CHEMOTHERAPY IN OESOPHAGEAL CANCER

CHEMOTHERAPIE BIJ SLOKDARMKANKER

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van
het College voor Promoties

De openbare verdediging zal plaatsvinden
op vrijdag 16 april 2004 om 13.30 uur

door

Marco B. Poleé

geboren te Rheden

PROMOTIECOMMISSIE:

Promotor:	Prof.dr. G. Stoter
Overige leden:	Prof.dr. H.W. Tilanus
	Prof.dr. E.J. Kuipers
	Prof.dr. J. Verweij
Co-promotor:	Dr. A. van der Gaast

ISBN 90 5677 125 6

Printed by Hellinga b.v. Leeuwarden, the Netherlands

Voor mijn ouders
Marjolein
Iris, Koen en Robert

CONTENTS

Chapter 1

Introduction

Introduction

The incidence of oesophageal cancer in the Netherlands has doubled in the period 1978-1996 (from 2.2 to 4.8 per 100.000 person-years) and at the end of this period the incidence of adenocarcinomas equalled the incidence of squamous cell carcinomas[1]. The main risk factors for squamous cell carcinomas are alcohol and tobacco. Adenocarcinomas of the oesophagus are associated with obesity[2], symptoms of gastric reflux[3] and to specialised columnar (Barrett's) epithelia[4]. In recent years several genetic events that occur within the oesophageal mucosa leading to oesophageal adenocarcinoma have been discovered[5,6]. However an overall understanding of the rising incidence remains incomplete.

The prognosis of patients with oesophageal cancer is poor. The 5-year survival rate of all patients with oesophageal cancer is below 10%. Surgery is considered the mainstay of treatment, however 40-60% of patients present with irresectable disease, distant metastases or are considered to be poor candidates for surgery because of coexistent morbidity. Pathological examination reveals that in 30% a resection is microscopically incomplete regardless the type of surgery that has been performed[7]. After resection the 5-year survival is 20-30% and the majority of patients relapse both loco regionally as well as at distant sites[8]. Chemotherapy alone or in combination with radiotherapy is therefore often used in an attempt to improve the resectability rate and the prognosis of these patients, or to palliate symptoms in patients with irresectable or metastatic disease.

Chemotherapy

Single agent chemotherapy

Many cytostatic agents have been tested for the treatment of patients with oesophageal cancer. Cisplatin, investigated as a single agent in 5 studies, induced a pooled response rate of 20%[9]. Carboplatin seemed to be less active (response rates 0-10%), although both platinum analogs have not been compared in a randomised study[10]. Response rates after treatment with other cytostatic agents such as bleomycin, 5-fluorouracil, methothrexate and etoposide are in the 10-30% range[11]. Paclitaxel has been studied in 50 patients with metastatic disease with an overall response rate of 32%[12].

Combination chemotherapy

Cisplatin based combination chemotherapy is most frequently used for patients with oesophageal cancer. These combinations generally yielded a 25 to 35% response rate in patients with metastatic disease and a 45 to 75% response rate in patients with loco-regional disease[9]. Cisplatin combined with 5-fluorouracil is by some authors considered the standard regimen. There is, however, a lack of randomised studies in which patients with locally

advanced or metastatic tumours are treated with chemotherapy or best supportive care or in which different chemotherapy regimens are compared.

NEOADJUVANT CHEMOTHERAPY

The goal of neoadjuvant chemotherapy is a reduction of recurrence from occult lymphatic and/or distant metastases with improvement of survival and possible tumour shrinkage with an increased resectability rate. The number of randomised phase III studies comparing preoperative chemotherapy followed by surgery versus surgery alone is limited. Furthermore, the results of some of these studies are difficult to interpret for reasons such as: only a small number of patients included, the used chemotherapy regime is nowadays not considered optimal or the results have not yet been fully published.

Noteworthy is the fact that the results of the 2 largest studies have a different outcome. In the Intergroup trial 440 patients with either adenocarcinomas or squamous cell carcinomas were randomised to pre-operative treatment with 3 courses of cisplatin and 5-fluorouracil followed by surgery or surgery alone[13]. Patients who had stable disease or an objective response after chemotherapy received also 2 post-operative courses of chemotherapy. The overall rate of clinical response (19%) to pre-operative chemotherapy was surprisingly low. The number of R0 resection was 62% after treatment with chemotherapy versus 59% after surgery alone; this difference was not significant. Survival after 2 years was also comparable in the two groups, 35% after pre-operative chemotherapy and 37% after surgery alone. The Medical Research Council (MRC) found a significantly improved survival following neoadjuvant chemotherapy[14]. In their study 802 patients with either squamous cell carcinoma or adenocarcinoma were randomised to receive pre-operative chemotherapy with 2 courses of cisplatin and 5-fluorouracil followed by surgery or surgery alone. The response rate after chemotherapy was not reported. A complete resection was achieved in 60% of patients in the chemotherapy group compared to 54 % in the surgery alone group. The 2-year survival rate was 43% for patients treated with pre-operative chemotherapy versus 34% after surgery alone (difference 9%, 3-14).

These dissimilar results are difficult to explain, particularly because in both studies comparable chemotherapy regimens were used. Possible explanations could be: patient selection, the type and adherence to the chemotherapy protocol of patients, chance and the type of surgical resection. In the Intergroup study an oesophagectomy through a thoracotomy was preferred while in the MRC study either a transhiatal resection or an oesophagectomy through a transthoracic approach was considered appropriate.

Palliative chemotherapy

Most patients with oesophageal cancer need palliative treatment for local recurrence and/or metastases at some stage of the disease. Dysphagia due to tumour obstruction is one of the most distressing symptoms. Intraluminal radiotherapy, intubation with self-expanding metal stents and laser therapy are all effective in palliation of dysphagia at the cost of acceptable morbidity[15,16]. Median survival after these types of treatment is 3-6 months, comparable to the survival of untreated patients. Despite palliation of dysphagia, quality of life usually rapidly deteriorates in most patients due to symptoms such as pain, fatigue, appetite loss and constipation[17,18]. In 2 studies the effect of chemotherapy on dysphagia was prospectively investigated, in both studies 80-90% of patients reported a relief of dysphagia after treatment with chemotherapy[19,20].

Introduction to the thesis

This thesis addresses the various roles of chemotherapy in the treatment of patients with oesophageal cancer. In chapter 2 the results of a phase II study with the combination of cisplatin, etoposide, 5-fluorouracil and folinic acid in patients with advanced squamous cell carcinoma of the oesophagus are reported. This study elaborated on a previous chemotherapy study performed at our department with the combination cisplatin and etoposide[21]. The addition of 5-fluorouracil and folinic acid seemed rational because of the few overlapping toxicities and because of a reported synergistic activity in preclinical studies[22,23].

In the next 4 chapters studies with weekly or biweekly administrations of paclitaxel and cisplatin or carboplatin are described. Weekly or biweekly administration of chemotherapy increases cell exposure to drugs and reduces the non-exposure interval, during which regrowth and neoangiogenesis occurs. Based on theoretical models, shortening of the interval between chemotherapy cycles is a method to increase dose-intensity[24]. A dose-finding study of weekly administrations of cisplatin and paclitaxel in patients with advanced oesophageal cancer is described in chapter 3. In previous studies we had shown that single agent therapy with cisplatin 80 mg/m^2/week was tolerated by most chemotherapy-naive patients and that cisplatin 70 mg/m^2/week could be combined with other agents such as etoposide[25,26,27]. In this study patients receives a fixed dose of cisplatin 70 mg/m2/week and escalating doses of paclitaxel. In chapter 4 we investigated the safety and effectivity of a biweekly schedule of cisplatin and paclitaxel for patients with advanced oesophageal cancer. This study was the successor of an earlier conducted phase I study in which cisplatin 60 mg/m^2 and paclitaxel 180 mg/m^2 administrated every 2 weeks was the recommended dose for further studying[28]. The high response rate and the favourable toxicity profile obtained with this biweekly regimen in patients with locally advanced or metastatic disease

were the reasons to test this regimen in a neoadjuvant setting. In this phase II study, presented in chapter 5, patients with a resectable squamous cell carcinoma of the oesophagus were treated with a biweekly chemotherapy regimen of cisplatin and paclitaxel before surgery. In chapter 6 a phase I and pharmacokinetic study of weekly carboplatin and paclitaxel administrations is described. Paclitaxel and carboplatin were both administered in one hour and pharmacokinetic analyses were performed at the highest dose levels.

In chapter 7 we present the results of an analysis to identify prognostic factors for survival in 350 patients with advanced oesophageal cancer all treated with cisplatin-based chemotherapy. Knowledge of such factors may be helpful in selecting the best treatment for these patients.

References

1 Wijnhoven BPL, Louwman WJ, Tilanus HW and Coebergh JWW. Increased incidence of adenocarcinomas of the gastro-oesophageal junction in dutch males since the 90`s. Eur J Gastroenterol Hepatol 2002; 14: 115-22.

2 Chow WH, Blot WJ, Vaughn TL et al. Body mass index and risk of adenocarcinoma on the oesophagus and gastric cardia. J Natl Cancer Inst 1998; 90: 150-5.

3 Lagergren J, Bergstrom R, Lindgren A, et al: Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999; 340: 825-31.

4 Jankowski J, Wright NA, Meltzer S, et al: Molecular evolution of the metaplasia dysplasia adenoma sequence in the esophagus (MCS). Am J Pathol 1999; 154: 965-74.

5 Bailey T, Biddlestone L, Shepherd N et al. altered cadherin and catenin complexes in the Barret's esophagus- dysplasia- adenocarcinoma sequence: correlation with disease progression and dedifferentiation. Am J Pathol 1998; 152: 135-44.

6 Huang Y, Boynton RF, Blount PL et al. Loss of heterozygossity involves multiple tumour suppressor genesin human esophageal cancers. Cancer Res 1992; 52: 6525-30.

7 Hulscher JBF, van Sandick JW, de Boer AGEM et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002; 347: 1662-9.

8 Millikan KW, Silverstein J, Hart V et al. A 15-year review of oesophagectomy for carcinoma of the esophagus and cardia. Arch Surg 1995; 130: 617-24.

9 Enzinger PC, Ilson DH, and Kelsen DP. Chemotherapy in esophageal cancer. Semin Oncol 1999; 26: 12-20.

10 Queisser W, Preusser P, Mross KB et al. Phase II evaluation of carboplatin in advanced esophageal carcinoma. Onkologie 1985; 13: 190-3.

11 Kok TC. Chemotherapy in Oesophageal cancer: a review. Cancer treatment reviews 1997; 23: 65-85.

12 Ajani JA, Ilson DH, Daugherty K et al. Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the oesophagus. J Natl Cancer Inst 1994; 86: 1086-91.

13 Kelsen DP, Ginsberg R, Pajak TF et al. Chemotherapy followed by surgery compared with surgery alone for localised esophageal cancer. N Engl J Med 1998; 339: 1979-84.

14 Medical Research Council Esophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in esophageal cancer: a randomised trial. Lancet 2002; 359: 1727-33.

15 Knyrim K, Wagner HJ, Bethge N, Keymling M, Vakil N. A controlled trial of an expansile metal stent for palliation of oesophageal obstruction due to inoperable cancer. N Engl J Med 1993; 329: 1302-7.

16 Low DE, Pagliero KM. Prospective randomised trial comparing brachytherapy and laser photoablation for palliation of oesophageal cancer. J Thorac Surg 1992; 104: 173-8.
17 Blazeby JM, Williams MH, Brookes ST, Alderson D, Farndon JR. Quality of life measurement in patients with oesophageal cancer. Gut 1995; 37: 505-8.
18 Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life in patients with oesophageal cancer. Cancer 2000; 88: 1781-7.
19 Ilson DH, Saltz L, Enzinger P et al. Phase II trial of weekly irinotecan plus cisplatin in advanced oesophageal cancer. J Clin Oncol 1999; 17: 3270-5.
20 Spiridonidis CH, Laufman LR, Jones JJ, Gray DJ, Cho CC, Young DC. A phase II evaluation of high dose cisplatin and etoposide in patients with advanced oesophageal adenocarcinoma. Cancer 1996; 78: 2070-7.
21 Kok TC, Van der Gaast A, Dees J et al. Cisplatin and etoposide in oesophageal cancer: a phase II study. Br J Canc 1996; 74: 980-4.
22 Nishiyama M, Yamamoto W, Park JS et al. Low dose cisplatin and 5-fluorouracil in combination can repress increased gene expression of cellular resistance determinants to themselves. Clin Cancer Res 1999 ; 5: 2620-8.
23 Hotta T, Tanimura H, Yamaue H et al. Etoposide enhances the antitumour effects of cisplatin in gastric cancer cells. Anticancer Res 1997; 17: 885-9.
24 Levaseur LM, Slocum HK, Rustum YM, Greco WR. Modelling of the time-dependency of in vitro drug cytotoxicity and resistance. Cancer Res 1998; 58: 5749-61.
25 Planting AST, Van der Burg MEL, De Boer-Dennert M et al. Phase I/II study of a short course of weekly cisplatin in patients with advanced solid tumours. Br J Cancer 1993; 68: 789-92.
26 Planting AST, de Mulder PHM, De Graeff A et al. Phase II study of weekly high-dose cisplatin for six cycles in patients with locally advanced squamous cell carcinoma of the head and neck. Eur J Cancer 1997; 33: 61-5.
27 Planting AST, Van der Burg MEL, De Boer-Dennert M et al. Phase I study of weekly high dose cisplatin combined with long term oral etoposide in advanced solid tumours. Ann Oncol 1994; 6:190-2.
28 Van der Gaast A, Kok TC, Kerkhofs L et al. Phase I study of a biweekly schedule of a fixed dose of cisplatin with increasing doses of paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 1999; 80: 1052-7.

CHAPTER 2

PHASE II STUDY OF THE COMBINATION CISPLATIN, ETOPOSIDE, 5-FLUOROURACIL AND FOLINIC ACID IN PATIENTS WITH ADVANCED SQUAMOUS CELL CARCINOMA OF THE ESOPHAGOUS

M.B. Polee[1], T.C. Kok[1], P.D. Siersema[2], H.W. Tilanus[3], T.A.W. Splinter[1], G. Stoter[1] and A. Van der Gaast[1]

Department of [1]Medical Oncology, [2]Gastroenterology and [3]Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands

Anti-Cancer Drugs 2001; 12: 513-7

Summary

Purpose: The objective of this study was to determine the toxicity and the efficacy of the combination of cisplatin, etoposide, 5-fluorouracil and folinic acid in the treatment of patients with advanced squamous cell carcinoma of the oesophagus.

Patients and methods: Patients received cisplatin 80 mg/m² i.v. on day 1, etoposide 125 mg/m² i.v. on day 1 and etoposide 200 mg/m² p.o. on days 3 and 5, 5-fluorouracil 375 mg/m²/day continuously i.v. combined with folinic acid 30 mg p.o. 6 times per day on days 1 to 4. Courses were repeated every 4 weeks until progression or up to a maximum of 6 courses. Patients were evaluated for response after every 2 courses.

Results: Sixty-nine patients received a total of 291 courses (median 4, range 1-6). The haematological toxicity consisted of leucocytopenia grade 3 or 4 in 17% and 16% of patients, respectively. Leucocytopenic fever was seen in 19 % of patients. Thrombocytopenia grade 3 or 4 was seen in 13% and 7% of patients, respectively. Non-haematological toxicity consisted of nausea/vomiting grade 3 in 32%, diarrhoea grade 3 in 6% and mucositis grade 3 or 4 in 23% of patients. The overall response rate was 34% (complete response 4%, partial response 30%), the median time to progression was 7 months in 13 patients who received no additional treatment. The median survival for all patients was 9.5 months with a 1-year survival rate of 36%. Ten patients with initially locally unresectable disease (N=2) or celiac or supraclavicular lymph node metastases (N=8) who received additional treatment (oesophageal resection 7 patients, radiotherapy 3 patients) after they had responded to chemotherapy had a three-year survival of 50%.

Conclusion: The combination cisplatin and etoposide combined with 5-fluorouracil and folinic acid is a safe and active regimen for patients with advanced squamous cell carcinoma of the oesophagus. Mucositis is the most prevalent toxicity.

Introduction

The prognosis for patients with carcinoma of the oesophagus or gastro-oesophageal junction is still poor. More than 50% of symptomatic patients have already locally advanced non-resectable tumours, overt metastatic disease or at least T3N0 or T3N1 tumours. The 5-year survival rate of patients who are thought to have resectable disease is in the range of 10-20%[1,2]. The pattern of relapse in resected patients is both locoregional as well as the development of distant metastases.

Cisplatin-based combination chemotherapy is moderately effective in the treatment of

metastatic oesophageal cancer. In combination with 5-fluorouracil response rates of 19-55%[3,4,5] are obtained and by some authors this combination is considered to be standard therapy[6].

Folinic acid is a biochemical modulator of 5-fluorouracil and is known to enhance 5-fluorouracil activity in the treatment of colorectal and gastric cancer[7,8]. We previously treated 29 patients with adenocarcinoma of the oesophagus with 5-fluorouracil (500 mg/m2/day for 5 days continuous infusion) and folinic acid (loading dose 4 x 90 mg followed by 6 x 60 mg for 5 days orally). This treatment was tolerated well with an overall response rate of 19%[9]. In patients with squamous cell carcinoma of the oesophagus a response rate of 17% was achieved with a comparable regimen[10]. We have also investigated cisplatin in combination with etoposide in a phase II study in patients with advanced squamous cell carcinoma of the oesophagus[11]. The overall response rate in 65 evaluable patients was 48%. Toxicity was manageable and consisted mainly of myelosuppression.

Based on the favourable toxicity profile of the cisplatin/etoposide combination we decided to add 5-fluorouracil and folinic acid to this regimen. A combination of cisplatin, etoposide and 5-fluorouracil seemed attractive since all three drugs are active as single agent against oesophageal cancer, and their toxicity profiles are only partially overlapping. Furthermore, these agents may have synergistic interactions[12,13]. We here report the toxicity and efficacy of this combination in the treatment of patients with advanced squamous cell carcinoma of the oesophagus.

Patients and methods

All patients who entered the study had inoperable or metastatic, histologically proven squamous cell carcinoma of the oesophagus. Further eligibility criteria were: age ≤ 75 years, performance status WHO 0-2, a life expectancy of more than 3 months, a reasonable food passage, bidimensionally measurable disease (or evaluable disease if the primary tumour was the only indicator lesion), white blood cell (WBC) count ≥ 3,0 x 10^9/L, platelets ≥ 100 x 10^9/L, creatinine clearance ≥ 60 ml/min. Prior chemotherapy was not allowed. Patients with overt brain metastases or an irradiated primary tumour as the sole indicator lesion were excluded. All patients gave informed consent.

The intravenous (i.v.) treatment consisted of pre-hydration with 1500 ml saline/glucose (0,45% / 2,5%) and 4 g of magnesium sulphate over 14 h, followed by etoposide 125 mg/m^2, dissolved in 500 ml 0,9% saline given over 2 h (day 1). Cisplatin (80 mg/m^2) dissolved in 1000 ml 0,9% saline was then administered over 4 h, followed by 5-fluorouracil (375 mg/m^2/ day) dissolved in 1000 ml 0,9% saline per day for four days. To prevent chemotherapy-induced phlebitis, 5000 E heparin was added to 5-fluorouracil infusion each day.

Oral treatment consisted of etoposide 200 mg/m²/day on days 3 and 5, divided in 3 doses on each day (at 10 a.m., 2 p.m. and 6 p.m.). In case of stenosis with dysphagia the content of the capsules was dissolved in lemonade. Folinic acid 30 mg was administered 6 times per day from day 1 (at the start of 5-fluorouracil infusion) until day 5 (at the end of 5-fluorouracil infusion).

In case the WBC nadir remained above 2,0x 10^9/L and / or the platelet nadir above 100 x 10^9/L the oral doses of etoposide were increased until a nadir (WBC 1,0-2,0 x 10^9/L and /or platelets 25-100 x 10^9/L) was reached in the subsequent courses. This was done in order to counterbalance possible differences in bio-availibility of oral etoposide. In case of WBC nadir <1,0 x 10^9/L and /or platelet nadir <25-100 x 10^9/L a 25% dose reduction of oral etoposide was carried out in the next and subsequent courses. Courses were postponed 1 week if WBC <3.0 x 10^9/L and /or platelets <100 x 10^9/L on day 1 of the next course. If after 2 weeks of delay WBC and/or platelets had not recovered, patients went off treatment. In case of severe mucositis (WHO grade ≥ 3), the dose of 5-fluorouracil was reduced by 25%. In case of severe neurotoxicity (WHO grade ≥ 3) or renal insufficiency (WHO grade ≥ 2), treatment was stopped permanently. Routine anti-emetic support consisted of 10 mg dexamethason before and after administration of cisplatin, in combination with ondansetron 8 mg twice daily. Courses were repeated every 4 weeks until progression, or up to a maximum of 6 courses.

Response evaluation was done according to standard WHO criteria[14]. Time to progression and survival were calculated from the first day of treatment. Patients were evaluated for response after two courses of chemotherapy or earlier if treatment was stopped due to severe toxicity. Response evaluation was performed after every second course. If progression of disease was evident after one course, the patients were classified as having early progressive disease. Toxicity was graded according to standard WHO criteria[13].

Results

Sixty-nine patients entered the study. Patient's characteristics are listed in *Table 1*. All patients were evaluable for toxicity; one patient was not evaluable for response because he refused further treatment after one course of treatment.

A total of 291 courses were given (median 4, range 1-6). Four patients discontinued treatment because of toxicity; 3 because of an episode of neutropenic fever and one because of neurotoxicity grade 3 after the fifth course. Fifteen cycles (7%) had to be postponed; 4 cycles because of leucocytopenia, 11 because of non-resolved non-haematological toxicity. The oral dose of etoposide had to be reduced in 20 patients; in 5 patients because of a WBC nadir <1 x 10^9/l, in 14 patients because of a platelet nadir < 25 x 10^9/l and in one patient because of both leucocytopenia and thrombocytopenia. The dose of 5-fluorouracil was reduced in 23 patients because of mucositis.

Table 1. Patients characteristics

Characteristic	No. of patients	%
Male	53	
Female	16	
Age (years)		
Median	55	
Range	28 – 71	
WHO performance Status (n=65)		
0	15	22
1	35	56
2	15	22
Weight loss (%)		
Median	9	
Range	0 – 35	
Extent of disease		
Locally advanced[13]	19	
Metastatic disease[50]	81	
Lymph nodes		
Supraclavicular	28	40
Mediastinal	8	12
Celiac[22]	30	
Lung	13	19
Liver	13	19
Other	6	6
Prior treatment		
Radiotherapy	4	6
Surgical resection[7]	10	
Endoprothesis	4	6

Toxicity

The haematological toxicity consisted of leucocytopenia WHO grade 3 in 17% and grade 4 in 16% of patients. Fourteen episodes of leucocytopenic fever occurred in 13 patients. Ten patients developed leucocytopenic fever after the first course, the other 4 episodes were seen after the second and fourth course of chemotherapy. All patients with leucocytopenic fever had also grade 3 or 4 mucositis except for 1 patient who had a pneumonia. All patients were admitted and recovered after treatment with antibiotics. There were no toxic deaths. Seven patients developed infections without leucocytopenia. Two of these patients were admitted: one patient with mediastinitis after dilatation of his oesophageal tumour and one patient with pneumonia. Both patients recovered. Thrombocytopenia grade 3 and 4 was seen in

13% and 7% of patients respectively. Four patients received platelet transfusions. Blood transfusions were administered to 18 patients.

The most important non-haematological toxicities are listed in *Table 2*. Grade 3 nausea and vomiting occurred in 32% of the patients. Most patients experienced this toxicity during the last 2 days of each cycle. Four patients had grade 3 diarrhoea, all 4 after the first course of treatment. Grade 3 mucositis was seen in 22% of the patients and 1 patient had to be admitted because of a grade 4 mucositis. Despite dose reductions of 5-fluorouracil/folinic acid and prophylactic measurements, grade 2 or 3 mucositis re-occurred in 12 patients after the second course and in 8 patients in the next courses. Neuropathy grade 1 or 2 was seen in 20 patients and one patient developed a grade 3 neuropathy. Three patients experienced grade 2 hearing toxicity; two of these patients had tinnitus. Nephrotoxocity grade 1 was observed in one patient. Alopecia was common. Three patients experienced retrosternal pain while they were at home. Two of these three patients had a previous history of cardiac disease. The third patient had an endoprothesis in the oesophagus. No EKG abnormalities or enzymatic changes were observed.

Table 2. ***Worst CTC grade non haematological toxicities (n = 24)***

CTC grade in % WHO grade	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Toxicity					
Nausea/Vomiting	23	16	29	32	0
Diarrhoea	67	19	9	6	0
Mucositis	28	20	29	22	1

Response and survival

The overall response rate in the 68 evaluable patients was 34% [95% confidence interval (CI) 22-46%], including 3 complete responses (CR, 4%) and 20 partial responses (PR, 30%). Twenty-six patients had stable disease (SD, 38%) and 19 patients progressive disease (PD, 28%). The duration of CR was 8 months in a patient with lung- and lymph node metastases who received no further treatment. One patient with an initially irresectable tumour and one patient with supraclavicular lymph node metastases who had a clinical complete response after chemotherapy were referred for surgery; no viable tumour was found after surgical resection of the oesophagus and both patients are still disease free after 53 and 76 months. The median response duration of the 18 patients with PR's was 9 months (range 3-16 months). Ten patients who had a PR or CR after chemotherapy and either locally advanced disease or lymph node metastases confined to the supraclavicular or celiac region received additional treatment. Three patients were treated with radiotherapy at a dose of 50-54 Gy on the oesophagus and supraclavicular or celiac regions. Seven patients

underwent a radical transhiatal oesophageal resection. The median time to progression in patients who received additional treatment was 15 months (range 8-76 months).

All patients, with the exception of the two patients who had pT0 resections after chemotherapy have died. The median survival time for all patients was 9.5 months (range 2-76+ months) and the 1-year survival rate was 36%. The median survival for responding patients was 17 months (range 7-76+ months), compared to a median survival of 6 months (range 2-18 months) in non-responding patients. The median survival of the 10 patients who received additional treatment (surgery or radiotherapy) was 36 months (range 11-76+months).

Discussion

Patients with oesophageal cancer frequently present with, or develop metastatic disease later in the course of their disease. Intubation, external beam radiotherapy, endo-oesophageal intraluminal brachytherapy and endoscopic lasertherapy or combinations of these modalities are most frequently used for symptomatic palliation[15,16,17]. Despite effective palliation of dysphagia, quality of life rapidly deteriorates as a result of pain, fatigue, appetite loss and constipation[18,19] and median survival after palliative treatment is 3 to 6 months.

In the current study we investigated the efficacy and toxicity of the combination 5-fluorouracil and folinic acid added to a chemotherapy schedule that was previously used by us with cisplatin and etoposide. The observed haematological toxicity consisted of leucocytopenia grade 3 or 4 in 33% and thrombocytopenia grade 4 in 7% of patients. Febrile leucocytopenia occurred in 19% of patients and all but one patient had also a concurrent mucositis. Compared to our previous study with cisplatin and etoposide[11] the rate of myelosuppression was not increased, however the incidence of leucocytopenic fever increased most probably as a result of the concurrent mucositis caused by the addition of 5-fluorouracil and folinic acid. In this study, we observed an overall response rate of 34% in 68 evaluable patients, a median survival of 9.5 months and a 1-year survival rate of 36%. In our study with cisplatin and etoposide, the overall response rate was 48% and the median survival 8.5 months and 26 % of patients survived for more than one year.

The combination of cisplatin, etoposide, 5-fluorouracil and folinic acid has also been studied by Stahl et al. as part of a multimodality treatment program which also comprised chemoradiotherapy and/or surgery[20,21]. In 2 phase II studies, these investigators treated 110 patients, mostly with locally advanced oesophageal cancer, with 3 or 4 cycles of cisplatin 30 mg/m^2, etoposide 100 mg/m^2, 5-fluorouracil 500 mg/m^2 and folinic acid 300 mg/m^2 each administered on days 1,2 and 3. Grade 3 or 4 leucocytopenia and thrombocytopenia was observed in, respectively, 52% and 51%, and leucocytopenic fever in 29% of patients. Surprisingly, mucositis and

diarrhoea grade 3 or 4 was reported in less than 10% of the patients. The overall response rate in both studies was almost 50%. Preoperative treatment with cisplatin 20 mg/m² days 1-5, 5-fluorouracil 900 mg/m² days 1-5 and etoposide 90 mg/m² days 1,3,5 without folinic acid in patients with resectable adenocarcinoma of the oesophagus resulted in a response rate of 49%[22]. Because of the combined modality approach the median survivals of these latter studies can not be compared with the median survival obtained in our study.

Eight patients with celiac or supraclavicular lymph node metastases and two patients with locally unresectable disease were additionally treated with radiotherapy or surgery and had a three-year survival rate of 50%. It seems that patients with M1a disease who respond to chemotherapy and who are additionally treated with radiotherapy or surgery, may achieve a prolonged survival. Concurrent chemotherapy and radiotherapy in patients with T4 or M1a disease resulted in a 3-year survival of 23% in one study but at the cost of significant toxicity[xiv].

Future improvement in the systemic treatment of oesophageal cancer might come from the incorporation of new drugs such as the taxanes and irinotecan. In a number of studies it has been demonstrated that these agents can be combined with cisplatin with relatively mild toxicity and that high response rates up to 50% may be achieved[24,25,26]. Mucositis is usually a less prominent side effect of these new drug combinations compared to 5-fluorouracil based combinations.

In conclusion, the combination of cisplatin, etoposide, 5-fluorouracil and folinic acid is a safe and active regimen in the treatment of advanced squamous cell carcinoma of the oesophagus. Mucositis is the most prevalent toxicity of this regimen. A select group of patients with M1a disease who respond to treatment and additionally are treated with radiotherapy or surgery had a 3-year survival of 50%.

References

1 Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg 1990; 77: 845-57.

2 Millikan KW, Silverstein J, Hart V et al. A 15-year review of oesophagectomy for carcinoma of the oesophagus and cardia. Arch Surg 1995; 130: 617-24.

3 Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG et al. Chemotherapy followed by surgery compared with surgery alone for localised oesophageal cancer. N Engl J Med 1998; 339: 1979-84.

4 Hilgenberg D, Carey RW, Wilkins EW, Choi NC, Mathisen DJ, Grillo HC. Preoperative chemotherapy, surgical resection, and selective postoperative therapy for squamous cell carcinoma of the oesophagus. Ann Thorac Surg 1988; 45: 357-63.

5 Bleiberg H, Conroy T, Paillot B et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 1997; 33: 1216-20.

6 Ajani JA. Contributions of chemotherapy in the treatment of carcinoma of the oesophagus: results and commentary. Semin Oncol 1994a; 21: 474-82
7 Advanced colorectal cancer meta-analysis project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol 1992; 10: 896-903.
8 Wilke H, Stahl S, Schmoll HJ et al. Biochemical modulation of 5-fluorouracil by folinic acid or alpha-interferon with and without other cytostatic drugs in gastric, oesophageal and pancreatic cancer. Sem Oncol 1992; 2:(suppl 3) 215-9.
9 Kok TC, van der Gaast A, Splinter TAW. 5-Fluorouracil and folinic acid in adenocarcinoma of the oesophagus or oesophago-gastric junction area. Ann of Oncol 1996; 7: 533-4.
10 Alberts AS, Schoeman L, Burger W, Greef F, Falkson G. A phase II study of 5-fluorouracil and leucovorin in advanced carcinoma of the oesophagus. Am J Clin Oncol 1992; 15: 35-6.
11 Kok TC, Van der Gaast A, Dees J et al. Cisplatin and etoposide in oesophageal cancer: a phase II study. Br J Canc 1996; 74: 980-4.
12 Nishiyama M, Yamamoto W, Park JS et al. Low dose cisplatin and 5-fluorouracil in combination can repress increased gene expression of cellular resistance determinants to themselves. Clin Cancer Res 1999; 5: 2620-8.
13 Hotta T, Tanimura H, Yamaue H et al. Etoposide enhances the antitumor effects of cisplatin in gastric cancer cells. Anticancer Res 1997; 17: 885-9.
14 World Health Organisation. WHO handbook for reporting results of cancer treatment. WHO Offset Publ. No.4. Geneva: World Health Organisation, 1979.
15 Knyrim K, Wagner HJ, Bethge N, Keymling M, Vakil N. A controlled trial of an expansile metal stent for palliation of oesophageal obstruction due to inoperable cancer. N Engl J Med 1993; 329: 1302-7.
16 Siersema PD, Dees J, van Blankenstein M. Palliation of malignant dysphagia from oesophageal cancer. Rotterdam oesophageal tumour study group. Scand J Gastroenterol Suppl 1998; 225: 75-84.
17 Low DE, Pagliero KM. Prospective randomised trial comparing brachytherapy and laser photoablation for palliation of oesophageal cancer. J Thorac Surg 1992; 104: 173-8.
18 Blazeby JM, Williams MH, Brookes ST, Alderson D, Farndon JR. Quality of life measurement in patients with oesophageal cancer. Gut 1995; 37: 505-8.
19 Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life in patients with oesophageal cancer. Cancer 2000; 88: 1781-7.
20 Stahl M, Wilke H, Meyer HJ et al. 5-Fluoro-uracil, folinic acid, etoposide, and cisplatin chemotherapy for locally advanced or metastatic carcinoma of the oesophagus. Eur J Canc 1994; 30A: 325-8.
21 Stahl M, Wilke H, Fink U et al. Combined preoperative chemotherapy and radiotherapy in patients with locally advanced oesophageal cancer. Interim analysis of a phase II trial. J Clin Oncol 1996; 14: 829-37.
22 Ajani JA, Roth JA, Ryan B et al. Evaluation of pre-and postoperative chemotherapy for resectable adenocarcinoma of the oesophagus or gastro-oesophageal junction. J Clin Oncol 1990; 7: 1231-8.
23 Ohtsu A, Boku N, Muro K et al. Definitive chemoradiotherapy for T4 and or M1 lymph node squamous cell carcinoma of the oesophagus. J Clin Oncol 1999; 17: 2915-21.
24 Kelsen DP, Ginsberg R, Bains M et al. A phase II trial of paclitaxel and cisplatin in patients with locally advanced metastatic oesophageal cancer: a preliminary report. Semin Oncol 1997; 24: S19: 77-81.
25 Van der Gaast A, Kok TC, Kerkhofs L, Siersema PD, Tilanus HW, Splinter TA. Phase I study of a biweekly schedule of a fixed dose of cisplatin with increasing doses of paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 1999; 80: 1052-7.
26 Ilson DH, Saltz L, Enzinger P et al. Phase II trial of weekly irinotecan plus cisplatin in advanced oesophageal cancer. J Clin Oncol 1999; 17: 3270-5.

CHAPTER 3

PHASE I STUDY OF A WEEKLY SCHEDULE OF A FIXED DOSE OF CISPLATIN AND ESCALATING DOSES OF PACLITAXEL IN PATIENTS WITH ADVANCED OESOPHAGEAL CANCER

M.B. Polee[1], J. Verweij[1], P.D. Siersema[2], H.W. Tilanus[3], T.A.W. Splinter[1], G. Stoter[1] and A. van der Gaast[1].

Department of [1]Medical Oncology, [2]Gastroenterology and [3]Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands.

Eur J Cancer 2002 ; 38: 1495-500

Summary

Purpose: The objective of this study was to determine the toxicities and maximum tolerated dose (MTD) of a dose-dense schedule with a fixed dose of cisplatin and escalating doses of paclitaxel in patients with metastatic or irresectable squamous cell-, adeno-, or undifferentiated carcinoma of the oesophagus.

Patients and methods: Patients received paclitaxel over 3 hours followed by a 3-hour infusion of a fixed dose of cisplatin of 70 mg/m^2 on days 1, 8, 15, 29, 36 and 43. The starting dose of paclitaxel was 80 mg/m^2. Patients were retreated if white blood cell count (WBC) was $\geq 1x10^9$, except for day 29 when the WBC had to be $\geq 3 \times 10^9$. Six patients were treated at each dose level. The dose of paclitaxel was increased by 10 mg/m^2 per level.

Results: Of the 24 patients enrolled, 13 had adenocarcinoma, 10 had squamous cell carcinoma and one had an undifferentiated carcinoma. All patients were evaluable for toxicity and 22 of 24 patients were evaluable for response. The paclitaxel dose could be escalated to 110 mg/m^2. At this dose 3 out of 6 patients developed dose limiting toxicity including neutropenic enterocolitis with sepsis, vomiting and diarrhoea. Diarrhoea grade 3 and 4 was seen in 4 (17%) patients. Two of these patients died of neutropenic enterocolitis. Neutropenia grade 3 or 4 was seen in 20 (83%) patients, but apart from the two patients with neutropenic enterocolitis no other infectious complications were seen. Mild to moderate sensory neurotoxicity was seen in 11 (46%) patients (grade 1 in 8 patients and grade 2 in 3 patients). Other toxicities were mild and easily manageable. Of the 22 evaluable patients, 11 (50%) patients achieved a partial or complete response with a median duration of 13 months. Ten patients with either locally advanced disease or supraclavicular or celiac lymph nodes received additional local treatment after response to chemotherapy, seven patients are still without evidence of disease after a median follow up of 32 months.

Conclusion: Paclitaxel at a dose 100 mg/m^2 infused over 3 hours followed by a 3 hour infusion of 70 mg/m^2 cisplatin can be recommended for further studies in patients with metastatic or unresectable oesophageal cancer. Occurring diarrhoea should be handled with caution because it may be a sign of neutropenic enterocolitis. The response rate of this dose-dense schedule seems encouraging.

Introduction

The majority of patients with squamous cell- or adenocarcinoma of the oesophagus either present with systemic disease or will relapse after prior surgery and the prognosis of these patients remains poor[1,2]. Response rates achieved with single agent chemotherapy are usually

modest, although with combination chemotherapy response rates of 35% in metastatic and 45-55% in locoregional disease can be obtained[3]. In most trials the reported median duration of response is short. Moreover the impact of chemotherapy on survival is unclear also because of a lack of randomised phase III studies of chemotherapy versus best supportive care.

Cisplatin is one of the most extensively studied drugs in oesophageal cancer yielding an overall response rate of 24%[4]. The combination of cisplatin and 5-fluorouracil, mainly studied as preoperative treatment, yielded response rates from 37-65%[5,6,7]. By some authors this combination is considered standard therapy, although this can be questioned based upon results of a small randomised study[6].

Paclitaxel is a new agent in the treatment of patients with oesophageal cancer. Ajani et al reported a response rate of 31% using paclitaxel 250 mg/m^2 every 3 weeks[8]. By adding cisplatin to paclitaxel response rates of 49%[9] and 52%[10] have been reported. The latter study involved a bi-weekly drug administration.

In vitro studies and clinical studies have suggested that a dose-response relationship for cisplatin may exist for solid tumours[11,12,13]. Therefore a further dose intensity increase might be attractive. Further shortening the interval between chemotherapy cycles is a possibility to increase this dose-intensity. Our group has previously demonstrated that single agent cisplatin at a dose of 80 mg/m^2/week was tolerated by most chemotherapy-naive patients[14,15]. Cisplatin at a dose of 70 mg/m^2/week could be combined with etoposide 50 mg administered orally on days 1-15 and 29-43[16]. Finally, in patients with ovarian cancer weekly cisplatin at a dose of 70 mg/m^2 could safely be combined with weekly paclitaxel at a dose of 90 mg/m^2 [17]. In the latter study there was no apparent difference in tolerance between pre-treated and non-pre-treated patients. The dose limiting toxicity was fatigue and the level of myelosuppression was remarkably low. The latter confirms the observation of minimal haematologic toxicity in studies using single agent weekly paclitaxel[18,19,20,21,22], in which schedule dose is limited by reversible neurotoxicity[21].

We now report the results of a dose finding study with a weekly schedule of a fixed dose of cisplatin and escalating doses of paclitaxel in patients with metastatic or unresectable cancer of the oesophagus or the oesophageal-gastric junction.

Patients and methods

Patient Selection

Eligibility included patients with metastatic or unresectable histologically proven squamous cell-, adeno-, or undifferentiated carcinoma of the oesophagus or oesophageal-gastric

junction area, a performance status (World Health Organisation) of 0-2, a life expectancy of more than 12 weeks, adequate haematological, renal and hepatic function defined as white blood cell count (WBC) ≥ 3 x 10^9/L, platelets ≥ 100 x 10^9/L, creatinine ≤ 120 mmol/L and total bilirubin ≤ 1.5 x upper normal limit. Patients with neurotoxicity > CTC grade 1 were not eligible. Prior radiation for primary or metastatic disease was allowed but not in the 4 weeks prior to study entry and not involving more than 30% of the bone marrow. Patients previously treated with chemotherapy were not eligible. The study was approved by the institutional ethics committee. All patients gave written informed consent.

Dose and Dose Escalation

Treatment consisted of weekly intravenous administrations of paclitaxel and cisplatin on days 1,8,15,29,36 and 43. Further treatment was left to the discretion of the treating physician. The cisplatin dose was fixed at 70 mg/m^2/administration and the starting dose of paclitaxel was 80 mg/m^2/administration. Six patients were to be treated at each dose-level. The paclitaxel dose was increased by 10 mg/m^2/administration per cohort. Treatment comprised of pre-hydration with one litre of normal saline administered over 3 hours followed by the calculated dose of paclitaxel diluted in 500 ml of normal saline infused over 3 hours. This was directly followed by the infusion of cisplatin diluted in 1000 ml of a mixture of 5% dextrose and 0,9% saline in 3 hours. This contrasted with our previous use of 250 ml of 3% saline. Post-hydration comprised the infusion of 3 litres normal saline with the addition of 20 mmol/L potassium chloride and 2 g/L magnesium sulphate over 24 hours. All patients were pre-medicated with dexamethason 20 mg orally 12 and 6 hours prior to paclitaxel treatment and clemastine 2 mg and ranitidine 50 mg intravenously 30 minutes before the paclitaxel infusion. Ondansetron 8 mg was administered intravenously before the cisplatin infusion and was repeated twice daily if necessary. Patients were retreated on days 8 and 15 provided the WBC was ≥ 1 x 10^9/L and platelets were ≥ 50 x 10^9/L, while prior to the start of the day 29 course the WBC had to be ≥ 3 x 10^9/L and platelets ≥ 100 x10^9/L. When these criteria were not met treatment was postponed for 1 week. If bone marrow recovery was insufficient after 1 week delay patients were taken off study.

Toxicity was graded using NCI-CTC criteria. Dose limiting toxicity (DLT) was defined as any of the following events occurring during the first 4 weeks of treatment: grade 3-4 leucocytopenia with infection or fever requiring parenteral antibiotics, grade 3-4 thrombocytopenia requiring 2 or more platelet transfusions, or resulting in ≥ grade 2 haemorrhage, or ≥ grade 3 non-haematologic toxicity with the exception of acute nausea and/or vomiting. Maximum tolerated dose (MTD) was defined as the dose level below the dose that induced DLT in three patients out of six during the first 4 weeks.

Treatment Assessment

Before therapy, a complete medical history was obtained and a physical examination was performed. A complete blood cell count (including WBC and differential counts) and serum

biochemistry (including sodium, potassium, calcium, phosphorus, urea, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT and gamma-glutamyltransferase) were assessed. Weekly evaluations included history, physical examination, toxicity assessment, complete blood cell counts and serum chemistry studies. Tumour evaluation was performed after 6 administrations by a CT-scan of the chest and upper abdomen. Patients with the primary tumour in situ were also evaluated by endoscopy. Response was assessed using World Health Organisation criteria for response[23]. Duration of response was calculated from the start of treatment.

Results

Twenty-four patients entered the study. All patients were eligible and all were evaluable for toxicity. Patient characteristics are listed in *Table 1 (see page 28)*. Nineteen (79%) patients received all scheduled six drug administrations.

The paclitaxel dose was increased from 80-110 mg/m^2. At the latter dose level one patient developed neutropenic enterocolitis and sepsis after the third administration of cisplatin and paclitaxel, and died despite intensive treatment. In addition, two other patients had dose-limiting vomiting and diarrhoea respectively. Because of this, this dose level could be classified as DLT. Cisplatin at a dose of 70 mg/m^2 with paclitaxel 100 mg/m^2 for each administration was therefore considered to be the maximum tolerated dose. In addition, the achieved dose intensity at this dose level was higher than with paclitaxel scheduled at 110 mg/m^2. The median dose intensity at the paclitaxel dose level of 100 mg/m^2 was 52 mg/m^2/week for cisplatin and 86 mg/m^2/week for paclitaxel versus, 46 mg/m^2/week and 85 mg/m^2/week, respectively, at the paclitaxel dose level of 110 mg/m^2.

A total of 134 cisplatin/paclitaxel administrations were given with a median number of 6 (range 2-6). Nine (6,7 %) administrations were delayed for a maximum of one week in 7 (29%) patients. Three administrations (administration numbers 4,4 and 5 respectively) had to be delayed due to unresolved leucocytopenia. Five patients had a treatment delay because of incomplete recovery of mostly gastrointestinal toxicity of the preceding administration. The other delay was related to required intercurrent other treatment. Treatment delays were seen at paclitaxel doses of 80 mg/m^2 (2 patients), 90 mg/m^2 (4 patients) and 110 mg/m^2 (3 patients).

Toxicity

Haematological toxicity could be assessed in 133 of the 134 cisplatin/paclitaxel administrations. Neutrocytopenia and thrombocytopenia did not appear to be related to paclitaxel dose (*Table 2, see page 29*). Neutrocytopenia mainly occurred one week after the last drug administration, while mild to moderate thrombocytopenia was only observed after the fifth

Table 1. ***Patient characteristics***

Characteristic		No. of patients	%
Total patients		24	
Sex	female	8	33
	male	16	67
Age,	years		
	median	55	
	range	30-71	
Performance status (Karnofsky)			
70%		5	21
80%		6	25
90%		8	33
100%		5	21
Histology			
adenocarcinoma		13	54
squamous cell carcinoma		10	42
undifferentiated carcinoma		1	4
Extent of disease			
locally advanced / unresectable		2	8
primary with distant metastases		15	63
metastases after primary resection		7	29
Metastatic sites			
supraclavicular lymph nodes		7	29
celiac lymph nodes		13	54
liver		6	25
retroperitoneum		4	17
other		6	25

and sixth administration. Haematological growth factors were not used. Grade 2 anaemia was seen in 11 patients and 3 patients received red blood cell transfusions.

Diarrhoea was a frequent finding and was dose limiting in 4 patients (*Table 3*). Unfortunately 2 of them died due to neutrocytopenic enterocolitis, 1 after completion of the full treatment at the paclitaxel dose of 90 mg/m^2, and 1 after the third administration of paclitaxel at the dose of 110 mg/m^2. The latter patient experienced a grade 2 diarrhoea after the second administration and he was prophylactically treated with loperamide after the third administration of chemotherapy. The other 3 patients with a grade 3 or 4 diarrhoea did not report a previous episode of diarrhoea. Apart from the sepsis coinciding enterocolitis in 2 patients, no other infectious complications were observed.

*Table 2. **Haematological toxicity, worst CTC grade per patient***

Paclitaxel Dose level	Nr of pts	Neutropenia Grade					Thrombocytopenia Grade				
		0	1	2	3	4	0	1	2	3	4
80 mg/m²	6	-	1	-	2	3	5	1	-	-	-
90 mg/m²	6	-	-	1	3	2	4	1	1	-	-
100 mg/m²	6	1	1	-	2	2	3	1	1	1	-
110 mg/m²	6	-	-	-	2	4	5	1	-	-	-

*Table 3. **Non-haematological toxicity, worst CTC grade per patient***

Paclitaxel Dose level	Nr of pts	Nausea Grade					Vomiting Grade					Diarrhoea Grade					Neurotoxicity Grade				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
80 mg/m²	6	1	1	3	1	-	1	2	3	-	-	2	3	1	-	-	4	1	1	-	-
90 mg/m²	6	-	1	5	-	-	-	3	-	2	1	2	2	1	-	1	3	3	-	-	-
100 mg/m²	6	1	1	4	-	-	1	1	4	-	-	1	3	1	-	1	3	2	1	-	-
110 mg/m²	6	-	2	2	2	-	1	2	1	1	1	4	-	-	1	1	3	2	1	-	-

Mild to moderate neurotoxicity, mostly characterised by paraesthesias and sensory loss, was seen in 11 patients (46%), and did not appear to be dose related. Only 5 patients with sensory neurotoxicity had a follow-up of more than 6 months, the neurotoxicity was reversible in 1 of these 5 patients. Two patients had reversible tinnitus. Three patients reported short lasting and reversible myalgia/arthralgia grade 1 and 6 reported grade 2. Three of the latter patients were treated at the highest paclitaxel dose level. Renal toxicity grade 1 was seen in 3 patients treated at paclitaxel dose levels of 80, 90 and 100 mg/m² respectively, being reversible in 2 of 3. Alopecia was seen in all patients who completed at least 3 administrations.

Response and Survival

Twenty-two of the 24 entered patients were evaluable for response. Two patients (9%) achieved a complete response. Both patients are still disease-free after a follow up of 32 and 27 months, respectively. Nine patients (41%) achieved a partial response with a median duration of 10 months (range 2-34+ months). Ten of 11 responding patients had bidimensionally measurable lesions and one patient had unidimensionally evaluable disease. All other 11 (50%) patients had stable disease with a median duration of 6 months (range 4- 34 months). Five patients underwent an oesophageal resection after response to chemotherapy and five patients received radiotherapy (50 Gy) on the primary tumour and/or supraclavicular or celiac lymph nodes. Of the 10 patients who received additional treatment 7 patients are alive and

disease-free (median follow up: 32 months). The overall response rate for patients with adenocarcinomas was 58% and for patients with squamous cell carcinomas 33%. The median survival for all 24 patients was 16 months (range 2-34+ months) with an 1 year survival of 58 %.

Discussion

Most patients who are diagnosed with oesophageal cancer will die of their disease. In addition, more than half of these patients have locally advanced or metastatic disease at first presentation and their median survival is only between 4 and 8 months. Conventional chemotherapy may offer these patients a chance of tumour regression and palliation of symptoms but in most cases only for a limited period of time. The efficacy of chemotherapy might potentially be improved by decreasing the time interval between consecutive treatments. Theoretically, such dose-dense schedules yield a more continuous exposure to cytotoxic agents and may herewith permanently impair growth-promoting intracellular signalling and DNA repair[24].

Our group has extensive experience with weekly scheduling of cisplatin, with or without the addition of oral etoposide[14,15,16,25]. However, paclitaxel may be a more attractive agent to combine with cisplatin in this respect. Frasci et al. treated 30 chemotherapy-naive patients with advanced solid tumours with a weekly schedule of escalating doses of cisplatin and paclitaxel[26]. The MTD found in this study was cisplatin 30 mg/m²/week in combination with paclitaxel 65 mg/m²/week. When G-CSF support was given the cisplatin dose could be increased to 40 mg/m²/week and the paclitaxel dose to 85 mg/m²/week. The encountered dose limiting toxicity consisted of neutropenia, conservatively defined as grade > 1 neutropenia on the day of retreatment. In a subsequent phase II study with the latter regimen, 43 women with advanced breast cancer were treated, and the observed toxicity was moderate and consisted predominantly of haematological and neurological toxicity especially in pre-treated patients[27]. Van de Burg et al. treated 24 patients with advanced ovarian cancer, mostly pre-treated, with cisplatin 70 mg/m²/week on days 1, 8, 15, 29, 36 and 43 and escalating doses of paclitaxel[17]. At paclitaxel 100 mg/m²/week the dose limiting toxicity consisted of fatigue. Neutropenia grade 3-4 was only seen in 19% of treatment cycles but no infectious complications occurred.

In the present study using a fixed dose of cisplatin of 70 mg/m² and escalating doses of paclitaxel administered on days 1, 8, 15, 29, 36 and 43, we encountered dose limiting toxicity at the paclitaxel dose of 110 mg/m². DLT was gastro-intestinal.

The difference in MTD between our current study and the study by Frasci et al. could be explained by their use of more restrictive haematological criteria. Furthermore we treated our patients for 3 weeks out of 4 weeks while Frasci et al. treated their patients for 6 consecutive

weeks followed by a two week break. The MTD reported by van der Burg et al. is also slightly lower compared to the current study but in that study more than half of the patients had previously received chemotherapy.

The frequency of diarrhoea in the current study was high, and sharply contrasts to other reports. Fifteen patients (63%) reported diarrhoea after one or more administrations, and 3 patients had grade 4 diarrhoea. Diarrhoea was not at all reported in the other phase 1 studies with the weekly combination of cisplatin and paclitaxel[26,27,17]. In patients treated with cisplatin 70 mg/m^2 weekly as a single agent the incidence of diarrhoea was 13% but mostly grade 1[25]. Severe diarrhoea is also uncommon in patients treated with weekly paclitaxel at doses up to 200 mg/m^2/week[19,20]. Gordon et al. treated patients with advanced ovarian cancer with a fixed dose of cisplatin and escalating doses of paclitaxel repeated every 3 weeks and in that study diarrhoea became the dose-limiting toxicity at a paclitaxel dose level of 275 mg/m^2 [28]. So the difference between our study and the one of Frasci in this respect may be explained by the difference in dose-intensity. The difference with the study of Van der Burg is more difficult to explain. Apart from a difference in patient population, in that study cisplatin was administered using hypertonic saline, while in the current study this was substituted for dextrose-saline. If and how this could explain for the difference in diarrhoea frequency remains to be elucidated.

Obviously the 2 cases of neutropenic enterocolitis could cause concern. Neutropenic enterocolitis is a necrotising inflammation of the colon, known to occur in patients treated with intensive chemotherapy schedules[29]. It is usually characterised by fever, abdominal pain, diarrhoea and localised tenderness to the right lower abdominal quadrant in combination with severe neutropenia[30]. The cause is probably a direct cytotoxic effect on mucosa whereas neutropenia itself is a contributing factor since neutropenic enterocolitis can also occur in patients with neutropenia unrelated to chemotherapy[31,32]. Taxane-based chemotherapy is known to be related to the occurrence of neutropenic enterocolitis[33,34], but it remains a relatively infrequent side effect. Since neutropenic enterocolitis was not seen at all in previous studies with weekly administrations of cisplatin and or paclitaxel, and 1 of the 2 cases observed in our study occurred at a dose intensity explored by others as well, it is quite possible that these 2 cases are incidental observations. Nevertheless, until experience has been expanded, caution is warranted. The other toxicities observed in this study were usually mild. There were no other infectious complications.

An overall response rate of 50% and a median response duration of 10 months seems to compare favourable to those reported in other studies on advanced oesophageal cancer. Since this regimen is active and can be administered over a short period of time it can be used as induction treatment as part of multi-modality treatment. Of interest, 10 of our patients initially had irresectable disease or lymph node metastases confined to the celiac or

supraclavicular region. They received subsequent local treatment and 7 of them are still alive and disease-free after a median follow up of 32 months.

In conclusion, cisplatin 70 mg/m² in combination with paclitaxel 100 mg/m² administered on days 1, 8, 15, 29, 36 and 43 is the recommended dose for untreated patients with advanced oesophageal cancer. Further evaluation of this regimen as induction treatment for resectable or locoregionally advanced oesophageal cancer and other tumour types is warranted.

References

1 Muller JM, Erasmi H, Stelzner M et al. Surgical therapy of oesophageal carcinoma. Br J Surg 1990; 77: 845-57.

2 Millikan KW, Silverstein J, Hart V et al. A 15-year review of oesophagectomy for carcinoma of the oesophagus and cardia. Arch Surg 1995; 130: 617-24.

3 Kok TC. Chemotherapy in oesophageal cancer: a review. Cancer treatment reviews 1997; 23: 65-85.

4 Ajani JA. Contributions of chemotherapy in the treatment of carcinoma of the oesophagus: results and commentary. Semin Oncol 1994a; 21: 474-82.

5 Hilgenberg D, Carey RW, Wilkins EW et al. Preoperative chemotherapy, surgical resection, and selective postoperative therapy for squamous cell carcinoma of the oesophagus. Ann Thorac Surg 1988; 45: 357-63.

6 Bleiberg H, Conroy T, Paillot B et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 1997; 33: 1216-20.

7 Ajani JA, Ryan B, Rich TA et al. Prolonged chemotherapy for localised squamous carcinoma of the oesophagus. Eur J Cancer 1992; 28A: 880-4.

8 Ajani JA, Ilson DH, Daugherty K et al. Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the oesophagus. J Natl Cancer Inst 1994; 86: 1086-91.

9 Kelsen DP, Ginsberg R, Bains M et al. A phase II trial of paclitaxel and cisplatin in patients with locally advanced metastatic oesophageal cancer: a preliminary report. Semin Oncol 1997; 24, S19: 77-81.

10 Van der Gaast A, Kok TC, Kerkhofs L et al. Phase I study of a biweekly schedule of a fixed dose of cisplatin with increasing doses of paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 1999; 80: 1052-7.

11 Perez RP, Hamilton TC, Ozols RF. Resistance to alkylating agents and cisplatin insights from ovarian carcinoma systems. Pharmacol Ther 1990; 48: 19-27.

12 Ozols RF, Ostchega Y, Myers CE et al. High-dose cisplatin in hypertonic saline in refractory ovarian cancer. J Clin Oncol 1985; 3: 1246-50.

13 Kaye SB, Lewis CR, Paul J et al. Randomised study of two doses of cisplatin with cyclofosfamide in epithelial ovarian cancer. Lancet 1992; 340: 329-33.

14 Planting AST, Van der Burg MEL, De Boer-Dennert M et al. Phase I/II study of a short course of weekly cisplatin in patients with advanced solid tumours. Br J Cancer 1993; 68: 789-92.

15 Planting AST, de Mulder PHM, De Graeff A et al. Phase II study of weekly high-dose cisplatin for six cycles in patients with locally advanced squamous cell carcinoma of the head and neck. Eur J Cancer 1997; 33: 61-5.

16 Planting AST, Van der Burg MEL, De Boer-Dennert M et al. Phase I study of weekly high dose cisplatin combined with long term oral etoposide in advanced solid tumours. Ann Oncol 1994; 6: 190-2.

17 Van der Burg MEL, De Wit R, Stoter G et al. Phase I study of weekly cisplatin (P) and weekly or 4-weekly Taxol(T): a highly active regimen in advanced epithelial ovarian cancer (OC). Proc Amer Soc Clin Oncol 1998; 17: 355a.
18 Loffler TM, Freund W, Lipke J et al. Schedule- and dose-intensified paclitaxel as weekly 1-hour infusion in pre-treated solid tumours: results of a phase I/II trial. Semin Oncol 1996; 23, S16: 32-4.
19 Akerley W, Choy H, Safran H et al. Weekly paclitaxel in patients with advanced lung cancer: preliminary data from a phase II trial. Semin Oncol 1997; 24, S12: 10-3.
20 Akerley W, Glantz M, Choy H et al. Phase I trial of weekly paclitaxel in advanced lung cancer. J Clin Oncol 1998; 16: 153-8.
21 Fennely D, Aghajanian C, Shapiro F et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 1997; 15: 187-92.
22 Hainsworth JD, Greco FA. Paclitaxel administered by 1-hour infusion. Cancer 1994; 74: 1377-82.
23 World Health Organisation. WHO handbook for reporting results of cancer treatment. WHO Offset Publ. No.4. Geneva: World Health Organisation, 1979.
24 Norton L. Kinetic concepts in the systemic drug therapy of breast cancer. Semin Oncol 1999; 26, S2: 11-20.
25 Planting AST, Catimel G, De Mulder PHM et al. Randomised study of a short course of weekly cisplatin with or without amifostine in advanced head and neck cancer. Ann Oncol 1999; 10: 693-700.
26 Frasci G, Comella P, Parziale A et al. Cisplatin-paclitaxel weekly schedule in advanced solid tumours: a phase I study. Ann Oncol 1997; 8: 291-3.
27 Frasci G, Comella P, D'Aiuto G et al. Weekly paclitaxel-cisplatin administration with G-CSF support in advanced breast cancer. A phase II study. Breast Cancer Res Treat 1998; 49: 13-26.
28 Gordon AN, Stringer CA, Matthews CM et al. Phase I dose escalation of paclitaxel in patients with advanced ovarian cancer receiving cisplatin: rapid development of neurotoxicity is dose-limiting. J Clin Oncol 1997; 15: 1965-73.
29 Song HK, Kreisel D, Canter R et al. Changing presentation and management of neutropenic enterocolitis. Arch Surg 1998; 133: 979-82.
30 Gomez L, Martino R, Rolston KV. Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. Clin Inf Dis 1998; 27: 695-9.
31 Rifkin G. Neutropenic enterocolitis and Clostridium septicum infection in patients with agranulocytosis. Arch Intern Med 1980; 140: 834-5.
32 Hopkins G, Kushner JP. Clostridial species in the pathogenesis of necrotising enterocolitis in patients with neutropenia. Am J Hematol 1983; 14: 289-95.
33 Ibrahim NK, Sahin AA, Dubrow RA et al. Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. Lancet 2000; 355: 281-3.
34 Kouroussis C, Samonis G, Androulakis N et al. Successful conservative treatment of neutropenic enterocolitis complicating taxane-based chemotherapy: a report of five cases. Am J Clin Oncol 2000; 23: 309-13.

CHAPTER 4

PHASE II STUDY OF BIWEEKLY ADMINISTRATION OF PACLITAXEL AND CISPLATIN IN PATIENTS WITH ADVANCED OESOPHAGEAL CANCER

M.B. Polee[1], F.A.L.M. Eskens[1], M.E.L. van der Burg[1], T.A.W. Splinter[1], P.D. Siersema[2], H.W. Tilanus[3], J. Verweij[1], G. Stoter[1] and A. van der Gaast[1].

Department of [1]Medical Oncology, [2]Gastroenterology and [3]Surgery, Erasmus Medical Centre, Rotterdam, The Netherlands.

Br J Cancer 2002; 86: 669-73

Summary

Background: In a phase I study we demonstrated the feasibility of a biweekly combination of paclitaxel 180 mg/m^2 with cisplatin 60 mg/m^2. In this study we further assessed toxicity and efficacy of this schedule in the treatment of advanced cancer of the oesophagus or the gastro-oesophageal junction.

Methods: Patients received paclitaxel 180 mg/m^2 administered over 3 hours followed by a 3-hour infusion of cisplatin 60 mg/m^2. Patients were retreated every 2 weeks unless granulocytes were < 0,75x10^9 or platelets <75 x10^9. Patients were evaluated after 3 and 6 cycles and responding patients received a maximum of 8 cycles.

Results: 51 patients were enrolled into the study. The median age was 56 years (range 32-78). WHO performance status were: 0 (19 patients); 1 (29 patients); 2 (3 patients). All patients received at least 3 cycles of chemotherapy and all were evaluable for toxicity and response. Haematological toxicity consisted of uncomplicated neutropenia grade 3 in 39% and grade 4 in 31 % of patients. Five patients (10%) were hospitalised, 3 patients because of treatment related complications and 2 patients because of infections without neutropenia. Sensory neurotoxicity was the predominant non-haematological toxicity; grade 1 and 2 neurotoxicity was observed in 43% and 20 % of patients, respectively. Response evaluation in 51 patients with measurable disease: complete response 4%, partial response 39%, stable disease 43% and progressive disease in 14% of the patients. The median duration of response was 8 months. The median survival for all patients was 9 (range 2-29+) months and the one-year survival rate was 43%. Four patients who received additional local treatment (2 patients surgery and 2 patients radiotherapy) are still disease free after a follow up of 20-29 months.

Conclusion: This bi-weekly treatment of paclitaxel and cisplatin is well tolerated by patients with advanced oesophageal cancer. The toxicity profile of this regimen compares favourable to that of previously used cisplatin-, and paclitaxel-based regimens. Trials are underway evaluating this biweekly regimen in a neo-adjuvant setting.

Introduction

The incidence of oesophageal cancer is rising in the United States and most Northern European countries, especially due to a rapid increase in the incidence of adenocarcinomas of the distal oesophagus or the gastro-oesophageal junction[1]. Although adenocarcinomas are known to be related to symptoms of gastric reflux[2] and to specialised columnar (Barrett's) epithelia[3] it is questionable whether this totally accounts for the rising incidence.

Many patients who present with symptoms of oesophageal obstruction already have locally advanced or metastatic disease. After surgery the 5-year survival is 20% and the majority of patients relapse both locoregionally as well as at distant sites[4]. Multimodality treatment plays an increasingly important role in the treatment of oesophageal cancer. Chemotherapy with concurrent radiotherapy has been shown to be superior to radiotherapy alone in patients with locoregional disease[5]. However, pre-operative treatment with chemotherapy remains still investigational because a number of randomised studies have provided conflicting results[6,7,8]. Chemotherapy can also be given for palliation of symptoms and improvement of quality of life in patients with metastatic disease[9,10].

Combination chemotherapy with cisplatin and 5-fluorouracil and /or etoposide or with bleomycin and vindesine has predominantly been used in patients with squamous cell carcinoma[11,12,13], yielding response rates of 45-75% in patients with locoregional disease and 25-35% in patients[14].

Single agent paclitaxel has been tested in squamous cell and adenocarcinomas of the oesophagus. Ajani et al. reported a response rate of 31% after treatment with paclitaxel 250 mg/m^2 administered every 3 weeks in combination with granulocyte colony-stimulating factor support[15]. In combination with cisplatin, also in a 3-week schedule, Kelsen et al. reported a response rate of 49% for patients with either locoregional or metastatic oesophageal cancer[16].

We previously performed a dose finding study with a fixed cisplatin dose (60 mg/m^2) and increasing doses of paclitaxel given every 2 weeks in patients with advanced oesophageal cancer[17]. The paclitaxel dose could be increased to 200 mg/m^2 without encountering dose limiting haematological toxicity. However sensory neurotoxicity was dose limiting at paclitaxel dose levels ≥ 190 mg/m^2. The recommended dose for further studies was paclitaxel 180 mg/m^2 in combination with cisplatin 60 mg/m^2. In view of the response rate of 52% observed in this dose finding study we performed a phase II study to further confirm the safety and activity of this biweekly regimen.

Patients and methods

Patients

Patients with histologically proven metastatic or unresectable adenocarcinoma, undifferentiated or squamous cell carcinoma of the oesophagus or gastro-oesophageal junction area were eligible for the study. Further eligibility requirements were: a life expectancy of more than 12 weeks; age ≥ 18 years; WHO performance status 0-2; written informed consent; adequate haematological, renal and hepatic functions defined as: granulocytes ≥ 1.5 x 10^9 /L, platelets ≥ 100 x 10^9/L, total bilirubin ≤ 1.5 x upper normal limit and creatinine ≤ 120 mmol/L. Patients

were required to have measurable or evaluable disease. Prior radiotherapy was allowed if not involving more than 30% of the bone marrow or was given within the 4 weeks prior to study entry. The study was approved by the institutional ethics committee.

Drug administration

Paclitaxel 180 mg/m^2 and cisplatin 60 mg/m^2 were administered intravenously (i.v.) every 2 weeks. After prehydration with at least one litre of normal saline, paclitaxel, diluted in 500 ml of normal saline, was infused over 3 hours and subsequently cisplatin was administered over 3 hours followed by post-hydration over 24 hours. All patients received premedication with dexamethasone 20 mg given orally 12 and 6 hours prior to the paclitaxel infusion. Thirty minutes before the paclitaxel infusion, the patients received 10 mg dexamethasone, 2 mg clemastine and 50 mg ranitidine, all given i.v. Ondansetron at a dose of 8 mg i.v. was given as anti-emetic prophylaxis. Patients were retreated after 14 days when the granulocytes were $\geq 0.75 \times 10^9$/L and the platelets were $\geq 75 \times 10^9$/L. When these criteria were not met, treatment was postponed for 1 week. A dose reduction was only made for patients with neutropenic fever; in that case paclitaxel was reduced to 75% in subsequent courses.

Treatment assessment

Pre-treatment evaluations consisted of a complete medical history, physical examination, complete blood cell count and serum biochemistry, computerised tomography (CT) scan of the chest and upper abdomen and ultrasonography of the supraclavicular nodes when appropriate. Patients with the primary tumour in situ were also evaluated by endoscopy. During treatment blood cell counts were assessed every week and physical examination, toxicity assessment and serum chemistry studies every 2 weeks. Toxicity was graded and reported using NCI-CTC criteria (version 2). For response evaluation the CT-scan, and also a ultrasonography and endoscopy when appropriate, were repeated after the third and sixth cycle and after discontinuation of therapy. Response was evaluated using WHO criteria[18] (WHO, 1979). A complete response (CR) required the disappearance of all known disease, determined by 2 observations not less than 4 weeks apart, and for patients with the primary tumour in place an endoscopic confirmation of a complete response with normal endoscopic biopsies. A partial response was defined as a decrease by at least 50% reduction in the sum of the products of the largest perpendicular diameters in all measurable lesions or at least a 30% reduction of the largest diameters in unidimensional disease (evaluable disease) for at least 4 weeks. It is not necessary for all lesions to have regressed to qualify for partial response, but no lesion should have progressed and no new lesion should appear. Stable disease was defined as less than 50% decrease and less than 25 % increase in tumour size. Progressive disease was a greater than 25% increase of one or more measurable lesions or the development of new lesions. The duration of response was defined as lasting from the start of treatment to documentation of the disease progression. Patients with stable disease received up to a maximum of 6 cycles of treatment. In patients achieving a partial or

complete response, an additional 2 cycles were allowed. Patients were followed for survival and disease progression every 3 months until death.

Statistical considerations

Patient enrolment followed a five-step sequential design. If no response was seen in the first 8 patients further accrual had to be halted. Otherwise an additional 6 patients could be entered and if at least 2 patients responded again 6 patients had to be entered. In the fourth step 10 more patients were entered if at least 4 responses were observed in the 20 patients that were treated. Finally when 30 patients were treated the trial was continued with an additional 20 patients if the observed number of responses was at least 50%. Under this design there is only an 18% chance of continuing the trial while the true response percentage is below 40%. Actuarial survival was calculated using the method of Kaplan and Meier.

Results

Fifty-one patients were entered in this study. Patient characteristics are listed in *Table 1 (see page 40)*. All patients received at least 3 cycles of chemotherapy and all were evaluable for toxicity and response. A total of 286 cycles were administered (median 6, range 3-8). Nine patients received only 3 cycles. Three of these 9 patients had progressive disease and in 5 patients with stable disease who had persistent dysphagia treatment was stopped and these patients were palliated by oesophageal stenting. One patient refused further treatment. Five of the remaining 42 patients did not complete 6 cycles of therapy. Two patients were not able to continue treatment after 4 cycles for reasons of toxicity mainly consisting of fatigue, one patient developed a cerebrovascular accident and 2 patients had progressive disease after the fourth and fifth cycle, respectively. Seven patients who had achieved a partial response received 8 cycles of treatment.

Seventy-one chemotherapy cycles (25%) were delayed. In 19 (37%) patients there was no treatment delay; one, two or more delays were required in respectively 7 (14%), 11 (22%) and 14 (27%) patients. Sixty-five cycles in 25 (49%) patients were delayed for 1 week because of a granulocyte count $<0.75 \times 10^9$/L. Four cycles were delayed for 1 week because of infections without neutropenia, one cycle was delayed for 1 week because of elevated liver-enzymes due to co-medication and 1 cycle was delayed for 3 weeks in a patient who developed a broncho-oesophageal fistula 4 days after the start of chemotherapy. The planned and achieved dose intensity were for cisplatin 30 mg/m²/week and 26 mg/m²/week, respectively, and for paclitaxel 90 mg/m²/week and 79 mg/m²/week, respectively.

Haematological toxicity

Neutropenia grade 3 and 4 were observed in 39% and 31 % of patients and in 23% and 10% of cycles, respectively. The nadir for granulocytes usually occurred after the fourth or fifth

Table 1. Patient characteristics (n=51)

Characteristic	No. of patients	(%)
Sex		
Male	37	73
Female	14	27
Age (years)		
Median	56	
Range	32-78	
WHO performance status		
0	19	37
1	29	57
2	3	6
Weight loss (%)		
0-5	13	25
5-10	15	29
>10	23	45
Histology		
Adenocarcinoma	31	61
Squamous cell carcinoma	16	31
Undifferentiated carcinoma	4	8
Prior therapy		
Oesophagectomy	11	22
Radiotherapy	0	0
Extent of disease		
Locally advanced/unresectable	5	10
Primary with distant metastases	35	69
Metastases after prior resection	11	22
Metastatic sites		
Celiac/supraclavicular lymph nodes	38	75
Liver	13	25
Other	3	6

cycle of treatment. Neutropenic infections were not observed. No thrombocytopenia was seen. Red cell transfusions were administered in 7 patients.

Grade 1 sensory neurotoxicity was observed in 22 patients (43%) and grade 2 in 10 patients (20%). Six of these in total 32 patients had a complete resolution of sensory neurotoxicity and in 11 patients neurotoxicity partially subsided. Five patients developed infections without neutropenia. Three of these patients were admitted because of a pneumonia, an urinary tract

infection and an infected subcutaneously implanted intravenous access device, respectively. All patients recovered after treatment with antibiotics. Two patients were admitted for gastro-intestinal toxicity. In total 5 patients (10%) were hospitalised, 3 patients because of treatment-related complications and 2 patients because of infections without neutropenia. There were no treatment-related deaths. Other toxicities were usually mild and are listed in *Table 2*.

Table 2. ***Worst CTC grade non-haematological toxicities (n = 51)***

	CTC grade				
	0	1	2	3	4
	(%)	(%)	(%)	(%)	(%)
Nausea	25	49	24	2	
Vomiting	51	25	18	4	2
Diarrhoea	86	12	2		
Mucositis	92	6	2		
Neurotoxicity	37	43	20		
Nephrotoxicity	96	4			
Myalgia	65	33	2		
Fatigue	60	20	20		

Responses and survival

All 51 patient had measurable disease. The overall response rate was 43%; 20 patients (39%) had a PR and two patients (4%) had a CR. Stable disease was observed in 21 patients (41%) and PD in 8 patients (16%). Twenty-one of 22 responding patients had bidimensionally measurable lesions and one patient had unidimensionally evaluable disease. In 15 of 22 responding patients the response was already documented after 3 courses of chemotherapy. The duration of complete response was 7 months in a patient with a local recurrence and lymph node metastases. The second patient who had a complete response received additional radiotherapy on the primary tumour and supraclavicular region and is still disease free 29 months after start of treatment. The median duration of response (measured from start of treatment) in the patients with a PR was 8 months (range 5-29+ months). Twenty-one patients (41%) had stable disease with a median duration of 6.5 months. After a response to chemotherapy definitive local therapy using either radiotherapy or surgery was attempted in 9 patients with either locally advanced disease or lymph node metastases confined to the celiac or supraclavicular region (M1a disease). Two patients with an irresectable tumour underwent an oesophageal resection, pathologic examination of the resected specimen showed tumour free margins and these patients are disease free 20 and 28 months, respectively, after surgery. Seven patients with M1a disease received radiotherapy at a dose of 50 Gy at the primary tumour and involved lymph nodes; two of these patients are disease

free after 24 and 29 months, respectively. The overall response rates for patients with adenocarcinoma, and squamous cell carcinoma were 39% and 44 %, respectively, and 3 of the 4 patients with an undifferentiated carcinoma achieved an objective response.

After a median follow up of 32 months (range 1-32 months) 12 patients (24%) are still alive. The median actuarial survival in all patients was 9 months (range 2-29+ months), with an 1-year survival rate of 43%. The median actuarial survival for responding patients is 12 months (range 6-29+ months), compared to 7 months (range 2-31+ months) in non-responding patients.

Discussion

Chemotherapy either alone or in combination with radiotherapy is frequently used preoperatively in patients with resectable disease. For patients with irresectable and/or metastatic disease chemotherapy may offer a chance of both tumour regression and palliation of symptoms. The effect of chemotherapy on survival in this group of patients is unclear due to a lack of randomised phase III studies comparing chemotherapy to best supportive care.

The combination cisplatin and 5-fluorouracil is probably the most frequently used combination in the treatment of oesophageal cancer. Pre-operative treatment with this combination was tolerated well by patients with resectable disease in two large randomised trials[7,8]. However in one of the few randomised studies performed in patients with metastatic disease, the toxicity of this regimen appeared to be severe[11]. In that trial 88 patients with metastatic oesophageal cancer received either cisplatin in combination with 5-fluorouracil or cisplatin alone. In the cisplatin/5-fluorouracil arm there were 16% treatment related deaths, mostly due to neutropenic sepsis, versus 0% in the cisplatin arm. Because of this high incidence of treatment-related deaths the higher response rates observed in the cisplatin/5-fluorouracil arm most likely did not translate in a significant survival benefit compared to treatment with cisplatin alone. The difference in tolerability of chemotherapy between patients with resectable disease and patients with metastatic disease could be explained by the fact that patients with metastatic disease often have an impaired performance status, substantial weight loss and co-morbidity.

Recently, several new agents such as the taxanes, irinotecan and vinorelbine, have shown promising activity in the treatment of oesophageal cancer. A further advantage of these new agents is that they cause less mucosal toxicity compared to the combination of 5-fluorouracil and cisplatin with or without leucovorin.

In a previous study we demonstrated the feasibility of cisplatin and paclitaxel administered in a treatment interval of 2 weeks[17]. We were able to decrease the treatment interval because

we retreated the patients when their granulocytes were above 0.75 x 10^9/L in stead of the more common used treshold for retreatment of 1.5 x 10^9/L. The safety of this approach was confirmed in the current study. Despite the fact that 70% of patients developed grade 3 or 4 neutrocytopenia, we did not observe any episode of neutropenic fever. The achieved dose intensity was for cisplatin 26 mg/m²/week and for paclitaxel 79 mg/m²/week.

Given the fact that most patients had metastatic disease the treatment was well tolerated. Only 5 patients (10%) were hospitalised, 3 patients because of treatment-related complications and 2 patients because of infections without neutropenia. In general gastro-intestinal toxicity was mild and grade 2 mucositis was observed in only 2 patients. Sensory neurotoxicity was the predominant non-haematological side-effect: grade 1 and 2 occurred in, respectively, 43 % and 20% of patients. In 19% of patients with neurotoxicity we observed a complete resolution and in 34% a partial improvement of neurotoxicity. The neurotoxicity observed with our biweekly regimen is comparable to the neurotoxicity observed with regimens of cisplatin and paclitaxel administered every 3 weeks. This may be explained by the fact that neurotoxicity due to cisplatin is correlated with the cumulative cisplatin dose and not with the dose-intensity of cisplatin[19]. The median cumulative dose of cisplatin in our study was only 360 mg/m².

The combination of cisplatin and paclitaxel with or without 5-fluorouracil was tested in patients with oesophageal cancer in 3 other studies. Ilson et al.[20] (1998) treated 61 patients with the combination of paclitaxel 175 mg/m² administered over 3 hours on day 1, cisplatin 20 mg/m² days 1-5 and 5-fluorouracil 1000 mg/m² days 1-5; 48 % of the patients had to be admitted for reasons of toxicity. In a subsequent study 5-fluorouracil was omitted and paclitaxel 200-250 mg/m² was administered over 24 hours followed by cisplatin 75 mg/m² [21]. Cycles were repeated every 3 weeks and all patients received granulocyte colony stimulating factor support. The toxicty in this study was also considerable and 50% of the patients had to be hospitalised due to toxicity and 11 % of the patients died from treatment-related complications. In our study we used, expressed as administered dose per week, a comparable dose of paclitaxel and a higher dose of cisplatin but observed no severe toxicity. The fact that we administered paclitaxel over 3 hours instead of 24 hours might explain this difference[22]. Petrasch et al.[23] treated 24 patients with cisplatin 50 mg/m² and paclitaxel 90 mg/m² (3-hour infusion), also administered every 2 weeks. Using this, although compared to our study, lower dose of paclitaxel they also observed no major toxicities.

The response rate of 43% with a median duration of response of 8 months observed in our study is in line with the results reported in the other studies with cisplatin and paclitaxel however with substantial less toxicity. Of the 20 responding patients 4 patients, who received additional radiotherapy or surgery, are still disease free after a follow up of 20-29 months.
In most studies on neo-adjuvant chemotherapy in patients with oesophageal cancer response to chemotherapy is an important prognostic factor. The tolerability of this biweekly

regimen and the high response rate observed in this study renders it attractive for use in a neo-adjuvant setting. One of the reasons for the negative results of the Intergroup trial[7] comparing chemotherapy followed by surgery to surgery alone in 440 patients with resectable adenocarcinomas or squamous cell carcinomas, might be the low response rate of 19% obtained with the combination of cisplatin and 5-fluorouracil. Contrasting the negative results of the Intergroup study are the results of a recently reported Medical Research Council (MRC) trial[8] randomising 802 patients to 2 pre-operative cycles of cisplatin and 5-fluorouracil followed by surgery or surgery alone, as well as one of our own previous studies randomising 163 patients to preoperative treatment with cisplatin and etoposide followed by surgery or surgery alone[6]. In both studies survival was significantly better in patients receiving pre-operative chemotherapy. Chemotherapy before surgery is therefore still an option for patients with resectable oesophageal cancer. A randomised study investigating the efficacy of this biweekly cisplatin/paclitaxel regimen as a preoperative treatment would therefore be appropriate.

In conclusion, cisplatin and paclitaxel administered every 2 weeks is an active combination in the treatment of patients with advanced oesophageal cancer. The toxicity profile of this regimen compares favourable to that of previously used cisplatin-, and paclitaxel- based regimens. Trials are underway evaluating this biweekly regimen in a neo-adjuvant setting.

References

1 Blot WJ and McLaughlin JK. The changing epidemiology of oesophageal cancer. Semin Oncol 1999; 26 (S15): 2-8.

2 Lagergren J, Bergstrom R, Lindgren A, and Nyren O. Symptomatic gastro-oesophageal reflux as a risk factor for oesophageal adenocarcinoma. N Engl J Med 1999; 340:825-31.

3 Jankowski J, Wright NA, Meltzer S, Triadafilopoulos G, Geboes K, Casson AG, Kerr D, Young LS. Molecular evolution of the metaplasia dysplasia adenoma sequence in the oesophagus (MCS). Am J Pathol 1999; 154: 965-74.

4 Millikan KW, Silverstein J, Hart V, Blair K, Bines S, Roberts J, Doolas A. A 15-year review of oesophagectomy for carcinoma of the oesophagus and cardia. Arch Surg 1995; 130: 617-24.

5 Herskovic A, Martz K, Al-Sarraf M, Leichman L, Brinle J, Vaitkevicius V, Cooper J, Byhardt R, Davis L and Emami B. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the oesophagus. N Engl J Med 1992; 326: 1593-8.

6 Kok TC, van Lanschot J, Siersema PD, van Overhagen H, Tilanus HW. Neoadjuvant chemotherapy in operable squamous cell cancer: final report of a phase III multicenter randomised trial. Proc Am Soc Clin Oncol 1997; 17: 984.

7 Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, Estes N, Haller DG, Ajani J, Kocha W, Minsky BD, Roth, JA. Chemotherapy followed by surgery compared with surgery alone for localised oesophageal cancer. N Engl J Med 1998; 339: 1979-84.

8 Clark P.I. Medical research council randomised trial of surgery with or without pre-operative chemotherapy in resectable cancer of the oesophagus. Ann of Oncol 2000; 11, suppl 4: 20.

9 Spiridonidis CH, Laufman LR, Jones JJ, Gray DJ, Cho CC, Young DC. A phase II evaluation of high dose cisplatin and etoposide in patients with advanced oesophageal adenocarcinoma. Cancer 1996; 78: 2070-7.
10 Ilson DH, Saltz L, Enzinger P, Huang Y, Kornblith A, Gollub M, O'Reilly E, Schwartz G, De Groff J, Gonzalez G, Kelsen PD. Phase II trial of weekly Irinotecan plus cisplatin in advanced oesophageal cancer. J Clin Oncol 1999; 17: 3270-75.
11 Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jacob JH, Bedenne L, Namer M, DeBesi P, Gay F, Collette L and Sahmoud T. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 1997; 33: 1216-20.
12 Kok TC, Van der Gaast A, Dees J, Eijkenboom WMH, van Overhagen H, Stoter G, Tilanus HW, Splinter TAW. Cisplatin and etoposide in oesophageal cancer: a phase II study. Br J Cancer 1996; 74: 980-4.
13 Kelsen DP, Minsky B, Smith M, Beitler J, Niedzwiecki D, Chapman D, Bains M, Burt M, Heelan R, Hilaris B. Preoperative therapy for oesophageal cancer: a randomisised comparison of chemotherapy versus radiotherapy. J Clin Oncol 1990; 8: 1352-61.
14 Enzinger PC, Ilson DH, and Kelsen DP. Chemotherapy in oesophageal cancer. Semin Oncol 1999; 26: 12-20.
15 Ajani JA, Ilson DH, Daugherty K ,Pazdur R, Lynch PM, Kelsen DP. Activity of Taxol in patients with squamous cell carcinoma and adenocarcinoma of the oesophagus. J Natl Cancer Inst 1994; 86: 1086-91.
16 Kelsen DP, Ginsberg R, Bains M, Cooper J, Arquette M, Forastiere AA, Ilson D. A phase II trial of paclitaxel and cisplatin in patients with locally advanced metastatic oesophageal cancer: a preliminary report. Semin Oncol 1997; 24, S19: 77-81.
17 Van der Gaast A, Kok TC, Kerkhofs L, Siersema PD, Tilanus HW and Splinter TAW. Phase I study of a biweekly schedule of a fixed dose of cisplatin with increasing doses of paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 1999; 80:1052-7.
18 World Health Organisation. WHO handbook for reporting results of cancer treatment. WHO Offset Publ. No.4. Geneva: World Health Organisation, 1979.
19 Hilkens PHE, van der Burg MEL, Moll JWB, Planting AST, van Putten WLJ, Vecht ChJ and van den Bent MJ. Neurotoxicity is not enhanced by increased dose intensities of cisplatin administration. Eur J Canc 1995; 31A: 678-81.
20 Ilson DH, Ajani J, Bhalla K, Forastiere A, Huang Y, Patel P, Martin L, Donegan J, Pazdur R, Reed C, Kelsen DP. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the oesophagus. J Clin Oncol 1998; 16: 1826-34.
21 DH, Forastiere A, Arquette M, Costa F, Heelan R Huang Y, Kelsen DP. A Phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the oesophagus. Cancer J 2000; 6: 316-23.
22 Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, Gianni L, Myles J, Van der Burg ME, Kerr I, Vermorken JB, Buser K, Colombo N. European-Canadian randomised trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. J Clin Oncol 1994; 12: 2654-66.
23 Petrasch S, Welt A, Reinacher A, Graeven U, König M and Schmiegel W. Chemotherapy with cisplatin and paclitaxel in patients with locally advanced, recurrent or metastatic oesophageal cancer. Br J Cancer 1998; 78: 511-4.

CHAPTER 5

PHASE II STUDY OF NEO-ADJUVANT CHEMOTHERAPY WITH PACLITAXEL AND CISPLATIN GIVEN EVERY TWO WEEKS FOR PATIENTS WITH A RESECTABLE SQUAMOUS CELL CARCINOMA OF THE OESOPHAGUS

M.B. Polee[1], H.W. Tilanus[2], F.A.L.M. Eskens[1], R. Hoekstra[1], M.E.L. Van der Burg[1], P.D. Siersema[3], G. Stoter[1] and A. Van der Gaast[1]

Department of [1]Medical Oncology, [2]Surgery and [3]Gastroenterology and Hepatology, Erasmus Medical Centre, Rotterdam, The Netherlands

Ann Oncol 2003; 14: 1253-7

Summary

Background: We have previously reported a favourable response rate in patients with advanced oesophageal cancer after treatment with a biweekly regimen of paclitaxel and cisplatin. In this study we investigate the feasibility and efficacy of this regimen in a neo-adjuvant setting.

Patients and Methods: Patients with resectable squamous cell carcinoma of the oesophagus received paclitaxel 180 mg/m^2 and cisplatin 60 mg/m^2 every two weeks. Patients received 3 courses and responding patients received 3 additional courses, thereafter patients were referred for surgery. Patient characteristics of 50 eligible patients were: male 60%, median age 62 years (45-78), median WHO PS 1 (0-2).

Results: Ninety-four percent of patients received at least 3 courses of chemotherapy. Haematological toxicity consisted of CTC grade 3 or 4 neutropenia in 71% of patients, with neutropenic fever occurring in only 2 patients (4%). The overall response rate was 59%. Pathological examination showed tumour free margins in 38 patients. In 7 patients no residual tumour was found. The median overall survival was 20 months and the 1- and 3- year survival were 68 and 30%, respectively.

Conclusion: This dose-dense schedule of paclitaxel and cisplatin administered biweekly is well tolerated and the observed overall and complete response rates are promising.

Introduction

Patients who present with oesophageal cancer have a poor prognosis. Most patients thought to have resectable disease have already extension into the adventia or through the oesophageal wall and/or regional lymph node involvement at the time of diagnosis. The 5-year survival rate of these patients after a surgical resection is only 20%[1,2]. The pattern of failure includes both local recurrence as well as distant metastases.

A way to improve the prognosis of patients with resectable oesophageal cancer might be the incorporation of neo-adjuvant chemotherapy. The goals of neo-adjuvant chemotherapy are a reduction of recurrence from occult lymphatic and/or distant metastases with improvement of survival and possible tumourshrinkage with an increased resectability rate.

Most studies on neo-adjuvant chemotherapy have demonstrated that patients achieving an objective response have a significant better survival compared to non-responding patients[3]. Nevertheless overall survival remains poor and therefore development of chemotherapy

regimens, with high response rates, and which can be administered to patients with a moderate performance score has a high priority. Paclitaxel has been found to be an active agent in oesophageal cancer, either alone or in combination with cisplatin. Ilson et al. investigated conventional 3-week schedules of cisplatin and paclitaxel with or without 5-fluorouracil in patients with advanced oesophageal cancer[4,5]. The reported response rates were 48 and 44%, respectively. However, in both studies the observed toxicity was substantial, including hospitalisation due to gastrointestinal and haematological toxicity in half of the patients. In our centre we have obtained experience with the use of dose-dense chemotherapy regimens with cisplatin and paclitaxel. In a phase I study, we treated patients with advanced oesophageal cancer with a biweekly administration of cisplatin 60 mg/m^2 and escalating doses of paclitaxel (3-hour infusion)[6]. The recommended dose for paclitaxel was 180 mg/m^2, because at higher doses of paclitaxel sensory neuropathy became the dose limiting toxicity. In a subsequent phase II study, we confirmed the feasibility of this regimen and the observed response rates in these two studies were 52 and 43 %, respectively[6,7] . Both the high response rates and the excellent clinical tolerability of this biweekly regimen of cisplatin and paclitaxel urged us to test this regimen in a neo-adjuvant phase II setting in patients with resectable squamous cell carcinoma of the oesophagus.

Patients and methods

Patients

Patients with histologically confirmed squamous cell carcinoma of the oesophagus and with no signs of irresectability and no evidence of metastatic disease were eligible for the study. The tumour had to be limited to the oesophagus and regional lymph nodes without involvement of the tracheobronchial tree or other structures. Further eligibility requirements were: age ≥ 18 years; no contraindications for extensive surgery; World Health Organisation (WHO) performance status 0-2; written and voluntary informed consent; adequate haematological, renal and hepatic functions defined as: granulocytes ≥ 1.5 x 10^9 /L, platelets ≥ 100 x 10^9/L, total bilirubin ≤ 1.5 x upper normal limit and creatinine ≤ 120 mmol/L. Exclusion criteria were: previous treatment with chemotherapy or radiotherapy; pre-existing neurotoxicity greater than CTC grade 1 and inadequate calorie- and/or fluid intake. The study was approved by the local ethics committee.

Initial evaluation

Initial evaluation included a complete medical history, physical examination, complete blood cell count and serum biochemistry endoscopy with biopsies, endoscopic ultrasonography, ultrasonography of the supraclavicular region and a computed tomography (CT) scan of the chest and abdomen.

Chemotherapy

Paclitaxel 180 mg/m^2 and cisplatin 60 mg/m^2 were administered by intravenous infusion (i.v.) every 2 weeks. After prehydration with at least one litre of normal saline, the calculated dose of paclitaxel, diluted in 500 ml of normal saline, was infused over 3 hours. Hereafter, the calculated dose of cisplatin was administered over 3 hours followed by post-hydration with 3 litres of normal saline over 24 hours. Thirty minutes prior to the paclitaxel infusion, the patients received 10 mg dexamethason, 2 mg clemastine and 50 mg ranitidine, all given intravenously. Ondansetron 8 mg i.v. was routinely given. Patients were retreated when the granulocytes were $\geq 0.75 \times 10^9$/L and the platelets $\geq 75 \times 10^9$/L. When these criteria were not met, treatment was postponed for 1 week.

Tumour response was assessed after the third course of chemotherapy and included a CT scan of chest and abdomen and an endoscopy. Non-responding patients were referred for surgery. Patients showing disease regression received 3 additional courses of chemotherapy. These patients were again evaluated after the sixth course and then referred for surgery.

Toxicity was graded and reported using NCI-CTC criteria (version 2) and response was evaluated using standard WHO criteria[8].

Surgery

For carcinomas proximal of the carina the oesophagus was resected by a right dorso-lateral thoracotomy. For more distal carcinomas the transhiatal approach was preferred. Accessible intra-abdominal, peri-oesophageal and subcarinal lymph nodes were sampled. Post-operative radiotherapy or chemotherapy was not given.

The tumour stage after resection was classified according to the TNM classification of the International Union Against Cancer (UICC, fifth edition, 1997). To describe the absence or presence of residual tumour after resection of the primary tumour, the following R(esidual) categories were used as appendices: R0 if all the surgical margins were free of tumour, R1 if there was microscopically residual tumour in any of the surgical margins and R2 if macroscopically residual tumour was detected.

Any type of complications occurring after surgery was considered postoperative morbidity. Treatment-related mortality was defined as any death that occurred before a patient was discharged or even after discharge when there was any possible correlation with the treatment itself.

Statistical considerations

Patient enrolment followed a four-step sequential design. If no response was seen in the first 8 patients further accrual had to be halted. Otherwise an additional 12 patients could be

entered. In the third step, 10 more patients were entered if at least 4 responses were observed in the 20 patients that were treated. Finally when 30 patients were treated the trial was to be continued with an additional 20 patients if the observed number of responses was at least 50%. Under this design there is only an 18% chance of continuing the trial while the true response percentage is below 40%.

Survival time was measured from date of inclusion to death or was censored at the time that the patient was last known to be alive. Median survival times and survival curves were estimated by using the method of Kaplan and Meier.

Results

From October 1997 to February 2000, 51 patients entered the study. One patient was ineligible because he had a carcinoma of the gastric cardia. Patient characteristics are listed in *Table 1*.

Table 1. ***Patient characteristics (n=50)***

Characteristic	No. of patients	(%)
Sex		
Male	30	60
Female	20	40
Age (years)		
Median	62	
Range	45-78	
WHO performance status		
0	20	40
1	26	52
2	4	8
Weight loss (%)		
0-5	21	42
5-10	10	20
>10	19	38
TNM-classification (endoscopic ultrasonography)		
T2N0	1	2
T3NO	10	20
T2N1	6	12
T3N1	21	42
No pass	12	24

Chemotherapy

Of 50 eligible patients, 47 patients (94%) received at least 3 courses of chemotherapy. One patient refused further treatment after 1 course of chemotherapy. This patient was considered not evaluable for toxicity and response. In two other patients treatment was stopped after 2 courses due to a grade 2 sensory neuropathy. Both patients were evaluated and referred for surgery. Thirteen patients with stable disease after 3 courses were referred for surgery according to the protocol. Treatment was continued in the remaining 34 patients who had at least objective tumour regression at evaluation, although not always qualifying for partial response. Seven of these patients did not receive the planned next 3 courses due to sensory neuropathy (4 patients) and deterioration of general condition mainly due to fatigue and myalgia (3 patients).

Sixty-three cycles (26%) were delayed for one week in 26 patients. The reason for the delay of treatment was in almost all cases a granulocyte count < 0,75 x 10^9 /L at the day of re-treatment. The planned and achieved dose intensity for cisplatin were 30 mg/m²/week and 26,6 mg/m²/week, respectively, and for paclitaxel 90 mg/m²/week and 79,8 mg/m²/week, respectively.

The predominant toxicities are listed in *Table 2*. Neutropenia grade 3 or 4 was observed in 35 patients (71%), with neutropenic fever occurring in only 2 patients (4%). Both patients recovered after treatment with broad-spectrum antibiotics. Non-haematological toxicities were usually mild. Sensory neuropathy, the most important non-haematological toxicity, was observed in 25 patients (51%) but never exceeded grade 2. The overall response rate in 49 evaluable patients was 59%; 7 patients (14%) had a complete response and 22 patients (45%) had a partial response. Stable disease was observed in 20 patients (41 %). No patient had disease progression during treatment.

Table 2. ***Worst CTC grade toxicities (n = 49)***

	CTC grade				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Granulocytopenia	4	10	14	18	53
Thrombocytopenia	96	4			
Nausea	45	37	14	4	
Vomiting	57	31	8	4	
Diarrhoea	90	8	2		
Mucositis	96	4			
Neurotoxicity	49	37	14		
Myalgia	47	35	18		
Fatigue	51	37	12		

Surgery

Three patients (6%) were not referred for surgery. These patients had large tumours located above the carina and enlarged mediastinal lymph nodes that remained unchanged during chemotherapy and were considered not fit enough for a thoracotomy due to co-morbidity and a deteriorated general condition. All 3 patients received radiation therapy up to a total dose of 50 Gy.

Forty-seven patients (94%) were referred for surgery. Surgery was performed between 4 and 6 weeks after completion of chemotherapy in all patients. In 45 patients (90%), a resection was carried out. In 2 patients, who had a locally irresectable tumour or intra- abdominal lymph node metastasis, a resection was not carried out. In 28 patients a transhiatal approach without thoracotomy was performed, while 17 patients underwent a transthoracic oesophagectomy.

Of the 45 patients that underwent an oesophageal resection, 38 patients (84%) had a R0 resection and 7 patients (16%) had a R1 resection. Pathologic examination of the resected specimens showed no residual tumour in seven patients. Five of these 7 patients had been clinically evaluated as complete responders. A comparison of the pre- and post-treatment staging of all 50 patients is listed in *Table 3*.

*Table 3. **Pre- and post-treatment stage**[1]*

Stage	pre- chemotherapy[2]		post- chemotherapy[3]	
	no.of patients (%)		no.of patients (%)	
T0N0	0		7	14
I	0		4	8
IIA	11	22	19	38
IIB	6	12	6	12
III	21	42	6	12
IV	0		3	6
No pass/unknown	12	24	5	10

[1] stage grouping according to the International Union Against Cancer, fifth edition

[2] staged by endoscopic ultrasonography

[3] staged by pathologic examination

Postoperative complications occurred in 26 of 45 patients (58%) (*Table 4, see page 54*). Two patients died in the post-operative period (4%). One patient died of cardiovascular complications directly after surgery and one patient died of respiratory complications three months after surgery.

Table 4. ***Postoperative course and morbidity***

Characteristic	No. of patients	(%)
Operative mortality	0	0
30-day hospital mortality	1	2
Median days of hospital stay (range)	15 (8-96)	
Postoperative course		
Uneventful	19	42
Complications	26	58
Respiratory	14	32
Sepsis	2	4
Anastomotic leakage	7	13
Bleeding	1	2
Vocal cord paralysis	12	27

Survival and pattern of failure

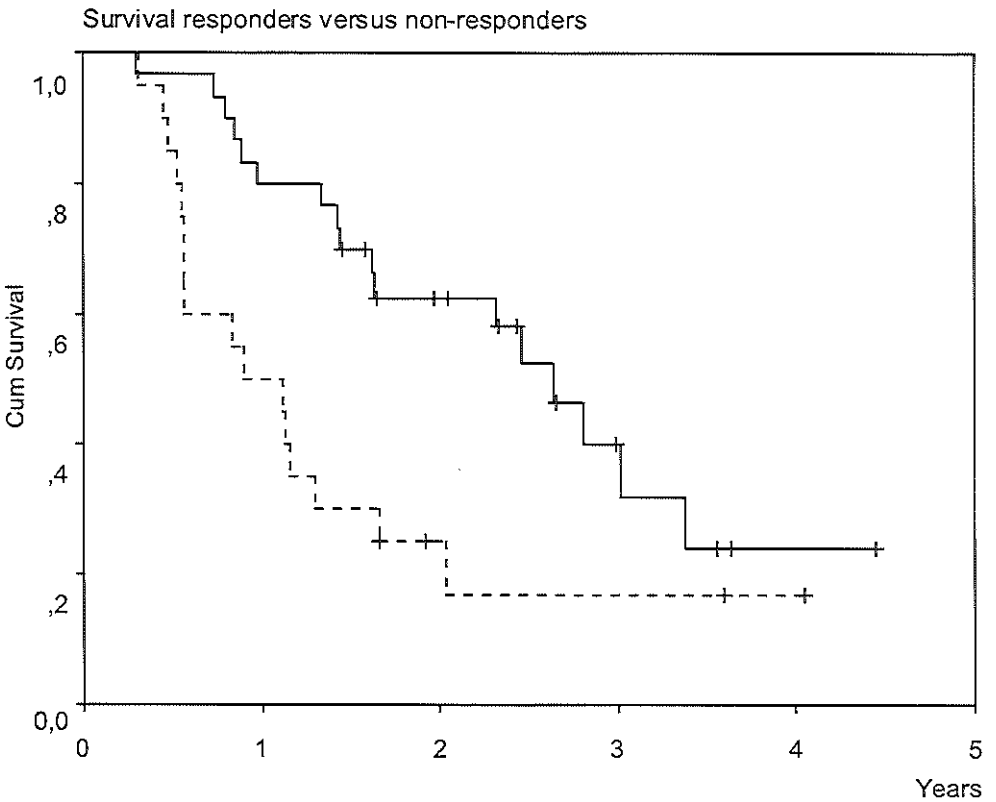
After a median follow-up period of 41 months (18 - 54 months) 18 of the 50 patients are alive, 17 of them showing no recurrence of disease. The median actuarial survival in all patients is 20 months (3 - 50+ months), with a 1- and 3-year survival rate of 68 and 32%, respectively. Responders had a significant better median survival than non-responding patients (32 versus 11 months, p= 0,009) (*Figure 1*). The pattern of disease recurrence in 27 patients was loco-regional recurrence in 6 patients, metastatic disease only in 17 patients and both locoregional and distant disease in 4 patients.

Discussion

Previous phase II studies with neo-adjuvant chemotherapy have shown encouraging results in patients with squamous cell carcinoma. Response rates of 15-60% with a complete pathologic response rate of 4-7 % after cisplatin-based combination chemotherapy have been reported[9]. Compared to historical controls the outcome seemed improved after treatment with pre-operative chemotherapy[10].

In 2 large randomised trials neo-adjuvant chemotherapy followed by surgery was compared with surgery alone[11,12]. Noteworthy are the conflicting results of the two largest trials. The Medical Research Council (MRC) found a significantly improved survival following neo-adjuvant chemotherapy[11]. In their study 802 patients with resectable oesophageal cancer were randomised to receive pre-operative chemotherapy with 2 courses of cisplatin and 5-fluorouracil followed by surgery or surgery alone. The median survival was 17 months for patients treated with pre-operative chemotherapy versus 13 months after surgery alone (P=0,004; hazard ratio 0,79; 95% CI 0,67-0,93). In the Intergroup trial 440 patients were

Figure 1. ***Kaplan Meier survival curve for responding (n=29) (—) and non-responding (n=20) (- -) patients, p (Log rank) = 0,008***



randomised to pre-operative treatment with 3 courses of cisplatin and 5-fluorouracil followed by surgery or surgery alone[12]. Median survival was comparable in the two groups, 15 months after pre-operative chemotherapy and 16 months after surgery alone (P=0,53; hazard ratio 1,07; 95% CI 0,87-1,32). The conflicting results of the randomised studies are difficult to explain, particularly because comparable chemotherapy regimens were used. A possible explanation could be the type of surgical resection. In the Intergroup study a transthoracic oesophagectomy was preferred while in the MRC study both the transthoracic oesophagectomy and the transhiatal oesophagectomy were considered appropriate, however the number of transhiatal resections has not been reported. A transthoracic approach makes a more extended lymph node resection possible and it could be that the benefit of preoperative chemotherapy in the positive studies was only the result of improved local control in patients treated with less extensive surgery. However, in a recently reported trial comparing transhiatal oesophagectomy with transthoracic oesophagectomy with extended lymphadenectomy there was only a trend toward improved long-term survival at five years with the extended transthoracic approach[13]. A transhiatal oesophagectomy was associated with lower morbidity.

In the current study, we treated 50 patients with a resectable squamous cell carcinoma of the oesophagus with a biweekly regimen of paclitaxel and cisplatin. This dose-dense treatment was well tolerated and achieved an overall clinical response rate of 59%. Despite the fact that 71% of patients developed grade 3 or 4 neutropenia, we observed only 2 episodes of neutropenic fever. The majority of patients included in our study had T3 tumours with positive regional lymph node involvement. Forty-five patients (90%) underwent an oesophageal resection and the mortality rate was not apparently increased. Pathological examination showed no residual tumour in 7 patients (14%) and a R0 resection in 38 patients (76 % of all patients and 83% of patients that underwent a resection). The median survival was 20 months and the 1- and 3- year survival were 68 and 32%, respectively.

Both the overall and the complete response rate observed in this study, 59 and 14%, respectively, seem to compare favourable to response rates observed in other studies with neo-adjuvant chemotherapy. In addition, this dose-dense regimen of cisplatin and paclitaxel was well tolerated and 94% of patients were able to complete the first 3 courses of chemotherapy. In the Intergroup study, for example, only 71% of patients completed the three pre-operative chemotherapy courses[12].
The design of our study and the chemotherapy regimen differed in several aspects from other studies. This is the first study investigating a neo-adjuvant regimen of dose-dense cisplatin and paclitaxel. Theoretical advantages of a dose-dense schedule could be that more cancer cells are being killed because there is less time for the tumour to regrow between drug administrations and that a more continuous exposure to cytotoxic agents may permanently impair growth-promoting intracellular signalling and DNA repair[14]. Furthermore the study design differed from that of the other trials because we administered 3 additional courses to responding patients. Although the optimal number of pre-operative chemotherapy courses has not been established, the administration of additional courses to responding patients could have resulted in an increased complete response rate and possible improved survival.

In conclusion, this dose-dense schedule of cisplatin and paclitaxel administered biweekly is well tolerated by patients with resectable squamous cell carcinoma of the oesophagus. The overall and complete response rates obtained with this combination are promising. Further evaluation comparing this treatment with other treatment strategies in a randomised trial is warranted.

References

1 Millikan KW, Silverstein J, Hart V, et al. A 15-year review of oesophagectomy for carcinoma of the oesophagus and cardia. Arch Surg 1995; 130: 617-24.

2 Muller JM, Erasmi H, Stelzner M, et al. Surgical therapy of oesophageal carcinoma. Br J Surg 1990; 77: 845-57.

3 Law S, Fok M, Chow S, et al. Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the oesophagus: a prospective randomised trial. J Thorac Cardiovasc Surg 1997; 114: 210-7.
4 Ilson DH, Ajani J, Bhalla K, et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the oesophagus. J Clin Oncol 1998; 16: 1826-34.
5 Ilson DH, Forastiere A, Arquette M, et al. A Phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the oesophagus. Cancer J 2001; 6: 316-23.
6 Van der Gaast A, Kok TC, Kerkhofs L, Siersema PD, Tilanus HW, Splinter TA. Phase I study of a biweekly schedule of a fixed dose of cisplatin with increasing doses of paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 1999; 80:1052-7.
7 Polee MB, Eskens FALM, van der Burg MEL, et al. Phase II study of a biweekly schedule of cisplatin and paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 2002; 86: 669-73.
8 World Health Organisation. WHO handbook for reporting results of cancer treatment. WHO Offset Publ No.4. Geneva: World Health Organisation, 1979.
9 Kelsen DP, Ilson DH. Chemotherapy and combined-modality therapy for oesophageal cancer. Chest 1995; 107: 224S-32S.
10 Hilgenberg AD, Carey RW, Wilkins EW Jr et al. Preoperative chemotherapy, surgical resection and selective postoperative therapy for squamous cell carcinoma of the oesophagus. Ann Thorac Surg 1988; 45: 357-63.
11 Medical Research Council Oesophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised trial. Lancet 2002; 359: 1727-33.
12 Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localised oesophageal cancer. N Engl J Med 1998; 339: 1979-84.
13 Hulscher JBF, van Sandick JW, de Boer AG, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the oesophagus. N Engl J Med 2002; 347, 1662-9.
14 Norton L. Kinetic concepts in the systemic drug therapy of breast cancer. Semin Oncol 1999; 26 S2: 11-20.

CHAPTER 6

PHASE I AND PHARMACOKINETIC STUDY OF WEEKLY PACLITAXEL AND CARBOPLATIN IN PATIENTS WITH METASTATIC OESOPHAGEAL CANCER

Marco B. Polee[1], Alex Sparreboom[2], Ferry A.L.M. Eskens[1], Ronald Hoekstra[1], Jacqueline van de Schaaf[1], Jaap Verweij[1], Gerrit Stoter[1] and Ate van der Gaast[1]

Department of [1]Medical Oncology and [2]Laboratory of Translational and Molecular Pharmacology, Erasmus Medical Center, Rotterdam, the Netherlands.

Accepted for publication in CLin Canc Res.

Abstract

Purpose: To determine the maximum-tolerated dose, toxicity profile, and pharmacokinetics of a fixed dose of paclitaxel followed by increasing doses of carboplatin, given weekly to patients with advanced oesophageal or gastric junction cancer.

Experimental design: Paclitaxel was administered on day 1 as a 1-hour infusion at a fixed dose of 100 mg/m² followed by a 1-hour infusion of carboplatin targeting an area under the curve (AUC) of 2 to 5 mg•min/mL, with cycles repeated on days 8, 15, 29, 36, and 43.

Results: Forty patients [36 males; median (range) age, 57 (40-74) years] were enrolled. Dose-limiting toxicity was observed at a carboplatin AUC of 5 mg•min/mL and consisted of treatment delay due to myelosuppression. No grade 3/4 treatment related non-haematological toxicity was observed. The highest dose intensity (> 95% of the planned dose over time) was achieved with a carboplatin AUC of 4 mg•min/mL. The mean (± SD) AUC of unbound (Cu) and total paclitaxel were 0.662 ± 0.186 and 7.37 ± 1.33 μM•h, respectively. Clearance of Cu was 188 ± 44.6 L/h/m², which is not significantly different from historic data (P = .52). Cremophor EL clearance was 123 ± 23.0 mL/h/m², similar to previous findings. Of 37 patients evaluable for response, 1 had complete response, 19 partial response, 10 had stable disease, accounting for an overall response rate of 54%.

Conclusions: This regimen is very tolerable and effective, and the recommended doses for further studies are paclitaxel (100 mg/m²) with carboplatin targeting an AUC of 4 mg•min/mL.

Introduction

Oesophageal cancer is among the 10 most frequently-occurring human malignancies in the world. While the incidence of squamous-cell cancer remains relatively constant, the incidence of adenocarcinoma of the distal oesophagus or the oesophageal-gastric junction is rapidly increasing in Western countries, including the United States[1]. This rising incidence is not completely explained, yet, but obesity, gastric reflux and the development of an intestinalised columnar epithelium (Barrett's oesophagus) in the squamous lining of the oesophagus have been identified as important risk factors for development of adenocarcinomas in the distal oesophagus[2,3,4]. Approximately 50% of the patients present with systemic disease and the majority of patients being treated for localised disease will develop metastatic disease with or without local recurrence after oesophageal resection.

Cisplatin based chemotherapy regimens are commonly used as pre-operative treatment for patients with resectable disease or for patients with advanced disease. In combination with 5-fluorouracil, response rates of 35% in metastatic and 45-55% in locoregional disease have been reported[5]. More recently, irinotecan and paclitaxel have been identified as new agents in the treatment of oesophageal cancer. The response rate after treatment with irinotecan, administered weekly as a single agent, was 15%[6] and in combination with cisplatin the response rate was 57%[7]. Combination therapy of cisplatin and paclitaxel, either administered weekly, biweekly or 3-weekly, in patients with advanced oesophageal cancer has been evaluated previously, with response rates ranging from 42 to 52%[8,9,10,11,12]. When paclitaxel was administered over 24 hours in combination with cisplatin with or without 5-fluorouracil, the predominant toxicity was myelosuppression[8,9]. Myelotoxicity was less severe when paclitaxel was administered over 3 hours in a weekly or biweekly schedule in combination with cisplatin, although the incidence and severity of sensory neurotoxicity increased[10,11,12].

Recently, the safety and efficacy of weekly administrations of paclitaxel in patients with breast cancer, ovarian cancer and lung cancer has been reported[13,14,15,16]. Doses of 100 to 175 mg/m^2/week are well tolerated with minimal haematological toxicity and reversible neurotoxicity[14]. Furthermore, it is possible to combine weekly paclitaxel administration with carboplatin either in a weekly schedule at a dose to produce a target area under the plasma concentration-time curve (AUC) of 2 mg/ml•min (AUC 2) or every 3-weeks at dose level targeting AUC 6[17]. Based on our favourable experience with dose-dense biweekly and weekly schedules of cisplatin and paclitaxel, we initiated a dose-finding study with a weekly schedule of a fixed dose of paclitaxel and escalating doses of carboplatin. The advantage of a paclitaxel-carboplatin regimen over a cisplatin-paclitaxel regimen is that it can be given as an out-patient treatment and that it probably induces less neurotoxicity. The objectives of this study were to assess the safety and toxicity of this combination; to determine the dose-limiting toxicities (DLT), maximum-tolerated dose (MTD), and recommended dose for further evaluation.

Patients and Methods

Eligibility

Patients with histological proven metastatic or unresectable adenocarcinoma, undifferentiated or squamous cell carcinoma of the oesophagus or gastro-oesophageal junction area were eligible for the study. Tumours invading adjacent structures (T4) or with proven distant metastases (M1a or M1b) were considered unresectable. Additional eligibility requirements included: life expectancy of more than 12 weeks; age ≥ 18 years; World Health Organization (WHO) performance status 0-2; adequate haematological (granulocytes ≥ 1.5 x 10^9/L, and platelets ≥ 100 x 10^9/L), renal (serum creatinine ≤ 120 mmol/L), and hepatic functions (total bilirubin ≤ 1.5 x upper normal limit). Patients with neurotoxicity graded > 1 according to the

National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2) were not eligible. Prior radiation for primary or metastatic disease was allowed but not in the 4 weeks prior to study entry and when not involving more than 30% of the bone marrow. Patients previously treated with chemotherapy were not eligible. The study was approved by the Erasmus MC ethics committee (Rotterdam, The Netherlands), and all patients provided written informed consent.

Pretreatment and Follow-up

Prior to treatment a complete medical history was taken, and physical examination, laboratory studies, electrocardiogram and imaging studies for tumour measurements were performed. Laboratory studies included a complete blood cell count analysis with white blood cell differential, sodium, potassium, calcium, phosphorus, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH).

History, physical examination and toxicity scoring according to NCI-CTC were performed weekly. Blood cell counts and serum chemistry studies were also performed weekly. Tumour measurements were performed after 6 administrations by a CT-scan of the chest and upper abdomen. Patients with the primary tumour *in situ* were also evaluated by endoscopy. Standard WHO response criteria were used[18]. Duration of response was calculated from the start of treatment.

Drug Administration

All patients received dexamethasone (10 mg), clemastine (2 mg), and ranitidine (50 mg), administered intravenously 30 minutes prior to paclitaxel infusion. Patients received paclitaxel as a 1-hour infusion diluted in 500 mL of sterile and isotonic (0.9%, vol/vol) sodium chloride solution (saline), with the total drug dose normalised to a patient's body-surface area. After the completion of the paclitaxel infusion, 100 mL of saline was infused over 30 minutes followed by an infusion of ondansetron (8 mg) diluted in 100 mL of saline given over 30 minutes. Hereafter, the total calculated dose of carboplatin, diluted in 500 mL of 5% (wt/vol) dextrose solution was administered over 1-hour.

Study Design

Paclitaxel and carboplatin were administered on days 1, 8, 15, 29, 36 and 43. The paclitaxel dose was fixed at 100 mg/m^2 per administration, and the starting dose of carboplatin was set at a targeted AUC of 2 according to a previously published formula[19]. The creatinine clearance was estimated by the Cockcroft-Gault equation. The carboplatin dose was escalated per cohort in steps targeting an increase in AUC of 0.5 mg/ml•min. In each cohort, three patients were treated until DLT was observed. If two or more DLTs were observed, that dose was considered too high. In the case of one DLT, the accrual of three additional patients

was required. If DLT was seen in no more than one patient at that dose level, the dose was to be further escalated. The dose level at which two or more patients experienced DLT was considered the MTD. The dose below MTD would be the recommended dose for further studies. DLT was defined as any of the following events occurring during treatment: grade 3-4 neutropenia with infection or fever requiring parenteral antibiotics; grade 3-4 thrombocytopenia requiring 2 or more platelet transfusions, or resulting in ≥ grade 2 haemorrhage; nonhaematological toxicity ≥ grade 3 with the exception of acute nausea and/or vomiting; and/or dose reductions and/or treatment delay for more than one week for reasons of toxicity.

Patients were retreated on days 8 and 15 provided the white blood count (WBC) was ≥ 1.0 x 10^9/L and platelets were ≥ 50 x 10^9/L, while prior to the start of the day 29 course the WBC had to be ≥ 3.0 x 10^9/L and platelets ≥ 100 x 10^9/L. When these criteria were not met, treatment was postponed for 1 week. If bone marrow recovery was still insufficient after this week, patients were taken off study. Dose reduction was performed in patients with neutropenic fever or grade 3-4 thrombocytopenia requiring 2 or more platelet transfusions or resulting in ≥ grade 2 haemorrhage; in that case patients were retreated at the preceding dose level. Responding patients could receive additional local therapy in case of limited lymph node metastasis or additional cycles of carboplatin and paxlitaxel in case of distant metastatic disease. These additional cycles could also be administered in a traditional 3-weekly schedule.

After establishing a recommended dose, 8 additional patients would be treated at this dose level. This was done in order to demonstrate the feasibility and to estimate the dose-intensity of this schedule. Pharmacokinetic analysis was performed in these patients.

Sampling Schedule and Drug Analysis

Blood volumes of 5 mL were drawn directly into Vacutainer tubes containing lithium heparin (Becton Dickinson, Meylin, France) from a peripheral venous access device. Samples were collected at the following time points: immediately before paclitaxel treatment; at 0.5 hours after start of infusion; 5 minutes before the end of infusion; and at 0.5, 1, 3, 7, and 23 hours after the end of infusion. Following centrifugation at 2000 x *g* for 5 minutes, the plasma fraction was separated, transferred into a clean polypropylene tube, and stored frozen at -20° C until analysis. Total concentrations of paclitaxel (ie, the total of bound and unbound) in plasma were determined by a validated reversed-phase high-performance liquid chromatographic assay with detection at a wavelength of 230 nm, as described previously[20]. This assay has a lower limit of quantitation of 10 ng/mL, with an accuracy (ie, percentage deviation from nominal concentrations) of ± 3.0%. Unbound concentrations of paclitaxel in plasma were obtained from an equilibrium dialysis method using generally tritium labeled paclitaxel as a tracer[21]. The analytical procedure for

Cremophor EL was based on a colorimetric dye-binding microassay using Coomassie-Brilliant Blue G-250 (Bio-Rad Laboratories, Munchen, Germany), according to a published procedure[22]. The lower limit of quantitation of this procedure was 0.50 mL/mL, with an accuracy of less than 6.5%.

Pharmacokinetic Data Analysis

The fractions unbound (fu) paclitaxel in each individual patient plasma sample, including the blank, were determined following analysis for total radioactivity (ie, [^{3}H]paclitaxel) by liquid-scintillation counting. The unbound drug concentrations (Cu) were calculated from the fraction unbound drug (fu) and the total drug concentration (Cp) (i.e., the total of unbound, protein bound and Cremophor EL associated), as Cu = fu x Cp. Estimates of pharmacokinetic parameters for unbound paclitaxel and total paclitaxel in plasma were derived from individual concentration-time data sets by a linear multi-compartmental analysis using the software package Siphar version 4.0 (InnaPhase, Philadelphia, PA). This program determines the slopes and intercepts of the logarithmically plotted curves of multiexponential functions using non-linear least-squares, iterative steps. Initial parameter estimates were determined by an automated curve-stripping procedure. The mathematical equations describing the drug concentration $C_{(t)}$ at any time t during and after i.v. administration are given by $C_{(t)} = S\{C_i / (l_i \times T_{Inf}) \times (1 - e^{(-l_i \times t)})\}$ and $C_{(t)} = S\{C_i / (l_i \times T_{Inf}) \times (e^{(-l_i \times [t - Tinf])} - e^{(-l_i \times t)})\}$, respectively. In these equations, l_i is the component of the *i*-th exponential term, C_i is the initial concentration of the *i*-th component of the curve, and T_{Inf} is the infusion duration. In all cases, paclitaxel-concentration-time curves were best described with a tri-exponential model, which gave the lowest Akaike information criterion, without any demonstration of saturable behavior (R^2 = 0.996 ± 0.002, root mean square error = 14 ± 3.5%). The curve fitting procedure with this model yields the parameters C_1, C_2, C_3, l_1, l_2, and l_3. The AUC values were determined on the basis of the parameters of the equations with extrapolation to infinity using the terminal disposition rate constant. The clearance was defined as dose (expressed in μmole/m^2) divided by AUC. The volume of distribution at steady-state was calculated as the product of clearance and the mean residence time, also estimated from the equations. Peak plasma concentrations were put on par with observed (experimental) drug levels immediately following the end of infusion.

Estimates of pharmacokinetic parameters for Cremophor EL in plasma were derived from individual concentration-time data sets by noncompartmental analysis using the software package WinNonLin version 3.0 (Pharsight Corporation, Mountain View, CA). The peak plasma concentrations and the time to peak were the observed values. The AUC was calculated using the log-linear trapezoidal method from time zero to the time of the final quantifiable concentration (AUC[tf]). The AUC was also extrapolated to infinity by dividing the last measured concentration by the rate constant of the terminal phase (*k*), determined by linear-regression analysis of the last 3 measurable concentrations (R^2 = 0.983 ± 0.021). The systemic clearance

was calculated by dividing the administered dose (expressed in µL) by the observed AUC[inf], and the terminal disposition half-life was calculated as ln (2)/k.

All pharmacologic parameters are expressed as mean values ± SD, unless stated otherwise. Interindividual variability in parameters was expressed as the coefficient of variation, calculated as the ratio of the SD and the observed mean, and multiplied by 100. The effect on the two different targeted carboplatin exposure levels (AUC of 4.0 and AUC of 4.5) on the generated data was evaluated statistically using a nonparametric Wilcoxon (2 group) test. A comparative analysis with data obtained from patients receiving single-agent paclitaxel with those obtained in the current trial was performed using a nonparametric Kruskal-Wallis (multiple group) test. The level of significance was set at $P < 0.05$. All statistical calculations were performed using JMP version 3.2.6 (SAS Institute Inc., Cary, NC; 1999).

Pharmacodynamic analysis was not performed because the number of patients that were analysed was too small.

Results

Patients and Toxicity Profiles

A total of 40 eligible patients entered the study. Patient characteristics are shown in *Table 1 (page 66)*. Two patients had pulmonary embolism 2 weeks after start of treatment, both patients recovered and were able to complete treatment. As these patients had a treatment delay due to other reasons than chemotherapy-induced toxicity, they were considered not to be fully assessable for toxicity. One patient refused further treatment after 2 courses of chemotherapy.

The carboplatin dose was increased from the first dose level (AUC 2) to dose level AUC 5. At dose level AUC 4, one patient had DLT after 3 administrations, consisting of neutropenic fever and grade 3 diarrhoea. She had to be admitted and recovered after treatment with intravenous broad-spectrum antibiotics. At the dose level AUC 4.5, another patient had a DLT. This patient developed neutropenic fever after the third course of treatment and also recovered after antibiotic treatment. Both patients treated at carboplatin dose level AUC 5 had a treatment delay related DLT. These 2 patients were not able to continue treatment at day 29 and treatment had to be delayed for 2 and 3 weeks, respectively, due to protracted myelosuppression and consequently this dose level was considered to be the MTD. As per protocol 8 patients were additionally treated at carboplatin level AUC 4.5 and pharmacokinetic analyses were performed. However, treatment delay frequently occurred at this dose level and therefore 6 additional patients were treated at carboplatin dose AUC 4. Pharmacokinetic analyses were also performed at this latter dose level.

Table 1. ***Patient characteristics***

Characteristic	No. of patients	(%)
Sex		
Male	4	
Female	36	
Age (years)		
Median	57	
Range	40-74	
ECOG performance score		
0	19	48
1	17	42
2	4	10
Weight loss (%)		
0-5	17	42
5-10	14	36
>10	9	23
Histology		
Adenocarcinoma	34	85
Squamous cell carcinoma	5	13
Undifferentiated carcinoma	1	3
Extent of disease		
Locally advanced/unresectable	0	
Primary with distant metastases	30	75
Metastases after prior resection	10	25
Metastatic sites		
Lymph nodes only	7	18
Liver	18	45
Other	15	38

Abbreviation: ECOG, Eastern Cooperative Oncology Group

Toxicity data are shown in *Tables 2 and 3.* Neutropenia grade 3 or 4 was observed in 25 (77%) patients. The granulocyte nadir usually occurred after the fifth or sixth treatment course. Thrombocytopenia grade 3 or 4 was observed in 4 patients, and occurred at carboplatin dose levels of AUC 4 and higher. Nonhaematological toxicity predominantly consisted of sensory neurotoxicity grade 1 or 2 occurring in 7 (19%) and 2 (5%) patients, respectively. Fatigue was observed in 24 (65%) patients and did not appear to be dose related. Nephrotoxicity did not occur. Alopecia was universal.

A total of 215 administrations was given. *Table 4* (see page 68) shows the achieved dose intensity and observed treatment delays. Thirteen (6%) administrations were delayed in 11

Table 2. Worst haematological toxicity per patient

Carboplatin	No. of pat./No. of	Neutropenia*					Thrombocotopenia*					Anaemia*				
Dose level	administrations	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
AUC 2	3 / 18	1	-	1	1	-	3	-	-	-	-	2	1	-	-	-
AUC 2.5	3 / 18	-	1	1	1	-	2	1	-	-	-	-	3	-	-	-
AUC 3	3 / 18	-	-	2	1	-	2	1	-	-	-	1	2	-	-	-
AUC 3.5	3 / 18	-	-	-	2	1	2	1	-	-	-	1	2	-	-	-
AUC 4	12 / 68	-	-	1	4	7	5	5	1	-	1	3	6	3	-	-
AUC 4.5	11 / 63	-	1	2	5	3	3	4	3	1	-	4	3	4	-	-
AUC 5	2 / 12	-	-	-	1	1	-	-	-	2	-	1	1	-	-	-

Abbreviation: AUC, area under the plasma concentration-time curve (in mg•min/ml)

* Graded according to National Cancer Institute common toxicity criteria.

Table 3. Worst nonhaematological toxicity per patient

Carbo-platin Dose level	No. of pat. / No. of Admini-strations	Nausea*					Vomiting*					Neuro-toxicity*					Diarrhoea*					Fatique*			
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
AUC 2	3 / 18	2	0	1	0	0	2	0	1	0	0	3	0	0	0	0	2	0	1	0	0	0	1	2	0	0
AUC 2.5	3 / 18	0	3	0	0	0	2	1	0	0	0	2	1	0	0	0	3	0	0	0	0	0	2	1	0	0
AUC 3	3 / 18	1	2	0	0	0	3	0	0	0	0	3	0	0	0	0	2	1	0	0	0	1	1	1	0	0
AUC 3.5	3 / 18	1	2	0	0	0	3	0	0	0	0	2	1	0	0	0	2	1	0	0	0	1	2	0	0	0
AUC 4	12 / 68	5	5	2	0	0	9	3	0	0	0	8	3	1	0	0	5	4	2	1	0	4	4	4	0	0
AUC 4.5	11 / 63	3	4	4	0	0	8	3	0	0	0	8	2	1	0	0	9	1	1	0	0	4	6	0	1	0
AUC 5	2 / 12	1	1	0	0	0	2	0	0	0	0	1	1	0	0	0	1	1	0	0	0	1	1	0	0	0

* Graded according to National Cancer Institute common toxicity criteria.

(30%) patients, and almost all delays occurred at day 29. Five administrations had to be delayed due to unresolved thrombocytopenia, one administration due to leucocytopenia and five administrations because of both thrombocytopenia and leucocytopenia. One patient had two administrations delayed for one week because of fatigue. A treatment delay due to myelotoxicity also was observed in 8 of 11 patients treated at carboplatin dose level AUC 4.5. Therefore we considered carboplatin targeted at AUC 4 the recommended dose for weekly treatment in combination with paclitaxel administered at 100 mg/m^2. Since at this dose level only one patient had a treatment delay of one week, we achieved the highest dose intensity for paclitaxel and carboplatin. The median dose intensity at dose level AUC 4 after 6 courses calculated over an 8-week period was 75 mg/m^2/week for paclitaxel and AUC 3/week for carboplatin.

Table 4. ***Summary of treatment delays per dose level***

Carboplatin Dose level	No. of patients / No. of administr.	No. of patients with a delay (%)	No. of administr. with a delay (%)	Total no. of weeks delay	Dose intensity carboplatin (AUC/week)*
AUC 2	3 / 18	-	-	-	1.5
AUC 2.5	3 / 18	-	-	-	1.9
AUC 3	3 / 18	-	-	-	2.3
AUC 3.5	3 / 18	1	1	2	2.4
AUC 4	12 / 68	1 (8%)	1 (1%)	1	3.0
AUC 4.5	11 / 63	7 (64%)	8 (13%)	11	2.9
AUC 5	2 / 12	2 (100%)	3 (25%)	6	2.7

* Dose intensity calculated over 8 weeks.

Table 5. ***Demographics of patients sampled for pharmacologic analysis (n = 14)***

Characteristic	Median	Range
Baseline screening		
Age (years)	56	42 – 66
BSA, m^2	1.95	1.78 – 2.18
Height, cm	177	169 – 187
Weight, kg	80	65 – 99
Pretherapy haematology		
Haematocrit, L/L	0.40	0.36 – 0.46
Leukocytes, x 109/L	9.0	5.0 – 15
Neutrophils, x 109/L	6.2	3.2 – 13
Pretherapy clinical chemistry		
AST, units/L	25	12 – 38
ALT, units/L	24	12 – 38
ALP, units/L	105	72 – 160
GGT, units/L	70	19 – 208
Total serum bilirubin, mmol/L	8	4 – 14
Serum creatinine, mmol/L	71	52 – 82

Abbreviations: n, total number of patients studied; BSA, body-surface area; AST, aspartate amino-transferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl-transferase.

Drug Disposition

Pharmacokinetic analysis of unbound and total paclitaxel was performed during the first cycles of treatment in fourteen patients treated at a carboplatin AUC of 4 or 4.5 (*Table 5*). A summary of the plasma pharmacokinetic parameters is presented in *Table 6*. Moderate interindividual variability in paclitaxel AUC was noted, both for the unbound fraction (ie, ~28%) as well as for total drug (ie, ~18%). The exposure to unbound paclitaxel was not significantly different in patients receiving either carboplatin targeted at an AUC of 4 or AUC of 4.5, with mean values of 0.611 ± 0.108 *vs* 0.690 ± 0.219 mM•h, respectively [mean difference (± SE), 0.078 ± 0.105; 95% confidence limits, -0.151 and 0.308; $P = .47$]. Likewise, the AUC of total paclitaxel was similar in both groups, with mean values of 7.60 ± 1.47 *vs* 6.96 ± 1.04 mM•h, respectively [mean difference (± SE), 0.63 ± 0.75; 95% confidence limits, -1.00 and 2.26; $P = .42$]. The absolute clearance of unbound paclitaxel was also not significantly different from historic data obtained in 15 patients treated with single-agent paclitaxel as a 1-hour infusion at 100 mg/m² ($P = .52$)[23].

Table 6. ***Summary of paclitaxel pharmacokinetic parameters (n = 14)****

Parameter	Mean ± SD	Range
Paclitaxel dose, mg	195 ± 12.7	178 – 216
Infusion duration, hours	1.05 ± 0.10	1.00 – 1.38
Unbound paclitaxel		
C_{max}, µM	0.349 ± 0.121	0.231 – 0.696
AUC, µM•h	0.662 ± 0.186	0.425 – 1.18
CL, L/h/m²	188 ± 44.6	99.6 – 276
V_{ss}, L/m²	1250 ± 661	649 – 3210
$T_{1/2,z}$, hours	9.69 ± 4.91	5.55 – 25.7
AUC_u/AUC_p, %	8.9 ± 1.1	7.6 – 12
Total paclitaxel		
C_{max}, µM	3.98 ± 1.07	2.95 – 7.04
AUC, µM•h	7.37 ± 1.33	5.60 – 10.2
$T_{1/2,z}$, hours	8.84 ± 1.79	7.09 – 13.53

* All patients received paclitaxel as a 1-hour infusion at a dose of 100 mg/m², followed by carboplatin at a dose targeting an AUC of 4 mg•min/mL (n = 5) or AUC 4.5 mg•min/mL (n = 9). Data were calculated using a 3-compartment model.

Abbreviations: n, total number of patients studied; C_{max}, peak plasma concentration; AUC, area under the plasma concentration-time curve; CL, plasma clearance; V_{ss}, volume of distribution at steady-state; $T_{1/2,z}$, half-life of the terminal disposition phase; AUC_u / AUC_p, ratio of unbound to total drug on the basis of AUC.

Cremophor EL concentrations in plasma from one patient remained undetectable beyond 8 hours after the end of infusion, this was not the result of technical errors but of interindividual pharmacokinetics of Cremophor EL. Pharmacokinetic parameters for this patient are not listed in *Table 7*. Disappearance of Cremophor EL from the plasma compartment was characterised by elimination in an apparent biexponential manner, with a mean overall clearance of 123 ± 23.0 mL/h/m². The AUC of Cremophor EL was similar to that reported in patients treated with paclitaxel in the absence of carboplatin co-administration [70.5 ± 16.4 (range, 54.6 – 107) *vs* 80.2 ± 24.2 (range, 46.3 – 123) mL•h/mL; $P = .21$][3].

Table 7. ***Summary of cremophor EL pharmacokinetic parameters (n = 13)****

Parameter	Mean ± SD	Range
Cremophor EL dose, mL	16.4 ± 1.04	14.8 – 18.0
Infusion duration, hours	1.02 ± 0.03	1.00 – 1.08
C_{max}, µL/mL	2.67 ± 0.33	2.06 – 3.15
AUC, µL•h/mL	70.5 ± 16.4	54.6 – 107
CL, mL/h/m²	123 ± 23.0	78.1 – 153
V_{ss}, L/m²	4.49 ± 0.54	3.71 – 5.56
$T_{1/2,z}$, hours	27.1 ± 8.06	19.9 – 50.3

* All patients received paclitaxel as a 1-hour infusion at a dose of 100 mg/m², followed by carboplatin at a dose targeting an AUC of 4 mg•min/mL (n = 5) or AUC 4.5 mg•min/mL (n = 8). Data were calculated using noncompartmental analysis.

Abbreviations: n, total number of patients studied; C_{max}, peak plasma concentration; AUC, area under the plasma concentration-time curve extrapolated to infinity; CL, plasma clearance; V_{ss}, volume of distribution at steady-state; $T_{1/2,z}$, half-life of the terminal disposition phase.

Response and Survival

Thirty-seven patients were evaluable for response. All these patients had bi-dimensionally measurable disease. One patient with a tumour in the proximal oesophagus and supraclavicular lymph node metastasis achieved a complete response. This patient received additional radiation therapy to a total dose of 50 Gray, and he is alive without evidence of disease after a follow-up of 19 months. A partial response was observed in 19 patients (51%). The median duration of partial and complete responses was 9 months (range, 5 - 30 months). Ten patients had stable disease and 7 patients had progressive disease. The overall response rate was 54%. Two responding patients with adenocarcinomas of the distal oesophagus and celiac lymph node metastases underwent an oesophageal resection after chemotherapy. Both patients had radical resections and are currently alive without evidence of disease after a follow-up of 18 and 16 months, respectively. Eleven patients with a partial response after chemotherapy and 4 patients with stable disease received additional treatment with chemotherapy. The median survival for all 40 patients was 11 months (range, 3 - 30 months), with a one-year survival rate of 46 %.

Discussion

Chemotherapy with or without radiotherapy is frequently used in the treatment of patients with resectable oesophageal cancer. Although the outcome of previously reported trials is contradictory, a recently reported large study on preoperative chemotherapy demonstrated a significant survival benefit[24]. The role of chemotherapy as palliative treatment for patients with recurrent or metastatic disease has been less well established. In one randomised study patients with advanced disease were randomised between treatment with cisplatin and 5-fluorouracil or cisplatin alone[25]. The higher response rate in the cisplatin/5-fluorouracil arm (37% versus 18%) did not translate in an improved survival, most likely because 16% treatment related deaths were observed in the cisplatin/5-fluorouracil arm compared to 0% in the cisplatin arm. In other randomised studies patients with oesophageal and gastric cancer are both included so it is difficult to draw conclusions[26,27].

In this phase I study we treated patients with metastatic oesophageal cancer with paclitaxel 100 mg/m^2 in combination with escalating doses of carboplatin administered on days 1, 8, 15, 29, 36 and 43. At carboplatin dose level AUC 5, the MTD was reached and consisted of a treatment delay of 2 or more weeks on day 29. The highest dose intensity was achieved at carboplatin dose level AUC 4 and therefore we recommend this dose level for further studies. In general this weekly schedule of carboplatin and paclitaxel was both well tolerated and convenient to administer in the outpatient setting. Although neutropenia grade 3 or 4 occurred in 77% of the patients, only 2 patients (5%) developed neutropenic fever. Therefore we consider the myelotoxicity to be acceptable. Other toxicities were either absent or mild.

Sehouli et al. recently reported on a phase I study in which patients with previously untreated ovarian cancer were treated with a weekly combination of paclitaxel 100 mg/m^2 (1-hour infusion) and escalating doses of carboplatin[28]. Patients were treated for 6 consecutives weeks followed by a 2-week break followed by another 6 weekly courses. Myelotoxicity was dose-limiting at carboplatin dose levels > AUC 2. The difference in MTD between this study and our study might be explained by the fact that we treated our patients for 3 consecutive weeks followed by a 1-week break. After a 1-week break myelotoxicity recovered in almost all patients treated at the recommended dose level. In addition, we administered only 6 weekly cycles and the MTD for carboplatin could be lower for 12 cycles due to cumulative myelotoxicity or neurotoxicity.

The achieved dose intensity calculated over 8 weeks at the recommended dose level of carboplatin AUC 3/ week and paclitaxel 75 mg/m^2/week is high in comparison with other schedules of carboplatin administered either as a single agent or in combination with paclitaxel. In patients with previously untreated ovarian cancer the MTD for 4 cycles of carboplatin as single agent was AUC 12 when carboplatin was administered every 4 weeks[29]

and AUC 7 when carboplatin was administered every 2 weeks with the use of granulocyte colony-stimulating factor[30], however at the cost of severe thrombocytopenia. In combination with paclitaxel 225 mg/m^2 the MTD for carboplatin was AUC 8 in a 3-weekly schedule, however also at the cost of considerable toxicity.

In previous clinical trials it has been demonstrated that concurrent carboplatin does not change the disposition of paclitaxel following 3-hour infusions[31,32]. Likewise, a number of reports documented unaltered pharmacokinetics of carboplatin due to pretreatment with paclitaxel at standard doses used in 3-weekly regimens[33,34]. Our current study adds to that knowledge by demonstrating that carboplatin also does not modulate paclitaxel disposition following shorter infusions. We also tested the hypothesis that carboplatin might alter the extent of paclitaxel protein binding, but found no effect on the fraction unbound paclitaxel relative to historic control data[23]. In line with several independent studies [reviewed in[35]], we noted that therapy-associated thrombocytopenia was less than expected in patients treated with the combination of paclitaxel and carboplatin. In the absence of a pharmacokinetic interaction, the reason for this phenomenon is still unclear, although several possible explanations have been invoked. Experimental studies have shown an antagonistic interaction between the two drugs in the megakaryoblast cell line MEG-01 as a model of a platelet precursor[36], which may involve induced production of haematopoietic cytokines, including thrombopoietin, possibly combined with gluthatione S-transferase-mediated detoxification of carboplatin[37]. Alternatively, we have recently shown that Cremophor EL, at concentrations achieved in the patients in the current study, acts as a protector for cisplatin-associated haematological side effects in both mice and cancer patients[38], presumably by modulation of accessory factors regulating haematopoietic progenitor cells through the operation of cytokine cascades[39]. Further studied beyond the scope of this trial will be required to fully elucidate the mechanisms underlying the platelet-sparing effect of the paclitaxel-carboplatin combination.
The overall response rate of 54% observed in this phase I study is high also in view of the fact that almost half of the patients had liver metastases. Because this regimen can be administered over a short period of time it is also attractive to explore its activity as induction treatment or as part of a combined-modality treatment.

In conclusion, carboplatin targeted at AUC 4 in combination with paclitaxel 100 mg/m^2 administered on days 1, 8, 15, 29, 36 and 43 is the recommended dose for untreated patients with advanced oesophageal cancer. Both the observed response rate and toxicity profile compare favourable to other cisplatin-based chemotherapy regimens used for patients with oesophageal cancer, and in addition to this, this regimen can be administered in an outpatient setting hereby improving patient convenience for this specific group of patients. Currently the recommended schedule is further examined in a randomised phase III study in patients with advanced ovarian cancer.

Refererences

1 Blot WJ, McLaughlin JK. The changing epidemiology of oesophageal cancer. Semin Oncol 1999; 26 (S15): 2-8.

2 Chow WH, Blot WJ, Vaughn TL et al. Body mass index and risk of adenocarcinoma on the oesophagus and gastric cardia. J Natl Cancer Inst 1998; 90: 150-5.

3 Lagergren J, Bergstrom R, Lindgren A et al. Symptomatic gastro-oesophageal reflux as a risk factor for oesophageal adenocarcinoma. N Engl J Med 1999; 340: 825-31.

4 Jankowski J, Wright NA, Meltzer S et al. Molecular evolution of the metaplasia dysplasia adenoma sequence in the oesophagus (MCS). Am J Pathol 1999; 154: 965-74.

5 Enzinger PC, Ilson DH, Kelsen DP. Chemotherapy in oesophageal cancer. Semin Oncol 1999; 26: 12-20.

6 Enzinger PC, Kulke MH, Clark JW et al. Phase II trial of irinotecan in patients with advanced adenocarcinoma of the oesophagus and stomach. (abstract) Proc Am Soc Clin Oncol 2000; 19: 1130.

7 Ilson D, Saltz L, Enzinger P et al. A phase II trial of weekly irinotecan plus cisplatin in advanced oesophageal cancer. J Clin Oncol 1999; 17: 3270-75.

8 Ilson DH, Ajani J, Bhalla K et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the oesophagus. J Clin Oncol 1998; 16: 1826-34.

9 Ilson DH, Forastiere A, Arquette M et al. A Phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the oesophagus. Cancer J 2000; 6: 316-23.

10 Van der Gaast A, Kok TC, Kerkhofs L et al. Phase I study of a biweekly schedule of a fixed dose of cisplatin with increasing doses of paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 1999; 80:1052-7.

11 Poleé MB, Eskens FALM, van der Burg MEL et al. Phase II study of a biweekly schedule of cisplatin and paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 2002; 86: 669-73.

12 Poleé MB, Verweij J, Siersema PD et al. Phase I study of a weekly schedule of a fixed dose of cisplatin and escalating doses of paclitaxel in patients with advanced oesophageal cancer. Eur J Cancer 2002; 38: 1495-500.

13 Fennely D, Aghajanian C, Shapiro F et al. Phase I and pharmacologic study of paclitaxel administered weekly in patients with relapsed ovarian cancer. J Clin Oncol 1997; 15: 187-92.

14 Akerley W, Glantz M, Choy H et al. Phase I trial of weekly paclitaxel in advanced lung cancer. J Clin Oncol 1998; 16: 153-8.

15 Perez EA, Vogel CL, Irwin DH et al. Multicentre phase II trial of weekly paclitaxel in women with metastatic breast cancer. J Clin Oncol 2001; 19: 4216-23.

16 Seidman AD, Hudis CA, Albanel J et al. Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. J Clin Oncol 1998; 16: 3353-61.

17 Belani CP. Interim analysis of phase II study of induction weekly paclitaxel/carboplatin regimens followed by maintenance weekly paclitaxel for advanced and metastatic non-small cell lung cancer. Semin Oncol 2001; 28 (4 suppl 14):14-8.

18 World Health Organisation. WHO handbook for reporting results of cancer treatment. WHO Offset Publ. No. 4. Geneva. World Health Organisation, 1979.

19 Calvert AH, Newell DR, Gumbrell LA et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7: 1748-56.

20 Sparreboom A, De Bruijn P, Nooter K et al. Determination of paclitaxel in human plasma using single solvent extraction prior to isocratic reversed-phase high-performance liquid chromatography with ultraviolet detection. J Chromatogr 1998; B 705: 159-64.

21 Brouwer E, Verweij J, De Bruijn P et al. Measurement of fraction unbound paclitaxel in human plasma. Drug Metab Dispos 2000; 28: 1141-5.

22 Brouwer E, Verweij J, Hauns B et al. Linearised colorimetric assay for Cremophor EL: application to pharmacokinetics after 1-hour paclitaxel infusions. Anal Biochem 1998; 261: 198-202.
23 Gelderblom H, Mross K, ten Tije AJ et al. Comparative pharmacokinetics of unbound paclitaxel during 1- and 3-hour infusions. J Clin Oncol 2002; 20: 574-81.
24 Medical Research Council Oesophageal Cancer Working Party: Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised trial. Lancet 2002; 359: 1727-33.
25 Bleiberg H, Conroy T, Paillot B et al. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 1997 ; 33: 1216-20.
26 Webb A, Cunningham D, Scarffe JH et al. A randomised trial comparing ECF with FAMTX in advanced oesophagastric cancer. J Clin Oncol 1997; 15: 261-7.
27 Vanhoefer E, Rougier P, Wilke H et al. Final results of a randomised phase III trial of sequential high dose methothrexate, fluorouracil and doxorubicin versus etoposide, leucovorin and fluorouracil versus infusional fluorouracil and cisplatin in advanced gastric cancer; a trial of the European Organisation for Research and Treatment of Cancer gastrointestinal tract cooperative group. J Clin Oncol 2001; 18: 2648-57.
28 Sehouli J, Stengel D, Elling D et al. First-line chemotherapy with weekly paclitaxel and carboplatin for advanced ovarian cancer: a phase I study. Gynecol Oncol 2002; 85:321-6.
29 Shapiro JD, Rothenberg ML, Sarosy GA et al. Randomised trial of dose-intensity with single agent carboplatin in patients with epithelial ovarian cancer. London Gynaecological Oncology Group. J Clin Oncol 1998; 16: 2426-34.
30 Lind MJ, Ghazal-Aswad S, Gumbrell L et al. Phase I study of pharmacologically based dosing of carboplatin with filgastrim support in women with epithelial ovarian cancer. J Clin Oncol 1996; 14: 800-5.
31 Aisner J, Belani CP, Kearns C et al. Feasibility and pharmacokinetics of paclitaxel, carboplatin, and concurrent radiotherapy for regionally advanced squamous cell carcinoma of the head and neck and for regionally advanced non-small cell lung cancer. Semin Oncol 1995; 5 (Suppl 12): 17-21.
32 Siddiqui N, Boddy AV, Thomas HD et al. A clinical and pharmacokinetic study of the combination of carboplatin and paclitaxel for epithelial ovarian cancer. Br J Cancer 1997; 75: 287-94.
33 Obasaju CK, Johnson SW, Rogatko A et al. Evaluation of carboplatin pharmacokinetics in the absence and presence of paclitaxel. Clin Cancer Res 1996; 2: 549-52.
34 Fujiwara K, Yamauchi H, Suzuki S et al. The platelet-sparing effect of paclitaxel is not related to changes in the pharmacokinetics of carboplatin. Cancer Chemother Pharmacol 2001; 47: 22-6.
35 Kearns CM, Egorin MJ. Considerations regarding the less-than-expected thrombocytopenia encountered with combination paclitaxel/carboplatin chemotherapy. Semin Oncol 1997; 1 (Suppl 2): S2-91-6.
36 Gaminski AD, Harnett PR, DeFazio A. Carboplatin and paclitaxel interact antagonistically in a megakaryoblast cell line – A potential mechanism for paclitaxel-mediated sparing of carboplatin-induced thrombocytopenia. Cancer Chemother Pharmacol 2001; 48: 229-34.
37 Pertussine E, Ratajczak J, Majka M et al. Investigating the platelet-sparing mechanism of paclitaxel/carboplatin combination chemotherapy. Blood 2001; 97: 638-44.
38 Gelderblom H, Loos WJ, Verweij J et al. Modulation of cisplatin pharmacodynamics by Cremophor EL: experimental and clinical studies. Eur J Cancer 2002 ; 38: 205-13.
39 Bertoncello I, Krieger AB, Woodcock DM et al. Haematopoietic radioprotection by Cremophor EL: a poly ethoxylated castor oil. Int J Radiat Biol 1995; 67: 57-64.

CHAPTER 7

PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH ADVANCED OESOPHAGEAL CANCER TREATED WITH CISPLATIN BASED COMBINATION CHEMOTHERAPY

M.B. Polee[1], W.C.J. Hop[2], T.C. Kok, F.A.L.M. Eskens[1], M.E.L. van der Burg[1], T.A.W. Splinter[1], P.D. Siersema[3], H.W. Tilanus[4], G. Stoter[1] and A. van der Gaast[1]

Departments of [1]Medical Oncology, [2]Epidemiology & Biostatistics, [3]Gastroenterology and Hepatology and [4]Surgery. Erasmus Medical Centre. Rotterdam, The Netherlands

Br J Cancer 2003; 89: 2045-50

Summary

Purpose: The objective of this study was to identify prognostic factors for survival in patients with advanced oesophageal cancer who are treated with cisplatin-based combination chemotherapy.

Methods: We analysed baseline characteristics of 350 patients who were treated in 6 consecutive prospective trials with one of the following regimens: cisplatin/etoposide, cisplatin/etoposide/5-fluorouracil, cisplatin/paclitaxel (weekly) and cisplatin/paclitaxel (biweekly). Predictive factors in univariate analyses were further evaluated using multivariate analysis (Cox regression).

Results: Median survival of all patients was 9 months. One, 2 and 5-year survival rates were 33%, 12% and 4%, respectively. The main prognostic factors were found to be: WHO performance status (0 or 1 versus 2), lactate dehydrogenase (normal versus elevated), extent of disease (limited disease defined as loco-regional irresectable disease or lymph node metastases confined to either the supraclavicular or celiac region versus extensively disseminated disease) in addition to type of treatment (weekly or biweekly cisplatin/paclitaxel regimen versus 4-weekly cisplatin/etoposide with or without 5-fluorouracil). Although weight loss, liver metastases and alkaline phosphatase were significant prognostic factors in univariate analyses, these factors lost their significance in multivariate analyses. Median survival for patients without any risk factors was 12 months compared to only 4 months in patients with WHO 2 plus elevated LDH and extensive disease.

Conclusion: Performance status, extent of disease, LDH and the addition of paclitaxel to cisplatin are independent prognostic factors in patients with advanced oesophageal cancer who are treated with cisplatin-based combination chemotherapy.

Introduction

The outlook for patients with oesophageal cancer is poor. Many patients who present with symptoms of oesophageal obstruction already have locally advanced or metastatic disease. The 5-year survival rate following surgery in patients thought to have localised disease is only 20%[1,2]. Most patients with oesophageal cancer need palliative treatment for local recurrence and/or metastases at some stage of the disease. Palliative surgery to relieve dysphagia carries a high morbidity and the median survival following surgery in these patients is 5-8 months. Therefore palliative surgery has been replaced by less aggressive treatments. Intraluminal radiotherapy, intubation with self-expanding metal stents and laser therapy are all effective in palliation of dysphagia and associated with less morbidity than surgery[3].

Median survival after these types of non-invasive palliative treatment is only 3-6 months, comparable to the survival of patients with untreated advanced oesophageal cancer[4,5]. Despite palliation of dysphagia, quality of life rapidly deteriorates in most patients due to disease related symptoms such as pain, fatigue, appetite loss and constipation[6,7].

Chemotherapy may offer palliation and/or prolongation of survival in patients with advanced oesophageal cancer. Combination chemotherapy, usually cisplatin based, has been evaluated in several phase II studies and response rates of 25-40% have been reported[8]. However, the impact of chemotherapy on survival and quality of life is unknown due to a lack of randomised phase III studies comparing chemotherapy to supportive care alone. Furthermore, it is unclear which patients will benefit from palliative chemotherapy and whether potential benefits outweigh the toxicities caused by such treatment. In one of the few randomised trials that have been performed in patients with metastatic disease the combination cisplatin and 5-fluorouracil was more effective than cisplatin alone but at the cost of severe toxicity[9]. In recent phase II studies, response rates after treatment with cisplatin combined with either paclitaxel[10] or irinotecan[11] seemed to be higher than after treatment with cisplatin and 5-fluorouracil; randomised studies, however, have not been performed thus far.

The outcome of chemotherapy and the prognosis of patients with oesophageal cancer most probably depends on both patient- and disease characteristics. Knowledge of these factors may be useful for patient and treatment selection. In this study we analysed a number of putative prognostic factors in patients who were treated in 6 consecutive prospective clinical trials with cisplatin-based chemotherapy.

Patients and methods

Patient population

Patients were entered in 6 consecutive prospective studies with cisplatin-based chemotherapy. The details of these studies are listed in *Table 1 (see page 78)*. All patients had either squamous cell carcinoma or adenocarcinoma of the oesophagus or oesophago-gastric junction. Eligibility criteria for all these trials included histologically proven metastatic or unresectable oesophageal cancer, a life expectancy of more than 12 weeks; age ≥ 18 years; WHO performance status 0-2; informed consent; adequate haematological, renal and hepatic functions defined as: granulocytes ≥ 1.5 x 10^9 /L, platelets ≥ 100 x 10^9/L, total bilirubin ≤ 1.5 x upper normal limit and creatinine ≤ 120 mmol/L. Prior radiotherapy was allowed if not involving more than 30% of the bone marrow. Prior chemotherapy was not allowed. Patients had no history of other malignancies except for non-melanomatous skin cancer or a cured malignancy more than 5 years prior to enrolment. Further exclusion criteria were: pre-existing neurotoxicity greater than Common Toxicity Criteria (CTC) grade 1, active

Table 1. ***Studies characteristics***

Study	Design (phase)	Tumour type	Patients no.	Chemotherapy	Schedule		Ref.
1	II	SCC	73	cisplatin	80 mg/m²	d1	
				etoposide	100 mg	d1,2	23
				etoposide	200 mg/m² p.o.	d3,5	
				administered every 4 weeks			
2	II	SCC	71	cisplatin	80 mg/m²	d1	
				etoposide	125 mg/m²	d1	
				etoposide	200 mg/m² p.o.	d3,5	24
				5-fluorouracil	375 mg/m²	d1-4	
				folinic acid	6x30 mg p.o.	d1-4	
				administered every 4 weeks			
3	II	adenoca	68	cisplatin	80 mg/m²	d1	
				etoposide	125 mg/m²	d1	
				etoposide	200 mg/m² p.o.	d3,5	25
				5-fluorouracil	375 mg/m²	d1-4	
				folinic acid	6x30 mg p.o.	d1-4	
				administered every 4 weeks			
4	I	SCC+ adenoca	64	cisplatin	60 mg/m²	d1	
				paclitaxel	100 mg/m² -	d1	26
				escalating to	200 mg/m²		
				administered every 2 weeks			
5	I	SCC + adenoca	24	cisplatin	70 mg/m²	d1	
				paclitaxel	80 mg/m² -	d1	27
				escalating to	110 mg/m²		
				administered every week			
6	II	SCC + adenoca	51	cisplatin	60 mg/m²	d1	
				paclitaxel	180 mg/m²	d1	28
				administered every 2 weeks			

Abbreviation: SCC: squamous cell carcinoma

infection or other serious underlying medical condition which would impair the ability of the patient to receive the planned treatment, inadequate calorie- and fluid intake and mental disorders not permitting adequate informed consent.

Pre-treatment evaluations consisted of a complete medical history, physical examination, complete blood cell count and serum biochemistry, computerised tomography (CT) scan of the chest and upper abdomen and ultrasonography of the supraclavicular nodes when appropriate. Patients with the primary tumour in situ were also evaluated by endoscopy. The response to chemotherapy was evaluated by CT scan, and by ultrasonography and endoscopy when appropriate. In patients with measurable or evaluable disease, response was evaluated using WHO response criteria[12].

Statistical Methods

Pre-treatment characteristics that were analysed for prognostic significance were: age, sex, performance status, weight loss (<5, 5 - 10, > 10 %), time from diagnosis to start of chemotherapy, histology (adenocarcinoma or squamous cell carcinoma), tumour grade, haemoglobin, alkaline phosphatase, lactate dehydrogenase (LDH), treatment with a dose-dense combination of cisplatin and paclitaxel (study 4,5,6) versus a combination of cisplatin, etoposide with or without 5-fluorouracil (study 1,2,3), extent of disease, and response to treatment.

Patients with locally irresectable disease without metastases were categorised as having loco-regional disease, patients with lymph node metastases confined to either the celiac or supraclavicular region as having limited disseminated disease and patients with distant metastases or lymph node metastases in both celiac and supraclavicular lymph nodes as having extensively disseminated disease.

Statistical analysis was performed using the SPSS software (SPSS inc, Chicago, IL). Survival was defined as the time elapsing from start of chemotherapy to death or to the date of last follow-up. All survival data had been updated to August 2001. Survival curves according to the putative prognostic factors were using the method of Kaplan and Meier[13] and were compared with the log-rank test[14]. The factors which were univariately significantly related to prognosis were further evaluated in multivariate analyses. The Cox proportional hazards model (Cox regression) was used with backward elimination to find the most important independent prognostic factors[15] (Cox 1972). P = 0.05 (two-sided) was considered the limit of significance.

To circumvent difficulties with respect to the time bias[16], the association between tumour response (partial or complete) and survival was assessed only in patients who survived 4 months after start of treatment. P = 0.05 (two-sided) was considered the limit of significance.

Results

A total of 351 patients were analysed. All patients received at least one course of cisplatin-based combination chemotherapy. One patient had no follow up and was excluded from further analysis. The characteristics of the remaining 350 patients are listed in *Table 2*. Patients included in the database were all registered before June 30, 1999 and the date of reference for the survival analysis was 31 August 2001. At the time of this analysis 27 patients were alive. The median survival of all patients was 9 months (95 % confidence interval 8-10 months). The 1, 2 and 5-year survival rates were 33%, 12% and 4%, respectively.

Table 2. ***Patient characteristics (n=350)***

Characteristic	No. of patients	(%)
Sex		
Male	278	79
Female	72	21
Age (years)		
Median	56	
Range	28-78	
WHO performance status		
0	66	19
1	219	63
2	63	18
Weight loss (%)		
< 5	121	35
5-10	91	26
> 10	131	37
Unknown	7	2
Histology		
Adenocarcinoma	145	41
Squamous cell carcinoma	199	57
Undifferentiated carcinoma	6	2
Extent of disease		
Locally advanced/unresectable	42	12
Limited disseminated disease[1]	138	39
Extensive disseminated disease[2]	170	49

[1] lymph node metastases confined to either the celiac or supraclavicular region

[2] distant metastases or lymph node metastases in both celiac and supraclavicular lymph nodes

*Table 3. **Univariate survival analysis***

Characteristic	Categories	Patients (no)	Survival Median (mo.)	1-year (%)	Logrank P
Age (years)	< 60	215	9	29	0,235
	> 60	135	11	39	
Gender	Female	72	11	42	0,390
	Male	278	9	30	
Performance-status (WHO)	0	66	12	45	< 0.001[a]
	1	219	10	35	
	2	63	5	13	
Weight loss (%)	< 5	121	12	39	0.006[a]
	5 - 10	91	9	32	
	> 10	131	9	29	
Tumour type	SCC	199	9	32	0.550
	Adenoca	145	10	32	
Tumour differentiation[b]	well/moderate	119	10	43	0.102
	poor	131	9	28	
Liver metastases	No	269	10	37	< 0.001
	Yes	81	7	21	
No. metastatic sites	0	42	10	36	0.02[a]
	1	190	10	34	
	> 1	118	7	31	
Extent of disease	loco regional	42	10	36	< 0.001[c]
	limited dissem.	138	12	41	< 0.001[c]
	extensive dissem.	170	7	26	
Interval between diagnosis and start treatment	< 6 months	295	10	34	0.65
	> 6 months	55	8	27	
Haemoglobin	normal	228	10	36	0.253
	abnormal	122	9	28	
Alkaline Phosphatase	normal	246	10	37	0.001
	elevated	104	7	24	
LDH	normal	296	11	46	<0.001
	elevated	54	8	16	
Paclitaxel	yes	139	10	40	0.002
	no	211	9	29	

[a] trend test, [b] tumour differentiation was unknown in 100 patients, [c] versus extended dissemination

Univariate analysis

Table 3 (see page 81) summarises the results of the univariate survival analyses. Significant variables related to survival were: performance status, weight loss, LDH, alkaline phosphatase, liver metastases, number of metastatic sites, extent of disease and treatment with a dose-dense cisplatin and paclitaxel chemotherapy regimen. Patients with loco-regional irresectable disease and patients with limited disseminated disease had a significantly better survival than patients with extensively disseminated disease.

Multivariate analysis

Multivariate analysis showed that good performance score, limited disseminated disease, normal LDH and treatment with a dose-dense schedule of cisplatin and paclitaxel were independent prognostic factors (*Table 4*). WHO performance status and extent of disease are the strongest predictors for survival. LDH was a relevant risk factor but was elevated in only 15% of patients. The type of treatment is an additional (external) factor determining prognosis.

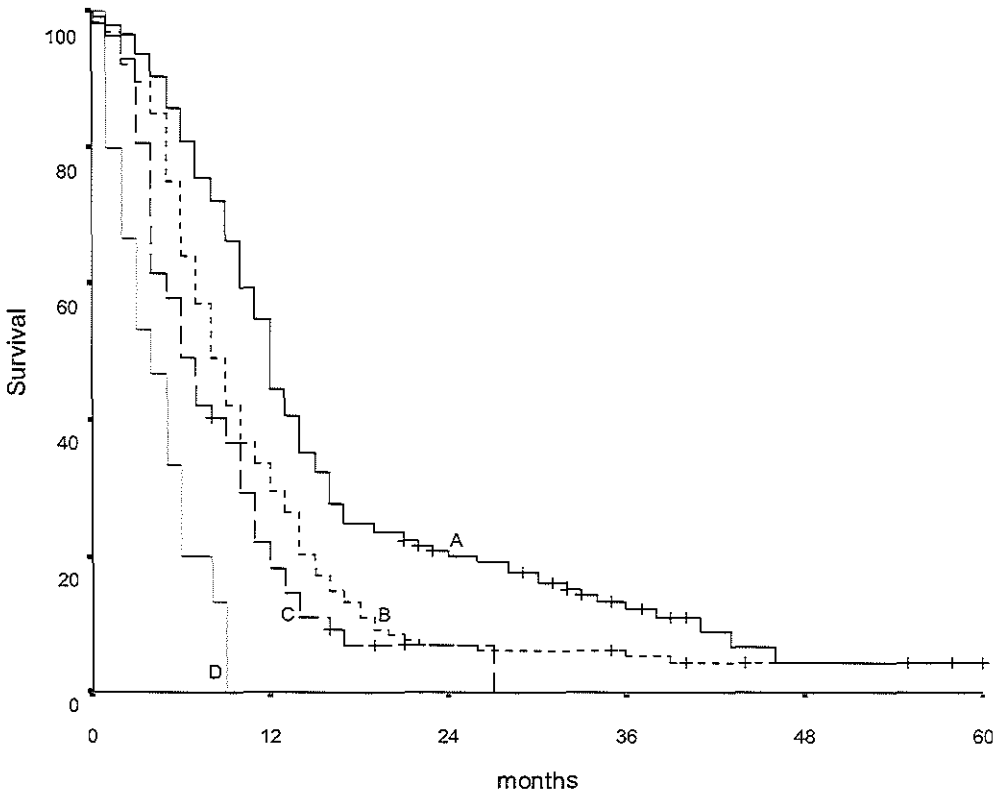
Table 4. ***Cox multivariate regression model***

Characteristic	RDR	95% CI RDR	P
Performance WHO			
0	1		
1	1.3	1.0 - 1,8	0.069
2	2.4	1.6 - 3.5	< 0.001
Extent of disease			
loco regional	0.7	0.5 - 1.0	0.08
limited dissemination	0.7	0.5 - 0.9	0.006
extensive dissemination	1		
LDH			
Normal	1		
Elevated	1.5	1.1 - 2.0	0.021
Paclitaxel			
Yes	1		
No	1.3	1.1 - 1.7	0.015

Abbreviations: RDR: relative death rate, CI: confidence interval

We combined the patient characteristics performance status, extent of disease and LDH to constitute 4 groups. WHO performance score of 2, extensive disseminated disease and an elevated LDH were risk factors for poor survival and the survival of patients with either 0, 1, 2 or 3 risk factors present was estimated. As is shown in *Figure 1* there is a large difference

Figure 1: ***Kaplan Meier survival curves for patients with 0-3 risk factors.***
(A = no risk factor, B = 1 risk factor, C = 2 risk factors, D = 3 risk factors).
The risk factors are: WHO 2, extensive disseminated disease and elevated LDH



in survival between these four patient groups. The median survival of patients with 0, 1, 2, and 3 risk factors was 12, 8, 6 and 4 months, respectively. The 1-year survival rates were 45%, 30%, 18% and 0%, respectively. In the group of patients with 3 risk factors no patient survived more than 9 months. Cox regression showed that the type of treatment did not significantly influence the relative differences in death rates between these four patient groups.

The relation between tumour response and survival was evaluated in patients who survived 4 months. Of the responding 137 patients the median survival was 15 months as compared to 8 months of the 146 non-responders (P< 0,001). Cox-regression showed that the response was a favourable prognostic factor independent of type of treatment and number of risk factors present. Adjusted for both these factors the death rate among responding patients was reduced by 70 percent (p< 0,001).

The characteristics of the group of patients with a survival of more than 3 years are listed in *Table 5*. The majority of these patients had the following characteristics: a performance status 0 or 1, limited disease, partial or complete response to chemotherapy and additional treatment after chemotherapy with either radiotherapy or surgery. Sixty of 178 patients with loco-regional disease or limited lymph node metastases received additional treatment, 31 patients received radiotherapy to a total dose of 50 Gy and 29 patients underwent an oesophageal resection. Seventeen of these 60 patients (28%) survived at least 3 years.

Table 5. ***Patient characteristics of patients with a survival of 3 years (n=20)***

Characteristic	No. of patients	(%)
WHO performance status		
0	10	50
1	8	40
2	2	10
Extent of disease		
loco-regional	5	25
limited disseminated	12	60
extensively disseminated	3	15
Response to chemotherapy treatment		
complete response	4	20
partial response	14	70
stable disease	2	10
Additional treatment after chemotherapy		
salvage surgery	13	65
radiotherapy	4	20
none	3	15

Discussion

Knowledge of prognostic factors is essential for the management of individual patients and these factors should be taken in account for in the design of randomised trails and in interpreting the results of such trials.

In patients with resectable oesophageal cancer survival correlates closely with the extent of tumour infiltration in the oesophageal wall and the presence or absence of lymph node metastases[17]. Weight loss has also been identified as an independent prognostic factor in patients who were surgically treated with or without pre-operative chemotherapy[18]. Performance status has been reported to be an important prognostic factor in patients

treated with radiotherapy alone[19]. In a number of studies the prognostic significance of biological factors such as oncogenes, tumour suppressor genes and growth factors has been studied. Overexpression of p53, p21 and vascular endothelial growth factor has been identified as prognostic factors by some authors[20,21] but the results of these studies are not always consistent and therefore these factors are currently not used in daily routine. Prognostic factor analyses in patients with locally advanced or metastatic oesophageal cancer treated with chemotherapy are scarce. Andreyev et al. identified weight loss as an independent prognostic factor in patients with several gastrointestinal malignancies but weight loss was not statistically significant in the subgroup of patients with advanced oesophageal cancer[22].

In this study we analysed pre-chemotherapy characteristics in 350 patients with locally advanced or metastatic oesophageal cancer who were treated with cisplatin-based chemotherapy. In multivariate analysis, performance status, extent of disease, LDH and the addition of paclitaxel to cisplatin were identified as the most important prognostic factors. Weight loss dropped out of the multivariate model when performance status was also included. This can be explained by the finding that most patients with a poor performance status also had significant weight loss. Metastatic involvement of the liver and the total number of metastatic sites lost their importance when studied with disease extent.

Based on performance score, LDH and extent of disease we were able to identify 4 prognostic groups. The median survival of patients with 0, 1, 2 and 3 risk factors was 12, 8, 6 and 4 months, respectively. Considering a median survival of 4 months for patients with 3 risk factors and the fact that none of these patients survived beyond 9 months it is unlikely that these patients had any benefit from chemotherapy, at least with respect to survival. Tumour response as a post-treatment factor was found to be a favourable prognostic sign which was independent of type of treatment and number of risk factors present. The objective merits of chemotherapy in the different patient groups can only be demonstrated in a randomised trial that includes stratification for risk factors and measurement of quality of life.

Patients with lymph node metastases confined to either the celiac or supraclavicular lymph nodes had a better survival than patients with more extensive disease. The 3-year survival rate of the 136 patients with lymph node metastases only was 11%. Most of the patients who survived more than 3 years after start of chemotherapy were additionally treated with surgery or radiotherapy.

We found that patients treated in the more recent studies with dose-dense schedules of cisplatin and paclitaxel had a significantly better survival compared to patients treated with cisplatin and etoposide with or without 5-fluorouracil. The dose dense schedules might bias the comparison of treatment schedules. Although the total dose of cisplatin was more or less

comparable the dose intensity (mg/m²/week) was significantly higher in the cisplatin and paclitaxel regimens. The improved outcome in the latter studies can be due to either the addition of paclitaxel or to the dose-dense character of these schedules.

In conclusion, performance score, extent of disease and LDH are independent prognostic factors in patients with advanced oesophageal cancer who are treated with cisplatin-based combination chemotherapy. Patients with a poor performance, extensive disseminated disease and an elevated LDH have a poor outcome and should not be treated with cisplatin-based combination chemotherapy.

References

1 Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. Br J Surg 1990; 77: 845-57.

2 Millikan KW, Silverstein J, Hart V, Blair K, Bines S, Roberts J, Doolas A. A 15-year review of oesophagectomy for carcinoma of the oesophagus and cardia. Arch Surg 1995; 130: 617-24.

3 Siersema PD, Dees J, van Blankenstein M. Palliation of malignant dysphagia from oesophageal cancer. Scand J Gastroenterol 1998; 33 suppl 225: 75-84.

4 Knyrim K, Wagner HJ, Bethge N, Keymling M, Vakil N. A controlled trial of an expansile metal stent for palliation of oesophageal obstruction due to inoperable cancer. N Engl J Med 1993; 329: 1302-7.

5 Low DE, Pagliero KM. Prospective randomised trial comparing brachytherapy and laser photoablation for palliation of oesophageal cancer. J Thorac Surg 1992; 104: 173-8.

6 Blazeby JM, Williams MH, Brookes ST, Alderson D, Farndon JR. Quality of life measurement in patients with oesophageal cancer. Gut 1995; 37: 505-8.

7 Blazeby JM, Farndon JR, Donovan J, Alderson D. A prospective longitudinal study examining the quality of life in patients with oesophageal cancer. Cancer 2000; 88: 1781-7.

8 Enzinger PC, Ilson DH, and Kelsen DP. Chemotherapy in oesophageal cancer. Semin Oncol 1999; 26: 12-20.

9 Bleiberg H, Conroy T, Paillot B, Lacave AJ, Blijham G, Jabob JH, Bedenne, Namer M, De Besi P, Gay F, Collette L, Sahmoud T. Randomised phase II study of cisplatin and 5-fluorouracil (5-FU) versus cisplatin alone in advanced squamous cell oesophageal cancer. Eur J Cancer 1997; 33: 1216-22.

10 Ilson DH, Forastiere A, Arquette M, Costa F, Heelan R, Huang Y, Kelsen PD. A Phase II trial of paclitaxel and cisplatin in patients with advanced carcinoma of the oesophagus. Cancer J 2000; 6: 316-23.

11 Ilson DH, Saltz L, Enzinger P, Huang Y, Kornblith A, Gollub M, O'Reilly E, Schwartz G, De Groff J, Gonzalez G, Kelsen PD. Phase II trial of weekly irinotecan plus cisplatin in advanced oesophageal cancer. J Clin Oncol 1999; 17: 3270-5.

12 World Health Organisation. WHO handbook for reporting results of cancer treatment. WHO Offset Publ. No.4. Geneva: World Health Organisation, 1979.

13 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-81.

14 Mantel N. Evaluation of survival data and two new rank order statistics in its consideration. Cancer Chemother Rep 1966; 50: 163-70.

15 Cox DR. Regression models and life-tables (with discussion). J R Stat Soc Ser B 1972; 34: 187-220.

16 Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumour response. J Clin Oncol 1983; 1: 710-9.

17 Kato H, Tachimori Y, Watanabe H, Iizuka T. Evaluation of the new (1987) TNM Classification for thoracic oesophageal tumours. Int J Cancer 1993; 53: 220-3.
18 Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, Estes N, Haller DG, Ajani J, Kocha W, Minsky BD, Roth JA. Chemotherapy followed by surgery compared with surgery alone for localised oesophageal cancer. N Engl J Med 1998; 339: 1979-84.
19 Coia LR, Minsky BD, Berkey BA, John MJ, Haller D, Landry J, Pisansky TM, Willett CG, Hoffman JP, Owen JB, Hanks GE. Outcome of patients receiving radiation for cancer of the oesophagus: results of the 1992-1994 patterns of care study. J Clin Oncol 2000; 18: 455-62.
20 Ikeda G, Isaji S, Chandra B, Watanabe M, Kawarada Y. Prognostic significance of biologic factors in squamous cell carcinoma of the oesophagus. Cancer 1999; 86: 1396-405.
21 Shimada H, Takeda A, Nabeya Y, Okazumi SI, Matsubara H, Funami Y, Hayashi H, Gunji Y, Suzuki T, Ochiai T. Clinical significance of serum vascular endothelial growth factor in oesophageal squamous cell carcinoma. Cancer 2000; 92: 663-9.
22 Andreyev HJN, Norman AR, Oates J and Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies. Eur J Cancer 1998; 34: 503-9.
23 Kok TC, Van der Gaast A, Dees J, Eijkenboom WMH, Van Overhagen H, Stoter G, Tilanus HW, Splinter TAW. Cisplatin and etoposide in oesophageal cancer: a phase II study. Br J Cancer 1996; 74: 980-4.
24 Polee MB, Kok TC, Siersema PD, Tilanus HW, Splinter TAW, Stoter G, Van der Gaast A. Phase II study of the combination cisplatin, etoposide, 5-fluorouracil and folinic acid in patients with advanced squamous cell carcinoma of the oesophagus. Anticancer Drugs 2001; 12: 513-7.
25 Kok TC, Splinter TAW, Van der Gaast A. Phase II study of the combination cisplatin, etoposide, 5-fluorouracil and folinic acid in patients with adenocarcinoma of the oesophagus. Proc Amer Soc Clin Oncol 1997; 16.
26 Van der Gaast A, Kok TC, Kerkhofs L, Siersema PD, Tilanus HW, Splinter TAW. Phase I study of a biweekly schedule of a fixed dose of cisplatin with increasing doses of paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 1999; 80: 1052-7.
27 Polee MB, Verweij J, Siersema PD, Tilanus HW, Splinter TAW, Stoter G, Van der Gaast A. Phase I study of a weekly schedule of a fixed dose of cisplatin and escalating doses of paclitaxel in patients with advanced oesophageal cancer. Eur J Cancer 2002; 38: 1495-500.
28 Polee MB, Eskens FALM, van der Burg MEL, Splinter TAW, Siersema PD, Tilanus HW, Verweij J, Stoter G, Van der Gaast A. Phase II study of a biweekly schedule of cisplatin and paclitaxel in patients with advanced oesophageal cancer. Br J Cancer 2002; 86: 669-7.

Chapter 8

Summary, conclusions and perspectives

SUMMARY, CONCLUSIONS AND PERSPECTIVES

The incidence of oesophageal cancer is rising, especially due to a rapid increase of the incidence of adenocarcinomas in the distal oesophagus and gastro-oesophagal junction. The prognosis of patients with oesophageal cancer remains poor as most patients present with irresectable tumours and/or metastatic disease. Even patients with seemingly localised disease treated with a radical resection have a relatively poor prognosis due to the development of local recurrence and / or metastatic disease. Therefore there is a potential role for chemotherapy in the treatment of oesophageal cancer, either as part of multi-modality treatment in patients with localised disease or as palliative treatment in patients with advanced disease. This thesis describes several phase I and II studies exploring new chemotherapy regimens in the treatment of oesophageal cancer.

The first study was based on the traditional presumption that the activity of a combination regimen can be improved by the addition of other active agents. In a previous study the combination of cisplatin and etoposide showed promising activity and acceptable toxicity in the treatment of patients with advanced squamous cell carcinoma of the oesophagus. The addition of 5-fluorouracil and leucovorin to this regimen seemed rational.

Chapter 2 describes this phase II study of the combination of cisplatin, etoposide, 5-fluorouracil and folinic acid in patients with advanced squamous cell carcinoma of the oesophagus. Myelosuppression and mucositis were the predominant toxicities. The observed haematological toxicity consisted of leucocytopenia grade 3 or 4 in 33% and thrombocytopenia grade 4 in 7% of patients. Febrile leucocytopenia occurred in 19% of patients and all but one patient had also a concurrent mucositis. In this study, we observed an overall response rate of 34% in 68 evaluable patients, a median survival of 9 months and a 1-year survival rate of 36%. Although not investigated in a randomised study, leucocytopenic fever seemed to occur more frequently after treatment with this 4-drug combination than after treatment with cisplatin and etoposide alone. This was most probably a result of the concurrent mucositis caused by the addition of 5-fluorouracil and folinic acid.

In the next 4 studies we investigated dose-dense combinations of paclitaxel in combination with either cisplatin and carboplatin. Weekly or biweekly administration offers a chance to increase the dose-intensity of these agents. This is particularly interesting for cisplatin, since a dose-response relationship for this agent has been suggested. Dose-dense administration could also be attractive for a phase specific agent as paclitaxel, because more frequent exposure may enhance its apoptotic an anti-angiogenic effects. It has been shown that paclitaxel can be administered weekly with surprisingly mild myelotoxicity.

Chapter 3 presents a phase I study with the combination of cisplatin and paclitaxel administered weekly to patients with advanced oesophageal cancer. Patients received escalating doses of paclitaxel in combination with a fixed dose of cisplatin of 70 mg/m² on days 1,8,15,29,36 and 43. Dose limiting toxicity was observed at a paclitaxel dose of 110 mg/m². Gastrointestinal toxicity, especially diarrhea, appeared to be dose limiting. Two patients died of neutropenic enterocolitis. The relatively high frequency of severe diarrhea in this study was unexpected and remained unexplained. An overall response rate of 50%, a median survival of 16 months and a 1-year survival rate of 58 % seemed to compare favourable to those reported in other studies on advanced oesophageal cancer. Ten patients with irresectable disease or lymph node metastases confined to the celiac or supraclavicular region received additional local treatment and 7 of these patients were disease free after a median follow up of 32 months. We conclude that cisplatin 70 mg/m² in combination with paclitaxel 100 mg/m² administered on days 1, 8, 15, 29, 36 and 43 is the recommended dose and that further evaluation of this regimen as induction treatment is warranted.

In **chapter 4** a biweekly combination of cisplatin 60 mg/m² and paclitaxel 180 mg/m² was evaluated in a phase II study in patients with advanced oesophageal cancer. Fifty-one patients were included and all patients were able to complete 3 cycles of treatment. Responding patients received up to 8 cycles. Haematological toxicity consisted of grade 3 or 4 neutropenia in 70% of patient, however neutropenic fever did not occur. Sensory neurotoxicity was the predominant non-haematological toxicity; grade 1 and 2 neurotoxicity was observed in 43% and 20 % of patients, respectively. The overall response rate was 43% with a median response duration of 8 months. The median survival for all patients was 9 months and the 1-year survival rate was 43%. The observed response rates are in line with response rates reported in other studies exploring cisplatin, paclitaxel and/or 5-fluorouracil combinations. However, the observed toxicity in our study, especially the absence of neutropenic fever and other severe complications, compares favourably to those reported in other studies.

In **chapter 5** this biweekly cisplatin and paclitaxel combination was investigated in a neo-adjuvant setting in 50 patients with a resectable sqamous cell carcinoma of the oesophagus. Patients were evaluated after 3 cycles, non-responding patients were referred for surgery and responding patients received 3 additional cycles before surgery. The treatment was well tolerated and 94 % of patients completed 3 cycles of chemotherapy. The overall response rate was 59 %. Forty-five patients (90%) underwent an oesophageal resection and the mortality rate was not apparently increased. Pathological examination showed no residual tumour in 7 patients (14%) and a radical resection in 38 patients (76 % of all patients). The median survival was 20 months and the 1- and 3- year survival were 68 and 32%, respectively. The high number of complete responses could be either the result of the dose-dense cisplatin and paclitaxel regimen or the fact that we administered additional cycles of

chemotherapy to responding patients. Further evaluation comparing this treatment with other treatment regimens in a randomised trial is warranted.

Chapter 6 describes a phase I study of weekly administration of carboplatin and paclitaxel in patients with metastatic oesophageal cancer. The advantage of a paclitaxel/carboplatin regimen over a cisplatin/paclitaxel regimen is that it can be given as an outpatient treatment and probably induces less neurotoxicity. The paclitaxel was administered over 1 hour at a fixed dose of 100 mg/m^2 per administration, and the starting dose of carboplatin was set at a targeted AUC of 2 mg•min/mL. Dose-limiting toxicity was observed at a carboplatin AUC of 5 mg•min/mL and consisted of treatment delay due to myelosuppression. The highest dose intensity (> 95% of the planned dose over time) was achieved with a carboplatin AUC of 4 mg•min/mL. Haematological toxicity consisted of neutropenia grade 3 or 4 in 77% of the patients, however neutropenic fever in only 5% of patients. Non-haematological toxicity was usually mild. Pharmacokinetic analysis showed that carboplatin does not change the disposition of paclitaxel following 1-hour infusion. The observed overall response rate was 54%. The median duration of response was 9 months. The median survival for all 40 patients was 11 months, with a 1-year survival rate of 46 %. The achieved dose intensity is high in comparison with other schedules of carboplatin administered either as a single agent or in combination with paclitaxel. This weekly combination of carboplatin and paclitaxel seems to be an attractive induction regimen because it is well tolerated, convenient to administer in the outpatient setting and it can be administered in a short period of time.

The role of cisplatin-based combination chemotherapy in the palliation of advanced oesophageal cancer is unclear due to a lack of randomised studies that compare treatment with chemotherapy versus best supportive care. It is also unknown which patient- and disease characteristics are important in the decision to treat these patients with chemotherapy.

Chapter 7 presents a retrospective study in which we analysed a number of putative prognostic factors in 350 patients who were treated in 6 consecutive clinical trials with cisplatin-based chemotherapy. In multivariate analysis, performance status, extent of disease and Lactate Dehydrogenase (LDH) were identified as independent prognostic factors. Based on these 3 factors we were able to identify 4 prognostic groups. The median survival of patients with 0, 1, 2 and 3 risk factors was 12, 8, 6 and 4 months, respectively. The clear difference in median survival between these groups demonstrates the importance of these prognostic factors in the design of randomised trails and in interpreting the results of such trials. Moreover it is clear that it is impossible to compare results of different phase II studies with respect to survival.

Conclusions

Cisplatin-based combination chemotherapy has been shown to be moderately effective in the treatment of oesophageal cancer. However, this treatment was often poorly tolerated, especially by patients with advanced disease. The combination regimens we investigated were different from those that were previously used in 2 aspects: firstly we added paclitaxel to a platinum analogue and secondly we designed dose-dense combination regimens. Weekly and biweekly administration resulted also in high dose-intensities of the investigated agents. The question whether these new regimens are more effective than traditional regimen such as cisplatin/5-fluorouracil can only be answered by a randomised trial. However the observed toxicity after treatment with biweekly cisplatin/paclitaxel or weekly carboplatin / paclitaxel is surprisingly mild and suggests a favourable toxicity profile compared to the most frequently used traditional regimens. Noteworthy is the low frequency of neutropenic fever and the fact that only few patients had to be admitted for reasons of toxicity after treatment with biweekly cisplatin/paclitaxel or weekly carboplatin/paclitaxel. This last combination is particularly interesting because it can be administered in an outpatient setting.

Performance score, extent of disease and LDH are independent prognostic factors in patients with advanced oesophageal cancer that can be used in treatment and patient selection.

Perspectives

Theoretically there are several ways to improve the prognosis of patients with oesophageal cancer. By means of a strict follow-up of patients with high-grade dysplastic oesophageal lesions and early detection of (pre) malignant lesions, patients can be diagnosed in an early stage of disease with a more favorable prognosis. The increasing knowledge of the molecular evolution of the metaplasia – dysplasia – adenocarcinoma sequence will allow us to identify patients who have a high risk to develop a malignancy. These early stages of disease can probably be adequately treated by local treatments such as mucosal resection, laser therapy and photodynamic treatment and thereby avoiding an oesophageal resection.
For those patients who present with more advanced tumors surgery until now remains the mainstay of treatment. Treatment in a specialised center with a well equipped multidisciplinary team, optimised pre- and postoperative care and perhaps the use of minimal invasive surgical techniques may all be helpful in reducing the morbidity and mortality associated with oesophageal surgery.
Many patients with T2-3N0-1 tumors treated with a surgical resection alone experience a loco-regional relapse and/or develop distant metastases. The aim of combined modality treatment is to decrease the number of loco-regional recurrence and to eradicate distant (micro) metastases. However in a number of randomised trials on pre-operative chemotherapy

no or only a modest survival benefit is shown. Randomised trials with pre-operative chemoradiotherapy suggest a survival benefit but the sample size of these studies is too small to reach definitive conclusions. The concept of combined modality treatment therefore remains attractive and further randomised trials using perhaps more effective agents or combinations with biologic agents have to be initiated. The accuracy of staging should be enhanced to improve stratification of patients to appropriate prospective trials and minimise stage migration, which may obscure potential benefits of pre-operative treatment. FDG-PET can probably be helpful in the process to identify those patients who might benefit from combined modality treatment[1].

It has become clear that expression of Vascular Endothelian Growth Factor[2] and Epidermal Growth factor[3] has prognostic significance in oesophageal cancer and studies using small molecules or monoclonal antibodies against these factors are underway. Overexpression of p53 seems to be related to a diminished survival and lower response to chemotherapy, although conflicting results are sometimes reported[4]. Cyclooxygenases (COXs) are key enzymes that mediate the production of prostaglandines from arachidonic acid. Preclinical and clinical data suggest an important role for COX-2 in gastrointestinal carcinogenesis. Selective inhibition of COX-2 suppresses growth and induces apoptosis in human oesophageal adenocarcinoma cells[5,6]. Selective COX-2 inhibitors have been reported to enhance the tumor response to radiation and chemotherapy.

For the many patients who present with metastatic disease or who relapse after surgery or definitive chemoradiotherapy no curative options are available. In this patient group palliation of dysphagia and of symptoms such as pain and fatigue are important goals. Although not always reported as an endpoint chemotherapy can alleviate symptoms of dysphagia in 80-90% of patients and most of these patients also experienced an improvement in quality of life[7,8]. However, especially cisplatin-based chemotherapy may also cause considerable toxicity in unselected patients. The utilization of simple clinical prognostic factors such as performance status, extent of disease and serum Lactate Dehydrogenase will enable us to select with a higher accuracy those patients who will benefit from treatment. Promising results have been reported in phase I - II studies using dose-dense chemotherapy combinations with paclitaxel or irinotecan and a platinum compound. However the value of these newer regimens has to be confirmed in randomised phase III studies with quality of life as an important endpoint.

The emerging understanding of the molecular biology of oesophageal cancer and the development of targeted biological agents offer new challenges for the treatment of patients with oesophageal cancer. Eventually this will result in the use of tailor made treatments who provide the best benefit for the individual patient with this until now highly lethal disease.

References

1 Downey RJ, Akhurst T, Ilson D et al. Whole body 18FDG-PET and the response of oesophageal cancer to induction therapy: results of a prospective trial. J Clin Oncol 2003; 21: 428-32.

2 Shimada H, Hoshino T, Okazumi S et al. Expession of angiogenic factors predicts response to chemoradiotherapy and prognosis of oesophageal squamous cell carcinoma. Br J Canc 2002; 86: 552-7.

3 Inada S, Koto T, Futami K, Arima S, Iwashita A. Evaluation of malignancy and the prognosis of oesophageal cancer based on an immunohistochemical study (p53, E-cadherin, epidermal growth factor receptor). Surg Today 1999; 493-503.

4 Sarbia M, Stahl M, Fink U et al. Expression of apoptosis-regulating proteins and outcome of oesophageal cancer patients treated by combined therapy modalities. Clin Cancer Res 1998; 4: 2991-6.

5 Souza RF, Shewmake K, Beer DG, Cryer B, Spechler SJ. Selective inhibition of cyclooxygenase-2 suppresses growth and induces apoptosis in human oesophageal carcinoma cells. Cancer Res 2000; 60: 5767-72.

6 Buskens CJ, Van Rees BP, Sivula A et al. Prognostic significance of elevated cyclooxygenase 2 expression in patients with adenocarcinoma of the oesophagus. Gastroenterology 2002; 122: 1800-7.

7 Spiridonidis CH, Laufman LR, Jones JJ, Gray DJ, Cho CC, Young DC. A phase II evaluation of high dose cisplatin and etoposide in patients with advanced oesophageal adenocarcinoma. Cancer 1996; 78: 2070-7.

8 Ilson DH, Saltz L, Enzinger P et al. Phase II trial of weekly irinotecan plus cisplatin in advanced oesophageal cancer. J Clin Oncol 1999;17: 3270-5.

SAMENVATTING, CONCLUSIES EN VOORUITZICHTEN

The incidentie van het oesophaguscarcinoom neemt toe, vooral ten gevolge van een snelle stijging van de incidentie van adenocarcinomen in de distale oesophagus en de gastro-oesophageale overgang. De prognose van patiënten met oesophaguscarcinoom blijft slecht doordat veel patiënten zich presenteren met irresectabele tumoren en/of gemetastaseerde ziekte. Ook patiënten met een ogenschijnlijk lokale ziekte die worden behandeld met een radicale resectie hebben een slechte prognose ten gevolge van het frequente optreden van een lokaal recidief en/of metastasen. De potentiële rol voor chemotherapie in de behandeling van het oesophaguscarcinoom kan enerzijds een onderdeel zijn van een multi-modaliteits behandeling voor patiënten met een resectabele ziekte, en anderzijds een palliatieve behandeling voor patiënten met een meer uitgebreide ziekte. Dit proefschrift beschrijft een aantal fase I en II studies waarbij nieuwe chemotherapiecombinaties worden onderzocht in de behandeling van het oesophaguscarcinoom.

De eerste studie was gebaseerd op de veronderstelling dat de werkzaamheid van chemotherapie mogelijk kan worden vergroot door de toevoeging van andere actief middel. In een voorafgaande studie waren patiënten met een gemetastaseerd plaveiselcelcarcinoom van de oesophagus behandeld met een combinatie van cisplatina en etoposide en deze combinatie bleek werkzaam te zijn terwijl de bijwerkingen acceptabel waren. De toevoeging van 5-fluorouracil en folinezuur aan deze combinatie leek daarom zinvol.

In **hoofdstuk 2** wordt deze fase II studie met de combinatie van cisplatina, etoposide, 5-fluorouracil en folinezuur voor patiënten met gevorderd plaveiselcelcarcinoom van de oesophagus beschreven. Myelosuppressie en mucositis waren de belangrijkste bijwerkingen van dit schema. De hematologische bijwerkingen bestonden uit leucocytopenie graad 3 of 4 bij 33% en thrombocytopenie graad 4 bij 7% van de patiënten. Leucopene koorts werd gezien bij 19% van de patiënten en vrijwel al deze patiënten hadden een bijkomende mucositis. Het responspercentage in deze studie was 34% van de 68 evalueerbare patiënten, de mediane overleving voor de hele groep bedroeg 9 maanden met een 1-jaarsoverleving van 36%. Hoewel dit niet onderzocht is in een gerandomiseerd onderzoek lijkt leucopene koorts frequenter voor te komen na behandeling met deze combinatie dan na behandeling met cisplatina en etoposide alleen. Waarschijnlijk is dit het gevolg van het optreden van mucositis ten gevolge van de toevoeging van 5-fluorouracil en folinezuur.

In de volgende 4 studies onderzochten wij dosis-dense combinaties van paclitaxel gecombineerd met cisplatina of carboplatin. Door middel van wekelijkse of 2-wekelijkse toedieningen is het mogelijk de dosisintensiteit van deze cytostatica te verhogen. Vooral voor cisplatina is dit interessant aangezien voor dit middel een relatie tussen dosering en respons wordt gesuggereerd. Voor een fase-specifiek cytostaticum zoals paclitaxel lijkt een fre-

quentere toediening ook voordelen te bieden, omdat hierdoor de apoptotische en anti-angiogenetische effecten van dit middel kunnen worden vergroot. Eerder onderzoek had al aangetoond dat paclitaxel wekelijks kan worden toegediend zonder dat dit gepaard ging met het optreden van ernstige bijwerkingen.

Hoofdstuk 3 beschrijft een fase I studie met wekelijkse toedieningen van cisplatina en paclitaxel aan patiënten met een oesophaguscarcinoom. Aan achtereenvolgende patiënten werden oplopende doseringen van paclitaxel in combinatie met een gefixeerde dosis cisplatin van 70 mg/m² toegediend op dag 1, 8, 15, 29, 36, en 43. Dosislimiterende bijwerkingen traden op bij een paclitaxel-dosis van 110 mg/m² in de vorm van gastrointestinale bijwerkingen en in het bijzonder ernstige diarree. Twee patiënten overleden onder het beeld van een neutropene enterocolitis. De relatief hoge frequentie van ernstige diarree in deze studie was onverwacht en kon niet geheel worden verklaard. Het responspercentage van 50%, de mediane overleving van 16 maanden en een 1-jaarsoverleving van 58% steken gunstig af ten opzichte van de resultaten van andere onderzoeken bij patiënten met een oesophaguscarcinoom. Tien patiënten met irresectabele ziekte of uitzaaiingen in de lymfeklieren beperkt tot de truncus coeliacus of supraclaviculaire regio werden aanvullend lokaal behandeld, 7 van deze patiënten waren ziektevrij na een mediane follow-up van 32 maanden. De conclusie van deze studie was dat cisplatina 70 mg/m² in combinatie met paclitaxel 100 mg/m² toegediend op dag 1, 8, 15, 29, 36 en 43 de aanbevolen dosering is voor verdere studies.

In **hoofdstuk 4** wordt een fase II studie met een 2-wekelijkse toediening van cisplatina 60 mg/m² en paclitaxel 180 mg/m² beschreven bij patiënten met een oesophaguscarcinoom. In deze studie werden eenenvijftig patiënten geïncludeerd en alle patiënten kregen tenminste 3 kuren toegediend. Patiënten met een respons ontvingen maximaal 8 kuren. De hematologische bijwerkingen bestonden uit graad 3 en 4 neutropenie bij, respectievelijk, 43% en 20% van de patiënten. Het totale responspercentage bedroeg 43% met een mediane responsduur van 8 maanden. Dit responspercentage komt overeen met de percentages zoals genoemd in andere studies waarin de combinatie van cisplatin, paclitaxel en/of 5-fluorouracil werd onderzocht. Echter, de bijwerkingen zoals waargenomen in onze studie en vooral de afwezigheid van febriele neutropenie en andere ernstige complicaties, steken gunstig af ten opzicht van de bijwerkingen gerapporteerd in de andere studies.

In **hoofdstuk 5** werd deze 2-wekelijkse combinatie onderzocht als neo-adjuvante therapie bij 50 patiënten met een resectabel plaveiselcelcarcinoom van de oesophagus. Patiënten werden geëvalueerd na 3 kuren, niet responderende patiënten werden verwezen voor chirurgie, responderende patiënten ontvingen nog 3 aanvullende kuren voorafgaande aan de chirurgie. De behandeling werd goed verdragen en 94% van de patiënten kreeg tenminste 3 kuren toegediend. Het responspercentage was 59% en bij vijfenveertig patiënten (90%)

werd een oesophagusresectie verricht. De postoperatieve mortaliteit was niet duidelijk verhoogd. Pathologisch onderzoek liet geen resttumor zien bij 7 patiënten (14%) en resectievrije marges bij 38 patiënten (76% van alle patiënten). De mediane overleving was 20 maanden en de 1- en 3-jaarsoverleving waren, respectievelijk, 68 en 32%. Het hoge aantal complete remissies is mogelijk het gevolg van het dosis-dense cisplatin-paclitaxel schema of het gevolg van het feit dat responderende patiënten extra kuren kregen toegediend. Een gerandomiseerd onderzoek waarin deze combinatie wordt vergeleken met andere behandelschema's is gewenst.

Hoofdstuk 6 beschrijft een fase I studie waarin carboplatin en paclitaxel wekelijks worden toegediend aan patiënten met gemetastaseerd oesophaguscarcinoom. Voordelen van een combinatie van carboplatin en paclitaxel ten opzichte van cisplatin en paclitaxel combinatie zijn dat de behandeling poliklinisch toegediend kan worden en dat er waarschijnlijk minder neurotoxiciteit optreedt. De paclitaxel werd toegediend in 1 uur in een gefixeerde dosering van 100 mg/m^2 en de startdosis van carboplatin was berekend op een AUC van 2 mg min/mL. Dosislimiterende bijwerkingen traden op bij een berekende carboplatin dosering van AUC 5 mg/min/mL en bestonden uit uitstel van behandeling ten gevolge van myelosuppressie. De hoogste dosisintensiteit (> 95% van de geplande dosis) werd bereikt met een berekende carboplatin dosering van AUC 4 mg/min/mL. Hematologische bijwerkingen bestonden uit neutropenie graad 3 of 4 bij 77% van de patiënten, echter febriele neutropenie trad slechts bij 5% van de patiënten op. Niet-hematologische bijwerkingen waren over het algemeen mild. Pharmacokinetisch onderzoek toonde aan dat carboplatin de dispositie van paclitaxel toegediend in 1 uur niet beïnvloedde. Het responspercentage bedroeg 54%. De mediane overleving voor de 40 behandelde patiënten was 11 maanden en de 1-jaarsoverleving 46%. De bereikte dosisintensiteit is hoog vergeleken met andere schema`s waarbij carboplatin wordt toegediend als monotherapie of in combinatie met paclitaxel. De wekelijkse combinatie van carboplatin en paclitaxel lijkt geschikt voor een inductieschema aangezien de behandeling goed wordt verdragen, poliklinisch kan worden toegediend en in korte tijd kan worden voltooid.
De betekenis van cisplatina bevattende combinatiechemotherapie als de palliatie voor patiënten met een gemetastaseerd oesophaguscarcinoom is onduidelijk mede door een gebrek aan gerandomiseerde studies waarin een behandeling met chemotherapie wordt vergeleken met andere vormen van palliatie. Verder is het ook niet bekend welke patiënt- en ziekte-gerelateerde kenmerken belangrijk zijn voor de afweging om een behandeling met chemotherapie aan te vangen.

Hoofdstuk 7 betreft een retrospectief onderzoek naar een aantal mogelijke prognostische factoren in een groep van 350 patiënten die in 6 opeenvolgende studies behandeld waren met cisplatina bevattende chemotherapie. In een multivariate analyse werden performance status, uitgebreidheid van de ziekte en lactaat dehydrogenase (LDH) geïdentificeerd als

onafhankelijke prognostische factoren. Gebaseerd op deze 3 factoren konden wij 4 prognostische groepen onderscheiden. De mediane overleving van patiënten met 0, 1, 2 of 3 risicofactoren was, respectievelijk, 12, 8, 6 en 4 maanden. Dit duidelijke verschil in mediane overleving tussen de groepen kan van belang zijn bij het opzetten van gerandomiseerde studies en bij de interpretatie van deze studies. Bovendien is het een indicatie dat het niet mogelijk is om zondermeer de resultaten van verschillende fase II studies te vergelijken wat betreft de overleving.

Conclusies

Cisplatina bevattende combinatiechemotherapie is redelijk effectief in de behandeling van oesophaguscarcinoom. Echter deze behandeling wordt vaak slecht verdragen vooral door patiënten met vergevorderde ziekte. De chemotherapiecombinaties die wij hebben onderzocht verschilden in 2 opzichten van eerder onderzochte schema's: ten eerste werd paclitaxel gecombineerd met cisplatina of carboplatin en ten tweede maakten wij gebruik van dosisdense behandelschema's. Wekelijkse en 2-wekelijkse toedieningen van de onderzochte cytostatica resulteerden in een hoge dosisintensiteit. De vraag of deze nieuwe regimes ook effectiever zijn dan de traditioneel gebruikte regimes kan alleen worden beantwoord wanneer dit in een gerandomiseerd onderzoek verder wordt onderzocht. Wel kan worden gesteld dat de bijwerkingen van de 2-wekelijkse toedieningen van cisplatin en paclitaxel of na wekelijkse toedieningen van carboplatin/paclitaxel opvallend mild waren, dit suggereert een gunstig bijwerkingprofiel vergeleken met vele andere gebruikte chemotherapieschema's. Vermeldenswaardig is de lage frequentie van het optreden van neutropene koorts en het feit dat slechts een beperkt aantal patiënten wordt opgenomen in verband met bijwerkingen na de behandeling. De combinatie van carboplatin en paclitaxel is ook aantrekkelijk omdat deze behandeling poliklinisch kan worden toegediend.

Performancestatus, uitgebreidheid van de ziekte en LDH zijn onafhankelijke prognostische factoren voor patiënten met gevorderd oesophaguscarcinoom, deze factoren kunnen als leidraad dienen wanneer men overweegt deze patiënten te behandelen met chemotherapie.

Vooruitzichten

De prognose van patiënten met oesophaguscarcinoom kan theoretisch op verschillende manieren worden verbeterd. Door middel van een nauwkeurige controle van patiënten met dysplastische afwijkingen in de slokdarm kan een tumor in een vroeg stadium worden gediagnosticeerd, wat de kans op genezing vergroot. De toename van kennis betreffende de moleculaire evolutie van de metaplasie - dysplasie tot adenocarcinoom zal ons uiteindelijk

in staat stellen om patiënten met een hoog risico om een carcinoom te ontwikkelen te identificeren. De vroege stadia van een oesophaguscarcinoom kunnen waarschijnlijk adequaat worden behandeld met een mucosaresectie, laserbehandeling en/of fotodynamische behandeling, waardoor zodat een oesophagusresectie vermeden kan worden.

Voor patiënten met een lokaal meer uitgebreid oesophaguscarcinoom is een oesophagusresectie een essentieel onderdeel van de behandeling. Een behandeling in een gespecialiseerd centrum met een multidisciplinair team gericht op het optimaliseren van de pre- en postoperatieve zorg en het gebruik van minimaal invasieve technieken kan bijdragen in het verlagen van de morbiditeit en mortaliteit ten gevolge van de chirurgische behandeling.

Veel patiënten met T2-3N0-1 tumoren die worden behandeld met alleen een oesophagusresectie krijgen een locoregionaal recidief en/of metastasen op afstand. Het doel van een multimodaliteitsbehandeling is om het aantal recidieven te verkleinen en om (micro) metastasen te eradiceren. Echter in het beperkte aantal gerandomiseerde studies betreffende preoperatieve chemotherapie wordt geen of slechts een beperkt overlevingsvoordeel aangetoond. Gerandomiseerde onderzoeken waarin preoperatieve concomitante chemoradiotherapie werd vergeleken met chirurgie alleen suggereren een overlevingsvoordeel maar het aantal geïncludeerde patiënten in deze studies is te klein om een definitief oordeel te geven over de waarde van pre-operatieve chemoradiotherapie. Het concept van de multimodaliteitsbehandeling blijft echter aantrekkelijk en het is belangrijk dat nieuwe gerandomiseerde studies, waarin gebruik wordt gemaakt van effectievere chemotherapie eventueel met toevoeging van niet-cytotoxische celgroeiremmende medicijnen, worden opgezet. De nauwkeurigheid van het stageringsonderzoek zou moeten worden vergroot zodat patiënten correct gestratificeerd kunnen worden en waardoor de waarde van een preoperatieve behandeling in het kader van een gerandomiseerde studies beter kan worden beoordeeld. FDG-PET zal mogelijk kunnen bijdragen tot een juiste selectie van patiënten die in aanmerking komen voor een multimodaliteitsbehandeling[1].

Het is aangetoond dat expressie van Vascular Endothelial Growth Factor[2] en Epidermal Growth Factor[3] een prognostische betekenis heeft en de mogelijkheden van een behandeling gericht tegen deze factoren met bijvoorbeeld antilichamen worden thans onderzocht. Overexpressie van P53 lijkt geassocieerd te zijn aan een verminderde overleving en een kleinere responskans op chemotherapie, echter resultaten van de studies zijn tegenstrijdig[4]. Cyclooxygenases zijn sleutelenzymen voor de productie van prostaglandines uit arachnidonzuur. Preklinische en klinische onderzoeksresultaten suggereren een belangrijke rol voor de cyclooxygenases in de gastrointestinale carcinogenese. Selectieve remming van COX-2 onderdrukt groei en induceert apoptosis in menselijke oesophagusadenocarcinoom cellen[5,6]. Het is beschreven dat selectieve COX-2 remmers de kans op een respons na een behandeling met chemotherapie of radiotherapie vergroten.

Voor de vele patiënten met slokdarmkanker die bij eerste presentatie al uitzaaiingen hebben of die na een resectie een recidief krijgen zijn geen curatieve opties voorhanden. Voor deze groep van patiënten is adequate palliatie van dysphagie maar ook van symptomen zoals moeheid en pijn van groot belang. Hoewel niet altijd als eindpunt in studies vermeld, kan een behandeling met chemotherapie symptomen van dysphagie verbeteren in 80-90% van de patiënten en bij de meeste van deze patiënten treedt er ook een verbetering van kwaliteit van leven op[7,8]. Echter, cisplatina bevattende chemotherapie kan gepaard gaan met ernstige bijwerkingen. Door gebruik te maken van simpele prognostische factoren zoals performance status, uitgebreidheid van de ziekte en het serum LDH is het mogelijk om patiënten te selecteren die mogelijk meer baat hebben van een dergelijke behandeling met chemotherapie.

Veelbelovende resultaten worden vermeld in fase I en II studies met een behandeling met dosis-dense chemotherapieschema's bestaande uit combinaties van paclitaxel of irinotecan met een platinum verbinding. De verhoogde werkzaamheid van deze nieuwe combinaties zal moeten worden aangetoond in gerandomiseerde fase III studies, kwaliteit van leven dient daarbij een belangrijk eindpunt te zijn. De toegenomen kennis over het ontstaan van slokdarmkanker op moleculair-biologisch niveau en de ontwikkeling van beter gerichte behandelingen biedt nieuwe kansen voor de behandeling van patiënten met slokdarmkanker. Uiteindelijk zal dit resulteren in behandelplannen toegespitst op de individuele patiënt met deze tot nu toe nog steeds zeer ernstige ziekte.

Referenties

1 Downey RJ, Akhurst T, Ilson D et al. Whole body 18FDG-PET and the response of esophageal cancer to induction therapy: results of a prospective trial. J Clin Oncol 2003; 21: 428-32.

2 Shimada H, Hoshino T, Okazumi S et al. Expession of angiogenic factors predicts response to chemoradiotherapy and prognosis of oesophageal squamous cell carcinoma. Br J Canc 2002; 86: 552-7.

3 Inada S, Koto T, Futami K, Arima S, Iwashita A. Evaluation of malignancy and the prognosis of esophageal cancer based on an immunohistochemical study (p53, E-cadherin, epidermal growth factor receptor). Surg Today 1999; 493-503.

4 Sarbia M, Stahl M, Fink U et al. Expression of apoptosis-regulating proteins and outcome of esophageal cancer patients treated by combined therapy modalities. Clin Cancer Res 1998; 4: 2991-6.

5 Souza RF, Shewmake K, Beer DG, Cryer B, Spechler SJ. Selective inhibition of cyclooxygenase-2 suppresses growth and induces apoptosis in human esophageal carcinoma cells. Cancer Res 2000; 60: 5767-2.

6 Buskens CJ, Van Rees BP, Sivula A et al. Prognostic significance of elevated cyclooxygenase 2 expression in patients with adenocarcinoma of the esophagus. Gastroenterology 2002; 122: 1800-7.

7 Spiridonidis CH, Laufman LR, Jones JJ, Gray DJ, Cho CC, Young DC. A phase II evaluation of high dose cisplatin and etoposide in patients with advanced esophageal adenocarcinoma. Cancer 1996; 78: 2070-7.

8 Ilson DH, Saltz L, Enzinger P et al. Phase II trial of weekly irinotecan plus cisplatin in advanced esophageal cancer. J Clin Oncol 1999;17: 3270-5.

Dankwoord

Dankwoord

Voor U ligt een proefschrift van iemand die altijd weinig wetenschappelijke pretenties had. Ik kwam naar Rotterdam om opgeleid te worden tot internist-oncoloog en patiëntenzorg ging mij meer aan het hart dan onderzoek. Op de afdeling Interne Oncologie in het Dijkzigt ontdekte ik dat onderzoek en goede patiëntenzorg juist met elkaar verbonden zijn. De relevantie van het onderzoek bleek elke dag weer bij de begeleiding van patiënten met slokdarmkanker. Deze patiënten met vaak ernstige klachten toonden een indrukwekkende strijdlust in een oneerlijke strijd. Ik ben deze patiënten niet alleen dankbaar voor hun bijdrage aan dit onderzoek; zij hebben ook een belangrijke rol gespeeld bij mijn vorming als internist-oncoloog.

Het voltooien van dit proefschrift is vooral te danken aan deskundige adviezen en begeleiding van een klein aantal personen en de morele steun van vele anderen.

Op de allereerste plaats wil ik vooral mijn copromotor Ate van der Gaast bedanken. Ate, mijn proefschrift is in belangrijke mate de oogst van wat jij gezaaid hebt. Zonder jouw adequate en plezierige begeleiding was het nooit zover gekomen. Ik bewonder je kennis en je vermogen om naar mensen te luisteren. Je bent rechtlijnig en direct, eigenschappen die ik later ook bij andere Friezen ben gaan waarderen.

Mijn dank gaat uit naar mijn promotor professor Gerrit Stoter die mij de gelegenheid bood om reeds lopend klinisch wetenschappelijk onderzoek voort te zetten. Gerrit, je hebt van enige afstand ons de ruimte gegeven om onze ideeën uit te werken zonder de regie uit het oog te verliezen. Je geduld wordt nu toch beloond.

De behandeling van slokdarmkanker is multidisciplinair en dat geld dus ook voor onderzoek over dit onderwerp. De Rotterdamse Slokdarm Werkgroep staat al jaren borg voor uitstekende samenwerking en is een bron voor belangrijk onderzoek op het gebied van slokdarmkanker. In het bijzonder wil ik professor Hugh Tilanus en Peter Siersema bedanken voor een stimulerende samenwerking.

Mijn medeauteurs professor Jaap Verweij, Alex Sparreboom en Wim Hop ben ik dankbaar voor de tijd die zij hebben genomen om mij te begeleiden bij uitwerking van respectievelijk fase I onderzoeken, farmaco-kinetisch onderzoek en statistische analyses.

Mijn directe collega's Ferry Eskens, Ronald Hoekstra, Maria van der Burg en Ted Splinter wil ik vooral bedanken voor een prettige samenwerking en gezelligheid. Daarnaast hebben jullie natuurlijk ook veel bijgedragen aan mijn onderzoek door de behandeling van patiënten met slokdarmkanker en door nuttige correcties van mijn manuscripten.

Tjebbe Kok stond aan de basis van de behandeling met chemotherapie bij slokdarmkanker in Rotterdam. Dank voor het verstrekken van de gegevens uit voorgaande onderzoeken.

Op de polikliniek interne-oncolgie op locatie Dijkzigt heb ik ruim 3 jaar met veel plezier gewerkt. Dat kwam door de prettige sfeer die vooral werd bepaald door een goede ploeg verpleegkundigen en doktersassistentes. Ik wil verder de research-verpleegkundigen en datamanagers bedanken voor hun ondersteuning. Connie Vollebrecht was behulpzaam met het leveren van gegevens over geopereerde patiënten. In de afgelopen jaren werd ik door vele secretaresses geholpen, ik wil met name Sandra Van den Bosch bedanken omdat zij zo veel voor mij heeft geregeld in de periode dat ik al naar Friesland was vertrokken.

Elsa Alingh Prins heeft al een hele reputatie opgebouwd bij het verzorgen van de lay-out voor proefschriften van specialisten werkzaam in het MCL. Dank voor de finishing touch.

Wilma en Jan, bedankt dat jullie mijn paranimfen wilden zijn. Het is fijn om op dit belangrijke moment te worden gesteund door zulke lieve en waardevolle personen.

Mijn ouders wil ik bedanken voor hun niet aflatende steun en stimulans. Een onbezorgde jeugd vormt de basis van mijn leven. Jullie zijn altijd zo trots op mij; vandaag vind ik dat goed.

Lieve Marjolein, bedankt dat jij wel steeds in een goede afloop hebt geloofd. Er waren de afgelopen jaren zoveel belangrijkere gebeurtenissen dan dit boekje en het was mooi om deze samen te beleven. Ik vind het geweldig zoals jij onze kinderen verzorgt, stimuleert, steunt en vermaakt. Lieve Iris, Koen en Robert. Het boekje is nu toch af, ondanks jullie prettige afleiding en veel onderbroken nachten. Jullie maken mij elke dag weer gelukkig.

PUBLICATIONS

Bilo HJG, Gans ROB, Poleé MB, Van der Maten J, Popp-Snijders C, Donker AJM. Catecholamines and blood glucose control in type 1 diabetes. Diabetic Medicine 1991; 8: S108-12.

Poleé MB, Kok TC, Siersema PD, Tilanus HW, Splinter TAW, Stoter G and Van der Gaast A. Phase II study of the combination cisplatin, etoposide, 5-fluorouracil and folinic acid in patients with advanced squamous cell carcinoma of the oesophagus. Anti-Cancer Drugs 2001; 12: 513-7.

Poleé MB, Verweij J, Siersema PD, Tilanus HW, Splinter TAW, Stoter G, Van der Gaast A: Phase I study of a weekly schedule of a fixed dose of cisplatin and escalating doses of paclitaxel in patients with advanced oesophageal cancer. Eur J Cancer 2002; 38: 1495-500.

Poleé MB, Eskens FALM, Van der Burg MEL, Splinter TAW, Siersema PD, Tilanus HW, Verweij J, Stoter G and Van der Gaast A. Br J Cancer 2002; 86: 669-73.

Polee MB, Eskens FALM, Van der Burg MEL, Splinter TAW, Siersema PD, Tilanus HW, Verweij J, Stoter G and Van der Gaast A. Phase II study of biweekly administration of paclitaxel and cisplatin in patients withs advanced oesophageal cancer. Br J Cancer 2002; 86: 669-73.

Poleé MB, Tilanus HW, Eskens FALM, Hoekstra R, Van der Burg MEL, Siersema PD, Stoter G and Van der Gaast A. Phase II study of neo-adjuvant chenotherapy with paclitaxel and cisplatin given every 2 weeks for patients with a resectable squamous cell carcinoma of the oesophagus. Ann Oncol 2003, 14: 1253-7.

Poleé MB, Hop WCJ, Kok TC, Eskens FALM, Van der Burg MEL, Splinter TAW, Siersema PD, Stoter G and Van der Gaast A. Prognostic factors for survival for patients with advanced esophageal cancer treated with cisplatin based combination chemotherapy. Br J Cancer 2003; 89: 2045-50.

Poleé MB, Sparreboom A, Eskens FALM, Hoekstra R, Van de Schaaf J, Verweij J, Stoter G and Van der Gaast A. Phase I and pharmacokinetic study of weekly paclitaxel and carboplatin in patients with metastatic esophageal cancer. Accepted for publication in Clin Cancer Res.

PUBLICATION OF THIS THESIS WAS FINANCIALLY SUPPORTED BY

Bristol-Myers Squibb
Abbott
Amgen
Astra Zeneca
Aventis
Glaxo Smith Kline
Lilly
Mundipharma
Novartis
Ortho Biotech
Pfizer
Pharmacia
Roche
Sanofi-Synthelabo
Schering-Plough
UCB Pharma

Curriculum Vitae

Marco Ben Poleé werd geboren op 20 juni 1965 te Dieren in Gelderland. Hij bezocht het Stedelijk Lyceum te Zutphen, alwaar hij in 1983 zijn OVWO diploma behaalde. In datzelfde jaar begon hij met de studie Geneeskunde aan de Vrije Universiteit in Amsterdam. In september 1990 ontving hij zijn arts-diploma en ging hij als AGNIO Interne geneeskunde werken in het Streekziekenhuis Hilversum (opleider Dr. F. van Kersen).
In januari 1993 begon de opleiding tot internist in Academisch Ziekenhuis Utrecht bij Prof. dr. D.W. Erkelens. In het eerste opleidingsjaar werd een stage verricht in Gomel, Wit-Rusland, in het kader van hulpverlening voor slachtoffers van Tjernobyl. Voor het perifere gedeelte van de opleiding ging hij van 1994 tot en 1996 naar het Ziekenhuiscentrum Apeldoorn, lokatie Lucasziekenhuis (opleider Dr. D.W. van Toorn). Het laatste gedeelte van de opleiding tot internist werd volbracht in het Academisch Ziekenhuis te Rotterdam, lokatie Dijkzigt. Alhier werd de vervolgopleiding tot internist-oncoloog voltooid onder begeleiding van Prof.dr. G. Stoter. Registratie tot internist vond plaats in 1999 en als internist-oncoloog in 2000. In 1999 werd aangevangen met het onderzoek dat geleid heeft tot dit proefschrift. Vanaf 2002 is hij werkzaam als internist met het aandachtsgebied oncologie in het Medisch Centrum Leeuwarden. Hij is gehuwd met Marjolein van den Brink, samen zijn zij de gelukkige ouders van Iris, Koen en Robert.