information on the number of stem-cell transplantations that are performed annually in the Netherlands it was shown that the budget received for these transplantations was approximately € 13 million while the actual costs were almost € 20 million. This shortage might explain the development that numbers of stem-cell transplantations lagged behind with our surrounding countries. The example presented in this chapter showed that periodic evaluation of the budgets for complicated procedures has added value. They can aid in understanding the evolution of these procedures and that they can contribute to maintaining the quality and continuity of care.

In **chapter 4** the results a cost-effectiveness study on different breast cancer interventions in epidemiologically different regions of Africa, North America and Asia are presented. In the literature, most cost-effectiveness analyses in breast cancer aimed at one single intervention in a developed country, so data to guide resource allocation decisions in developing countries are scarce. The aim of the study presented in chapter 4 was to broadly assess the cost-effectiveness of various forms of breast cancer control in different settings following a standardised methodology, developed by the World Health Organization (WHO). This approach makes comparisons to cost-effectiveness analyses performed for other healthcare interventions possible that follow the same methodology, thereby enabling use in priority setting. Using a mathematical model, six different interventions were compared: the effect of treating stage I, II, III or IV breast cancer individually, and of treating all four stages in the presence and absence of

an optimal breast cancer program (including down staging of stage at diagnosis by education and screening). The impact of implementing the six basic interventions for 10 years on the course of breast cancer in an open cohort of females of 15 years and older with a total follow-up period of 100 years was analysed. Each intervention was compared to a do nothing scenario called the counterfactual or null. The model distinguished six mutually exclusive health states: healthy, stage I, II, III or IV breast cancer and death. Regional population estimates on incidence, prevalence, percentage of prevalent cases treated and background mortality were based on the WHO burden of disease study. The key elements of the model were stage distribution of incident and prevalent cases and case fatality rates for treated and untreated patients. Outcome measures were life years adjusted for disability (DALYs), costs (in 2000 U.S. dollars) of treatment and follow-up and cost-effectiveness ratios (CERs). Treating stage I patients resulted in 23.41, 12.25, and 19.25 DALYs averted in Africa, North America and Asia, respectively. The corresponding mean CERs compared with no intervention were $78, $1,960 and $62. The number of DALYs averted with treatment decreased with increasing stage of disease at diagnosis; they were lowest for treating stage IV disease (0.18-0.19), with mean CERs of $4,986 in Africa, $70,380 in North America, and $3,510 in Asia. An optimal breast cancer program resulted in 16.14, 12.91 and 12.58 DALYs averted, with mean CERs of $75, $915 and $75. Treating stage I disease only or an optimal breast cancer program were the most cost-effective breast cancer interventions in the three studied regions.

In **chapter 5** the results of the cost-effectiveness study of melagatran/ximelagatran compared to enoxaparin in short-term (11 days) prophylaxis after elective knee or hip replacement are described. Patients undergoing major elective orthopaedic surgery are at an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), together referred to as venous thromboembolism (VTE). Therefore, patients undergoing elective orthopaedic surgery receive thromboprophylaxis to reduce this risk. Currently, thromboprophylaxis is given by low molecular weight heparins (LMWHs) or oral Vitamin K antagonists. These drugs have some limitation. The LMWHs have to be administered by daily subcutaneous injections and the vitamin K antagonists have a small therapeutic window requiring frequent monitoring. Ximelagatran a novel, oral direct thrombin inhibitor that transforms to its active form after administration was developed to overcome the current limitations. This cost-effectiveness analysis was carried out using a decision analytic model and was based on a clinical trial in which melagatran/ximelagatran started post-operatively was compared with the standard European LMWH regimen with enoxaparin started the evening before surgery. The model analysed costs (drugs, diagnosis/treatment of VTE, blood transfusions, long-term complications of DVT) and effects (symptomatic VTEs) over a period of three months, including costs of long-term complications of DVT. The total costs per 1000 patients were € 23,000 lower in the melagatran/ximelagatran group than in the enoxaparin group. The number of symptomatic VTEs was similar in the two groups but the number of blood transfusions was significantly lower in the melagatran/ximelagatran

group. Probabilistic sensitivity analysis showed that in almost 50% of simulations melagatran/ximelagatran was the dominant strategy. Melagatran/ximelagatran offers a cost-effective alternative to LMWHs for the prevention of VTE after major elective orthopaedic surgery with the advantage of oral administration and no need for laboratory monitoring,.

Chapter 6 deals with the incremental cost-effectiveness analysis of rituximab in diffuse large B-cell lymphoma (DLBCL) in older (over 60 years) and younger (under 60 years) patients in the Netherlands. This study was based on 4 years follow-up data of the Group d'Etude des Lymphomes de l'Adulte Non-Hodgkin's Lymphoma 98.5 randomized controlled trial. In this trial the relative increase in CR rate and relative risk reduction in disease-free and overall mortality associated with addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) for the treatment of DLBCL was determined. In the analysis, two outcomes after initial treatment were defined, CR and no CR. Patients over 60 years of age not reaching CR received palliative treatment while younger patients were eligible for second induction chemotherapy with- or without high-dose chemotherapy and autologous stem-cell rescue. After a follow-up of 15 years there was a difference in undiscounted overall survival of 1.2 years in the older group and 1.1 in the younger group of patients. The differences in discounted QALYs were 0.96 and 0.88 in favour of the R-CHOP arms of both groups. The discounted costs were € 15,860 higher in the older patients and € 12,343 higher in the younger group when rituximab was added to CHOP. This resulted in an incremental cost-effectiveness ratio (ICER) of € 13,983 for the younger and € 17,933 for the older patients per QALY gained. Taking severity of disease into account, addition of rituximab to CHOP for the treatment of DLBCL is recommended on the basis of these results.

Chapters 7 and 8 present the results of two cost-effectiveness analyses in which imatinib as first- and second-line treatment option for patient with Chronic Myeloid Leukaemia (CML) in the chronic phase was studied. In **chapter 7** the average cost-effectiveness ratios of first-line treatment with Interferon alpha-2a (IFN) or second-line imatinib following IFN failure were determined. There was no information on second-line treatment other than with imatinib after IFN failure available and therefore no direct comparator was available. In order to have some benchmark it was therefore decided to perform an analysis in which both first- and second-line treatment for CML were analysed. A cost-effectiveness model was constructed that consisted of two phases: an induction phase of eight months, in which patients were treated with IFN or imatinib, and a chronic treatment phase wherein patients were treated according the result of the induction phase. With, a maximum follow-up of 25 years, second-line treatment with imatinib resulted in 6.67 quality adjusted life years (QALYs) and first-line treatment with IFN in 4.98 QALYs. Average costs were considerably higher in the imatinib group, € 140,765 per patient, versus € 53,257 - € 76,969 for IFN treatment (depending on IFN dosage). Costs per QALY were € 21,082, € 10,687 and € 15,445 respectively. This study showed that although

imatinib was given later in time, namely after IFN failure, its introduction resulted in an increase in the number of QALYs at a considerable cost.

Chapter 8 presents the results of the incremental cost-effectiveness analysis of Interferon alpha-2a plus low-dose cytarabine (IFN+Ara-C) versus imatinib as first-line treatment option for CML in the chronic phase. This study was based on the pivotal phase III registration study of imatinib in the first-line. Due to the large difference in response and side-effect profile between both arms in this clinical trial a large cross over occurred from the IFN+Ara-C arm to the imatinib arm. As a consequence the results from the IFN+Ara-C arm could not be used in the comparison. Effectiveness data for the IFN+Ara-c arm survival estimates must be derived from studies with a similar patient group.

For this cost-effectiveness analysis a simulation model with a lifetime time horizon was constructed. The primary analysis was structured around attaining cytogenetic response (CR) after two years. Patients with a CR when treated with imatinib were assumed to have the same survival as patients treated with IFN+Ara-C reaching CR. Patients were treated with IFN+Ara-C or imatinib until disease progression or intolerance after reaching CR. In case of no CR patients were treated with IFN+Ara-C. After progression, 5% of patients received induction chemotherapy. In additional scenario-analyses, two other second-line treatment options for the imatinib group were studied. The costs and effects of including the possibility of allogeneic stem-cell transplantation (SCT) or treatment with a double dose of imatinib till disease progression (when SCT was not an option) as a second-line treatment option are included. In the primary analysis, treatment with imatinib resulted in an increase in overall undiscounted survival of 6.1 years, imatinib 15.2 years and IFN+Ara-C 9.1 years. The number of discounted QALYs gained was 5.7. The total discounted costs per patient in the imatinib arm were € 262,754, € 164,389 higher than in the IFN+Ara-C group. This resulted in an incremental cost-effectiveness ratio of € 49,012 per QALY gained. The results of the additional second-line treatment option in the scenario analysis resulted showed an increase in survival of 3.4 years or 2.9 QALYs compared to the other second-line treatment option (IFN+Ara-C) at an additional cost of € 207.000. Combination with the results of the imatinib patients with CR, resulted in exclusion of the imatinib with second-line treatment with IFN+Ara-C strategy through extended dominance arm and an incremental cost-effectiveness ratio of € 51,328 versus the IFN strategy of the primary analysis. This analysis showed that the introduction of imatinib as first-line treatment option in CML resulted in a considerable improvement of survival but that more can be gained by the choice of second-line treatment.

Chapter 2 to 8 present the results of different economic evaluations. Although performed differently, these all have one mutual goal; to support decision-making by delivering information on the relation between costs and effects to make a rational decision on allocation of resources. The study presented in **chapter 9** approaches this same goal in a different way.

The objective was to investigate to what extent differences in regulation and financing of new innovative drugs influenced their introduction in 8 different European countries. Analysis of IMS data since introduction of three innovative drugs in the field of haematology (Imatinib, Rituximab and Bortezomib) showed great differences in both the introduction and diffusion, especially for innovative drugs for inpatient use. Analysis of the different healthcare systems showed variation in healthcare financing, budgeting and regulation of both inpatient and outpatient drugs. This study furthermore described a number of approaches that were taken in other European countries to reduce inequality of access to innovative drugs. Although many of these cannot be translated directly to the Netherlands, these offer ways of research that might decrease the current inequality. This study also raised a number of relevant questions regarding the impact of prescribing culture and within country variation, it would be worthwhile to study these in combination with the regulatory and financial aspects related to the introduction and diffusion of innovative drugs.

SAMENVATTING

Dit proefschrift is gebaseerd op een aantal studies waarin verschillende gezondheidseconomische evaluaties worden uitgevoerd. In deze samenvatting zullen de belangrijkste resultaten van deze studies worden samengevat.

Hoofdstuk 2 beschrijft de gedetailleerde kostenanalyse van HLA-identieke stamceltransplantaties van verwante en onverwante donoren bij volwassenen met acute myoleloïde leukemie of acute lymphoblastische leukemie. Deze analyse was uitgevoerd om de werkelijke kosten van allogene stamceltransplantaties te bepalen en om deze te vergelijken met de historisch vastgestelde budgetten die voor deze aandoening beschikbaar worden gesteld. De gemiddelde kosten per getransplanteerde patiënt waren € 98.334 (BMT), € 151.754 (VUD-SCT) and € 98.977 (PBSCT) gedurende de eerste twee jaren na transplantatie. Het grootste gedeelte van deze kosten werd gemaakt voor het vinden van een geschikte donor en voor de ziekenhuisopname in de transplantatiefase. Bij VUD-SCT werd eenderde van de totale kosten gemaakt voor het vinden van een geschikte donor. Deze studie bevestigt dat het huidige budget voor allogene stamceltransplantaties (€ 70.038 voor verwante donoren en € 76.826 voor onverwante donoren) onvoldoende is om alle kosten van dergelijke transplantaties af te dekken.

Hoofdstuk 3 is een extensie van de kostenanalyse gepresenteerd in hoofdstuk 2. Het illustreert de rol die kostenanalysen kunnen spelen in de evaluatie van de ontwikkeling van medische technologieën. Op basis van het geld dat nodig is om op adequate wijze stamceltransplantaties uit te kunnen voeren en met behulp van het aantal stamceltransplantaties dat jaarlijks in Nederland wordt uitgevoerd is aangetoond dat het ontvangen budget ongeveer € 13 miljoen was terwijl de werkelijk gemaakte kosten € 20 miljoen zijn. Dit tekort kan wellicht de verschillen in ontwikkeling van het aantal stamceltransplantaties ten opzichte van ons omringende landen verklaren. Het voorbeeld gepresenteerd in dit hoofdstuk laat zien dat een periodieke evaluatie van de budgetten voor gecompliceerde medische interventies toegevoegde waarde heeft. Zij kunnen bijdragen aan het begrip van de evolutie van deze interventies en zij kunnen bijdragen aan het waarborgen van kwaliteit en continuïteit van zorg.

In **hoofdstuk 4** worden de resultaten van een kosten-effectiviteitsstudie van verschillende interventies voor borstkanker in epidemiologisch verschillende regio's van Afrika, Noord Amerika en Azië gepresenteerd. De meeste kosten-effectiviteitsanalyses in de literatuur zijn gericht op 1 enkele interventie in een ontwikkeld land. Hierdoor zijn data om de allocatie van middelen in ontwikkelingslanden te ondersteunen schaars. Het doel van de studie, gepresenteerd in hoofdstuk 4, was om de globale kosten-effectiviteit van een zestal interventies bij borstkanker, volgens een gestandaardiseerde methodologie, ontwikkeld bij de Wereldgezondheidsor ganisatie (WHO), te bepalen. Deze gestandaardiseerde aanpak maakt vergelijkingen met

kosten-effectiviteitsanalyses van andere gezondheidszorginterventies die volgens dezelfde methodologie zijn uitgevoerd mogelijk. Hierdoor kunnen zij gebruikt worden bij het zetten van prioriteiten. Met behulp van een wiskundig model werden zes verschillende interventies vergeleken: het effect van de behandeling van borstkanker in stadium I, II, III of IV individueel of in combinatie met de aan- of afwezigheid van een optimaal borstkankerprogramma (vroegere diagnose door scholing en screening). De impact van het introduceren van deze zes basale interventies op borstkanker in een open cohort van vrouwen van 15 jaar en ouder met een totale follow-up van 100 jaar werd geanalyseerd. Iedere interventie werd vergeleken met niets doen, de zogenaamde 'counterfactual' of nul-interventie. Het model onderscheidt zes niet onderling vervangbare stadia: gezond, borstkanker stadium I, II, III of IV en dood. Regionale populatieschattingen voor wat betreft incidentie, prevalentie, percentage van behandelde patienten en de achtergrondmortaliteit zijn gebaseerd op de WHO ziektelaststudie. De belangrijkste elementen van het model zijn borstkankerstadium van incidente en prevalente gevallen en het sterftecijfer van behandelde en onbehandelde patienten. Uitkomsten waren voor ziekte gecorrigeerde levensjaren (DALYs), kosten (in 2000, US dollar) van behandeling en follow-up en kosten-effectiviteitsratio's (CERs). De behandeling van stadium I patienten resulteerde in respectievelijk 23,41, 12,25, en 19,25 voorkomen DALYs in Afrika, Noord Amerika en Azie. De corresponderende CERS ten opzichte van niets doen waren $78, $1.960 en $62. Het aantal voorkomen DALYs nam af bij toenemend stadium bij diagnose en deze waren het laagst bij de behandeling van stadium IV (0,18-0,19), met gemiddelde CERs van $4.986 in Afrika, $70.380 in Noord Amerika en $3.510 in Azië. Een optimaal borstkankerprogramma voorkomt 16,14, 12,91 en 12,58 DALYs, met gemiddelde CERs van $75, $915 en $75. Het behandelen van stadium I borstkanker of de introductie van een optimaal borstkankerprogramma waren de meest kosten-effectieve borstkankerinterventies in de drie bestudeerde regio's.

In **hoofdstuk 5** worden de resultaten beschreven van de kosten-effectiviteitsstudie van melagatran/ximelagatran vergeleken met enoxaparine bij kortdurende (11 dagen) profylaxe na electieve knie- of heuptransplantaties. Patiënten die zware electieve orthopedische chirurgie ondergaan hebben een verhoogd risico op het ontwikkelen van diep veneuze thrombose (DVT) en longembolie (PE), gezamenlijk veneuze thromboembolie (VTE) genoemd. Om dit risico te verkleinen krijgen patiënten die dergelijke operaties ondergaan thromboprofylaxe met laag moleculaire heparines (LMWHs) of vitamine K antagonisten. Deze geneesmiddelen hebben echter enkele beperkingen. De LMWHs moeten met dagelijkse subcutane injecties worden toegediend terwijl de vitamine K antagonisten een beperkt therapeutisch werkingsgebied hebben waardoor frequente monitoring noodzakelijk is. Ximelagatran, een nieuwe, orale, directe thrombineremmer die omgezet wordt in zijn actieve vorm na toediening is ontwikkeld om de huidige beperkingen te verhelpen. Deze kosten-effectiviteitsanalyse was gebaseerd op een klinische studie waarin postoperatief gestart melagatran/ximlelagatran werd vergeleken met LMWH gestart op de avond voor de operatie hetgeen de Europese standaard is. Het model

analyseert kosten (geneesmiddelen, diagnose en behandeling van VTE, bloedtransfusies en langetermijn complicaties van DVT) en effecten (symptomatische VTEs) over een periode van drie maanden waarbij de lange termijn kosten van DVT-complicaties ook worden meegenomen. De totale kosten per 1000 patienten waren € 23.000 lager in de melagatran/ximelagatran groep in vergelijking met de enoxaparine groep. Het aantal symptomatische VTEs was vergelijkbaar in beide groepen maar het aantal bloedtransfusies was significant lager in de melagatran/ximelagatran groep. Probabilistische gevoeligheidsanalyse laat zien dat melagatran/ximelagatran in 50% van de simulaties de dominante strategie is. Melagatran/ximelagatran is een kosten-effectief alternatief voor LMWHs voor de preventie van VTE na zware electieve orthopedische chirurgie met het voordeel van orale toediening en het ontbreken van de noodzaak voor monitoring.

Hoofdstuk 6 bespreekt de incrementele kosten-effectiviteitsanalyse van rituximab in diffuus groot B-cel lymfoom (DLBCL) in oudere (ouder dan 60 jaar) en jongere (jonger dan 60 jaar) patiënten in Nederland. Deze studie was gebaseerd op 4-jaars follow-up gegevens van de Group d'Etude des Lymphomes de l'Adulte Non-Hodgkin's Lymphoma 98.5 gecontroleerd gerandomiseerde studie. In deze studie werd de relatieve toename in complete respons en de relatieve risicoreductie van ziektevrije en algehele overleving geassocieerd met de toevoeging van rituximab aan cyclofosfamide, doxorubicine, vincristine en prednison (CHOP) voor de behandeling van DLBCL bepaald. In de analyse werden twee uitkomsten na initiële therapie gedefinieerd: complete respons CR en geen CR. Patiënten ouder dan 60 jaar die geen CR behaalden ontvingen palliatieve therapie terwijl patiënten jonger dan 60 jaar die geen CR behaalden in aanmerking kwamen voor tweedelijns inductie chemotherapie met of zonder hoge dosis chemotherapie en stamceltransplantatie. Na een follow-up van 15 jaar was er een verschil in onverdisconteerde overleving van 1,2 jaar in de oudere groep en 1.1 jaar in de jongere groep patiënten. Het verschil in verdisconteerde QALYs was 0,96 and 0,88 in het voordeel van de rituximab + CHOP arm. De verdisconteerde kosten waren € 15.860 hoger in de oudere patiënten en € 12.343 in de jongere patiënten. Dit resulteerde in een incrementele kosten-effectiviteitsratio van € 13.983 voor de jongere en € 17.933 voor de oudere patiënten. Wanneer ernst van de ziekte wordt meegenomen is de toevoeging van rituximab aan CHOP bij de behandeling van DLBCL aan te bevelen op basis van deze resultaten.

Hoofdstuk 7 en 8 presenteren de resultaten van twee kosten-effectiviteitsanalyses waarin imatinib als eerste- of tweedelijns behandeling voor patiënten met Chronische Myeloïde Leukemie (CML) in de chronische fase werd ingezet. In **hoofdstuk 7** zijn de gemiddelde kosten-effectiviteitsratio's van eerstelijns behandeling met Interferon alpha-2a (IFN) of tweedelijns behandeling met imatinib bepaald. Er was geen informatie betreffende een andere dan tweedelijns behandeling met imatinib na eerstelijns IFN falen en derhalve was er geen directe vergelijkende behandeling. Om toch een benchmark te hebben was besloten om een analyse

uit te voeren waarin zowel eerste- als tweedelijns behandeling van CML werd bestudeerd. Een kosten-effectiviteitsmodel dat bestond uit twee fases was geconstrueerd: een inductie fase van acht maanden, waarin patiënten werden behandeld met IFN of imatinib, en een chronische behandelfase waarin patiënten werden behandeld op geleidde van de uitkomst van de initiële behandeling. Met een maximale follow-up van 25 jaar resulteerde tweedelijns behandeling met imatinib in 6,67 QALYs en eerstelijns behandeling met IFN in 4,98 QALYs. De gemiddelde kosten waren aanzienlijk hoger in de imatinib arm, € 140.765 per patient tegenover € 53.257 - € 76.969 voor IFN behandeling. Kosten per QALY waren respectievelijk € 21.082, € 10.687 en € 15.445. Deze studie liet zien dat imatinib, hoewel later in het behandeltraject gegeven, resulteert in een toename van het aantal QALYs maar dat dit tegen aanzienlijke kosten gebeurt.

Hoofdstuk 8 presenteert de resultaten van de incrementele kosten-effectiviteitsanalyse, gebaseerd op de fase III registratie studie, van IFN plus lage dosis cytarabine (IFN+Ara-C) versus imatinib als eerstelijns behandeling van CML in de chronische fase. Vanwege het grote verschil in respons en bijwerkingenprofiel tussen de behandelarmen was er een grote mate van cross-over naar de imatinib arm. Derhalve konden de resultaten van de IFN+Ara-C arm niet gebruikt worden voor deze analyse en zijn hiervoor de effectiviteitsdata van andere studies met een vergelijkbare patiëntenpopulatie gebruikt. Voor deze analyse is een simulatie model met een levenslange follow-up ontwikkeld. De primaire analyse is gestructureerd rondom het behalen van cytogenetische respons (CR) na twee jaar. Patiënten met een CR in de imatinib-arm werden verondersteld dezelfde overleving te hebben als IFN+Ara-C behandelde patiënten met een CR. Patiënten werden behandeld met imatinib of IFN+Ara-C tot aan ziekteprogressie of intolerantie voor deze behandeling bij het behalen van een CR. Indien geen CR werd behaald werden patiënten behandeld met IFN+Ara-C. Na progressie werd 5% van de patiënten behandeld met inductie chemotherapie. In additionele scenario-analyses werden twee andere tweedelijns behandelopties in de imatinib arm bestudeerd. Dit waren, de kosten en effecten van een behandeloptie waarin patiënten een allogene stamceltransplantatie of behandeling met een dubbele dosering imatinib kregen (indien stamceltransplantatie geen optie was). In de primaire analyse resulteerde behandeling met imatinib tot een toename van onverdisconteerde overleving met 6,1 jaar, 15,2 jaar in de imatinib groep en 9,1 in de IFN+Ara-C groep. De toename in het aantal QALYs (verdisconteerd) was 5,7. De totale verdisconteerde kosten waren € 262.754 per patiënt, € 164.389 hoger dan in de IFN+Ara-C groep. Dit resulteerde in een incrementele kosten-effectiviteitsratio van € 49.012 per gewonnen QALY. De resultaten van de additionele tweedelijns behandeloptie in de scenario analyse lieten een toename van 3.4 jaar of 2,9 QALYs zien ten opzichte van de base case tweedelijns behandeloptie (IFN+Ara-C) met additionele kosten van € 207.000. Combineren van de resultaten uit de scenario analyse met de imatinib behandelde patiënten die wel een CR behaalden lieten zien dat de imatinib-arm uit de basis analyse wordt uigesloten op basis van 'extended dominance' en dat de incrementele kosteneffe ctiviteitsratio van de scenario-analyse ten opzichte van de IFN+Ara-C uit de base case analyse €

51.328 was. Deze analyse liet zien dat de introductie van imatinib als eerstelijns behandeloptie van CML een grote toename in overleving geeft maar dat, blijkens de scenario analyse, er nog winst is te behalen bij de keuze van de tweedelijns behandeloptie.

De hoofdstukken 2 tot en met 8 presenteren de resultaten van verschillende economische evaluaties uitgevoerd voor verschillende actoren in de gezondheidszorg. Hoewel op een verschillende wijze uitgevoerd, hebben deze allemaal hetzelfde doel: het ondersteunen van beslissingen door het leveren van informatie over de relatie tussen kosten en effecten teneinde rationele keuzes bij de allocatie van middelen mogelijk te maken. De in **hoofdstuk 9** gepresenteerde studie benadert ditzelfde doel op een andere wijze. Het doel van deze studie was om te onderzoeken op welke wijze verschillen in regulatie en financiering van nieuwe innovatieve geneesmiddelen in acht Europese landen hun introductie en diffusie beïnvloedt. Analyse van IMS data sinds de introductie van drie innovatieve geneesmiddelen binnen de hematologie (imatinib, rituximab en bortezomib) laten grote verschillen in zowel de introductie als diffusie zien, met name voor geneesmiddelen die in het ziekenhuis worden gebruikt. Analyse van de verschillende gezondheidszorgsystemen toonde een variatie in financiering, budgettering en regulatie van geneesmiddelen die binnen en buiten het ziekenhuis werden gebruikt. Deze studie liet tevens een aantal manieren zien waarmee in andere Europese landen wordt getracht de ongelijkheid bij de toegang tot dergelijke geneesmiddelen te voorkomen. Hoewel deze niet direct naar Nederland vertaald kunnen worden bieden deze wel aanknopingspunten waarmee de huidige ongelijkheid kan worden onderzocht. Deze studie roept tevens een aantal interessante vragen betreffende het voorschrijfgedrag en variatie binnen een land op waarvan het de moeite waard zou zijn om deze samen met de regulerings- en financiële aspecten te bestuderen in relatie tot de introductie en diffusie van innovatieve geneesmiddelen.

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CURRICULUM VITAE

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