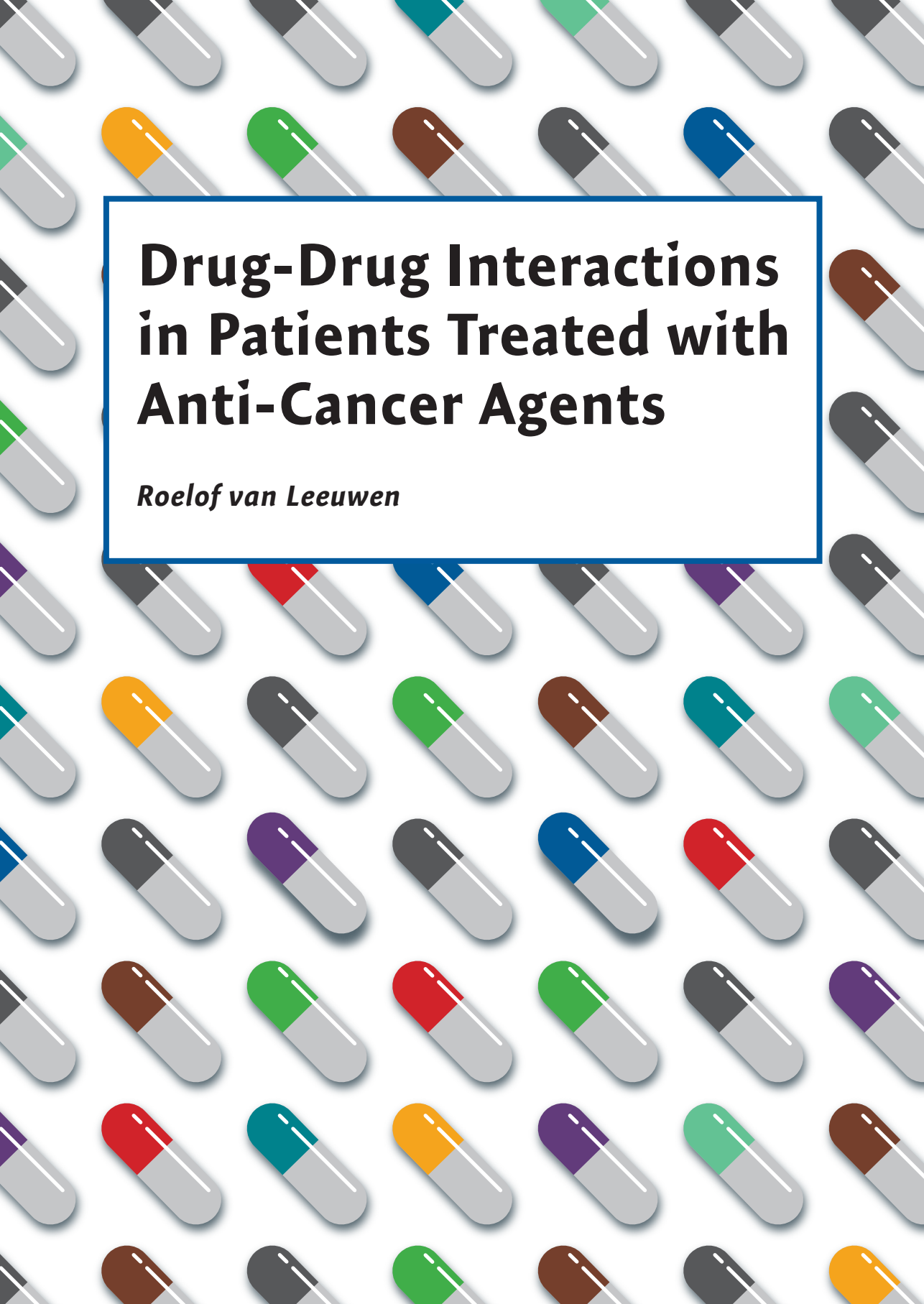

Drug-Drug Interactions in Patients Treated with Anti-Cancer Agents

Roelof van Leeuwen

Drug-Drug Interactions in Patients Treated with Anti-Cancer Agents

Geneesmiddel interacties bij patiënten die behandeld worden met antikanker geneesmiddelen

Roelof van Leeuwen

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Erasmus University Rotterdam

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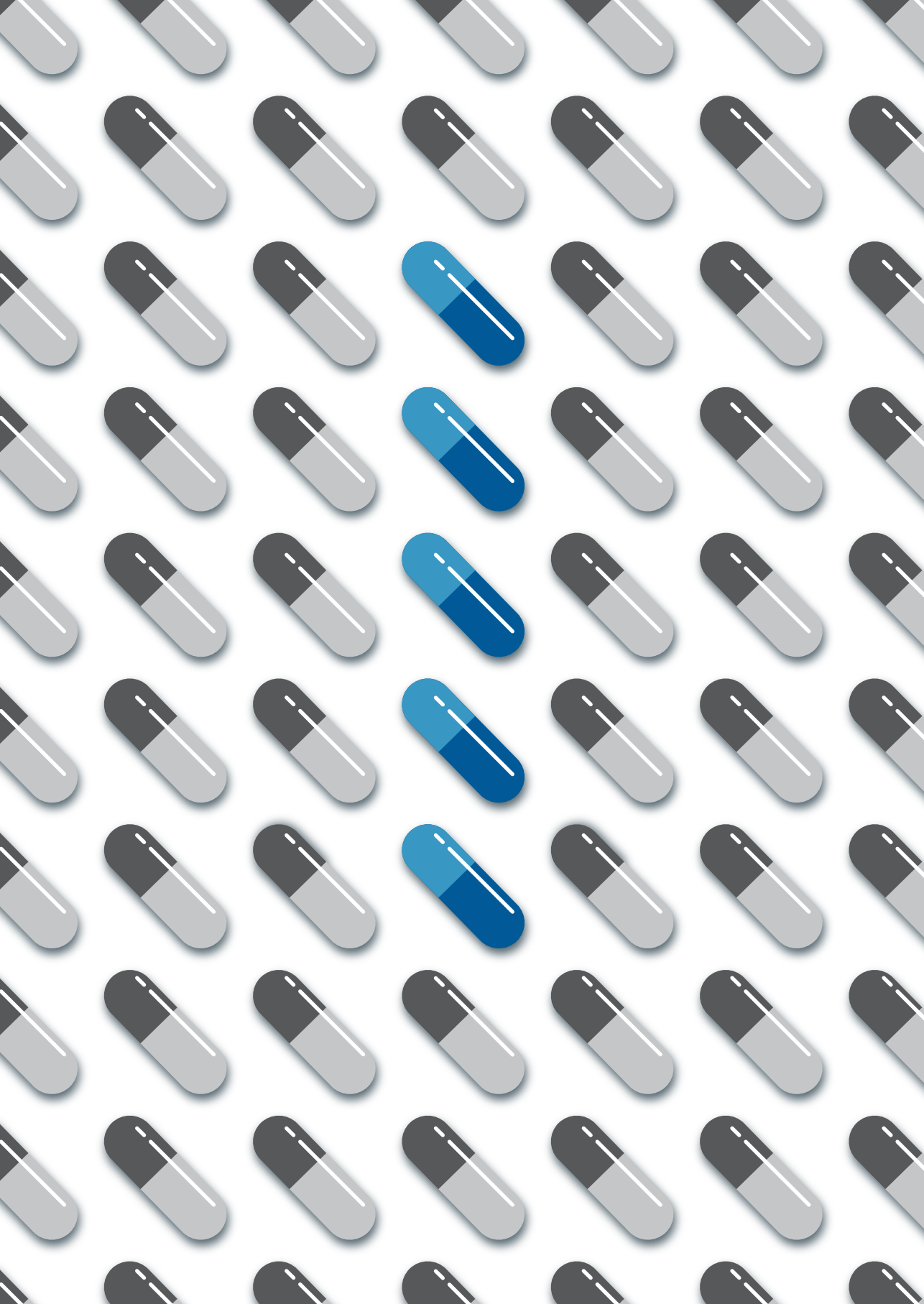
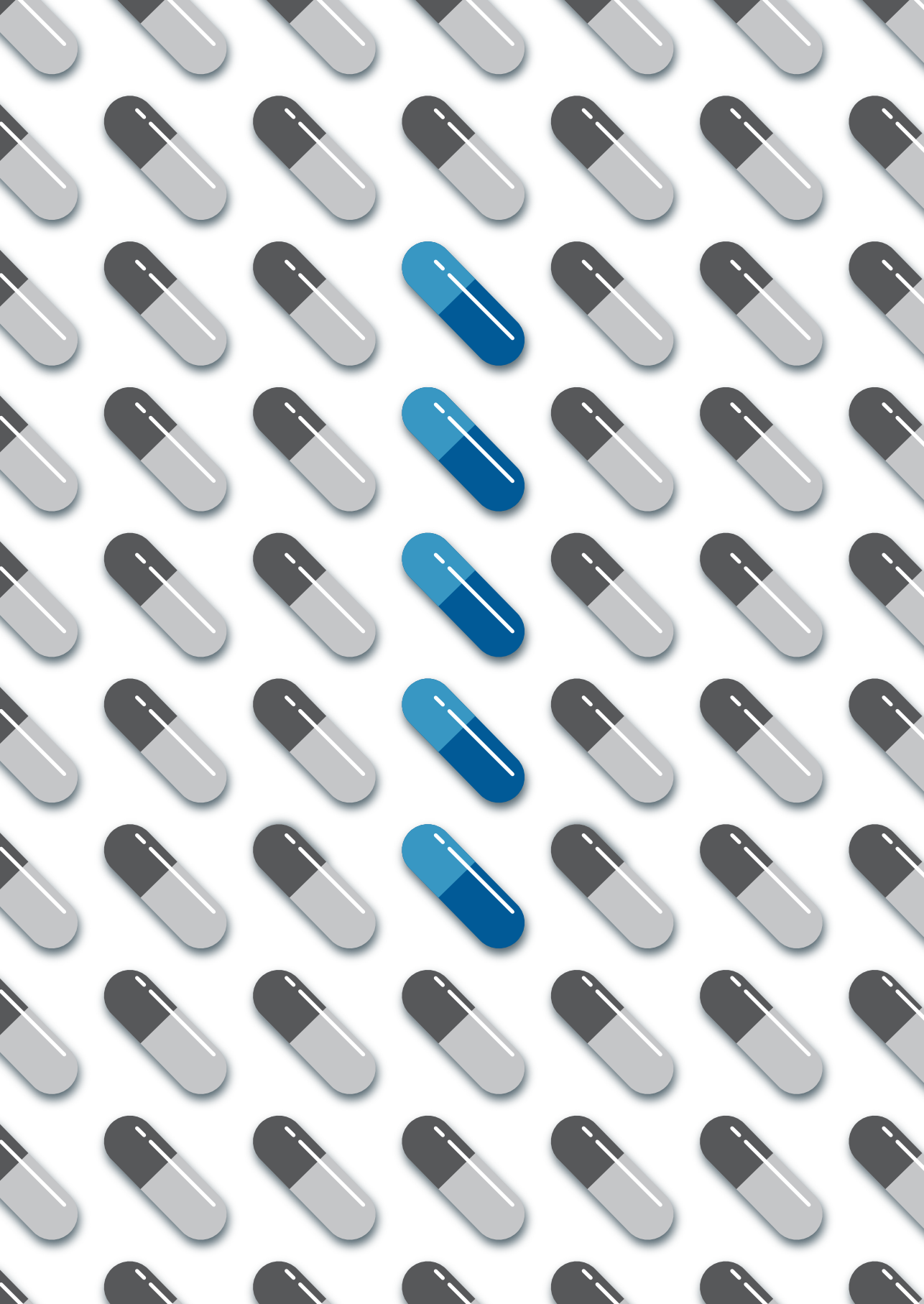


Chapter 1

1

GENERAL INTRODUCTION AND AIMS OF THIS THESIS



CANCER

Cancer is a significant and leading public health burden and a major cause of morbidity and mortality among men and women worldwide. Especially due to growth, aging and adaptation of deleterious behavior and lifestyle of the worldwide population, this burden is expected to grow in the coming years.[1] Although treatment options such as cytotoxic chemotherapy, (anti)hormone therapy and the more recent targeted agents are rapidly evolving, anticancer treatment is still associated with many challenges. Since most anticancer drugs have narrow therapeutic windows it is important to "get the dose right" in order to optimize drug exposure and effect and minimalize side effects.[2] To accomplish this goal there is a shifting paradigm towards individualized dosing rather than flat-fixed dosing in order to optimize cancer therapy. Along with other factors, such as life style, genetic factors and organ (dys)function, the use of comedication and the subsequent risk for drug-drug-interactions (DDIs) is one of the key factors influencing systemic drug exposure in cancer patients (figure 1).[2]

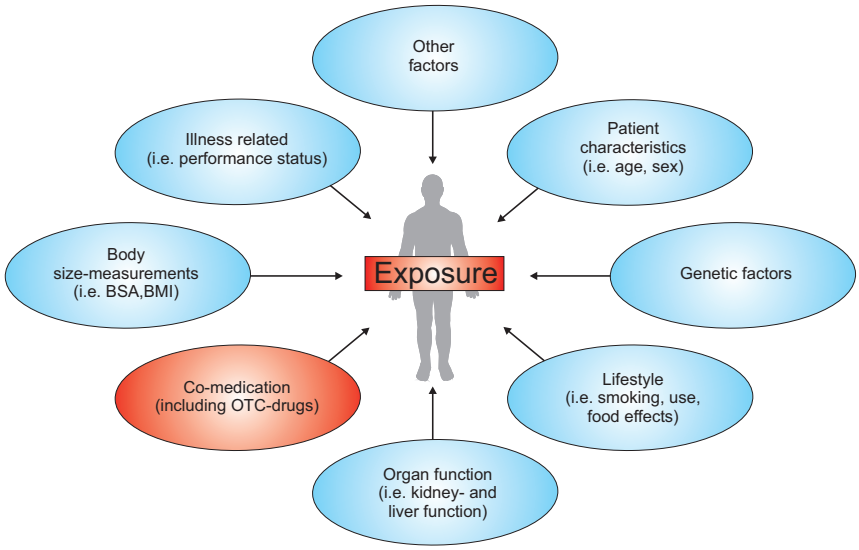


Figure 1: Key factors influencing the systemic exposure to an anticancer drugs

Abbreviations: BMI: body-mass index; BSA: body-surface area; CAM: complementary and alternative medicine; PPI: proton-pump inhibitor; SNPs: single-nucleotide polymorphisms.

DRUG-DRUG INTERACTIONS IN CANCER PATIENTS

DDIs in vivo, defined as a modification of the effect of a drug when administered with another drug in a given patient, can be divided into two main groups: *i*) pharmacokinetic and *ii*) pharmacodynamic DDIs.[3]

Pharmacokinetic DDIs can be further subdivided into DDIs concerning the pharmacokinetic properties Absorption, Distribution, Metabolism or Excretion (ADME principle; see also figure 2). When any of these parameters is modified by comedication, systemic exposure of the anticancer drug might be affected and the patient may be deprived from optimal therapy.

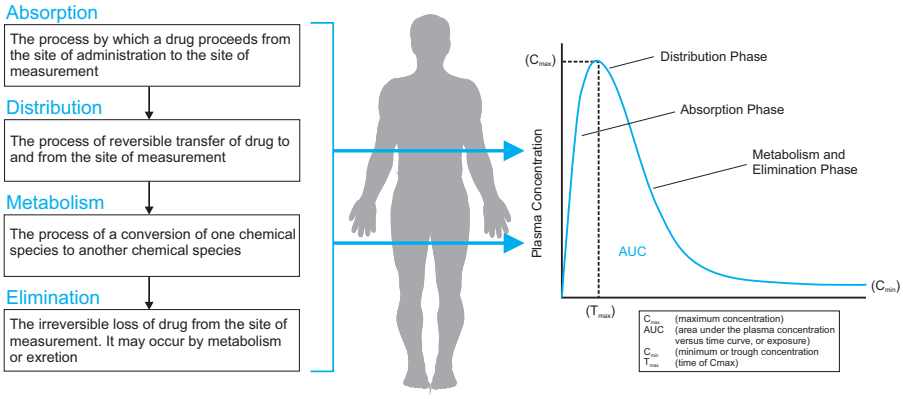


Figure 2: The ADME-principles

Abbreviations : ADME (Absorption, Distribution, Metabolism, Elimination)

Absorption

Gastrointestinal absorption of an anticancer drug primarily depends on its general chemical characteristics, but can also be significantly influenced by DDIs. Important factors that may influence drug absorption are: *i*) changes in stomach pH (e.g. due to coadministration of acid suppressive agents) and *ii*) the inhibition of drug transporters (e.g. P-gp) and intestinal enzymes (e.g. cytochrome P450 iso-enzyme 3A4; CYP3A4). Acid reducing drugs, like proton pump inhibitors (PPIs), increase the intragastric pH. As a result, the solubility and thereby the biological availability and systemic exposure of certain anticancer drugs is decreased. After dissolution, in the stomach and proximal intestine, an anticancer drug has to be transported across de intestinal lumen to reach the portal blood circulation. This transport is a complex multifactorial process predominantly mediated by passive diffusion, drug transporters (e.g. P-glycoprotein) and intestinal metabolic enzymes (CYPs). Either inhibition or induction of these drug transporters and intestinal metabolic enzymes may substantially influence bioavailability and systemic exposure of an orally taken anticancer drug. DDIs concerning absorption do have little effect on the pharmacokinetic parameters of intravenously given anti-cancer therapy. However, these DDIs are of significant importance with orally administered anticancer drugs such as tyrosine kinase inhibitors (eg. DDIs between PPIs and TKIs).

Distribution

After absorption, distribution of the drug to the target, is largely measured by blood flow and binding affinity to plasma protein (e.g. albumin). If two or more highly plasma protein bound drugs are used concomitantly, one drug can displace the other from its protein binding site, thereby increasing the fraction of unbound and pharmacologically active drug. Although many anticancer drugs are highly plasma protein bound (≥99%), there is little evidence to support a clinically relevant DDI on the basis of protein completion and displacement (eg. DDIs between TKIs and vitamin K antagonists).[4]

Metabolism

The phase I oxidative cytochrome P450 pathway (CYPs) in the liver is the primary route of drug enzymatic metabolism in humans. Alterations in metabolism, through CYP inhibition or induction, has emerged as an important factor in the occurrence of DDIs in cancer therapy as most anticancer drugs are entirely or partly metabolized by CYPs. CYP induction is the process by which concomitant use of certain drugs (e.g. rifampicin[5]) results in accelerated CYP enzyme metabolism. Accelerated anticancer drug metabolism may result in a clinically relevant decrease in exposure and drug efficacy. Through CYP inhibition (e.g. ketoconazole[5]) CYP enzyme metabolism of anticancer agents is decreased, which may result in elevated serum levels and toxicity. On the other hand, for anticancer drugs whose pharmacological activity requires CYP metabolism, CYP inhibition can lead to decreased efficacy (e.g. combined tamoxifen and paroxetine treatment[6]).

Elimination

DDIs concerning elimination generally occur due to renal impairment during the concomitant use of nephrotoxic comedication. Although some anticancer drugs are highly dependent on renal elimination (platina compounds and methotrexate), most anticancer drugs are eliminated through liver metabolism and subsequent excretion into the feces. Because anticancer drugs are predominately excreted through hepatic metabolism, DDIs concerning elimination seem to be of minor significance.

Pharmacodynamic DDIs

Pharmacodynamic DDIs are characterized by an additive, synergistic or antagonistic effect during concomitant use of two or more drugs which may result in either toxic or antitumor effect. As anticancer drugs are usually given in combination regiment pharmacodynamic DDIs are used, intentionally, to reduce resistance, reduce toxicity and improve antitumor activity of the anticancer drug in an additive or even synergistic manner. Nevertheless, pharmacodynamic DDIs can also have negative effects during cancer therapy. Many anticancer drugs prolong the QT_c interval (e.g. anthracyclines) which substantially increases the risk for Torsades the Pointes (TdP).[7] Concomitant use of comedication that prolong the QT_c interval in an additive or synergistic way may further increase the risk of TdP and sudden heart death during anticancer therapy. Although rare, these QT_c DDIs can be severe and are highly significant in daily practice.

DRUG-DRUG INTERACTIONS IN CANCER PATIENTS; EPIDEMIOLOGY AND MANAGEMENT

Since anticancer drugs are usually potent and toxic agents with a narrow therapeutic window (figure 3) DDIs are of major concern in oncology.[2, 3]

They seem to be responsible for 20-30% of all adverse events and may be the cause of death in 4% of all cancer patients, where others may be deprived from optimal anticancer therapy through reduced pharmacologic effects.[3,8] In addition, as cancer patients often take many comedication beside their anticancer therapy they are particularly at risk for DDIs. However, only limited data are available on the prevalence of DDIs in patients being treated

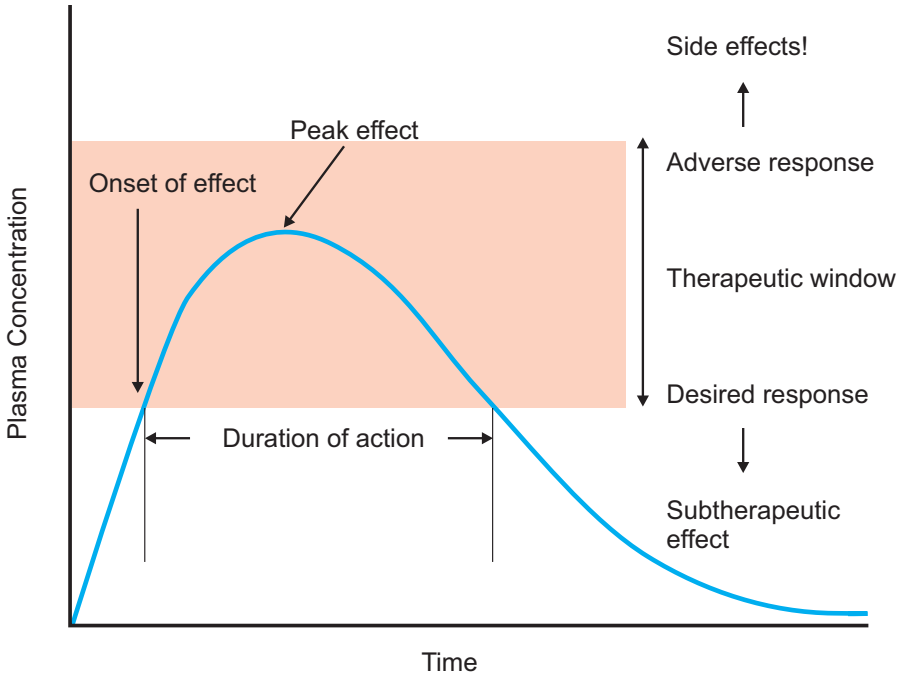


Figure 3: Therapeutic window of drugs

The Therapeutic window of a certain drug is a range in blood concentration which can treat disease effectively without having toxic effects (e.g. side effects). Below a minimum concentration the drug is inactive, while above a certain concentration toxicity appears. The most effective drug concentration (and dose) should be within the therapeutic window.

with anticancer drugs. In a study in ambulatory cancer patients, 27% of cancer patients were exposed to DDIs involving anticancer drugs.[9] To our knowledge, there is no study available that has included over-the-counter (OTC)-drugs. When DDIs in cancer patients are not properly managed in clinical practice the patients may be deprived from optimal therapy through overdosing or under treatment. Remarkably, most cancer patients are not routinely checked for DDIs during anticancer treatment. Cancer patients are often treated multidisciplinary and a profound overview of all prescribed drugs, including herbal and OTC-drugs, is not always available. Furthermore, documenting all drugs, including OTC-drugs in one national electronic patient record is not common practice in most countries.

NEW CHALLENGES

Historically, conventional cytotoxic drugs were predominantly administered intravenously on a non-continuous bases (e.g. once every 3 weeks). However, in the past decade there is a shifting paradigm towards specific targeted therapies that are predominately administered orally and that are continued over much longer periods of time (years). Especially, tyrosine kinase inhibitors (TKIs) have rapidly become an established factor in daily oncology practice. At present, there are 25 TKIs approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).[10, 11] The oral route of administration for these targeted agents is flexible, convenient and improves the quality of life during cancer therapy.[12] Despite this advantage, there are new challenges that arise in the use of these novel targeted anticancer agents. TKIs are generally characterized by a poor and variable bioavailability, resulting in significant between-patients variability in plasma levels and exposure. This variability is the result of an interplay of factors, including tissue permeability, membrane transport and enzymatic metabolism.[13] Furthermore, since TKIs are used chronically and are metabolized predominantly by CYP enzymes, patients on TKIs are at considerable risk for DDIs. Due to the oral administration route of TKIs, new DDIs concerning gastrointestinal absorption become apparent.[14] As nowadays this new class of drugs is extensively used, and considering its narrow therapeutic window, there is an increasing chance of serious drug interactions.

AIMS AND OUTLINE THESIS

The work described in this thesis aim to create awareness for DDIs in cancer therapy by describing the incidence, clinical relevance and giving specific recommendations to guide medical oncologists and pharmacists through the process of managing DDIs in cancer therapy in daily clinical practice.

In **chapter 2**, this thesis provides an overview of DDIs in TKI therapy as these group of targeted anticancer drugs is highly prone to DDIs (see figure 1). The focus of this review will be on the most important DDIs during TKI therapy: *i*)TKIs and acid reducing agents, *ii*) CYP-inhibitors/inducers and *iii*) QT_c interactions. Furthermore, a profound pharmacological background is given, several other important issues concerning DDIs in TKI therapy are addressed and clear recommendations for the management in clinical practice are given. In **chapter 3** and **chapter 4**, data are presented regarding the prevalence of DDIs in either intravenous and oral anticancer therapy, respectively. The purpose of these two studies is to generate data on the prevalence of DDIs and to create clinical awareness for potentially harmful drug combinations during prescribing anticancer drugs concomitant with other comedication. Due to the retrospective design, there remains an unmet need to assess the clinical relevance of DDIs in cancer therapy.

Therefore, as a sequel to **chapter 3** and **chapter 4** and since studies on the clinical relevance of DDIs have not yet been performed, in **chapter 5** a prospective study was designed to identify DDIs leading to actual clinical interventions during cancer therapy. The results of this study lead to a closer collaboration of clinicians to identify and manage these DDIs before the start and during anticancer treatment.

In the prospective study addressed in **chapter 5**, DDIs between TKIs and acid reducing agents (e.g. PPIs) were frequently seen. Although PPIs are extensively used during anti-cancer treatment, there is still no clear recommendations on how to manage DDIs between TKIs and PPIs.

As intragastric pH and subsequent pH dependent solubility is the "Achilles Heel" in TKI absorption, a practical way to by-pass the DDI between TKIs and PPIs could potentially be to temporarily lower the stomach pH by taking the TKI with an acidic beverage.[14] In **chapter 6** we therefore evaluated the impact of cola on the exposure of erlotinib (during or without PPI use) in patients with lung cancer. On the other hand, when all pharmacological characteristics of either TKIs and PPIs are considered, practical advices based on pharmacological principles can be given to manage this drug combination. In **chapter 7**, we considered the pharmacology of either TKIs and PPIs to develop practical guidelines to manage this drug interaction in clinical practice.

A Schematic outline of this thesis is presented in figure 4.

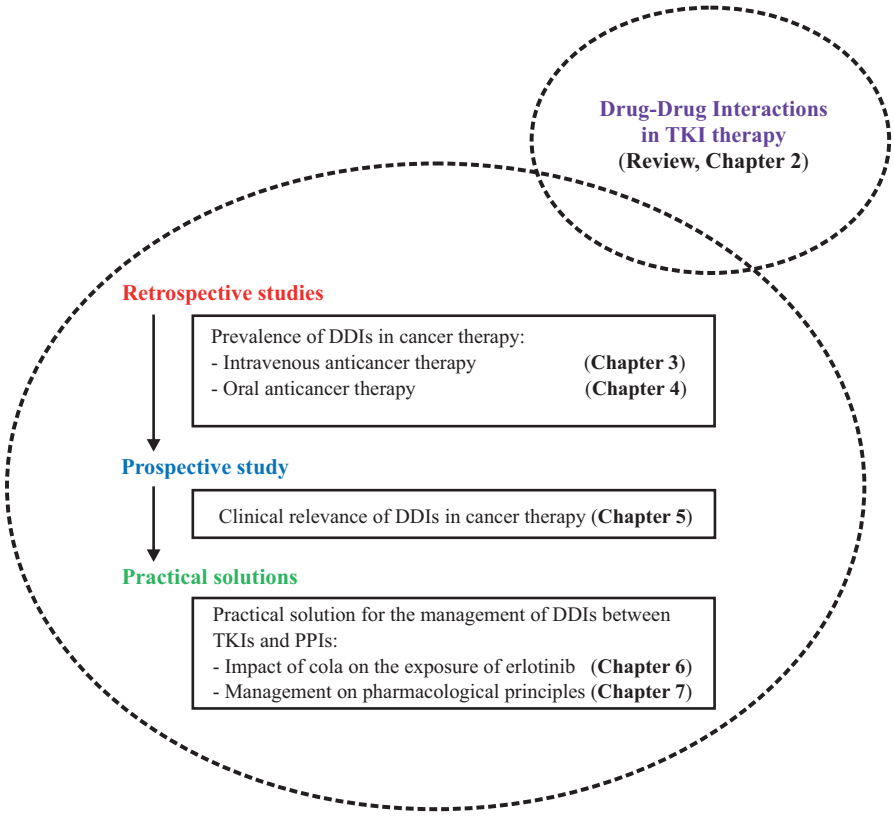


Figure 4: Schematic outline of this thesis

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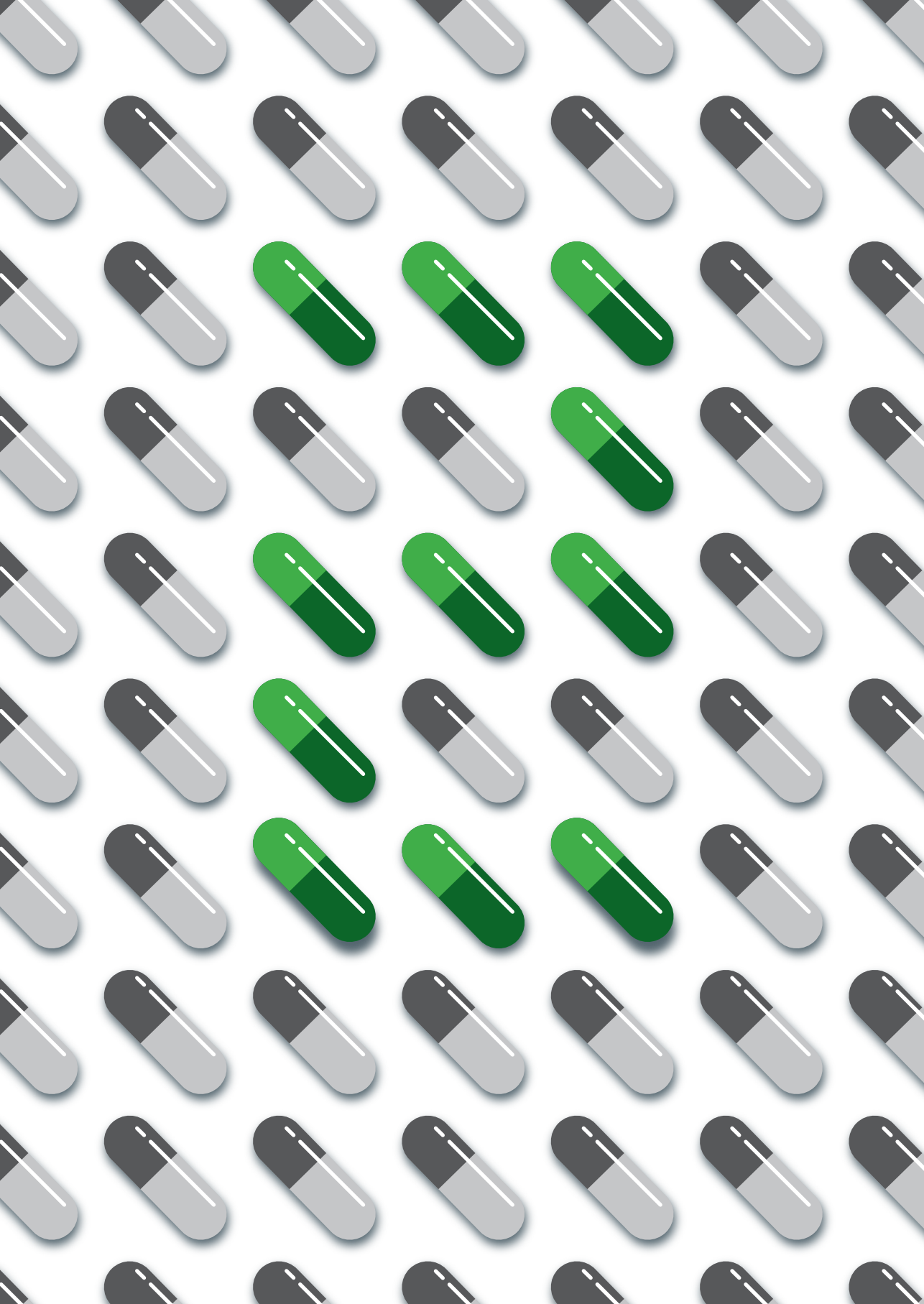

Chapter 2

DRUG-DRUG INTERACTIONS WITH TYROSINE-KINASE INHIBITORS: A CLINICAL PERSPECTIVE

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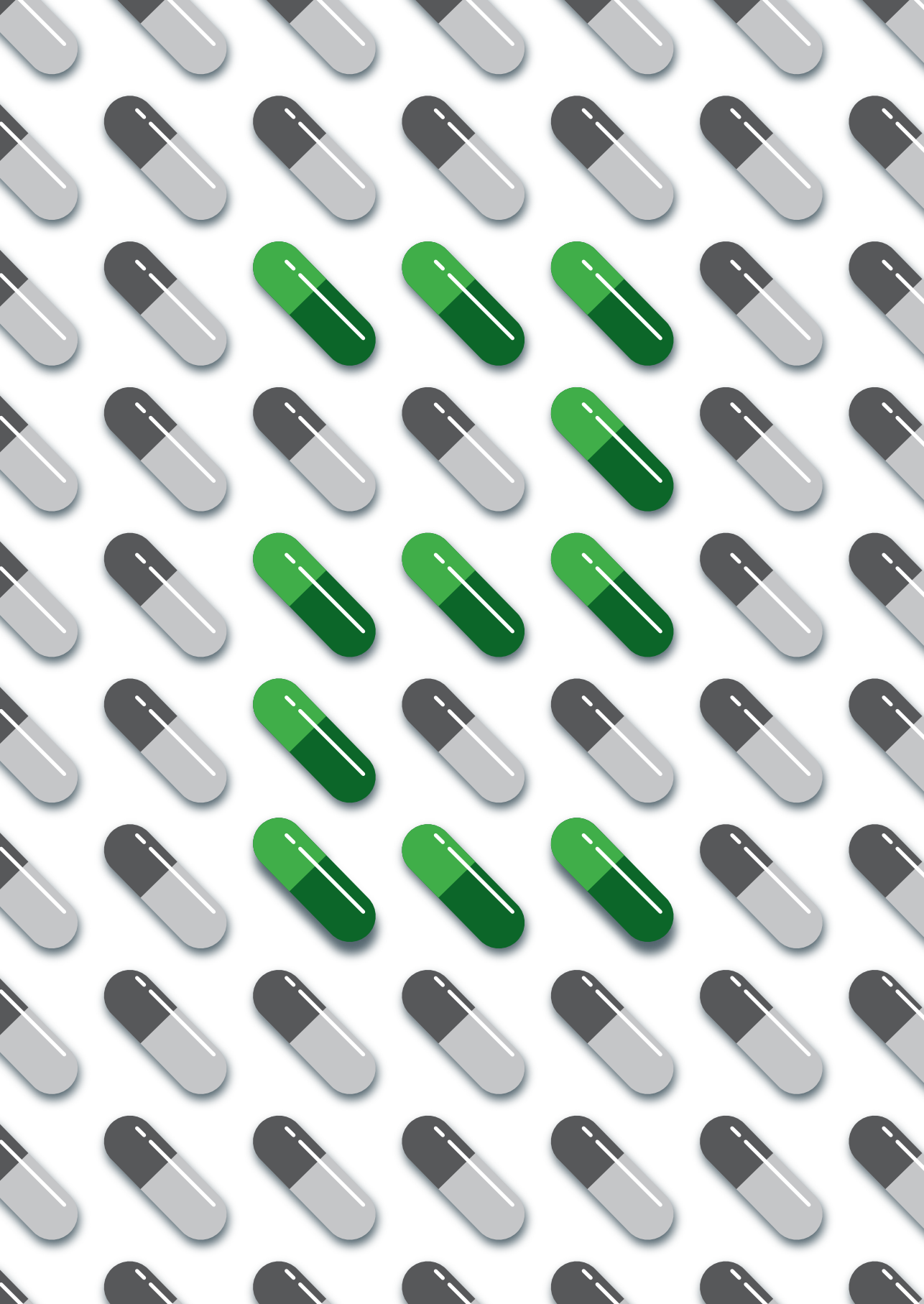

ABSTRACT

In the past decade, many tyrosine-kinase inhibitors have been introduced in oncology and haemato-oncology. Because this new class of drugs is extensively used, serious drug–drug interactions are an increasing risk. In this Review, we give a comprehensive overview of known or suspected drug–drug interactions between tyrosine-kinase inhibitors and other drugs. We discuss all haemato-oncological and oncological tyrosine-kinase inhibitors that had been approved by Aug 1, 2013, by the US Food and Drug Administration or the European Medicines Agency. Various clinically relevant drug interactions with tyrosine-kinase inhibitors have been identified. Most interactions concern altered bioavailability due to altered stomach pH, metabolism by cytochrome P450 isoenzymes, and prolongation of the QT_c interval. To guarantee the safe use of tyrosine-kinase inhibitors, a drugs review for each patient is needed. This Review provides specific recommendations to guide haemato-oncologists, oncologists, and clinical pharmacists, through the process of managing drug–drug interactions during treatment with tyrosine-kinase inhibitors in daily clinical practice.

INTRODUCTION

To improve effectiveness and reduce adverse events of cancer treatment, specific targets have been identified in oncology in the past decade. One of the most promising groups in targeted therapy are the tyrosine-kinase inhibitors.[1] Tyrosine kinases are key components of signal transduction pathways in the cell that relay information about conditions in the extracellular domain or the cytoplasm to pass on to the nucleus. As a result, tyrosine-kinase inhibitors affect gene transcription and DNA synthesis. Many tumour cells show abnormal activity of specific tyrosine kinases and are therefore an appealing target in oncology.[1]

All tyrosine-kinase inhibitors are given orally, which makes administration flexible and convenient, and improves quality of life. Another advantage of oral administration is that the tyrosine-kinase inhibitors are often taken on a continuous daily basis (compared with intermittent use of most chemotherapy), which usually improves the exposure time of the tumour to the active drug.
Although tyrosine-kinase inhibitors have some advantages compared with traditional chemotherapy, new challenges have arisen in the use of these novel targeted drugs. First, tyrosine-kinase inhibitors have specific toxicity profiles that differ from those of cytotoxic drugs.[2] Toxic effects can be severe (eg, cardiovascular side-effects) and some tyrosine-kinase inhibitors can even cause secondary tumours (eg, vemurafenib). Because the tyrosine-kinase inhibitors are used chronically and are metabolised by cytochrome P450 (CYP) isozymes, patients given these drugs are at substantial risk of having drug–drug interactions. Furthermore, because of the oral administration route of tyrosine-kinase inhibitors, new drug–drug interactions concerning gastrointestinal absorption have become apparent (eg, cotreatment with proton pump and tyrosine-kinase inhibitors).

Drug–drug interactions might be associated with serious or even fatal adverse events, or can lead to reduced therapeutic effects of either drug. Interactions can be classified into those that are pharmacokinetic and those that are pharmacodynamic.[3] Pharmacokinetic interactions arise when absorption, distribution, metabolism, or elimination of the involved drugs are altered, leading to changes in the amount and duration of drug availability at receptor sites. The most common pharmacokinetic drug–drug interactions concern absorption (incomplete drug absorption is a risk of drug interaction) and metabolisation by the cytochrome P450 isozymes. Pharmacodynamic interactions usually refer to

an interaction in which active compounds change each other's pharmacological effect. The effect can be synergistic, additive, or antagonistic.

In this Review we give an overview of existing data of known or suspected drug–drug interactions between tyrosine-kinase inhibitors approved by the US Food and Drug Administration or the European Medicines Agency and conventional prescribed drugs, over-the-counter drugs, and herbal medicines. Furthermore, we provide specific recommendations to guide oncologists, haemato-oncologists, and clinical pharmacists through the process of managing drug–drug interactions during treatment with tyrosine-kinase inhibitors in daily clinical practice.

SEARCH STRATEGY AND SELECTION CRITERIA

We screened the existing scientific literature about known or suspected drug–drug interactions between US Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved tyrosine-kinase inhibitors and conventional prescribed drugs, over-the-counter drugs, and herbal medicines. We identified references through searches of PubMed and Embase with the search terms [Drug interaction] OR [Drug combination] AND [Drug name]. We identified additional information was in the summary of product characteristics of the tyrosine-kinase inhibitors, that were FDA or EMA approved until Aug 1, 2013.[4,5] We reviewed only papers published in English. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

PHARMACOKINETIC DRUG INTERACTIONS: ABSORPTION

Gastrointestinal absorption of a drug depends on its inherent characteristics (eg, solubility), but can also be affected by drug–drug interactions. At the absorption level, these interactions mainly take place with tyrosine-kinase inhibitors that have incomplete absorption (eg, bioavailability <50%, first pass effect, or dependence on influx or efflux transporters). Important factors that can affect absorption of tyrosine-kinase inhibitors are a change in stomach pH due to coadministration of an H_2 antagonist, proton-pump inhibitor, or antacid, and the inhibition of P-glycoprotein and intestinal CYP3A4 in enterocytes.

Table 1: Effects of acid-suppressive compounds on the bioavailability of tyrosine-kinase inhibitors

TKI	Acid suppressive compound	Effect on TKI exposure C_{max}	Effect on TKI exposure AUC	Alternatives/recommendations	Refs.
Axitinib	Rabeprazol 20mg q.d.	42%↓	15%↓	H2As, PPIs and antacids can be used concomitantly with axitinib.	4, 5
Crizotinib	-	-	-	The solubility of crizotinib is pH dependent. Solubility sharply decreases from over the pH range 1•6–8•2 No drug interaction study has been conducted yet but effects can be expected. Acid suppressive agents should not be used concomitantly.	4, 5
Dasatinib	Famotidine 40mg, 10 hours before dasatinib	63%↓	61%↓	H2As: can be used 2 hours after dasatinib.	4,5,7
	Famotidine 40mg, 2 hours after dasatinib	-	-	Antacids: can be used 2 hours before and after Dasatinib.	
	Maalox 30ml, 2 hours before dasatinib	26%↓	-	PPIs: PPIs should not be used concomitantly with dasatinib.	
	Maalox 30ml, concomitantly with dasatinib	58%↓	54%↓		
	Omeprazole 40mg q.d. concomitantly with dasatinib	42%↓	43%↓		
Erlotinib	Omeprazole 40mg q.d. concomitantly with erlotinib.	61%↓	46%↓	H2As: can be used 2 hours after erlotinib. Ranitidine should be given in a 150mg b.i.d. regiment.	4, 5
	Ranitidine 300mg q.d. concomitantly with erlotinib	54%↓	33%↓	Antacids: can be used 4 hours prior or 2 hours after erlotinib.	
	Ranitidine 150mg b.i.d. concomitantly with erlotinib (erlotinib, 2 hours before and 10 hours after ranitidine	17%↓	15%↓	PPIs: should not be used concomitantly with erlotinib.	
Gefitinib	Two oral doses of 450 mg ranitidine (13 hours and 1 hour before gefitinib) followed by sodium bicarbonate was applied if a pH of ≥ 5 was not achieved.	71%↓	47%↓	H2As: should not be used concomitantly with gefitinib. Antacids: can be used 2 hours before or after gefitinib. PPIs: should not be used concomitantly with gefitinib.	4, 5
Imatinib	Omeprazole 40mg q.d., concomitantly with imatinib	-	-	H2As, PPIs and antacids can be used concomitantly with imatinib.	8, 9
	Maalox 20ml, 15 minutes before imatinib	-	-		
Lapatinib	Esomeprazole 40mg q.d., 12 hours prior to lapatinib	-	27%↓	H2As: should not be used concomitantly with lapatinib. Antacids: can be used 2 hours before or after lapatinib. PPIs: should not be used concomitantly with lapatinib.	4, 5

Table 1: Continued

TKI	Acid suppressive compound	Effect on TKI exposure C_{max}	Effect on TKI exposure AUC	Alternatives/recommendations	Refs.
Nilotinib	Esomeprazole 40mg q.d. concomitantly with nilotinib	27%↓	34%↓	H2As: can be used 10 hours before or 2 hours after nilotinib. Antacids: can be used 2 hours prior or after nilotinib. PPIs: nilotinib may be used concomitantly with PPIs.	10-12
	Famotidine 20mg b.i.d. concomitantly with nilotinib (given 2 hours after nilotinib)	-	-		
	Single oral dose of nilotinib and Maalox 20ml, where antacid was given 2 h before and after nilotinib	-	-		
Pazopanib	Esomeprazole (evening) concomitantly with pazopanib (in the morning)	42%↓	40%↓	H2As: pazopanib should be taken at least 2 hours before or 10 hours after a dose of an H2A. Antacids: can be used 4 hours before or 2 hours after pazopanib. PPIs: take the dose of pazopanib in the evening concomitantly with the PPI.	4, 5
Regorafenib	-	-	-	No study data available yet.	4,5
Ruxolitinib	-	-	-	H2As, PPIs and antacids can be used concomitantly with Ruxolitinib.	4, 5
Sorafenib	Esomeprazole concomitantly with sorafenib.	-	-	H2As, PPIs and antacids can be used concomitantly with imatinib.	4, 5
Sunitinib	-	-	-	Due to the high solubility, no effect on sunitinib would be expected during H2A, antacid or PPI use. Therefore, they may be used concomitantly.	4, 5
Vandetanib	-	-	-	H2A, antacids, PPIs may be concomitantly used with Vandetanib. Vandetanib demonstrates pH-dependent solubility but this is not clinically significant.	4, 5
Vemurafenib	-	-	-	H2A, antacids, PPIs may be concomitantly used with Vemurafenib. Vemurafenib demonstrates pH-dependent solubility but this is not clinically significant.	4, 5

H2As=H_2-antagonists, PPI=proton pump inhibitors, Refs = references

Alteration of stomach pH

Besides pH independent, chemical solubility properties, the most important factor that affects solubility and the resulting exposure to tyrosine-kinase inhibitors is stomach pH.

Because of their weakly basic properties, tyrosine-kinase inhibitors can be present in either the ionised or non-ionised form, depending on the pH in the stomach and the pK_a of the drug (ie, the pH at which the tyrosine-kinase inhibitor reaches equilibrium between the ionised and non-ionised form). Ionised forms normally dissolve more easily than do non-ionised forms. When a tyrosine-kinase inhibitor is coadministered with an acid suppressive drug (eg, a proton-pump inhibitor), the pH in the stomach will increase from 1 to about 4. Subsequently, the equilibrium of ionised or non-ionised drug will shift to the less soluble non-ionised form, and as a result, the bioavailability of the tyrosine-kinase inhibitor will decrease.[4] If the pK_a of a tyrosine-kinase inhibitor (eg, dasatinib) is near the pH range 1–4 the shift towards the non-ionised (less soluble) form, will be greater than that with an inhibitor with a higher pK_a (eg, sunitinib). As such, for tyrosine-kinase inhibitors with a pK_a of less than 4–5, co-administration of acid suppressive drugs (eg, antacids, proton-pump inhibitors, H_2-antagonists) will further reduce solubility and, subsequently, bioavailability and exposure to the tyrosine-kinase inhibitor.

In clinical practice, drug–drug interactions between acid suppressive drugs and tyrosine-kinase inhibitors can be clinically relevant. The oral absorption of crizotinib, dasatinib, erlotinib, gefitinib, lapatinib, and pazopanib is substantially altered by concomitant use of acid suppressive treatment. If possible, the combination of these tyrosine-kinase inhibitors and an H_2-antagonist, proton-pump inhibitor, or antacid should be avoided. Table 1 provides detailed recommendations for the clinical management of these drug–drug interactions.

Inhibition/induction of intestinal enzymes and drug transporters

A tyrosine-kinase inhibitor needs to be transported across the gut wall to reach the portal blood circulation. This transmembrane transport of the drug is a complex multifactorial process mediated by passive diffusion, organic anion and cation transporting peptides, multidrug resistance-associated proteins (eg, ATP-binding cassette [ABC] transporter G2), efflux transporters (eg, P-glycoprotein or multidrug resistance protein 1 [ABCB1]) and intestinal metabolic enzymes (eg, CYP3A4).

After passive diffusion or active transport through the gut lumen (or apical membrane), the tyrosine-kinase inhibitor enters the enterocyte where some tyrosine-kinase inhibitors undergo cytochrome p450 (CYP)-mediated metabolism. Subsequently, the drug or its (active) metabolite will undergo either active countertransport (or efflux) back into the gut lumen, or uptake into the portal vein by passive diffusion, or active transport through the basolateral membrane (figure 1).

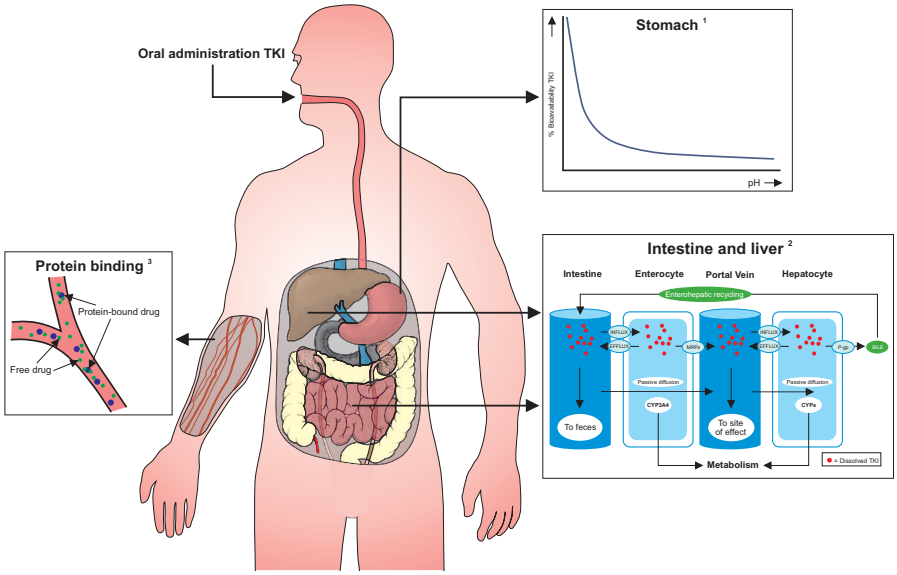

Figure 1: Major sites of pharmacokinetic drug–drug interactions in treatment with TKIs

TKI=tyrosine-kinase inhibitor. MRPs=multidrug resistance protein drug transporters, P-gp=P-glycoprotein. CYPs=cytochrome P450 enzymes. *With increasing stomach pH the bioavailability of TKIs decreases. †Protein-bound molecules are not available to exert pharmacological effects. ‡Shows the association between CYPs and drug transporters in TKI absorption or metabolism.

P-glycoprotein

The role of P-glycoprotein in the absorption of tyrosine-kinase inhibitors has been widely studied. Some tyrosine-kinase inhibitors (eg, crizotinib) are a substrate for P-glycoprotein, and consequently, inhibition or induction of this efflux transporter by coadministration of another drug might lead to a clinically relevant drug–drug interaction (table 2). Other tyrosine-kinase inhibitors (eg, pazopanib, lapatinib, and gefitinib) directly inhibit the activity of P-glycoprotein and can increase bioavailability of concomitantly used P-glycoprotein substrates. For instance, the area under the curve of digoxin is increased by 80% with P-glycoprotein inhibition by lapatinib.[5, 6] Another example is the rise in SN-38 exposure (the active metabolite of irinotecan), which has been attributed to inhibition of P-glycoprotein by lapatinib and gefitinib.[13, 14] The increased exposure to paclitaxel (roughly 26%) when used in combination with pazopanib can also be attributed to inhibition of P-glycoprotein by pazopanib.[5, 6] Furthermore, the pazopanib area under the curve was increased by 59% with P-glycoprotein-related inhibition of lapatinib. However, at reduced doses of both drugs, no changes were noted in bioavailability.[5, 6]

Intestinal CYP3A4

The intestinal metabolic enzyme CYP3A4 exerts its action in close proximity of P-glycoprotein in the enterocytes of the gut lumen (figure 1).[15] Simultaneous use of tyrosine-kinase inhibitors that are substrates for intestinal CYP3A4 together with CYP3A4 inhibitors and inducers can change the exposure and toxicity of tyrosine-kinase inhibitors. An example of a substance that inhibits intestinal CYP3A4 is grapefruit, which increases the area under the curve of sunitinib by 11%, or that of nilotinib by 29%.[16, 17] By contrast, grapefruit juice did not seem to affect the area under the curve of imatinib.[18] A possible explanation is that grapefruit juice not only enhances absorption of CYP3A4 substrates at the enterocyte level, but also decreases absorption of organic anion transporting peptides substrates.

Other drug-transporters

Besides P-glycoprotein, several tyrosine-kinase inhibitors (eg, imatinib) have been identified as substrates of other drug transporters (eg, organic anion transporting peptides, organic cation transporter, breast cancer resistance protein).[5, 6] Some drugs might inhibit organic anion transporting peptides (eg, ciclosporin) or breast cancer resistance protein (eg, lapatinib), but involvement of other mechanisms, such as CYP3A4, cannot be ruled out in these drug–drug interactions.[19] Evidence for drug–drug interactions with tyrosine-kinase inhibitors through inhibition or induction of transporters is not yet available.

Table 2: Pharmacological parameters of tyrosine-kinase inhibitors

TKI	Target	Absolute bioavailability	Protein binding	CYPs major	CYPs Minor and other	Inhibits	Inducer	P-glycoprotein
Axitinib	VEGFR 1,2,3	58%	>99%	CYP3A4	CYP1A2, CYP2C19, UGT	CYP1A2, CYP2C8	-	-
Crizotinib	HGFR; ALK	43%	91%	CYP3A4	CYP2D6, CYP2C19	CYP3A4	CYP2B6, CYP2C8, CYP2C9, UGT	Substrate, Inhibitor
Dasatinib	PDGFRβ; c-KIT; SRC; BCR-ABL; EPH	Unknown	96%	CYP3A4	CYP2C8, FMO and UGT	CYP3A4	-	-
Erlotinib	HER1-(EGFR)	60%	95%	CYP3A4	CYP1A2, CYP2C8, CYP1A1, CYP2D6	CYP3A4, CYP2C8, CYP1A1	-	Substrate
Gefitinib	HER1-(EGFR)	60%	90%	CYP3A4, CYP2D6	CYP1A1	CYP2D6, CYP2C19	-	-
Imatinib	PDGFRβ; c-KIT; FLT-3; BCR-ABL	98%	95%	CYP3A4	CYP2D6, CYP2C9	CYP3A4, CYP2D6, CYP2C9	-	-
Lapatinib	HER1(EGFR); HER2, AKT	Unknown	>99%	CYP3A4	CYP2C8, CYP2C19, CYP2C9, CYP1A2, CYP2D6	CYP3A4, CYP2C8	-	Substrate, Inhibitor
Nilotinib	PDGFRβ; c-KIT; BCR-ABL	31%	98%	CYP3A4	CYP2C8, CYP2C9, CYP1A1, CYP1A2, CYP2D6	CYP3A4	CYP2B6, CYP2C8, CYP2C9	-
Pazopanib	VEGFR 1,2,3; PDGFRβ; c-KIT	14-39%	99%	CYP3A4	CYP1A2, CYP2C8	CYP2D6, CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2E1	-	Inhibitor
Regorafenib	VEGFR; PDGFRβ; KIT; BRAF	69-83%	>99%	CYP3A4	UGT	CYP2C9; CYP2B6; CYP3A4; CYP2C8	-	Substrate Inhibitor
Ruxolitinib	JAK 1,2	Unknown	97%	CYP3A4, CYP2C9	-	CYP3A4	-	-
Sorafenib	VEGFR 2,3; PDGFRβ; c-KIT; FLT3; BRAF; CRAF	Unknown	99%	CYP3A4	-	CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4	-	-
Sunitinib	VEGFR 1,2,3; PDGFRβ; c-KIT; FLT3; SRC	Unknown	90-95%	CYP3A4	CYP1A2	-	-	Inhibitor
Vandetanib	VEGFR 2; HER1(EGFR); SRC	Unknown	90-94%	CYP3A4	FMO-1,3	CYP2D6	CYP3A4, CYP2C9, CYP1A2	-
Vemurafenib	BRAF	Unknown	>99%	CYP3A4*	-	CYP1A2, CYP2D6	CYP3A4, CYP2B6	Substrate, Inhibitor

This table is constructed from regulatory documents.[4,5]

*Only minor contribution of CYP3A4 (about 5%).

*Only minor contribution of CYP3A4 (±5%)

Other factors affecting absorption of tyrosine-kinase inhibitors

Another factor that might affect absorption of tyrosine-kinase inhibitors is the formation of an insoluble complex. For instance, bile salt-sequestering drugs such as cholestyramine can interfere with regorafenib absorption by formation of insoluble complexes. The clinical significance of these drug–drug interactions is unknown.[5, 6]

PHARMACOKINETIC DRUG INTERACTIONS, DISTRIBUTION

Distribution is largely measured by blood flow and the binding affinity for the plasma proteins albumin and α1-acid glycoprotein. If two drugs that are both highly bound to plasma proteins (>90%) are combined, one drug can displace the other from its protein binding site, therefore increasing the concentration of unbound drug (figure 1).

Although axitinib, lapatinib, and vemurafenib are all highly bound to plasma proteins (≥99%), and should theoretically be most susceptible for drug–drug interactions, little evidence is available to support a clinically relevant interaction on the basis of displacement of protein binding sites.[5, 6] Imatinib used concomitantly with clindamycin leads to altered imatinib exposure because of displacement of protein-bound imatinib. As a result, the increased free plasma concentration of imatinib leads to a rapid redistribution of the unbound drug into the extravascular volume. The clinical relevance of this interaction is unknown.[20]

All tyrosine-kinase inhibitors are fairly highly bound to plasma proteins (90% to >99%; table 2), which, in theory, makes these inhibitors prone to interactions with other highly bound drugs, such as warfarin and phenytoin.[5, 6, 21, 22] However, the evidence for drug–drug interactions concerning protein displacement is poor and, in reality, these interactions are more likely to be the consequence of other (metabolic) mechanisms.[23]

Table 3: Effects of CYP3A4 induction/inhibition on the exposure of TKIs

TKI	Inducing compound (CYP3A4)	Inhibitory compound (CYP3A4)	Effect on TKI exposure C_{max}	Effect on TKI exposure AUC	Alternatives and recommendations	Refs.
Axitinib	Rifampicin		71%↓	79%↓	Increase Axitinib dose gradually and monitor toxicity in order to obtain optimal efficacy.	4, 5, 24
		Ketoconazole	50%↑	106%↑	Lower axitinib dose to 2 mg b.i.d.	4, 5, 25
Crizotinib	Rifampicin		69%↓	82%↓	Increase crizotinib dose gradually and monitor toxicity in order to obtain optimal efficacy.	4, 5
		Ketoconazole	44%↑	216%↑	Avoid combination, if necessary extreme caution must be taken, dose should be lowered and toxicity must be monitored.	4, 5
Dasatinib	Rifampicin		81%↓	82%↓	Initially increase the dose 3-fold and then increase stepwise with 20mg based on patients tolerability and response.	4
		Ketoconazole	384%↑	256%↑	Lower the dasatinib dose to 20-40mg q.d.	4, 5, 26
Erlotinib	Rifampicin		29%↓	67-69%↓	Increase the dose to 300mg q.d., if well tolerated the dose can be increased after 2 weeks to 450mg q.d. under monitoring of side-effects.	4, 5
		Ketoconazole	102%↑	86%↑	If combination is indicated and erlotinib toxicity is observed, the erlotinib dose should be lowered with 50mg steps.	4, 5, 27
Gefitinib	Rifampicin		65%↓	83%↓	Increase gefitinib dose to 500mg q.d.	4, 5, 28
		Itraconazole	51%↑	78%↑	Avoid combination, if indicated gefitinib toxicity must be monitored, no clinical data available on the starting dose.	4, 5, 28
Imatinib	Rifampicin		54%↓	74%↓	Increase imatinib dose by at least 50%.	4, 5, 29
		Ketoconazole	26%↑	40%↑	No intervention is needed, but regular monitoring for toxicity is recommended.	4, 5, 30
Lapatinib	Carbamazepine		59%↓	72%↓	Gradually increase the lapatinib dose to 4500mg q.d. and monitor for liver toxicity.	4, 5, 31
		Ketoconazole	114%↑	257%↑	Lower the lapatinib dose to 500mg q.d.	4, 5, 31
Nilotinib	Rifampicin		64%↓	80%↓	Increase the dose gradually depending on patients toxicity and efficacy.	32
		Ketoconazole	84%↑	201%↑	Lower nilotinib dose to 400mg q.d.	32
Pazopanib	Phenytoin or Carbamazepine		50%↓	30%↓	Gradually increase the pazopanib dose with 200mg steps depending on patients tolerability	4,5
		Ketoconazole	45%↑	66%↑	Lower the dose by approximately 50% or 400mg q.d.	4,5

Table 3: Continued

TKI	Inducing compound (CYP3A4)	Inhibitory compound (CYP3A4)	Effect on TKI exposure C_{max}	Effect on TKI exposure AUC	Alternatives and recommendations	Refs.
Regorafenib	Rifampicin		50%↓	20%↓	Avoid the combination with strong CYP3A4 inducers, if indicated gradually increase the regorafenib dose and monitor toxicity in order to obtain optimal efficacy.	4,5
		Ketoconazole	33↑	40↑	Avoid the combination with strong CYP3A4 inhibitors, if indicated regorafenib toxicity must be monitored.	4,5
Ruxolitinib	Rifampicin		52%↓	71%↓	Increase the dose gradually depending on patients toxicity and efficacy.	4, 5, 33
		Ketoconazole	33%↑	91%↑	Lower the ruxolitinib dose by 50% and hematological toxicity must be monitored extensively (2 times a week).	4, 5, 33
Sorafenib	Rifampicin		-	37%↓	Combination can be used safely.	4, 5
		Ketoconazole	-	-	Combination can be used safely.	4, 5, 34
Sunitinib	Rifampicin		23%↓	46%↓	Gradually increase the sunitinib dose with 12,5mg steps, with a maximum of 87,5mg q.d. (GIST)	35
		Ketoconazole	49%↑	51%↑	Lower the sunitinib dose maximally to 25mg q.d.	35
Vandetanib	Rifampicin		-	40%↓	Co-administration of rifampicin results in a moderate increase in AUC of vandetanib. By contrast, the exposure to the mean active metabolite N-desmethylvandetanib was profoundly increased (AUC 266%). CYP3A4 inducers therefore need to be avoided during vandetanib therapy.	36
		Itraconazole	-	9%↑	Combination can be used safely.	36
Vemurafenib			-	-	No data on concomitant use of CYP3A4 inhibitors/inducers. Caution must be taken when co-administration of vemurafenib and CYP3A4 inhibitors or inducers is indicated.	4, 5

PHARMACOKINETIC DRUG INTERACTIONS, METABOLISM

Phase 1, mostly oxidative, metabolism by cytochrome P450 enzymes (CYPs) is the most important route of drug metabolism of drugs in vivo. Although some drugs are also metabolised by enterocyte CYP3A4 enzymes, the main site of metabolism in the human body is the liver (figure 1).
CYP enzymes can be inhibited in two ways: (1) competitive binding of two substrates at the same CYP-enzyme binding site and (2) uncompetitive inhibition of CYP enzymes by an inhibitor coadministered with a substrate for the same CYP enzymes, leading to an increase in the serum area under the curve of the CYP substrate. The net effect on the area under the curve of the CYP substrate is dependent on the inhibitory and inducing potency of the coadministered drug. Increased or decreased exposure by alteration of CYP activity might cause clinically relevant toxic effects or ineffectiveness of treatment with tyrosine-kinase inhibitors. Table 2 provides an overview of CYPs involved in metabolism of tyrosine-kinase inhibitors.

Because drug–drug interactions concerning strong CYP3A4-inhibition or induction play a crucial part in treatment with tyrosine-kinase inhibitors, they are usually well described in the regulatory assessment report of the manufacturer or in primary literature (table 3).

Other metabolic drug–drug interactions

Axitinib

The effects of strong CYP3A4 inhibition and induction on axitinib exposure have been thoroughly investigated. However, the effect on C_{max} and the area under the curve of moderate CYP3A4 inhibitors (eg, fluconazole) needs to be assessed in future studies. CYP1A2 and CYP2C19 have a minor role in axitinib elimination and so the risk of a clinical relevant drug–drug interaction via inhibition or induction of these enzymes is negligible. Furthermore, the effect of drug-transporter inhibitors (eg, ciclosporin) on the exposure of axitinib has not yet been investigated but deserves attention, because transporters of organic anion transporting peptide and breast cancer resistance protein might affect axitinib exposure.

Crizotinib

Crizotinib is a strong CYP3A4 inhibitor; it increases the area under the curve of midazolam by 270%.[5, 6] The combination of crizotinib and CYP3A4 substrates with a narrow therapeutic window (eg, ciclosporin or simvastatin) should therefore be avoided or closely monitored for toxic effects. For combined treatment with ciclosporin, therapeutic drug monitoring is recommended.[5, 6] The product label also warns about co-administration of crizotinib with CYP2B6, CYP2C8, CYP2C9, UGT1A1, P-glycoprotein substrates, and drug transporter inhibitors, but the clinical significance of these combinations is unknown.[5, 6]

Dasatinib

Strong inhibitors of CYP3A4 have a profound effect on dasatinib exposure.[5, 6] The effect of moderate CYP3A4 inhibitors on dasatinib exposure might also be clinically relevant, but such data are not available.[5, 6] The product label warns about the combination of dasatinib and simvastatin. Through (time-dependent) inhibition of CYP3A4 by dasatinib, simvastatin C_{max} is increased by 37%, and the area under the curve is increased by 20%.[5, 6] However, because dasatinib is a time-dependent inhibitor of CYP3A4 and the dose was not at steady state, the above findings could underestimate the CYP3A4 inhibition and the effect on simvastatin. The combination of dasatinib and CYP3A4 substrates with a narrow therapeutic window should therefore be avoided (eg, change from simvastatin to pravastatin), or approached with caution.[5, 6]

Erlotinib

Profound reduction in erlotinib exposure has been reported for the potent CYP3A4 inducer rifampicin,[5, 6] and reduced exposure of erlotinib might also take place with other strong inducers and moderate inducers (eg, enzalutamide, phenytoin, carbamazepine, barbiturates, or St John's wort).[5, 6] The exposure to erlotinib is increased with concomitant use of the CYP1A2 inhibitor ciprofloxacin (increased C_{max} and area under the curve of 17% and 39%, respectively). In the case of combined ciprofloxacin and erlotinib treatment, recommendations state that the erlotinib dose should only be lowered (using 50 mg steps) if specific toxic effects are observed.[5, 6] Because of competition for CYPs (3A4 and 1A2), erlotinib might increase the international normalised ratio in patients given warfarin,[22] increase simvastatin exposure (rhabdomyolisis),[37] and augment phenytoin toxicity,[21] but evidence to support these changes is poor. Nevertheless, caution and awareness of these potential interactions is needed when coadministering these drugs. Carboplatin exposure was increased when concomitantly used with erlotinib, whereas no effect was noted with paclitaxel exposure.[38]

Gefitinib

Concomitant gefitinib with phenytoin (a moderate-to-strong CYP3A4 inducer) results in a 26% decrease in C_{max}, and a 47% decrease in the area under the curve.[39] A potential drug–drug interaction has been reported between herbal CYP3A4/5 inducers (eg, ginseng) and gefitinib. After discontinuation of the herbal medicines, a patient turned from being a non-responder to a (partial) responder.[40] In theory, this interaction could also be expected with St John's wort (CYP3A4 inducer). If coadministration of gefitinib and a moderate-to-strong CYP3A4 inducer cannot be avoided, the gefitinib dose should be increased from 250 mg to 500 mg, both once daily. Through weak inhibition of CYP2D6, gefitinib can increase the C_{max} and the area under the curve of metoprolol by 10% and 35%, respectively, although increased metoprolol exposure does not seem to be clinically relevant.[28] Because of competition for CYP3A4, gefitinib might increase the international normalised ratio in warfarin treatment.[41] CYP3A4-inducing anti-epileptics significantly lowered gefitinib exposure.[42] Finally, sorafenib decreases the exposure to gefitinib (decrease in C_{max} and area under the curve of gefitinib by 38% and 26%, respectively) by an unknown mechanism, leaving sorafenib unaffected.[43]

Imatinib

Drug–drug interactions described with phenytoin, St John's wort, and enzyme-inducing anti-epileptic drugs show a consistent decrease in imatinib exposure.[44, 45, 46] If co-administration of imatinib and a strong CYP3A4 inducer is needed, the imatinib dose should be increased by at least 50%. Concomitant use of single-dose ketoconazole results in an non-significant increase in imatinib single-dose exposure.[30] Furthermore, because of CYP3A4 auto-inhibition by imatinib at steady state, coadministration of ritonavir did not have an effect on imatinib exposure.[47] By contrast, severe toxic effects have been noted when imatinib was concomitantly used with the strong CYP3A4 inhibitor voriconazole.[48] Taking the safety profile into account, coadministration of imatinib and strong CYP3A4 inhibitors should be possible without dose adjustments. However, caution is needed, and regular monitoring for toxic effects is recommended.[49] Ciclosporin and imatinib can also mutually affect each other's exposure, but changes are small and regarded as clinically irrelevant.[50] Liver toxicity was noted during concomitant use of ginseng (a CYP3A4 inhibitor) and imatinib, but this outcome could also be caused by ginseng itself.[51] Because of strong inhibition of CYP3A4 by imatinib, simvastatin exposure was markedly increased.[52] If the combination is needed, simvastatin should be switched to another weakly CYP3A metabolised statin, such as rosuvastatin.[53] CYP3A4 inhibition by imatinib might lead to high

nifedipine exposure, and thus form gallbladder stones; however, evidence is not convincing.[54] Through weak inhibition of CYP2D6, imatinib can increase the C_{max} and area under the curve of metoprolol by 8% and 23% respectively, but this finding has no clinical implications.[55] Because of possible competition for CYPs, imatinib might increase the international normalised ratio in warfarin treatment, but again, evidence is weak.[56]

Lapatinib

If coadministration of lapatinib and a strong CYP3A4 inducer is needed, the once daily lapatinib dose should be gradually increased stepwise from 1250–1500 mg (normal dose) to 4500 mg. Furthermore, if the lapatinib dose is increased to 4500 mg once daily, clinicians should be aware of the possible hepatotoxic effects of lapatinib metabolites with concomitant use of dexamethasone (a moderate CYP3A4 inducer).[57] CYP3A4 inducing anti-epileptics significantly lower lapatinib exposure.[58] When coadministered with irinotecan, the C_{max} of the active metabolite SN-38 was increased by 32% and the area under the curve was increased by 41%.[13] By contrast, no differences were noted in the exposure of lapatinib.[13] The reported effect is suspected to be multifactorial with contributions of, among others, inhibition of CYP3A4 by lapatinib.[13] When lapatinib was given in combination with paclitaxel, the exposure of both drugs was increased by 21% and 23%, respectively, possibly by inhibition of CYP2C8.[59] Because lapatinib is an inhibitor of CYP3A4 and CYP2C8, the product label recommends that the combination of lapatinib and CYP3A4 and CYP2C8 (eg, repaglinide) substrates with a small therapeutic window should therefore be avoided or approached with caution.[5, 6]

Nilotinib

By weak inhibition of CYP3A4, nilotinib can increase the C_{max} of midazolam by 20% and the area under the curve by 30%.[5, 6] Nilotinib did not have a significant effect on warfarin or imatinib exposure, and so can be used concomitantly.[60]

Pazopanib

By weak inhibition of CYP3A4 and CYP2D6, pazopanib might increase the exposure of midazolam and dextromethorphan.[61] In the same study, pazopanib did not have a significant effect on warfarin (CYP2C9 specific), omeprazole (CYP2C19 specific), and caffeine (CYP1A2 specific).[61] Coadministration of pazopanib eye drops with orally taken ketoconazole roughly doubled the pazopanib area under the curve.[5, 6] Pazopanib increased the area under the curve and C_{max} of paclitaxel (a substrate for CYP2C8, CYP3A4, and P-glycoprotein)

by 26% and 31%, respectively, without changing tolerability.[5, 6] In combination with lapatinib 1500 mg (moderate, competitive CYP3A4, P-glycoprotein, and breast cancer resistance protein inhibitor), the pazopanib (800 mg) area under the curve and C_{max} were increased by 59% and 51%, respectively. However, at a lower pazopanib (400 mg) and lapatinib dose (1000 mg), no statistically significant effect was seen for the area under the curve or C_{max}.[5, 6]

Regorafenib

When given concomitantly with ketoconazole, the area under the curve of regorafenib was increased by 33% and the C_{max} by 40%. Furthermore, a decrease of more than 90% was noted in the area under the curve and C_{max} of the (active) regorafenib metabolite. According to the package label, concomitant use of strong inhibitors of CYP3A4 activity should be avoided because their effect on the steady state exposure of regorafenib and its active metabolites has not been studied.[5, 6] Co-administration with the strong CYP3A4 inducer rifampicin resulted in a reduction in the area under the curve and C_{max} of regorafenib of 50% and 20%, respectively. Furthermore, an increase of three to four times was noted in exposure of regorafenib's active metabolites. Because the net effect of the combination of strong CYP3A4 inducer and regorafenib is unknown, these combinations should preferably be avoided.[5, 6] The inhibition of UGT1A1 by regorafenib resulted in an increase of 44% in area under the curve of SN-38 (active metabolite of irinotecan). An increase in area under the curve of irinotecan of roughly 28% was also noted. This finding shows that regorafenib can increase systemic exposure to UGT-substrates, such as irinotecan.[62] A study was done to evaluate the effect of regorafenib on probe substrates of CYP2C8 (rosiglitazone), CYP2C9 (s-warfarin), CYP2C19 (omeprazole), and CYP3A4 (midazolam). No effects were reported.[5, 6]

Ruxolitinib

Compared with strong CYP3A4 inhibitors, concomitant use of the moderate CYP3A4 inhibitor erythromycin results in a less profound increase in C_{max} of 8% and area under the curve of 27%. If coadministration with strong CYP3A4 inhibitors and inhibitors of both CYP3A4 and CYP2C9 (eg, fluconazole) is necessary, ruxolitinib dose should be reduced by 50% and haematological toxicity should be monitored extensively (eg, twice a week).[5, 6, 33] Concomitant use of the potent CYP3A4 inducer rifampicin decreased the area under the curve of ruxolitinib by 71%. However, only a 10% decrease in the overall pharmacodynamic activity was noted. This finding might be explained by the increased exposure to the active metabolites of ruxolitinib.[33]

Sorafenib

CYP3A4 inducers have an effect on sorafenib exposure.[5, 6] By contrast, strong CYP3A4 inhibitors did not seem to have any effect on the C_{max} and area under the curve of sorafenib. However, this study was not done at steady state of sorafenib and inter-individual variation was high, with an increase in the area under the curve noted for some participants, and a decrease noted for others after co-administration of sorafenib with ketoconazole.[34] Substrates of CYP2C19 (omeprazole), CYP2D6 (dextromethorphan), and CYP3A4 (midazolam) were co-administered with sorafenib, with only minor, clinically insignificant, effects.[63] However, sorafenib reduced gefitinib exposure (C_{max} was reduced by 26% and area under the curve by 38%), but gefitinib had no effect on sorafenib exposure.[43] Sorafenib exposure was significantly decreased in the presence of CYP3A4-inducing anti-epileptic drugs.[64] The international normalised ratio should be monitored during concomitant use of warfarin and sorafenib.[65] When sorafenib was continuously coadministered with paclitaxel or carboplatin, increases in the area under the curves of paclitaxel, 6-OH paclitaxel, and sorafenib were reported,[5, 6] although the pharmacokinetics of carboplatin were unaffected.[5, 6] Coadministration of paclitaxel and carboplatin with sorafenib, with a 3 day break in sorafenib dosing (2 days before and on the day of paclitaxel and carboplatin administration), had no significant effect on the pharmacokinetics of paclitaxel.[5, 6] Thus, a drug–drug interaction might be bypassed by the introduction of a 3 day break from sorafenib. When co-administered with sorafenib, the area under the curve of doxorubicin was increased by 21%.[5, 6] Furthermore, coadministration of capecitabine and sorafenib had no significant effect on sorafenib exposure, but increased the area under the curve exposure of capecitabine by 15–50%, and increased fluorouracil exposure by 0–52%.[5, 6] The clinical significance of these findings is unknown, but changes in exposure of up to 50% could have an effect on clinical outcome. After co-administration of irinotecan with sorafenib (400 mg), the area under the curve of SN-38, roughly doubled.[5, 6] Concomitant administration of low doses of sorafenib (100 mg or 200 mg twice daily) did not result in significant changes in SN-38.[5, 6] In a small study in six patients, irinotecan had no significant effect on sorafenib exposure when sorafenib was given in low doses (100–200 mg twice daily), but when sorafenib was given at 400 mg twice daily together with 125 mg/m^2 irinotecan, sorafenib exposure increased by 68%.[5, 6] Coadministration of sorafenib and dacarbazine led to decreased exposure of dacarbazine (the area under the curve reduced by 23%), but the clinical relevance of this drug–drug interaction remains unknown.[66] Neomycin decreased the area under the curve of sorafenib by 54%, probably because of eradication of gastrointestinal bacterial glucorinidase activity, resulting in a decrease in the enterohepatic recycling of sorafenib.[5, 6]

Sunitinib

Coadministration of sunitinib and ifosfamide (CYP3A4 inducer) led to a significant decrease in sunitinib exposure.[67]

Vandetanib

Co-administration of rifampicin results in a moderate decrease of 40% in the area under the curve. By contrast, the exposure to the most important active metabolite N-desmethylvandetanib was profoundly increased during coadministration of rifampicin (increases of 266% in area under the curve and 414% in C_{max}).[36] Because of the net effects of the decrease of vandetanib, and the major increase of its active metabolite are unknown, CYP3A4 inducers should be avoided during vandetanib treatment.[36] By contrast with the CYP3A4 inducer rifampicin, the CYP3A4 inhibitor itraconazole had no effect on vandetanib exposure. This finding implies that the effect of rifampicin on vandetanib exposure might be mediated by metabolic pathways other than CYP3A4, such as P-glycoprotein. The product label warns about the drug–drug interaction with warfarin, but no clinical evidence is available to support this.[5, 6]

Vemurafenib

No clinical data are available about the effect on vemurafenib exposure when concomitantly used with strong CYP3A4 inhibitors or inducers, and so caution should be taken when giving vemurafenib with either.[5,6] Vemurafenib had moderate, clinically insignificant, effects on exposure of dextromethorphan (CYP2D6), midazolam (CYP3A4), or caffeine (CYP1A2), and no effects on omeprazole (CYP2C19) or warfarin (CYP2C9).[5,6]

Summary

In summary, all tyrosine-kinase inhibitors are metabolised by CYP enzymes, which make them prone to metabolic drug–drug interactions.[5, 6] Regulatory assessment reports mainly investigate interactions with the most potent CYP inducers and inhibitors. Additional clinical studies should be done to fully assess the effect of moderate and strong CYP inducers and inhibitors at steady state, next to the present extrapolation of kinetic data from single-dose studies. On the basis of these results, adequate guidelines can be developed for dose adjustments of tyrosine-kinase inhibitors to counter drug–drug interactions.

P-glycoprotein

Some tyrosine-kinase inhibitors are substrates or inhibitors of P-glycoprotein. In theory, the exposure of some tyrosine-kinase inhibitors (eg, erlotinib) could increase during coadministration of P-glycoprotein inhibitors (eg, verapamil or ciclosporin). Furthermore, because of P-glycoprotein inhibition by sunitinib, colchicines-related toxic effects were noted.[68] Clinical data are scarce and more research is needed to fully understand the role of P-glycoprotein in exposure to tyrosine-kinase inhibitors.

PHARMACOKINETIC DRUG INTERACTIONS, ELIMINATION

Drug–drug interactions related to elimination generally occur due to renal impairment, either caused by the parent drug or during concomitant use of other nephrotoxic comedication. Most tyrosine-kinase inhibitors are eliminated by liver metabolism and subsequently excreted in faeces as metabolites or unchanged, with minor contributions of renal clearance. Because tyrosine-kinase inhibitors are largely eliminated by hepatic metabolism, drug–drug interactions that take place through changes in renal elimination seem to be of minor importance. However, drug transporters (eg, P-glycoprotein, organic anion transporting peptides, organic cation transporter, and breast cancer resistance protein), that are also found in the kidneys, are important for the elimination of tyrosine-kinase inhibitors.[69] Because of the possible inhibition of the organic cation transporter by erlotinib, cellular accumulation of cisplatin in renal tubular cells might be restricted and, as a result, specific cisplatin-based nephrotoxic effects might be prevented.[70] Furthermore, the drug–drug interaction between imatinib and methotrexate might affect methotrexate transport and elimination.[71] More research is needed to fully assess the positive effect of changes in expression of renal drug transporters on the pharmacokinetics of tyrosine-kinase inhibitors.

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic drug–drug interactions can happen when the pharmacological effect of one drug is changed by another through action on mechanisms associated with the same physiological process or effect. Although pharmacodynamic interactions can be used intentionally (eg, methotrexate and folic acid), they can also be harmful (eg, cisplatin and lisdiuretics).

Some case reports describe pharmacodynamic interactions between tyrosine-kinase inhibitors and other drugs. For instance, imatinib can increase methotrexate toxicity by causing fluid retention, and sunitinib and imatinib can antagonise levothyroxine treatment by interference with thyroid hormones at the pituitary level.[72, 73] Furthermore, concomitant use of antibiotics that affect the flora of the gastrointestinal tract might interfere with the enterohepatic circulation of regorafenib and might decrease regorafenib absorption.[5, 6] Other, mainly additive, pharmacodynamic drug–drug interactions have been described between tyrosine-kinase inhibitors and other anticancer drugs, but this event is beyond the scope of this Review.

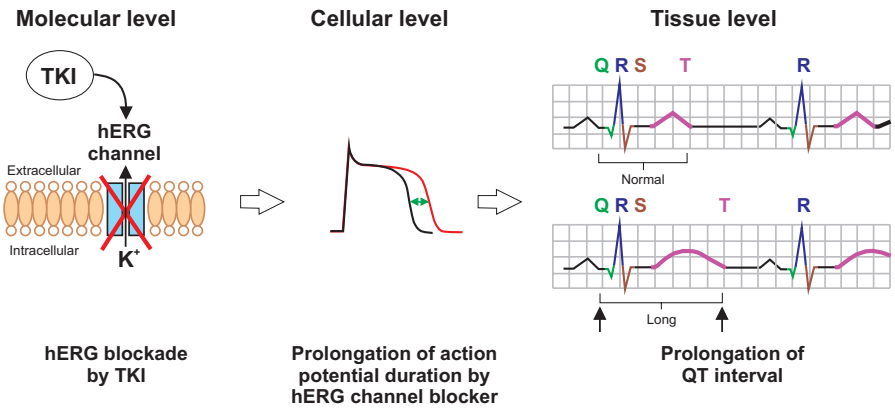

Figure 2: Mechanism of action of QTC prolongation of TKIs, at the molecular, cellular, and tissue level

TKI=tyrosine-kinase inhibitor.

Prolongation of the QT_c interval

Many classic anticancer drugs can prolong the QT_c interval (eg, anthracyclines). This prolongation is also frequently reported with use of tyrosine-kinase inhibitors,[5, 6] which is probably caused by interaction with hERG K^+ channels. This interaction results in a change in electrical flow and delayed pulse conduction, and therefore, QT_c prolongation (figure 2).[74]

The potential of a tyrosine-kinase inhibitor to prolong the QT_c interval is usually related to its chemical structure and plasma concentration. Such QT_c prolongation might be further increased by CYP3A4 inhibition by another drug, or by the simultaneous use of another drug that can prolong the QT_c interval (eg, sotalol) alongside a tyrosine-kinase inhibitor.[74] Table 4 lists the QT_c interval prolonging properties of tyrosine-kinase inhibitors. The Arizona CERT Index lists tyrosine-kinase inhibitors (eg, vandetanib, nilotinib, lapatinib, and sunitinib), and other drugs that might affect the QT_c interval.[75]

Although rare, prolongation of the QT_c interval and subsequent development of Torsades de pointes is a severe, life-threatening side-effect of treatment with tyrosine-kinase inhibitors. Medical oncologists should be better informed about the risk of coadministration of drugs that prolong the QT_c interval in patients given tyrosine-kinase inhibitors. Pharmacists should routinely check for concomitant use of such prolonging drugs and CYP3A4 inhibitors. Special attention should given to QT_c interval-prolonging $5HT_3$ antagonists, antibiotics, antifungals, and over-the-counter drugs (eg, domperidone), because these drugs are frequently used by patients with cancer concomitantly with tyrosine-kinase inhibitors. Unless absolutely necessary, coadministration QT_c-prolonging tyrosine-kinase inhibitors and drugs that prolong the QT_c interval and CYP3A4 inhibitors should be avoided. If needed, an ECG should be obtained 24–48h before, and 1 week after, the start of the concomitant treatment.

Table 4: QT_c-interval prolonging properties of tyrosine-kinase inhibitors

	QT_c-interval prolongation		Events*	
TKI	Yes	No	Yes	No
Axitinib		•		•
Crizotinib	•			•
Dasatinib		•		•
Erlotinib		•		•
Gefitinib	•			•
Imatinib		•		•
Lapatinib	•			•
Nilotinib	•		•	
Pazopanib	•		•	
Regorafenib		•		•
Ruxolitinib		•		•
Sorafenib	•			•
Sunitinib	•		•	
Vandetanib	•		•	
Vemurafenib	•			•

This table is constituted from regulatory documents.4,5
*Torsades de pointes or sudden (heart) death.

RECOMMENDATIONS FOR CLINICAL PRACTICE

In the past few years, tyrosine-kinase inhibitors have rapidly become an established part of oncology practice, but have also presented new challenges, such as the increased risk of drug–drug interactions.

Apart from sorafenib and vandetanib, tyrosine-kinase inhibitors' exposures are greatly affected by CYP3A4 inhibitors and inducers, and clinical intervention is often needed (table 3). Furthermore, acid-reducing drugs, such as proton-pump inhibitors, can profoundly affect the bioavailability of most tyrosine-kinase inhibitors and need clinical attention (table 1).

Drug–drug interactions that lead to prolongation of the QT_c interval are rare, but can have fatal consequences and should be accounted for (table 4). Table 5 lists the main points about drug–drug interactions.

P-glycoprotein substrates with a narrow therapeutic window (eg, digoxin, ciclosporin, and tacrolimus) should be extensively monitored (eg, by therapeutic drug monitoring) during the use of tyrosine-kinase inhibitors that inhibit P-glycoprotein (table 2). The combination of grapefruit juice and sunitinib or nilotinib should be avoided.[16, 17] Other product labels discourage intake of grapefruit juice only on theoretical assumptions (eg, pazopanib and lapatinib).[5, 6]

To improve the safe use of tyrosine-kinase inhibitors in clinical oncology, a profound assessment of co-prescribed drugs, herbal supplements, lifestyle food and drinks (eg, grapefruit juice), cardiac risk factors, and physical examination is needed. To undertake this assessment, oncologists and haemato-oncologists should collaborate closely with clinical pharmacists, family doctors, and other medical specialists (eg, cardiologists). Additionally, more clinical research is needed (with for instance the new anti-androgen enzalutamide; a strong CYP3A4 inducer) about drug–drug interactions in treatment with tyrosine-kinase inhibitors to provide a profound basis for drug reviews and to fully understand the interaction potential of these inhibitors. In case of a suspected interaction, and if pharmacokinetic data are not available, physicians and pharmacists should balance the available evidence, if possible, extrapolate available pharmacokinetic data for an individual patient, and monitor closely for toxic effects and response.

Table 5: Highlights of the most significant DDIs in TKI therapy

TKIs prone to significantly interact with:	Assessment of clinical relevance:
Acid suppressive agents (PPIs, H2As and antacids) crizotinib, dasatinib, erlotinib, gefitinib, lapatinib and pazopanib	Concomitant use of acid suppressive agents can significantly affect the drug absorption of these TKIs. If possible, the combination must be avoided or the time of drug intake must be split by at least several hours
Strong CYP3A4 inhibitors* and strong CYP3A4 inducers** axitinib, crizotinib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sunitinib, vemurafenib	Concomitant use of strong CYP3A4 inhibitors/inducers can significantly influence the exposure to these TKIs. Dose adjustments are highly recommended
Other QT_c-interval prolonging drugs crizotinib, gefitinib, lapatinib, nilotinib, pazopanib, sorafenib, sunitinib, vandetanib, vemurafenib	Concomitant use of other QT_c-interval prolonging drugs along with these TKIs can significantly prolong the QT_c-interval. If indicated, it is strongly recommended that an ECG is obtained 24-48 hours before and one week after initiating the concomitant therapy

This table only shows the highlights and is constituted from table 1,3 and 4. For more detailed information, see table 1,3 and 4.
H2As=H_2-antagonists, PPI=proton pump inhibitors
*ketoconazole, itraconazole and voriconazole
** rifampicin and enzalutamide

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Chapter 3

POTENTIAL DRUG INTERACTIONS IN CANCER THERAPY: A PREVALENCE STUDY USING AN ADVANCED SCREENING METHOD

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ABSTRACT

Introduction

In cancer patients, drug interactions may intensify adverse events or reduce antitumour effects. We assessed the prevalence of potential drug interactions (PDIs) among ambulatory cancer patients on i.v. treatment using an advanced screening method.

Methods

Data on drugs used for comorbidities, anticancer agents, over-the-counter (OTC) drugs, and comorbidities were collected by means of a structured interview among the patients and review of medical charts. PDIs were identified using electronic (Drug Interaction Facts software, version 4.0) and manual screening methods (peer-reviewed reports).

Results

In this study, 278 patients were enrolled. We identified 348 PDIs. Of all patients, 161 (58%) had at least one PDI. Of all PDIs, 34% was classified as major and 60% as moderate. Coumarins, quinolones, antiepileptics, and hydrochlorothiazide were frequently part of a PDI. Interactions that potentially cause QT interval prolongation, gastrointestinal toxicity, and central nervous system depression were also common. In multivariate analysis, an increasing number of drugs [odds ratio (OR) = 1.4, confidence interval (CI) 1.23–1.52; $P < 0.001$] and the use of an OTC drug (OR = 0.56, CI 0.32–0.97; $P = 0.045$) were risk factors.

Conclusions

PDIs are common in patients treated for an (haemato-) oncological disease. Screening for potential interactions should take place routinely before administering chemotherapy.

INTRODUCTION

The pharmacological treatment of patients with cancer is associated with multiple side-effects.[1] Although the cause of side-effects usually lies in the toxicity of the drugs themselves, drug interactions can reinforce or intensify adverse events and even seem to be the cause of death in 4% of cancer patients.[2] Cancer patients are particularly susceptible for drug interactions as they often use several drugs as part of the cancer treatment on top of the medication prescribed to manage comorbidities.[3]

Potential drug interactions (PDIs) in nature are subdivided into pharmacokinetic and pharmacodynamic interactions.[4] Pharmacokinetic interactions alter the absorption, distribution, metabolism, or excretion of a drug. The majority of pharmacokinetic interactions are the result of inhibiting or inducing the cytochrome P450 liver enzymes.[3] Since many anticancer agents are metabolised via this mechanism, PDIs involving cytochrome P450 may occur.[5] A pharmacodynamic interaction is characterised by an additive, synergistic, or antagonistic effect, thereby influencing the response of a drug.[4]

The occurrence of PDIs in general clinical practice and their determinants has extensively been studied.[2, 6–9] However, only limited data are available on the occurrence of PDIs in patients being treated with anticancer agents and, to our knowledge, there is no study available that has included over-the-counter (OTC) medication. In a Canadian study in ambulatory cancer patients, it has been shown that 27% of cancer patients were exposed to PDIs involving anticancer agents.[3] Certain types of cancers (mainly brain tumours) and comorbidities appeared to be risk factors. In hospitalised cancer patients, the use of eight or more drugs and a hospital stay of >6 days were identified as risk factors for PDIs.[10] OTC medication is popular in cancer patients, either to prevent or treat symptoms of disease or to promote health and well-being.[11]

Due to the lack of information about the drugs in use to treat comorbidities, prescribing oncologists may not always be aware of PDIs in their patients. In addition, since the community pharmacy is usually not informed by the oncologist on the treatment with anticancer agents, general practitioners may not be aware of PDIs when prescribing drugs for a new complaint. OTC medication is not always identified. Although computer-based medication prescription systems are in use in hospitals as well as in community pharmacies, they are not linked. Electronic identification of PDIs between drugs to treat comorbidities and anticancer agents is not yet available.

The aim of the present study was to gain more insight into the prevalence of PDIs among ambulatory cancer patients on i.v. treatment of an (haemato-) oncological disease using a novel more extensive screening method. The prevalence of PDIs with OTC drugs was also analysed. Possible risk factors for the occurrence of these potential drug-related problems were investigated as well.

METHODS

Study design

A two-centre cross-sectional study of the epidemiology of PDIs was carried out during a 5-month period in 2009 among all ambulatory cancer patients treated i.v. with anticancer agents at the (haemato-) oncology outpatient day care department of the VU University Medical Center and the Zaans Medical Center. The VU University Medical Center is a large tertiary referral hospital, while the Zaans Medical Center is a small community hospital situated in the Amsterdam area. The study was registered under number NTR2238.

Patients

All patients with a solid tumour or a haematological malignancy on i.v. treatment with anticancer agents were asked to participate in the study. Exclusion criteria were as follows: unable to fill out questionnaires, the use of clinical trial medication, a lack of command of the Dutch language, and age <18 years. All participating patients were asked to sign an informed consent. The study was approved by the medical ethics review board of both institutes.

Table 1: Classification of potential drug interactions

Classification	Description
Level severity	
1	Major: life-threatening or permanent damage
2	Moderate: deterioration of patient's status, treatment is required
3	Minor: bothersome or little effect
Level documentation	
1	Established: proven to occur in well-controlled studies
2	Probable: very likely, but not proven clinically
3	Suspected: may occur; some good data, but needs more study
4	Possible: could occur, but data are very limited
5	Unlikely: doubtful; no good evidence of a clinical effect

Procedures

Patients were asked questions by means of a structured interview (RWFVL). Questions concerned comorbidities and the use of OTC drugs. To determine the type of comedication, an overview of drugs prescribed over the previous 6 months was obtained from the community pharmacy. The actual use, both on a continuous base and an incidental use, was discussed with the patient. Data on the type of anticancer agents, diagnosis, aim of treatment (palliative/adjuvant), treatment start date, and comedication in use for administration of anticancer agents were collected by means of a medical chart review and, if necessary, by means of an interview of the prescribing doctor. Data on renal function (creatinine) and liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (γ-GT)] were obtained from the laboratory database of the hospital. We defined a laboratory abnormality as an increase of 50% or higher above the upper limit of normal as measured within the 4 weeks preceding the interview (upper normal limits: AST ≤35 U/l, ALT ≤40 U/l, γ-GT ≤44 U/l, creatinine ≤99 μmol/l).

Drugs were subdivided into four groups: 'anticancer agents, supportive care drugs, drugs to treat comorbidity, and OTC drugs. We defined 'anticancer agents' as medication to treat solid tumours or haematological malignancies, 'supportive care agents' as medication to treat cancer- and/or therapy-related symptoms, 'drugs to treat co-morbidity' as a noncancer clinical condition that required pharmacological treatment, and 'OTC drugs' as (alternative) drugs and

food supplements used by the patients on their own initiative without prior consultation of a doctor. For each patient, we counted the number of drugs by group. If a drug contained two or more pharmacologically active ingredients, each drug was counted individually in the analysis (e.g. sulfamethoxazole combined with trimethoprim). The drug was counted only once when a patient was taking the same medication in more than one formulation (e.g. long- and short-acting morphine).

Drugs were screened for PDIs by the Drug Interaction Facts software (Facts and Comparisons, version 4.0)[12], which has been shown to have an accuracy of >95% in detecting interactions.[13] The Drug Interaction Facts software for PDIs classifies interactions by the level of severity and the level of scientific evidence (Table 1). The potential severity of a PDI was classified as major if the effects are potentially life threatening or capable of causing permanent damage; moderate, when the effects may cause a deterioration in a patient's clinical status or if an additional treatment, hospitalisation, or an extended hospital stay may be necessary; or minor, if the effects are usually mild and should not significantly affect the therapeutic outcome. The level of scientific evidence of a PDI was classified on a five-point documentation scale. Level 1 means that a PDI was supported by well-controlled human studies and level 5 means that the documentation of a PDI is of poor quality or only theoretical. Of note, PDIs that might result in reduced anticancer activity were not scored as severe if the interaction would lead to lower toxicity, such as the combination of irinotecan and St John's wort.[14]

Drugs were also screened by a clinical pharmacologist for combinations of drugs with potential QT interval prolongation and/or torsades de pointes-inducing properties using the Arizona Center for Education and Research on Therapeutics system and peer-reviewed reports on scientific evidence for potential QT interaction. Because of the potentially severe consequences, we classified all drug combinations with risk for QT interval prolongation as major.[15] Drugs associated with an increased risk of falling [central nervous system (CNS) depressant agents] were identified manually using handbooks and peer-reviewed reports on scientific evidence. A combination of two CNS depressant agents was counted as one interaction, defined as a CNS interaction in the analysis. All CNS interactions were classified as moderate. Drugs were also screened for the combination between nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, anticoagulants, aspirin, or selective serotonin reuptake inhibitors (SSRIs) defined as gastrointestinal (GI) interaction using

the Drug Interaction Facts software and peer-reviewed reports on scientific evidence. These combinations are known to increase the risk for GI bleeding. Because of the potentially severe consequences, all GI interactions were classified as major.

To identify PDIs involving OTC drugs, pharmacology handbooks and peer-reviewed reports were screened manually. Theoretical interactions were not included in the analysis. Because of lack of clinical significance, interactions of minor severity were also excluded. The medication screened for PDIs were the drugs in the four groups mentioned above: anticancer agents, supportive care drugs, drugs to treat comorbidity, and OTC drugs. A PDI was only counted in the analysis when an anticancer agent or a supportive care drug was involved.

Statistical analysis

Descriptive statistics (mean ± standard deviation or median) were applied to characterise the whole study sample with regard to demographics, cancer type, treatment objective, type of anticancer agents, comorbidities, number of drugs per patient, laboratory abnormalities, and interaction characteristics (severity, level of scientific evidence, onset, and mechanism).

Univariate and multivariate logistic regression analyses were carried out to identify the potential risk factors for the occurrence of PDIs. The number of potential interactions per patient was the dependent variable. Covariables were age, number of drugs, study centre (Zaans Medical Center and VU University Medical Center), treatment intent, treatment type, presence of comorbidities, cancer type, tumour type (haemato-oncology/oncology), laboratory abnormalities, and the use of an OTC drug. Gender was not included as a covariable due to the fact that certain cancer types only occur in men or women. For binary or nominal variables, the largest group was taken as the reference. Variables with univariate P values <0.05 were included in the multivariate analysis. In the multivariate analysis, a P value of <0.05 was considered statistically significant. The data were adjusted for confounders and effect modifiers.

Table 2: Baseline characteristics

	N	%
Study population	278	100
Age in years*	61 (19-82)	-
Sex		
Female	124	45
Male	154	55
Hospital		
VU University Medical Center	158	56.8
Zaans Medical Center	120	43.2
Cancer type		
Oncology	223	80.2
Haemato-oncology	55	19.8
Cancer type oncology		
Gastrointestinal	75	27.0
Breast	66	23.7
Lung	23	8.3
Genitourinary	21	7.6
Gynaecological	21	7.6
Other	17	6.0
Cancer type haemato-oncology		
Malignant lymphoma	26	9.3
Plasma cell dyscrasia	12	4.3
Leukaemia	11	4.0
Myelodysplastic syndrome	5	1.8
Immunocytoma	1	0.4
Treatment intent		
Curative/Adjuvant	131	47.1
Palliative	147	52.9
Cancer treatment		
Chemotherapy	195	70.1
Monoclonal antibodies	36	12.9
Hormone therapy	1	0.36
Combinations	46	16.5
No. of drugs used per patient*	9 (2-22)	-
No. of drugs used per patient per group*		
Anti-cancer agents	2 (1-5)	-
Supportive care drugs	2 (0-6)	-
Drugs for co-morbidities	3 (0-14)	-
OTC drugs	1 (0-7)	-
No. of co-morbidities per patient*	1 (0-6)	-
Total laboratory abnormalities**	98	40.0
Laboratory values*		
Creatinine	72 (39-354)	-
Aspartate aminotransferase	27 (11-204)	-
Alanine aminotransferase	26 (5-266)	-
Gamma-glutamyltransferase	40 (2-1205)	-

*Median (range)

**Because of missing data, denominator is 245

OTC=over the counter

RESULTS

Patient characteristics

Between August and December 2009, a total of 278 patients were asked to participate in the study; there were no refusals. Table 2 lists the baseline characteristics of the patients. The mean age of the patients was 61 years (range 19–82 years) and 45% were female. The patients used nine (range 2–22) drugs per patient and 82% of the patients used at least one OTC drug. Fifty-eight percent of the patients had at least one comorbidity.

Drug interactions

For 278 patients, 348 PDIs were identified (Table 3). In 161 patients (58%) [95% confidence interval (CI) 52% to 64%], at least one PDI was found. In 34% of all cases, the interaction was classified as major and in 60% as moderate. In 40% and 60%, an anticancer agent and a supportive care drug, respectively, were involved. In 11% of all 348 interactions, an OTC drug was part of the PDI. Sixty-four percent of all PDIs concerned a pharmacodynamic interaction; thirty-three percent of the PDIs concerned a CNS interaction. For 83% of the major and moderate PDIs, the level of scientific evidence was 2 (probable) or 3 (suspected).

The PDIs for combinations including an anticancer agent or a supportive care drug are shown in Tables 4 and 5, respectively. Almost 20% of all PDIs could be attributed to a drug combination with coumarins, quinolones, antiepileptics, or hydrochlorothiazide. The other 80% of the PDIs showed a wide variety of drug classes. PDIs that may result in QT interval prolongation, GI toxicity, and CNS depression (falling) accounted for, respectively, 16%, 11%, and 33% of all PDIs.

Potential risk factors

In the univariate analysis, the number of drugs, the presence of comorbidities, and the use of OTC drugs were associated with a higher number of PDIs (Table 6). Age was not associated with a higher number of PDIs ($P = 0.223$). When patients were divided into two groups comprising younger and older than 61 years, age was also without effect. Although this subgroup was small, the use of mAbs as monotherapy showed a lower risk. After adjustment for confounders, the effect of the number of drugs and the use of an OTC drug remained significant ($P < 0.001$ and $P = 0.045$, respectively).

Table 3: Prevalence, classification and mechanism of potential drug interactions (PDIs) among cancer patients

PDIs	N	%
Total	348	100
Potential drug interaction per patient*	1 (0-7)	-
Drug interactions by group		
Anti-cancer agent involved	138	39.7
Supportive care drug involved	210	60.3
Level of severity		
Major	118	33.9
Moderate	210	60.3
Minor	20	5.7
Level of scientific evidence		
1	0	0
2	242	69.9
3	46	13.2
4	47	13.5
5	11	3.7
Drug interaction mechanism		
Pharmacodynamic	224	64.4
QT-interval prolongation	56	16.1
GI-interaction	39	11.2
CNS-interaction	116	33.3
Other PD-interactions	13	3.7
Pharmacokinetic	92	26.4
Unknown	32	9.2

*median (range)

GI=gastro-intestinal, CNS=central nervous system, PD=pharmacodynamic

Table 4: Potential drug interactions involving anticancer agents

Potential drug interactions between anti-cancer agents and supportive care drugs				
	N	**Description**	**Severity**	**Scientific evidence**
Ondansetron + Doxorubicin/Epirubicin/ Tamoxifen [15,24]	37	Drug combinations can prolong QT-interval	Major	2
Potential drug interactions between anti-cancer agents and drugs to treat co-morbidities				
Coumarine + Capecitabine/Etoposide/ Carboplatin/Gemcitabine [25,26,27]	11	Chemotherapy-induced protein displacement and inhibition of coumarines metabolism with higher risk of bleeding	Major	2
Doxorubicin + Sotalol/Amiodarone/ Clarithromycin/Levofloxacin [15,24]	6	Drug combinations can prolong QT-interval	Major	2
Bleomycin + (PEG)Filgrastim [28]	4	Possible pulmonary toxicity	Major	3
Methotrexate + Prednisolone [29]	1	Prednisolone may decrease the total clearance of methotrexate.	Major	4
Methotrexate + Aspirin [30]	1	Aspirin may increase plasma concentrations of methotrexate with an increased risk of bone marrow and hepatic toxicity	Major	3
Quinolones + Carboplatin/Etoposide/ Mitoxantrone/Vincristine/ Cisplatin/Cyclophosphamide/ Doxorubicin [31]	13	Absorption of quinolones may be decreased due to damaged gastrointestinal mucosa	Moderate	5
Coumarine + Cyclophosphamide/Fluorouracil/ Paclitaxel [32,33,34]	10	Chemotherapy-induced protein displacement and inhibition of coumarines metabolism with higher risk of bleeding	Moderate	2
Hydrochlorothiazide + Cyclophosphamide/ Fluorouracil [35]	7	Myelosuppression may be increased by thiazides	Moderate	4
CNS-interactions*	7	Combinations of CNS-depressant drugs may increase the risk of falling	Moderate	2/3
Phenytoin + Cyclophosphamide/Etoposide/ Vincristine/Doxorubicin [36,37]	5	Plasma concentrations and therapeutic effect of phenytoin or cytotstatic agent may be altered	Moderate	3/4
Valproic acid + Cisplatin/Doxorubicin/ Bleomycin [38]	4	Lower AUC valproic acid possibly due to disturbed gastrointestinal absorption or increased metabolism	Moderate	4
Cyclophosphamide + Allopurinol [39]	2	Toxicity (bone marrow depression) may be increased	Moderate	4
Other§	7	-	Moderate	3/4
Potential drug interactions between anti-cancer agents and OTC drugs				
Methotrexate + Ibuprofen [30]	2	Toxicity of methotrexate may be increased by ibuprofen	Major	3
Folic acid + Capecitabine/Fluorouracil [40]	18	Toxic effects of capecitabine may be increased by folic acid	Moderate	4
Irinotecan + St.John's Wort [14]	2	Plasma concentrations and pharmacological effects of irinotecan may be decreased	Moderate	3

* Azacitadine+Levocetirizine, Codeine+Procarbazine, Thalidomide+Levocetirizine/Tramadol/ Oxycodon/Morphine and Oxazepam+Procarbazine.

§ Flurouacil+Metronidazole, Claritromycine+Vinorelbine, Claritromycine+Irinotecan, Cyclophosphamide+Digoxin, Doxorubicine+Digoxin, Docetaxel+Metronidazole and Metronidazole+Paclitaxel.

Table 5: Potential drug interactions involving supportive care drugs

Potential drug interactions between multiple supportive care drugs				
	N	**Description**	**Severity**	**Scientific evidence**
CNS-interactions*	23	Combinations of CNS-depressant drugs may increase the risk of falling	Moderate	2/3
Potential drug interactions between supportive care drugs and drugs to treat co-morbidities				
Dexamethasone + Diclofenac/Naproxen/ Rofecoxib/Indomethacin/ Prednisolone [41]	25	Combinations of corticosteroids and NSAIDs may cause gastrointestinal toxicity	Major	2
Ondansetron + Levofloxacine/Sotalol/ Amiodaron/Clarithromycin/ Flecainide [15]	14	Drugs combinations can prolong QT interval	Major	2
Aprepitant + Ethinylestradiol [42]	1	Plasma concentrations and pharmacological effects of ethinylestradiol may be decreased	Major	3
Aprepitant + Fentanyl [43]	1	Aprepitant may increase plasma concentrations of fentanyl	Major	3
Fluvoxamine + Metoclopramide [44]	1	Serotonin syndrome with extrapyramidal movements may occur	Major	3
CNS-interactions§	85	Combinations of CNS-depressant drugs may increase the risk of falling	Moderate	2/3
Coumarine + Dexamethasone/Aprepitant [45,46]	12	The anticoagulation effect of coumarines may be in/decreased	Moderate	3
Quinolones + Dexamethasone [47]	7	The risk of ciprofloxacin induced tendon rupture may be increased	Moderate	3
Dexamethasone + Ethinylestradiol [48]	5	Pharmacological effects of dexamethasone may be increased	Moderate	3
Other±	3	-	Moderate	3/4
Potential drug interactions between supportive care drugs and OTC drugs				
Dexamethasone + Ibuprofen/Naproxen [41]	14	Combinations of corticosteroids and NSAIDs may cause gastrointestinal toxicity	Major	2
Ginkgo biloba + Metoclopramide	1	Combinations of CNS-depressant drugs may increase the risk of falling	Moderate	3

* Clemastine+Metoclopramide and Lorazepam+Metoclopramide

§ Clemastine+Temazepam/Oxazepam/Morphine/Codeine/Diazepam/Fentanyl/Levocetirizine/Lorazepam/Pregabaline/Cetirizine/Levetiracetam/Loperamide/Mirtazapine/Olanzapine/Oxycodon/Paroxetine/Sertraline/Tramadol Metoclopramide+Fentanyl/Oxazepam/Temazepam/Levocetirizine/Oxycodon/Amitriptyline/Diazepam/Midazolam/Mirtazapine/Zolpidem/Zopiclon/Pregabaline/Valproic acid Lorazepam+Temazepam/Morphine/Hydrochlorothiazide/Nitroglycerine/Oxycodon/Zopiclon Dexamethasone + Oxazepam

± Cyclosporine+Metoclopramide, Clarithromycin+Dexamethasone and Dexamethasone+Phenytoin

OTC=Over-The-Counte

Table 6: Univariate and multivariate analyses of risk factors for the occurrence of potential drug interactions

Variable	Unadjusted OR (95% CI)	Unadjusted P value	Adjusted OR (95% CI)	Adjusted P value
Age	0.99 (0.97-1.01)	0.223		
No. of drugs	1.41 (1.27-1.56)	<0.001	1.36 (1.23-1.52)	<0.001
Hospital				
VU University Medical Center	1.0 (reference)			
Zaans Medical Center	0.78 (0.50-1.29)	0.357		
Treatment intent				
Curative/adjuvant	1.06 (0.66-1.71)	0.805		
Palliative	1.0 (reference)			
Cancer type		0.327		
Gastrointestinal	1.0 (reference)			
Breast	1.92 (0.97-3.79)	0.060		
Lung	1.93 (0.73-5.08)	0.186		
Genitourinary	1.37 (0.52-3.63)	0.528		
Gynecological	0.93 (0.35-2.46)	0.890		
Other oncology	2.47 (0.79-7.69)	0.120		
Haemato-oncology	1.07 (0.53-2.14)	0.859		
Tumour type				
Oncology	1.0 (reference)			
Haemato-oncology	0.92 (0.50-1.67)	0.774		
Treatment type		0.021		0.280
Chemotherapy	1.0 (reference)		1.0 (referent)	
Mabs	0.37 (0.17-0.78)	0.010	0.51 (0.21-1.22)	0.130
Combinations	1.13 (0.64-1.97)	0.681	1.06 (0.56-2.00)	0.851
Presence of co-morbidities				
Yes	1.0 (reference)		1.0 (referent)	
No	0.50 (0.31-0.81)	0.005	0.83 (0.48-1.46)	0.833
Laboratory abnormality				
Yes	1.0 (reference)			
No	1.11 (0.66-1.87)	0.705		
Treatment duration (months)	1.00 (0.99-1.01)	0.511		
Use of [3]1 OTC drugs				
Yes	1.0 (reference)			
No	0.42 (0.26-0.71)	0.001	0.56 (0.32-0.97)	0.045

OR= odds ratio, CI= confidence interval. Mabs=Monoclonal antibodies, OTC=Over-The-Counter

DISCUSSION

This study showed that the occurrence of PDIs in ambulatory cancer patients was high, with more than half of the patient group presenting with at least one PDI. This situation is even more alarming because one-third of the patients had a major PDI that may result in serious clinical consequences. The majority of the major and moderate PDIs were supported by scientific evidence of level 2 or 3 (probable or suspected). We also found that 80% of the patients used OTC drugs, which resulted in 10% of cases with a PDI. This is particularly alarming because the use of OTC drugs is generally not registered either in the patient's medical chart or at the community pharmacy.

Another important finding in this study was the high prevalence of PDIs that may result in serious adverse events, including QT interval prolongation, GI toxicity, and CNS depression (falling). This has not previously been described in literature and is of particular concern because of the high risk of harm to the patients' quality of life and increase of health care costs.

Numerous drugs representing a wide range of pharmacological classes have been associated with QT interval prolongation. The possibly serious and even fatal consequences of drug combinations that may cause prolongation of the QT interval have resulted in the recommendation to avoid the prescription of many drug combinations.[15] Due to the extensive use of QT interval prolongation drugs, such as quinolones, doxorubicin, and ondansetron by cancer patients, QT interactions may form a significant problem in (haemato-) oncology.

Falling in elderly patients is a major public health concern. Prescribed CNS depressant medication is an important contributor to the risk of falling in elderly people and the use of multiple CNS depressant agents may even increase this risk.[41, 42] Several commonly used drugs (e.g. psychotropic and cardiovascular drugs) are identified as a risk factor for falls.[43-45] These CNS interactions may be specifically harmful in cancer patients due to the high prevalence of osteoporosis and thereby the risk for hip fractures.[46]

NSAIDs are frequently prescribed for pain related to cancer. However, their use should be restricted because of potential GI toxicity. Additional pharmacological risk factors for the development of NSAID-related ulcers include concomitant use of corticosteroids, anticoagulants, aspirin, and SSRIs.[47, 48] Due to the extensive use of corticosteroids and anticoagulants, these PDIs are of particular concern in (haemato-) oncology.

The number of drugs and the use of one or more OTC drugs were associated with an increased risk for the occurrence of PDIs. It is to be expected that the number of drugs is a determinant, simply because the number of drug combinations is increased. This finding is in agreement with other studies.[3] The association of OTC drugs with the increased number of PDIs shows that these drugs are often involved in PDIs.

The strength of this study is the high response since all patients were willing to participate. In addition, the study was carried out in two hospitals. These factors increase the representativeness of the data. We also used an advanced screening method for the detection of PDIs, which led to more valuable data on the occurrence of PDIs. The inclusion of OTC drugs in the analysis resulted in findings that are unique on their own. The cross-sectional design forms another strength of the study. The patients were interviewed on the basis of their medication overview obtained from the community pharmacy and their medical chart, which increased the validity of the data on drugs taken. However, a prospective study would provide the opportunity to investigate the clinical consequences of PDIs. PDIs not involving an anticancer agent or a supportive drug were excluded in this study but may also be a subject for future analysis.

In conclusion, the present study shows a high prevalence of PDIs in ambulatory cancer patients. It is not known to what extent medical doctors were aware of these PDIs and whether they had made attempts to avoid a particular combination of drugs or took measures to prevent complications of PDIs. Buajordet et al. have suggested that drug interactions are responsible for the death of 4% of hospitalised cancer patients.[2] Therefore, oncologists might largely be unaware of interactions of anticancer agents or supportive care drugs with medication to treat comorbidities or the use of OTC drugs or they may underestimate the risk of a PDI. Professional insight into the clinical consequences of PDIs in cancer patients is not well known and should be further explored. Physicians and clinical pharmacists must collaborate to develop a routine computer-based screening method to identify PDIs upon drug prescription, which includes the awareness of the use of OTC drugs.

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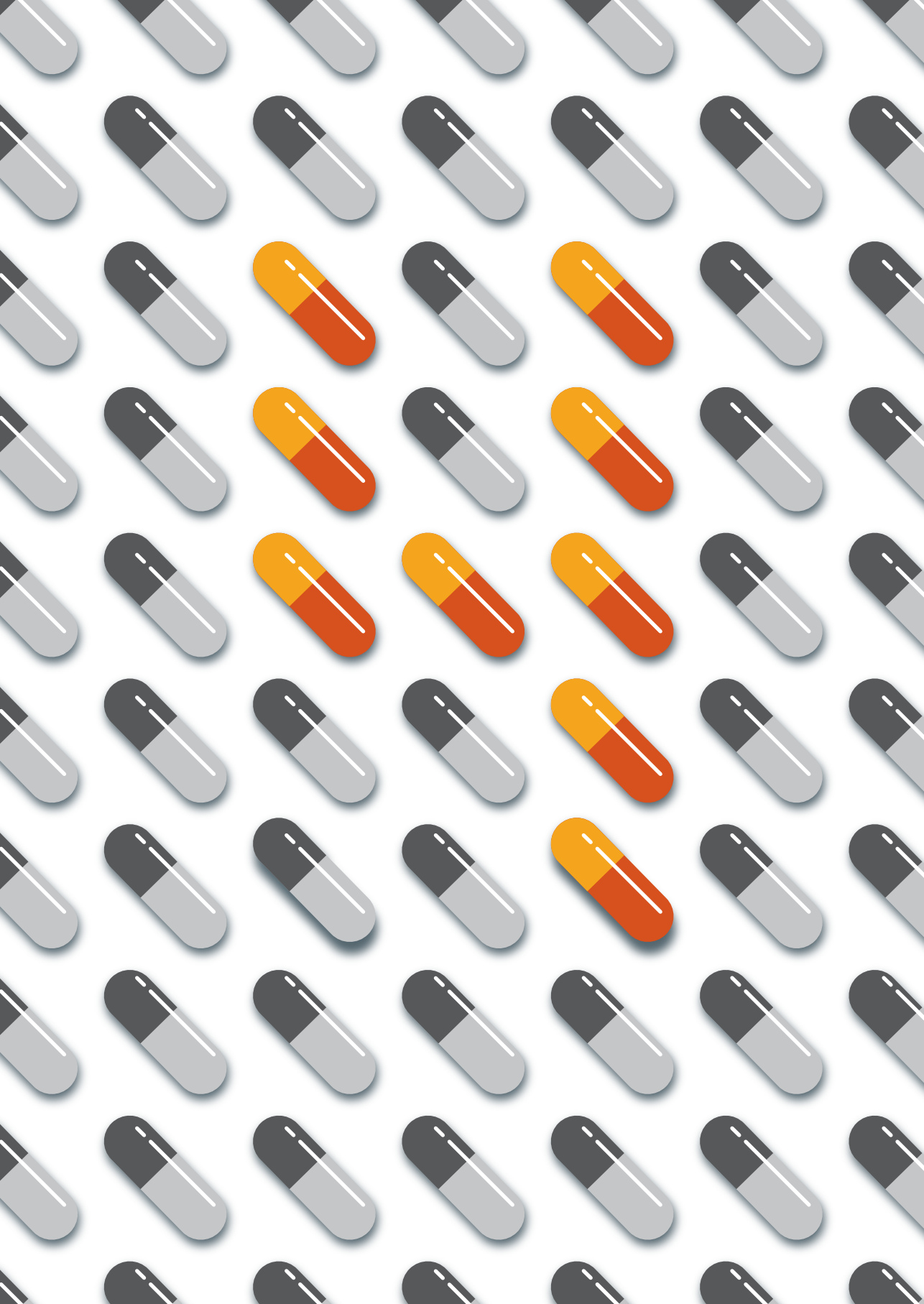

Chapter 4

PREVALENCE OF POTENTIAL DRUG-DRUG INTERACTIONS IN CANCER PATIENTS TREATED WITH ORAL ANTI-CANCER DRUGS

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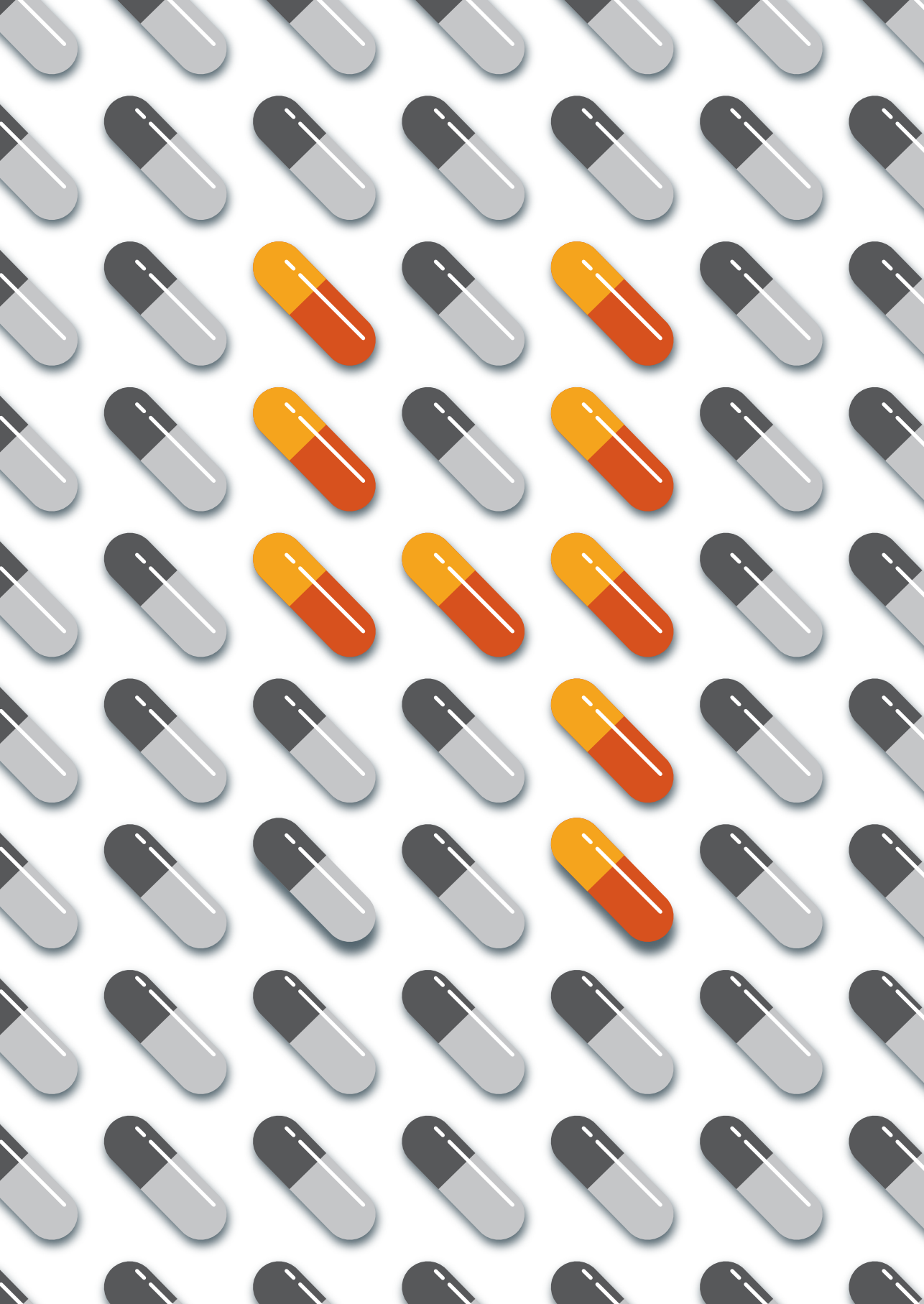

ABSTRACT

Introduction

Potential drug–drug interactions (PDDIs) in patients with cancer are common, but have not previously been quantified for oral anticancer treatment. We assessed the prevalence and seriousness of potential PDDIs among ambulatory cancer patients on oral anticancer treatment.

Methods

A search was conducted in a computer-based medication prescription system for dispensing oral anticancer drugs to outpatients in three Dutch centres. Potential drug–drug interactions were identified using electronic (Drug Interaction Fact software) and manual screening methods (peer-reviewed reports).

Results

In the 898 patients included in the study, 1359 PDDIs were identified in 426 patients (46%, 95% confidence interval (CI)=42–50%). In 143 patients (16%), a major PDDI was identified. The drug classes most frequently involved in a major PDDI were coumarins and opioids. The majority of cases concerned central nervous system interactions, PDDIs that can cause gastrointestinal toxicity and prolongation of QT intervals. In multivariate analysis, concomitant use of more drugs (odds ratio (OR)=1.66, 95% CI=1.54–1.78, $P<0.001$) and genito-urinary cancer (OR=0.25, 95% CI=0.12–0.52, $P<0.001$) were risk factors.

Conclusions

Potential drug–drug interactions are very common among cancer patients on oral cancer therapy. Physicians and pharmacists should be more aware of these potential interactions.

INTRODUCTION

Drug–drug interactions in patients with cancer are common, and most drug–drug interactions can cause considerable adverse drug reactions (ADRs)[1]. In the general population, it has been reported that 20–30% of all ADRs are caused by drug–drug interactions.[1] Drug–drug interactions are estimated to be the cause of death in ~4% of cancer patients.[2] Patients treated systemically for cancer are particularly at risk for drug–drug interactions. Typically, patients with cancer receive a high number of drugs concomitantly, including cytotoxic agents, hormonal agents, targeted agents, and supportive care agents among medication prescribed to treat comorbidities. An additional problem is that the mean age of cancer patients is increasing. Older patients generally have more comorbidities for which they also receive drug treatment.[3] The risk for drug–drug interactions in elderly cancer patients is further increased because of altered age- and comorbidity-related physiologic changes (e.g., altered drug absorption due to mucositis or altered excretion due to renal and hepatic impairment).[4]

Here, a potential drug–drug interaction (PDDI) was defined as the occurrence of a potentially harmful combination of prescribed drugs in a given patient, rather than the occurrence of an actual adverse event for a patient.

In clinical practice, PDDIs can be distinguished as pharmaceutical, pharmacokinetic, and pharmacodynamic interactions[4]. Pharmaceutical PDDIs occur for instance when two chemically or physically incompatible compounds are combined (e.g., cisplatin and mesna)[5]. Pharmacokinetic interactions refer to an influence on the absorption, distribution, metabolism, or elimination of the drug itself or a combination of drugs. A common pharmacokinetic interaction concerns drugs metabolised by the cytochrome P450 (CYP) enzymes. By inhibition or induction of CYP iso-enzymes, blood and tumour concentrations, antitumoural effects, and toxicities of specific anticancer therapies may be altered. Other pharmacokinetic interactions may result from, that is, inhibition of the ABCB1 efflux-transporter (or P-glycoprotein); by altering the activity of ABCB1, the bioavailability of anticancer drugs may be influenced. Pharmacodynamic drug interactions usually occur when two or more drugs have a similar mechanism of action. The effect can be synergistic, additive, or antagonistic. Pharmacodynamic drug interactions can be beneficial (e.g., enhanced pharmacologic effects with fluorouracil and leucovorin), but may also be potentially harmful (e.g., ototoxicity with furosemide and cisplatin)[6].

In general medicine, the prevalence of PDDIs and their determinants has been evaluated in several studies.[7-9] By contrast, data on the prevalence of PDDIs with anticancer drugs are scarce. Two studies, conducted in ambulatory cancer patients, found that 27–58% of all patients had at least one PDDI.[10, 11] Determinants for PDDIs were an increasing number of drugs, the use of OTC drugs, type of medication (drugs to treat comorbid conditions only), and the presence of brain tumours. However, these studies included only outpatients receiving intravenous anticancer treatment at a day-treatment facility.[10, 11] A retrospective database study, involving cancer patients on oral anticancer therapy, found that 5% of all patients had at least one potentially interacting drug combination.[12]

In the last decade, the availability and use of oral anticancer agents has increased dramatically. In comparison with parenteral treatment, the administration of oral agents is usually believed to be more convenient for the patient.[13] However, due to chronic use and the fact that most anticancer drugs are metabolised by CYPs, patients on oral anticancer agents are at considerable risk for PDDIs.[4] Moreover, a relative lack of collaboration between medical oncologists, pharmacists, and general practitioners, and the fact that computer-based medication prescription systems in hospitals and community pharmacies are usually not connected leads to PDDIs frequently going unnoticed.[13]

At present, epidemiological data regarding harmful PDDIs during oral anticancer therapy are scarce in the literature. Therefore, the aim of this study was to investigate the prevalence of PDDIs among ambulatory cancer patients on oral anticancer treatment, with the primary intent to create awareness among oncologists and pharmacists regarding the risk of potentially harmful drug–drug interactions. The secondary objective was to obtain more insight into possible determinants for the occurrence of these PDDIs.

METHODS

Study design and patients

A multicentre cross-sectional study of the prevalence of PDDIs was conducted in ambulatory cancer patients treated with oral anticancer drugs in three Dutch centres: the Maastricht University Medical Center (Maastricht), St. Radboud University Medical Centre (Nijmegen), and Deventer Teaching Hospital (Deventer). All ambulatory patients with the diagnosis of a solid tumour or a haematological malignancy, who were receiving one of more oral anticancer therapies (with or without additional intravenous anticancer drugs), were included in the study. Exclusion criteria were (i) the use of (oral) experimental trial agents, (ii) age <18 years, and (iii) the use of oral anticancer drugs for non-malignant diseases. This study was registered under number ISRCTN01739090, and was approved by the medical ethics boards of all three participating institutes.

Procedures

A retrospective search was conducted in the computer-based medication prescription system of the hospital pharmacy in these three centres for the dispensing of oral anticancer drugs to outpatients over a period of 12 months (between 1 October 2010 and 1 October 2011). Medications were classified into three groups; 'anticancer drugs', 'supportive care drugs', and 'drugs to treat additional diseases/ comorbidities'. Anticancer drugs were defined as oncolytic drugs (Anatomical Therapeutic Chemical code (ATC-code) L01) and antihormonal agents (ATC-code L02). In addition, data on supportive care and co-medication were collected using the same computer-based medication prescription system of the hospital pharmacy. Supportive care drugs included antiemetic and analgesic drugs. Drugs for chronic and incidental use (e.g., dexamethasone during chemotherapy) were included in this study as long as they were used concurrently as was defined by Tobi et al.[14] Information concerning type of cancer and comorbidities was collected by medical chart review. In this study, comorbidities were defined as all other diseases an individual patient might have, other than the primary disease of interest (cancer).

Renal function [creatinine] and liver function parameters (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyl-transferase (γ-GT)) were extracted from the laboratory database of the hospital while an individual patient was receiving an oral anticancer agent. Laboratory abnormalities were defined as an increase of >50% above the upper limit of normal (upper normal limits in all three medical centres: ASAT$\leqslant$35 U/L, ALAT$\leqslant$40 U/L, γ-GT$\leqslant$44 U/L, creatinine$\leqslant$99 μmol/L).

Potential drug–drug interactions between drugs and over-the-counter (OTC) medication were not studied. When a drug formulation contained two or more pharmacologically active ingredients each drug was counted individually in the analysis (e.g., tramadol/acetaminophen). However, when a patient was taking the same medication in more than one formulation (e.g., long- and short-acting morphine) the drug was counted only once.

In this study, we have identified drug–drug combinations, within the same patient, for drugs that are known for having interacting effects, rather than the occurrence of an actual adverse event in an individual patient. Potential drug–drug interactions were identified by using the Drug Interaction Facts software (Facts and Comparisons, version 4.0, 2006)[15], which is a commonly used and reputable source. It has been shown to have an accuracy of over 95% in detecting interactions.[16] Drug Interaction Facts software classifies interactions by the level of severity and the level of scientific evidence. A detailed classification of level of severity and scientific evidence is shown in Figure 1.

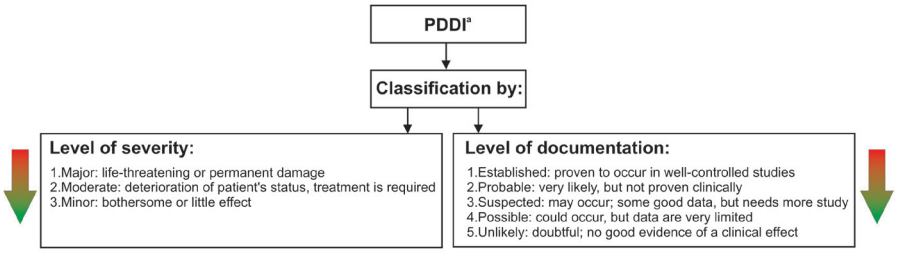

Figure 1: Classification of potential drug–drug interactions (Drug Interaction Facts[15]).

[a] Potential drug-drug interaction

The medication regimen of each patient was also screened for:

1 Drug combinations with potential QT-interval prolongation and/or *torsades de pointes* inducing properties using the Arizona CERT system list 1 (risk of torsades) and list 2 (possible risk of torsades).[17] Because of the potentially severe consequences, all drug combinations with risk for QT prolongation were classified as major (QT interaction). The QT-interval prolonging potential of drugs is generally well documented and QT interactions were classified as 'probable' as was defined in Figure 1.
2 Drugs associated with an increased risk of falling (central nervous system (CNS)-depressant agents). First, the medication regimen of each patient was manually screened for CNS-depressant agents by using handbooks and peer-reviewed reports on scientific evidence.[18-23] A combination of two CNS-depressant agents was counted as one interaction and defined as CNS interaction in the analysis. All CNS interactions were classified as moderate. The CNS-depressant potential of drugs is described in the literature, and CNS interactions were classified as 'probable' as was defined in Figure 1.
3 Drug combinations between non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, anticoagulants, aspirin, bisphosphonates, or selective serotonin reuptake inhibitors (SSRIs). These combinations were defined as a gastrointestinal (GI) interaction and were identified by using the Drug Interaction Facts software and peer-reviewed reports on scientific evidence.[15, 24-26] The GI interactions may increase the risk of GI bleeding. Due to the potentially severe consequences all GI interactions were classified as major. The GI interactions are generally well documented, and were classified as 'probable' as was defined in Figure 1.

A PDDI was only counted in the analysis when an 'anticancer agent' or a 'supportive care drug' was involved; thus, PDDIs resulting from the treatment of comorbidities were disregarded. Interactions of minor severity, being clinically not relevant, were not included in the analysis.

Statistical analysis

To compute patient demographics, cancer type, comorbidities, number of drugs used per patient, laboratory abnormalities, and drug interaction characteristics (severity, scientific evidence, and mechanism), descriptive statistics were used. Subsequently, univariate and multivariate binary logistic regression analyses were performed to identify the potential risk factors for the occurrence of PDDIs. The occurrence of at least one DDI per patient was called the dependent variable. Predictor variables tested included age, number of drugs, presence of comorbidities (yes/no), cancer type, treatment type, solid tumour or haemato-oncology disease and laboratory abnormalities. Gender was not included as a predictor variable as certain cancer types only occur in men or women. The largest group per predictor variable was taken as the reference (Ref.) for binary or nominal variables. In the multivariate analysis predictor, variables with univariate *P*-values <0.1 were included. Predictor variables in the multivariate analysis with a *P*-value of <0.05 were considered statistically significant. The data were adjusted for confounders and effect modifiers. Data were collected and analysed in SPSS version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient

A total of 898 patients were included in this study, with a median age of 61 years (range 18–95 years), of which 58% were female. The median number of drugs used per person was five (range 1–24 drugs). Demographic characteristics are listed in Table 1. In 898 patients, a total of 31 different oral anticancer drugs were identified as stated in Table 2.

Drug interactions

In total, 1359 PDDIs were identified in 426 patients (46%, 95% CI=42–50% Figure 2). In 143 patients (16%) at least one major PDDI was identified. Of all PDDIs, 15% and 83% were classified as major and moderate PDDIs, respectively. In 14% of all PDDIs, anticancer drugs were involved. A pharmacodynamic PDDI was found in 86% of all cases. The majority of cases concerned CNS interactions (*n*=848), GI interactions (*n*=97), and QT interaction (*n*=45). Most PDDIs (86%) were supported by level 2 (probable) or level 3 (suspected) scientific evidence. A stratification of the identified PDDIs by 'level of severity', 'level of scientific evidence', and 'mechanism of drug interaction' is listed in Figure 2.

Table 1: Demographic characteristics

	n	%
Study population	898	100
Age in years[a]	61 (18-95)	-
Sex		
Female	518	57.7
Male	380	42.3
Hospital		
Radboud University Medical Center	463	51.6
University Hospital Maastricht	362	40.3
Deventer Hospital	73	8.1
Cancer type		
Solid Malignancy	766	85.3
Haemato-oncology	132	14.7
Cancer type solid malignancy		
Breast	273	30.4
Gastro-intestinal (GI)	257	28.6
Genito-urinary (GU)	102	11.4
Neurological	79	8.8
Lung	28	3.1
Gynaecologic	13	1.4
Other	15	1.6
Cancer type haemato-oncology		
Leukaemia	40	4.5
Myeloproliferative disease	36	4.0
Malignant lymphoma	32	3.5
Plasma cell dyscrasia	15	1.7
Myelodysplastic syndrome	8	0.9
Immunocytoma	1	0.1
No. of drugs used per patienta	5 (1-24)	-
No. of drugs used per patient per groupa		
Oral anti-cancer agents	1 (1-3)	-
Supportive care drugs[b]	1 (0-9)	-
Other	2 (0-17)	-
No. of co-morbidities per patient[a,c]	1 (0-8)	-
Laboratory valuesa		
Creatinine	72 (26-568)	-
Aspartate aminotransferase	27 (4-1188)	-
Alanine aminotransferase	23 (5-845)	-
Gamma-glutamyltransferase	39 (8-1712)	-
Total laboratory abnormalities[d]	110	12.2

[a] Median (range)

[b] Antiemetics and pain medication

[c] As we retrospectively retrieved co-morbidity data from the oncology patient files the real number of co-morbidities could have been higher

[d] Because of missing data, the denominator is *n*=690. Liver failure (94), kidney failure (14), combination (2)

Table 2: Oral anticancer drugs identified

Drug class (ATC-code)	Drugs (n)
Oncolytics (L01)	
Alkylating agents	Temozolomide (75), Chlorambucil (34), Cyclophosphamide (26), Lomustine (9), Melphalan (9), Procarbazine (9), Busulfan (1)
Antimetabolites	Capecitabine (258), Hydroxyurea (41), Fludarabine (9), Mercaptopurine (8), Thioguanine (3), Uracil-Tegafur (2), Methotrexate (1)
Protein kinase inhibitors	Imatinib (30), Sunitinib (27), Erlotinib (10), Dasatinib (9), Nilotinib (8), Sorafenib (4), Everolimus (4), Thalidomide (1)
Topoisomerase inhibitors	Etoposide(19), Topotecan (1)
Other oncolytics	Tretinoin (3)
Antihormonal agents (L02)	
Anti-oestrogens	Tamoxifen (171)
Enzyminhibitors	Anastrozole (75), Letrozole (29), Exemestane (5)
Anti-androgens	Bicalutamide (76), Flutamide(3)

Abbreviations: ATC code=Anatomical Therapeutic Chemical code.

Table 3: Major drug-drug interactions found in the database search

Potential drug-drug interactions involving anti-cancer agents				
	n	**Description**	**Severity**	**Scientific evidence**
Tamoxifen + Ondansetron/ Granisetron/ Sotalol/ Erythromycin/ Levofloxacin/ Methadone/ Risperidone/ Azithromycin[a] [17]	28	Drug combinations can prolong QT-interval.	Major	2
Coumarines + Capecitabine/Tamoxifen/ Etoposide[27, 28]	17	Hypoprothrombinemic effects of coumarines may be increased, bleeding may occur.	Major	2
Methotrexate + Sulfamethoxazole/ Trimethoprim/ Acetylsalicylic acid[29, 30]	12	Increased pharmacologic effects of methotrexate with an increased risk of bone marrow and hepatic toxicity.	Major	2
(Es)omeprazole + Dasatinib/Nilotinib[31]	4	Proton Pump Inhibitors may decrease the plasma concentration of Tyrosine Kinase Receptor Inhibitors	Major	3
Methotrexate + Prednisolone[32]	2	Prednisolone may decrease the total clearance of methotrexate.	Major	2
Methotrexate + Amoxicillin/Clavunate[33]	1	Penicillins may decrease the total clearance of methotrexate.	Major	4
Perphenazine + Tamoxifen[34]	1	Pharmacologic effects of tamoxifen may be decreased by Perphenazine Coadministration may increase the risk of breast cancer recurrence.	Major	4
Potential drug-drug interactions involving supportive care drugs				
NSAIDs[b] + Corticosteroids[c]/ SSRIs[d]/ Dipyridamole/ Clopidogel/ Alendronate[24, 25]	98	Increased risk of GI bleeding.	Major	2
SSRI's + Metoclopramide/ Tramadol[35, 36]	16	Serotonin syndrome is a potential risk with this combination.	Major	4
Fentanyl + Fluconazole/ Aprepitant/ Ketoconazole/ Diltiazem/Itraconazole[37, 38]	12	Increased pharmacologic effects and plasma concentrations of fentanyl	Major	2
Haloperidol + Granisetron/Metoclopramide Ofloxacin + Methadone[17]	5	Drug combinations can prolong QT-interval.	Major	2
Fluconazole + Methadone[39]	1	Increased plasma concentration and pharmacologic effects of methadone.	Major	4

Abbreviations: GI=gastrointestinal; NSAIDs=non-steroidal anti-inflammatory drugs; PDDI=potential drug–drug interaction; SSRIs=selective serotonin reuptake inhibitors.

[a] References in this table are only mentioned to clarify for the identification of a PDDI. For a comprehensive overview of all references, go to Facts&Comparisons15

[b] NSAIDs: Acetylsalicylic acid, Diclofenac, Ibuprofen, Meloxicam, and Naproxen

[c] Corticosteroids: Budesonide, Dexamethasone, and Prednisolone

[d] SSRIs: (Es)citalopram, Fluoxetine, Paroxetine, and Venlafaxine

Potential drug–drug interactions involving anticancer drugs and supportive care agents are listed in Table 3. As the variety of drug classes is diverse, only PDDIs with potentially major consequences are reported. The drug classes most commonly involved in major PDDIs were coumarins and opioids. The QT interactions and GI interactions were also observed frequently.

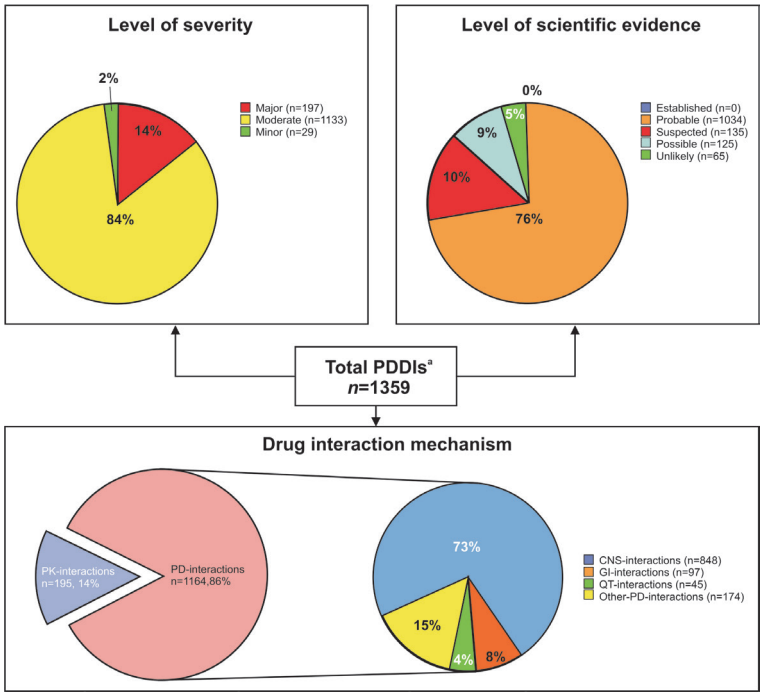

Figure 2: Prevalence, classification, and mechanism of potential drug interactions.

[a]Potential drug-drug interactions.

Risk factors

All patients were included in the binary logistic regression analysis. In the univariate analysis, the number of drugs, treatment type, cancer type, and the presence of comorbidities were associated with higher risk for PDDIs. No statistically significant association was found for age (P=0.124), tumour type (solid/non-solid malignancy; P=0.327), or laboratory abnormalities (P=0.295). Results of the univariate and multivariate binary logistic regression analyses are listed in Table 4. After adjustment for confounders, the number of drugs (odds ratio (OR) 1.66 (1.54–1.78); P<0.0001) and cancer type (genito-urinary cancer, OR 0.25 (0.12–0.52); P<0.0001) remained statistically significant.

Table 4: Univariate and multivariate binary logistic regression analysis

Variable	Unadjusted OR (95% CI)	Unadjusted *P* value	Adjusted OR (95% CI)	Adjusted *P* value
Age	1.01 (1.00-1.02)	0.124	-	-
No. of drugs	1.65 (1.54-1.76)	< 0.0001	1.66 (1.54-1.78)	< 0.0001[a]
Treatment type				
Oncolytics	1.0 (Ref.)	-	1.0 (Ref.)	-
Antihormonal agents	0.39 (0.29-0.52)	< 0.0001	0.61 (0.29-1.29)	0.196
Others	2.12 (0.79-5.66)	0.134	1.27 (0.32-5.05)	0.735
Cancer type				
Breast	1.0 (Ref.)		1.0 (Ref.)	
Gastrointestinal	2.35 (1.66-3.34)	< 0.0001	0.65 (0.29-1.44)	0.290
Haemato-oncology	1.69 (1.10-2.58)	< 0.016	0.45 (0.19-1.06)	0.067
Genito-urinary	0.53 (0.31-0.91)	0.021	0.25 (0.12-0.52)	< 0.0001a
Neuro-oncological	1.32 (0.79-2.20)	0.293	0.59 (0.24-1.49)	0.264
Other oncology	2.99 (1.66-5.41)	< 0.0001	1.10 (0.45-2.68)	0.832
Tumour type				
Oncology	1.0 (Ref.)	-	-	-
Haemato-oncology	1.20 (0.83-1.75)	0.327	-	-
Presence of co-morbidities				
No	1.0 (Ref.)	-	1.0 (Ref.)	-
Yes	2.06 (1.58-2.70)	< 0.0001	1.02 (0.70-1.48)	0.923
Laboratory abnormality				
No	1.0 (Ref.)	-	-	-
Yes	1.24 (0.83-1.87)	0.295	-	-

Abbreviations: CI=confidence interval; OR=odds ratio; Ref.=Referent

[a] Statistically significant

DISCUSSION

To our knowledge, this is the first study to investigate the prevalence of PDDIs among cancer patients that are on oral anticancer treatment. In this analysis, we detected a high prevalence of PDDIs with 46% of all patients being exposed to at least one PDDI. More importantly, these PDDIs were not just theoretical in nature, 16% of all patients had at least one major PDDI that may have had harmful side effects and which usually would have needed intervention or intensive monitoring.

Most PDDIs (86%) were supported by level 2 or level 3 scientific evidence. In the majority of PDDIs, a supportive care agent was involved (86%). Potential drug–drug interactions with coumarins, whose anticoagulant effects may be altered, and fentanyl, through which plasma concentrations and toxicity of fentanyl may be increased, were most frequently registered. This also counted for drug combinations that may have led to QT-interval prolongation, or to GI toxicities. The highest prevalence concerned CNS interactions that accounted for up to 73% of all PDDIs.

The drug–drug combinations of coumarins with certain oral anticancer agents (e.g., capecitabine) may result in altered anticoagulant effects and haemorrhage due to the increased hypoprothrombinemic effects of coumarins.[27, 28, 40] In case of a PDDI, anticoagulant effects should be closely monitored and the dose of coumarins must be adjusted accordingly. Combinations of strong CYP3A4 iso-enzyme inhibitors/inducers and anticancer drugs can be potentially harmful.[41, 42] In this study, the combination of fentanyl and strong CYP3A4 iso-enzyme inhibitors (e.g., itraconazole) was frequently found. This CYP3A4 inhibitor may decrease the metabolic elimination of this opioid, resulting in increased plasma concentrations and pharmacologic effect of fentanyl. Closely monitoring for signs of excessive narcotic effects of fentanyl is indicated and dosage reduction may be required.[37, 38]

Drug combinations that could lead to QT-interval prolongation, or to GI toxicity, can have serious or even fatal consequences, like *torsade de pointes* and NSAIDs induced ulcers, respectively.[17, 24, 25] Due to the extensive use of QT-prolonging drugs (e.g., ondansetron) and drugs that can cause GI toxicity (e.g., NSAIDs) in (haemato)-oncology these PDDIs may cause significant health risks. Concerning QT interactions, there is very little information to guide clinicians about the risks of concomitantly using QT-prolonging drugs, and how

these PDDIs should be managed. Moreover, the evidence for risk of *Torsades de point* is often imperfect. Nevertheless, QT interactions are presumed to have the potential for life-threatening consequences. Drug–drug combinations that could lead to QT-interval prolongation or to GI toxicity should, if possible, be avoided.

The high prevalence of CNS interactions is of particular concern, since injuries resulting from balance disorders may have a major impact on public health. The authors acknowledge that a large number of cancer patients need CNS depressant medication (e.g., opioids, antidepressants, and benzodiazepines). However, due to the increased risk of osteoporosis and the extensive use of CNS-depressant drugs, cancer patients are particularly at risk for fractures.[22] Prescribed CNS-depressant drugs can result in an up to 47% increased risk of falls.[43] Prescription of combinations of CNS-depressant drugs may even further increase this risk.[21] Although combinations of CNS-depressant drugs are often used for therapeutic reasons, oncologists and other health-care professionals should minimise the number of CNS depressant drugs prescribed, or at least carefully assess combinations of CNS-depressant drugs and monitor for signs of balance disorders.

In this study, the number of drugs used concomitantly has been identified as a risk factor for the occurrence of PDDIs. Genito-urinary cancer showed a lower risk. It is not surprising that an increasing number of drugs used is associated with an increased risk of PDDIs and is in agreement with other studies.[10, 11] Patients with genito-urinary cancers were less likely to be exposed to PDDIs. A plausible explanation for this lower risk could be the relatively mild interaction profile of bicalutamide, which was predominately used for the oral treatment of prostate cancer in our studied population. However, many medical centres still use flutamide and nilutamide for the treatment of prostate cancer, which do have interacting potentials. This questions the generalisability of prostate cancer as a risk factor.

A great strength of this study was that the medication data in the computer-based medication prescription system were based on ‘actual concurrent use’.[14] If an oral anticancer drug was dispensed in the hospital pharmacy, then the actual use of other drugs (e.g., supportive care drugs’ and ‘drugs to treat additional diseases/comorbidities’), both on a continuous base and an incidental use, was always discussed with the patient and registered in the computer-based medication prescription system. Other strengths of our study included

the large multicentre sample size, cross-sectional design, use of a large variety of oral anticancer agents, objective identification of PDDIs based on highly sensitive screening software (Facts and Comparisons, version 4.0, 2006; and the additional screening for QT, GI, and CNS interactions).[16] These factors increase the validity and representativeness of this study.

A major limitation of this study is that it does not investigate the clinical impact of the PDDIs. Although Buajordet *et al* estimated that PDDIs are responsible for the death of 4% of hospitalised cancer patients, insights into the clinical consequences of PDDIs in cancer patients remains largely unknown and should be further explored in prospective studies.[2] Also, the true relevance of some drug–drug interactions identified by Drugs Interaction Facts software or the additional manual search may sometimes be questioned (e.g., NSAIDs and bisphosphonates or NSAIDs and SSRIs). Furthermore, it is not known to what extent precautions (e.g., dosage adjustments) were taken by the health-care professionals to prevent potentially harmful PDDIs. Since these precautions are not being accounted for in this study, this may lead to an over-detection of PDDIs by electronic PDDI databases, as was concluded by Chan *et al*.[44] Another limitation of this study was that we did not study PDDIs between prescription drugs and OTC medication. In our previous study, OTC drugs were involved in 11% of all PDDIs.[11] Although drug combinations with OTC drugs were not investigated in this study (due to the retrospective search in the computer-based medication prescription system), PDDIs with OTC drugs are relevant and can be potentially harmful.[42, 45]

Our findings were largely in accordance with other studies.[10, 11] Conversely, a comparable retrospective database study, conducted in Eastern cancer patients using oral anticancer therapy, found that only 5% of all patients had at least one PDDI.[12] A possible explanation for the higher prevalence of PDDIs in our study may be the additional search for QT, GI and CNS interactions. Nevertheless, the existence of potentially harmful PDDIs should not be neglected and needs the explicit attention of pharmacists and medical doctors.

CONCLUSIONS

Over the past years there has been a sharp shift and focus towards oral anticancer drugs. The present study shows that besides their possible benefits, cancer patients on oral anticancer therapy are at considerable risk for PDDIs. It remains unknown to what extent pharmacies and medical doctors were actually aware of these PDDIs and whether they took adequate measures to prevent potentially harmful drug–drug combination. Therefore, the impact of the identified PDDIs on clinical outcomes remains partly unknown and should be further investigated in detail in future prospective studies. In the Erasmus University Medical Centre, a prospective clinical trial such as this to explore important remaining questions recently closed for patient accrual. For instance, the effects of duration of anticancer drug treatment and the dose of the drugs that may interact will be studied in detail.

This is particularly relevant as with the increasing numbers of new oral anticancer agents that become available, the risk for PDDIs will consequently increase. Despite this fact, in current daily practice medication review is not always common practice. We realise that many combinations of interacting drugs are unavoidable and may be administered together if appropriate precautions are taken (e.g., monitoring and dosage adjustment). However, this requires a solid medication review of all drugs used at every patient visit by an oncologist or pharmacist. Therefore, in an ideal situation, all drugs prescribed by oncologists, general practitioners, and other health-care professionals should be documented electronically, including patient's medical status, in computer-based patient records to identify and prevent potentially harmful PDDIs.

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Chapter 5

DRUG-DRUG INTERACTIONS IN PATIENTS TREATED FOR CANCER: A PROSPECTIVE STUDY ON CLINICAL INTERVENTIONS

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ABSTRACT

Introduction

Drug–drug interactions (DDIs) are of major concern in oncology, since cancer patients typically take many concomitant medications. Retrospective studies have been conducted to determine the prevalence of DDIs. However, prospective studies on DDIs needing interventions in cancer patients have not yet been carried out. Therefore, a prospective study was designed to identify DDIs leading to interventions among ambulatory cancer patients receiving anticancer treatment.

Methods

Patients starting with a new treatment regimen with i.v. or oral anticancer medication were asked to participate. The patients' medication was checked for DDIs by using drug interaction software. An expert team of clinical pharmacologists evaluated the relevance of these identified DDIs. If a DDI was qualified as potentially clinically relevant, an intervention was proposed to the treating (hemato)oncologist. Several variables were studied as determinants for performing an intervention. Descriptive statistics and uni- and multivariate logistic regression analyses were carried out.

Results

In this study, 302 patients were included. A total of 603 DDIs were identified by the drug interaction software and judged by the expert team. Of all 603 DDIs, 120 DDIs were considered potentially clinically relevant. These 120 DDIs, present in a total of 81 patients, resulted in a clinical intervention already executed by the (hemato) oncologist in 39 patients (13%), while an additional intervention was proposed by a clinical pharmacologist in 42 patients (14%). The number of comorbidities and the number of 'over-the-counter' drugs were identified as determinants.

Conclusions

Clinical interventions on DDIs are frequently required among patients starting with anticancer therapy. Structured screening for these potentially clinically relevant DDIs, by (hemato)oncologists in close collaborations with clinical pharmacologists, should take place before the start and during anticancer treatment.

INTRODUCTION

Drug–drug interactions (DDIs), defined as the occurrence of a harmful combination of prescribed drugs in a given patient, are preventable medication errors associated with serious or even fatal adverse events.[1] *In vivo* DDIs can be classified into two groups: pharmacokinetic and pharmacodynamic DDIs.[2] In pharmacokinetic DDIs, the pharmacokinetic properties (absorption, distribution, metabolism or excretion) of a certain drug are altered by another drug. In pharmacodynamic DDIs, an additive, synergistic or antagonistic effect occurs when two drug are used concomitantly (e.g. fluorouracil and leucovorin).

DDIs are of major concern in oncology, since patients typically use many drugs beside their anticancer therapy.[3, 4] In addition, most anticancer drugs are potent and toxic drugs with a narrow therapeutic index.[5] Remarkably, in most countries, cancer patients are not routinely checked for DDIs. Despite these concerns, only three retrospective studies have been conducted on the prevalence of DDIs involving anticancer drugs.[3, 4, 6] Two of these studies were conducted in ambulatory cancer patients receiving i.v. anticancer treatment and, in these studies, it was concluded that 27%–58% of all patients had at least one DDI.[4, 6] Comparable results were found in a multicenter study on ambulatory cancer patients treated with oral anticancer medication.[3] Several studies also identified determinants for DDIs in anticancer therapy: the number of co-medications, the use of over-the-counter (OTC) drugs, the type of (anticancer) medication and the presence of certain tumors were associated with the occurrence of DDIs.[3, 4, 6] However, due to the retrospective setting of these studies, it is unknown whether these DDIs were true medication errors, or if these DDIs represented drug–drug combinations selected intentionally by the (hemato) oncologist (and handled e.g. by intensive monitoring). Therefore, a prospective study was designed to identify DDIs leading to clinical interventions among ambulatory cancer patients starting a new oral and/or i.v. anticancer regimen. The secondary objective of this study was to obtain more information on potential determinants for DDIs leading to interventions.

METHODS

Study design and patients

A prospective intervention study was designed for patients treated with anticancer drugs at the Erasmus MC Cancer Institute (Rotterdam, The Netherlands). All patients treated in the outpatient department with oral or i.v. anticancer drugs, starting a new regimen between April 2013 and February 2014, were asked to participate. Exclusion criteria were: age <18 years, language barrier and the use of anticancer drugs for nonmalignant disease. This study was approved by the medical ethics committee of the Erasmus Medical Center.

Procedures

Patients were asked to participate in this study before the start of a new treatment regimen of anticancer therapy. Data on demographic characteristics, use of co-medication, OTC drugs, relevant consumption of food (supplements), such as grapefruit juice, and comorbidities were collected in a structured interview with the patient. To help identify the actual use of the co-medication, a 6-month overview of prescribed medication was collected from the community pharmacy. Data on the use of anticancer drugs, supportive care drugs, diagnosis and treatment intent (palliative/curative) were collected by medical chart review. Patients were also asked if the medical oncologist had already conducted a medication-related intervention on the day of the last outpatient visit.

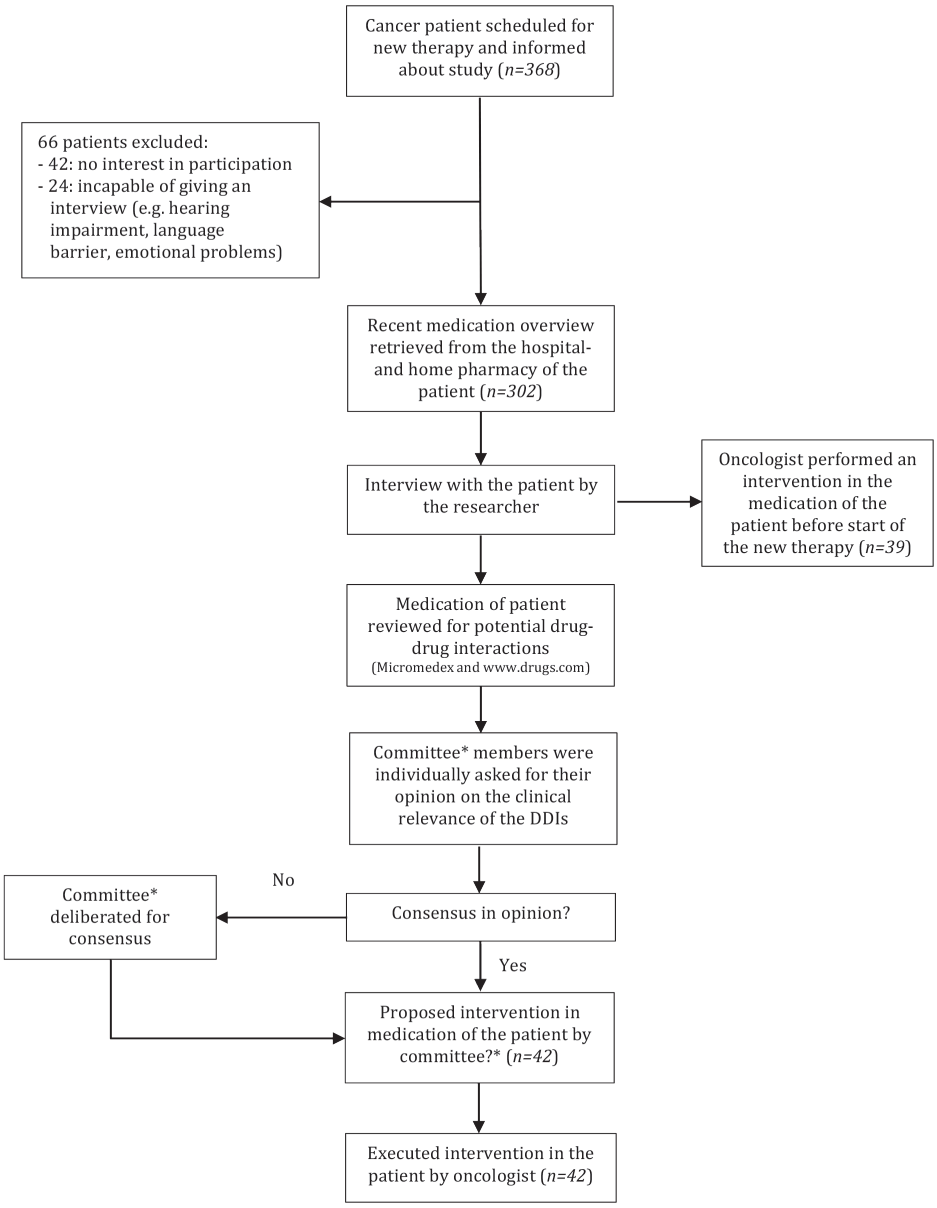
The types of medication were subdivided into four categories: 'anticancer drugs', 'supportive care drugs', 'drugs to treat comorbidities' and 'OTC drugs [including food (supplements)]. Anticancer drugs were defined as all cytostatic, antihormonal and targeted drugs to treat malignancies, while supportive care drugs were defined as all drugs supporting the anticancer treatment (e.g. antiemetics). Drugs to treat comorbidities were defined as all agents used for noncancer disease. OTC drugs included all (herbal) drugs, food (supplements) and vitamins that were used without prescription at the time of the interview. Drugs were counted as pharmacologically active components. If one formulation contained multiple pharmacologically active ingredients, these ingredients were each counted individually in the analysis. When a drug was taken in different dosages or administration routes, it was counted as one drug.

Following the interview, the patient's medication was checked for DDIs by use of the Micromedex drug–drug interaction software program.[7] To maximize accuracy, an additional medication review was conducted by using a second drug–drug interaction software program 'www.drugs.com'.[8]

DDIs were classified by mechanism in three major groups: pharmacokinetic DDIs, pharmacodynamic DDIs and DDIs with unknown mechanisms. Pharmacodynamic DDIs were subdivided into: (i) central nervous system (CNS) interactions, defined as combinations of drugs associated with drowsiness an increased risk of falling, (ii) QT_c interactions, defined as drug combinations with potential QT_c interval prolongation and/or *Torsades de pointes* inducing properties, (iii) Gastrointestinal (GI) interactions, defined as drug combinations that may increase the risk of GI-bleeding and (iv) Other pharmacodynamic DDIs.

DDIs found in either one or both databases were counted once in the analysis. A DDI was only included in the analysis when either an 'anticancer drug' or a 'supportive care drug', as defined above, was involved. An overview of the patient's demographic characteristics, comorbidities and identified DDIs, was sent to an expert team consisting of three certified clinical pharmacologists. The expert team members first assessed the DDI lists for the need to intervene in a certain DDI based on the used medication and the individual characteristics of the patient. If the individual advices of the expert team were inconsistent, consensus had to be reached. If a DDI was identified as needing an intervention, an advice on how to manage this DDI was sent to the (hemato)oncologist in charge of the patient. In close collaboration with the expert team, the (hemato) oncologist responsible for the patient, decided whether to carry out the proposed intervention. If an intervention was carried out, the DDI was considered to be potentially clinically relevant (Figure 1).

Figure 1: Study flowchart



*Committee: expert team consisting of three clinical pharmacologists

Statistical analysis

Descriptive statistics were used to analyze the patients' demographics, cancer type, comorbidities, number of drugs and DDI characteristics. Univariate and multivariate binary logistic regression analyses were used to identify potential determinants for DDIs leading to interventions. The dependent variable was 'the occurrence of at least one intervention per patient by the expert team' and predictor variables included age, number of drugs, number of OTC drugs, tumor type, treatment intent, type of therapy and number of comorbidities. Predictor variables with univariate P values <0.05 were stepwise included in the multivariate analysis. When the predictor variable changes the β coefficient with >10%, it was included in the multivariate model.

The primary end point in this exploratory study was the percentage of clinical intervention due to DDIs. It was estimated that DDIs would led to an intervention in 8% of all ambulatory cancer patients. With a sample size of 300 patients and an estimated intervention percentage of 8%, the 95% confidence interval for assessment of this percentage would be 5%–12%.

RESULTS

Patient characteristics

A total of 368 patients were asked to participate, of which 302 patients (82%) were included in this study (Figure 1). The mean age was 61 years (range 22–84 years) and half of all patients were male (Table 1). In total, 87% of the patients were diagnosed with a solid malignancy of which gastrointestinal, breast and genito-urinary malignancies were most frequently seen. The median number of drugs used per patient was 10 (range 1–25) and 81% of all patients used at least one OTC drug. The median number of comorbidities per patient was 1 (range 0–7) and 57% of all patients suffered from at least one comorbidity.

Drug-drug interactions

In total, 603 DDIs were identified and assessed for the need for interventions (Table 2). Of all DDIs, 120 DDIs with a wide variety of pharmacological classes, were considered potentially clinically relevant. These 120 DDIs, present in a total of 81 patients, resulted in a clinical intervention already executed by the (hemato) oncologist in 39 patients (13%, see Figure 1), while an additional intervention was proposed by a clinical pharmacologist in 42 patients (14%). The (hemato) oncologist executed all interventions (100%) that were proposed by the expert team. On the other hand, all interventions already executed by the (hemato) oncologist where retrospectively judged as potentially clinically relevant by the

Table 1: Baseline characteristics of patients included in the study

	n	%
Study population	302	100
Age (years)a	61 (22-84)	-
Sex		
Male	152	50.3
Female	150	49.7
No. of comorbidities per patientb	1 (0-7)	-
Cancer type		
Solid malignancy	264	87.4
Haemato-oncology	38	12.6
Cancer type solid malignancy		
Gastrointestinal (GI)	121	40.1
Breast	58	19.2
Genito-urinary (GU)	29	9.6
Gynaecologic	17	5.6
Neurological	14	4.6
Other	25	8.3
Cancer type haemato-oncology		
Malignant lymphoma	21	7.0
Plasma cell dyscrasia	11	3.6
Leukaemia	4	1.3
Myelodysplastic syndrome	2	0.7
Treatment intent		
Palliative	151	50.0
Curative	151	50.0
Cancer treatment		
Chemotherapy	153	50.7
TKIs/mTORi	21	7.0
mABs	13	4.3
Anti-hormonal therapy	2	0.7
Combination[c]	113	37.3
No. of drugs used per patientb	10 (1-25)	-
No. of drugs used per patient per groupb		
Anti-cancer agents	2 (1-6)	-
Supportive care drugs	3 (0-7)	-
Drugs for comorbidities	4 (0-15)	-
OTC and herbal drugs[d]	1 (0-9)	-

[a] Mean (range).
[b] Median (range).
[c] Combination anticancer drugs and/or radiotherapy.
OTC drugs= over-the-counter drugs.

expert team. Coumarins, corticosteroids and NSAIDs were frequently involved in the interventions. Also OTC drugs, herbal substances and food supplements (e.g. grapefruit juice) were extensively used and frequently involved in a DDI leading to an intervention. Interestingly, none of the identified CNS interactions ($n = 187$) was considered to require an intervention by the expert team nor by the treating (hemato) oncologist. In one case, a DDI (mercaptopurine and allopurinol) was identified by the drug interaction software program and scored as potentially clinically relevant by the expert team. Due to unfortunate logistic problems, the hemato-oncologist was informed only after 7 days. Despite an intervention, the patient developed bone marrow suppression, which recovered without sequela. An overview of all DDIs with an intervention conducted is given in Table 3 and Table 4, respectively.

Table 2: Identified drug–drug interactions (DDIs) and drug–drug interactions with an Intervention

DDIs	*n*	%
Total no.	603	100
Drug interaction mechanism		
Pharmacodynamic	407	67.5
CNS-interaction	187	31.0
QT-interaction	110	18.2
GI-interaction	81	13.5
Other pharmacodynamics interaction	29	4.8
Pharmacokinetic	126	20.9
Unknown	70	11.6
DDIs with an intervention	***n***	**%**
Total no.	120	19.9[a]
Drug interaction mechanism		
Pharmacodynamic	52	8.6
QT interval prolongation	10	1.7
GI interaction	26	4.3
Other pharmacodynamics interaction	16	2.6
Pharmacokinetic	34	5.6
Unknown	34	5.6
Number of patients ≥1 intervention	***n***	**%**
Carried out by the medical oncologist:		
Based on recommendation of clinical pharmacologists	42	13.9[b]
On own initiative of medical Oncologist	39	12.9[b]

[a] Denominator is 603 DDIs [b] Denominator is 302 patients

Table 3: Interventions on drug-drug interactions performed by the medical oncologist on own initiative

	n	Description	Intervention
Drug interactions involving anticancer agents			
Chemotherapeutics + Herbal substances[a]	14	The influence of herbal substances on chemotherapeutics is unknown, but may be harmful	Stop herbal substances on theoretical basis
Chemotherapeutics + Immunosuppressant[a]	4	Concomitant use of Immunosupressants and chemotherapeutics may have an undesired additional effect on immunosuppressive load	Stop immunosuppressant on theoretical basis
Coumarins[a] + Imatinib/ Everolimus/ Paclitaxel/ Irinotecan [9]	4	Chemotherapy-induced protein displacement and inhibition of coumarins metabolism with higher risk of bleeding	Intensify INR monitoring
Pazopanib + Antacid [10]	1	Exposure to pazopanib may be decreased	Stop antacid
Chemotherapeutics + Valproic acid	1	Valproic acid may cause future drug-drug interactions in cancer patients	Replace valproic acid
Drug interactions involving supportive care drugs			
Corticosteroids[b] + NSAIDs[c] [11]	18	Combination may result in increased risk of GI ulcerations or bleeding	Add PPI and/or stop NSAID
Acenocoumarol + Dexamethasone/ Ranitidine [9,12]	4	Combination may result in increased risk of bleeding or diminished effect of coumarins	Additional INR monitoring

Abbreviations: INR=international normalized ratio; ECG=electrocardiogram; GI=gastro-intestinal; PPI=proton pump inhibitor; TDM=therapeutic drug monitoring; NSAID: non-steroidal anti-inflammatory drug.

[a] DDIs on theoretical bases, no reference available

[b] Corticosteroids: dexamethasone and prednisolone

[c] NSAIDs: Acetylsalicylic acid, ibuprofen, naproxen and diclofenac

Table 4: Drug-drug interactions leading to interventions based on recommendation by clinical pharmacologists

	n	Description	Intervention
Drug interactions involving anticancer agents			
Grapefruit + Cyclophosphamide/ Vinblastine/ Doxorubicin/ Vincristine/ Docetaxel [9]	13	Grapefruit may increase the plasma concentrations of these chemotherapeutics by CYP3A4 inhibition	Stop grapefruit
Coumarins[a] + Carboplatin/ Doxorubicin/ Bortezomib [9]	7	Chemotherapy-induced protein displacement and inhibition of coumarin metabolism with higher risk of bleeding	Intensify INR monitoring
Capecitabine + Herbal substances[b,c]	5	The influence of herbal substances on capecitabine is unknown, but may be harmful.	Stop herbal substances on theoretical basis
Doxorubicin + Sotalol/ Granisetron/ Ondansetron; Sunitinib + Sotalol [14]	4	Additive QT-prolongation may occur	ECG monitoring
Corticosteroids[d] + Tiaprofenic acid/ Ibuprofen/ Acetylsalicylic acid [11]	3	Combination may result in increased risk of GI ulcerations or bleeding	Add PPI
Pazopanib + Antacid [10]	2	Exposure to pazopanib may be decreased	Stop antacid
Carbamazepine + Paclitaxel [15]	1	CYP3A4 inducing properties of carbamazepine may lead to a decreased exposure to paclitaxel	TDM of carbamazepine
Diltiazem + Paclitaxel [15]	1	CYP3A4 inhibition of diltiazem may lead to an increased plasma concentration of paclitaxel	Inform oncologist about this interaction
Imatinib + Simvastatin [16]	1	Imatinib may increase the plasma concentrations of simvastatin by inhibiting CYP3A4	Replace simvastatin by pravastatin
Allopurinol + Mercaptopurine [17]	1	Toxicity (bone marrow suppression) may be increased	Replace allopurinol
Vincristine + Fluconazole [18]	1	Exposure to vincristine may be increased	Replace fluconazole
Irinotecan + Magnesium citrate [19]	1	Irinotecan causes diarrhea in the majority of treated patients. Using a laxative might therefore be unfavorable	Stop magnesium citrate
Methotrexate + Naproxen [20]	1	May result in increased plasma concentrations of methotrexate and increased methotrexate toxicity	Stop naproxen

Table 4: Continued

	n	Description	Intervention
Drug interactions involving supportive care drugs			
Corticosteroids[c] + NSAIDs[e] [11]	5	Combination may result in increased risk of GI ulcerations or bleeding	Add PPI
Dexamethasone + Grapefruit [21]	9	Induction of CYP3A4 may lead to changes in dexamethasone plasma concentrations	Stop grapefruit on theoretical basis
Dexamethasone + Blood glucose lowering agents[f] [22]	6	The hyperglycemic effects of dexamethasone may interfere with blood glucose control	Recommend close clinical monitoring of glycemic control.
Anti-emetics[g] +Flecainide/ Sotalol/ Quetiapine [14]	6	Additive QT-prolongation may occur	ECG monitoring
Acenocoumarol + Corticosteroids[d]/ Ranitidine [9]	5	Combination may result in increased risk of bleeding or diminished effect of coumarins	Additional INR monitoring
Dexamethasone + Echinacea [24]	1	Effectiveness of dexamethasone may be decreased	Stop Echinacea

INR=international normalized ratio; ECG=electrocardiogram; GI=gastro-intestinal; PPI=proton pump inhibitor; TDM=therapeutic drug monitoring; NSAID: non-steriodal anti-inflammatory drug.
[a] Coumarins: fenprocoumon and acenocoumarol; [b] Herbal substances: Camu camu, Bitter melon, Curcuma, Graviola, Catsclaw; [c] DDIs on theoretical bases, no reference available; [d] Corticosteroids: dexamethasone and prednisolone;[e] NSAIDs: Acetylsalicylic acid, ibuprofen and naproxen; [f] Blood glucose lowering agents: insulin, metformin and glimepiride; [g] Anti-emetics: granisetron, ondansetron

Potential risk factors

Binary logistic regression was used to assess potential determinants for performing an intervention. An overview is given in Table 5. In the univariate binary logistic regression analysis, number of comorbidities, number of drugs, number of OTC drugs and tumor type were associated with an increased risk for DDIs leading to an intervention. No association was found for age, treatment intent and treatment type. In the multivariate binary logistic regression analysis, number of comorbidities [odds ratio (OR) 1.40 (95% confidence interval (CI) 1.00–1.96)] and number of OTC drugs [OR 1.41 (95% CI 1.13–1.78)] remained statistically significant.

Table 5: Univariate and multivariate logistic analysis of determinants for performing an intervention

Determinant	Unadjusted OR (95% CI)	Unadjusted *P value*	Adjusted OR (95% CI)	Adjusted *P value*
Age	0.99 (0.96-1.02)	0.371		
No. of comorbidities	1.47 (1.12-1.93)	0.006	1.40 (1.00-1.96)$^{\Sigma}$	0.048*
No. of drugs	1.14 (1.06-1.24)	0.001	1.03 (0.93-1.14)$^{\pi}$	0.590
No. of OTC drugs	1.42 (1.16-1.74)	0.001	1.41 (1.13-1.78)$^{¥}$	0.003*
Tumour type				
Oncology	1.00 (reference)			
Haemato-oncology	2.59 (1.15-5.83)	0.022	2.50 (0.99-6.34)$^{\alpha}$	0.053
Treatment intent				
Palliative	1.00 (reference)			
Curative	1.40 (0.72-2.70)	0.320		
Treatment type				
Chemotherapy	1.0 (reference)			
TKIs/mTORi	1.05 (0.28-3.87)	0.944		
Combination	1.19 (0.60-2.36)	0.616		

*statistically significant
$^{\Sigma}$ Adjusted for No. of drugs, No. of OTC drugs and Tumour Type
$^{\pi}$ Adjusted for No. of comorbidities, No. of OTC drugs and Tumour Type
$^{¥}$ Adjusted for No. of comorbidities and Tumour Type
$^{\alpha}$ Adjusted for No. of comorbidities and No. of OTC drugs

No.= number
OTC drugs= over-the-counter drugs
TKIs= tyrosine kinase inhibitors
mTORi= mammalian Target Of Rapamycin inhibitors

DISCUSSION

To our knowledge, this is one of the first studies that prospectively investigated the need for interventions due to DDIs in oncology. In total, 120 DDIs were considered to be potentially clinically relevant. More importantly, next to the intervention already carried out by the (hemato)oncologists themselves, this resulted in additional interventions proposed by the clinical pharmacologist in 42 patients (14%).

The prevalence of DDIs is largely in accordance with similar studies.[3, 4, 6] A possible explanation for the relatively high median number of drugs used by the patients in our study might be the inclusion of herbal and other OTC drugs and the inclusion of both oral and i.v. anticancer drugs. A prospective study that looked into DDIs affecting anticancer agents concluded that the frequency of pharmacokinetic DDIs that were associated with a published clinical effect was low. However, they solely screened for pharmacokinetic DDIs and the study methods and population was highly different from the current study (e.g. different drug interaction software used, no tyrosine kinase inhibitors included and different tumor types) which may explain the relative low percentage of relevant DDIs in that study.[9]

Coumarins and GI interactions (especially the combination of corticosteroids with NSAIDs), where frequently involved in an intervention, as were combinations of drugs that are known to cause QT_c interval prolongation. Coumarins, which are routinely used for the treatment of thrombosis, are highly prone for DDIs with anticancer drugs. In case of a DDI between coumarins and anticancer drugs, the anticoagulant effect may be altered and a clinical intervention (by intensified monitoring of the anticoagulant effect and possible dose adjustment) is recommended. Also, NSAIDs and corticosteroids are extensively used in (hemato)oncology. When used concomitantly, gastrointestinal ulcerations or bleedings may occur and, based on patient characteristics and risk factors, an intervention (e.g. adding a proton pump inhibitor) is often required.[10] Combinations of QT_c interval prolonging drugs are also frequently seen in (hemato)oncology practice. The risk of QT_c interval prolongation increases by the concomitant use of more QT_c interval prolonging drugs and by CYP inhibition due to another drug. Especially antiemetics (e.g. domperidone and $5HT_3$-antagonists) and certain anticancer drugs (tamoxifen, tyrosine kinase inhibitors and anthracyclines) have the capacity to prolong the QT_c interval.[11] Although rare, these drug combinations can lead to QT_c interval prolongation

and *Torsades de pointes*; and may therefore have severe consequences. ECG monitoring is recommended 24–48h before, and 1 week after, the start of the concomitant use of QT_c interval prolonging drugs.[2]

In accordance with previous studies, the prevalence of drug combinations, with the ability to increase the risk of falling (CNS interactions), was high in this study.[3, 4] Since co-administration of multiple central nervous depressant drugs is frequently seen and cancer patients already have an increased risk of fractures due to osteoporosis, one might expect that some of these CNS interactions were identified as potentially clinically relevant. Nevertheless, none of these CNS interactions were identified as such by the expert group. A possible explanation might be that in most cancer patients, in a certain stage of their disease, the benefits of central nervous depressant drugs, (e.g. morphine or benzodiazepines) in order to treat therapy- and disease-related side-effects, are considered to outweigh the increased risk of falling. However, withdrawal from central nervous depressant drugs may be an effective method in the prevention of falling.[12] In the future, the rational use of multiple central nervous depressant drugs in (hemato)oncology should be determined.

In order to increase accuracy, two web-based databases were used in this study to identify DDIs.[7, 8] Although Micromedex has proven to be highly accurate, a more sensitive detection of QT_c, GI and CNS interactions was seen when 'Drugs.com' software was used concomitantly.[13] On the other hand, 'drugs.com' software is random in identifying other DDIs than QT_c, GI and CNS interactions, which results in the detection of many irrelevant DDIs. Therefore, we recommend for future studies to use Micromedex as the basis for detecting DDIs, with additional screening for QT_c, GI and CNS interactions by the 'Drugs.com' software. Even then, many clinically irrelevant DDIs will be detected, so more specific screening tools need to be developed. Clinical rules, combining DDIs with patient data (such as renal function) may be helpful.[14]

The number of comorbidities and the number of OTC drugs used concomitantly with anticancer drugs were identified as potential determinants for performing an intervention. This is consistent with other studies and not surprising since (hemato)oncologists are often not aware of the use of OTC drugs (such as complementary and alternative medicine) and that these drugs are extensively used by cancer patients and frequently involved in DDIs.[4, 5, 15] Surprisingly, the number of concomitantly used drugs was not identified as a determinant. This may be caused by the fact that the number of concomitantly used drugs and the number of comorbidities are usually highly correlated in multivariate analyses. A strength of our study is that, for the first time, DDIs leading to an intervention by clinical pharmacologists were prospectively studied in cancer patients. Based on the actual concurrent medication used by the patient, a profound assessment was made whether to intervene or not. Also, the inclusion of OTC drugs in the analysis was important. OTC drugs are frequently used by cancer patients, are often involved in DDIs and might lead to harmful side-effects.[4, 15]

One of the limitations of this study is the lack of a control group. Due to the fact that we did not include a group in whom DDIs were identified but not reacted upon, it is not possible to assess whether or not the interventions averted any adverse drug events. More research is necessary to fully explore the effect of DDIs on adverse drug events and clinical outcome (e.g. to compare hospitalization rates). Furthermore, therapeutic drug monitoring (TDM), where blood drug concentrations and pharmacokinetic parameters are matched with pharmacodynamics (such as toxicity and clinical outcome) is a possible way to investigate the true clinical relevance of DDIs in oncology. The implementation of TDM in oncology should be further explored.[5]

Screening of DDIs by a clinical pharmacologist doubled the number of clinical interventions that were already executed by a medical oncologist. Cancer patients are often treated multidisciplinary and a sound overview of all (newly) prescribed drugs, including OTC drugs, is not always available. Subsequently, documenting all drugs, including OTC drugs in one electronic patient record and close collaboration between (hemato)oncologists and clinical pharmacologists, is necessary to facilitate a profound medication review.

In this study, the prevalence of DDIs that need intervention is high. To maximize safe and effective concomitant drug use, the Erasmus MC cancer Institute is currently implementing medication review, before and during anticancer therapy, in clinical oncology practice for all patients.

In conclusion, the present prospective study shows that, next to the intervention already carried out by the (hemato)oncologists, in 14% of patients, interventions were carried out based on recommendations of clinical pharmacologists. As the complexity of prescription process increases, more specific screening tools for the detection of DDIs are necessary, in order to increase the efficiency and cost-effectiveness of the medication review by clinical pharmacologists and (hemato)oncologists. The results of this study will help physicians and clinical pharmacologists to be more aware of DDIs in (hemato)oncology and should lead to a closer collaboration to identify and manage these DDIs before the start and during anticancer treatment.

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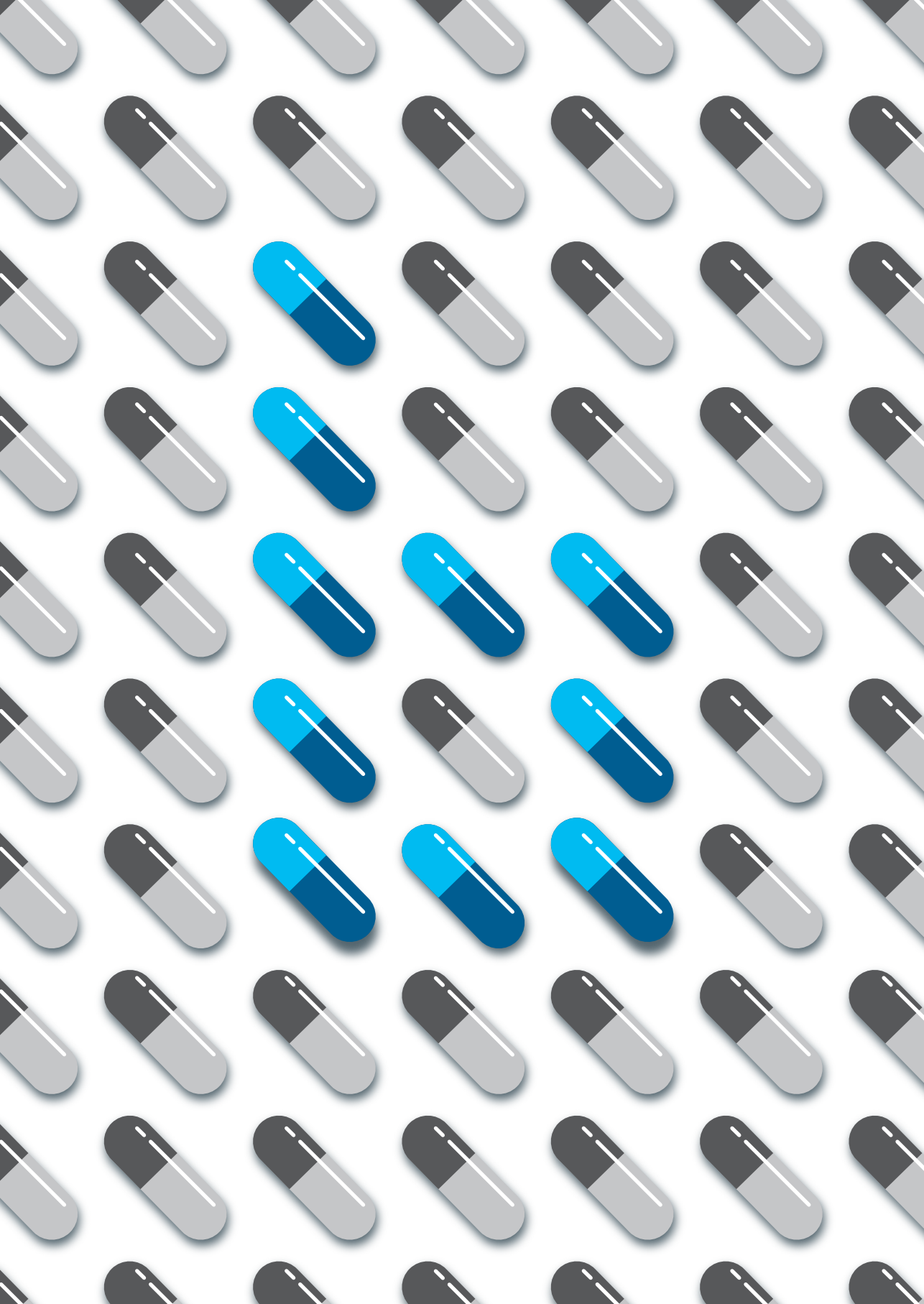

Chapter 6

INFLUENCE OF THE ACIDIC BEVERAGE COLA ON THE ABSORPTION OF ERLOTINIB IN PATIENTS WITH NON-SMALL-CELL LUNG CANCER

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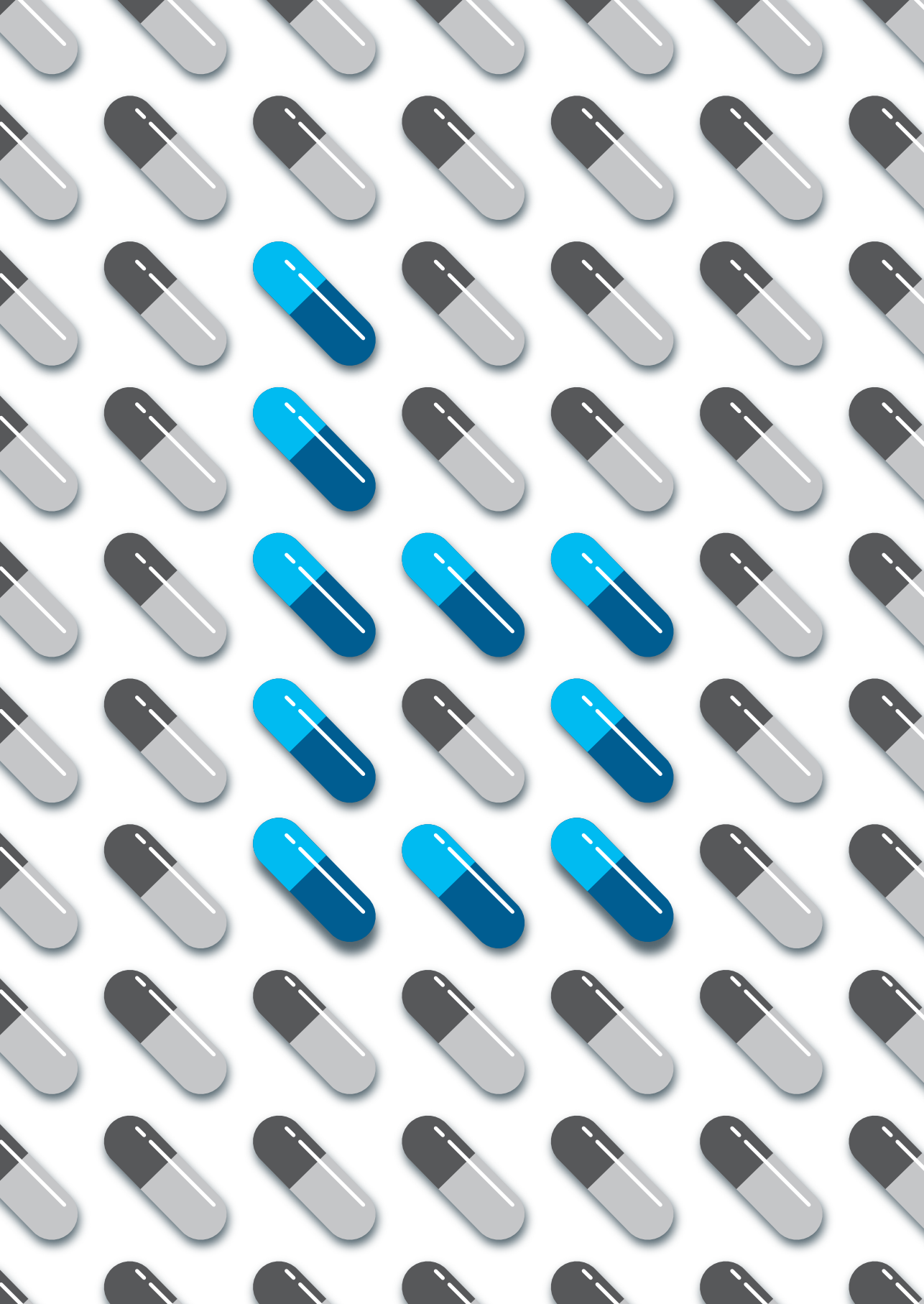


ABSTRACT

Introduction

Erlotinib is dependent on stomach pH for its bioavailability. When erlotinib is taken concurrently with a proton pump inhibitor (PPI), stomach pH will increase, resulting in a clinically relevant decrease of erlotinib bioavailability. In this study, we hypothesized that this drug-drug interaction (DDI) could be reversed by taking erlotinib with the acidic beverage cola. Also in patients without a PPI, effects of cola on erlotinib bioavailability were studied.

Methods

In this randomized cross-over pharmacokinetic study in non-small cell lung cancer (NSCLC) patients, we studied intra-patient differences in absorption ($AUC_{0\text{-}12h}$) after a 7 day period of concomitant treatment of erlotinib, with or without esomeprazole, for 7 days with either Coca-Cola Classic or water. At the 7^{th} and 14^{th} day, patients were hospitalized during 1 day for PK sampling.

Results

Twenty-eight evaluable patients were included in the analysis. In the patients taking erlotinib and esomeprazole with cola, the mean $AUC_{0\text{-}12h}$ increased with 39% (range -12% up to +136%; P=.004) whereas in patients without a PPI, the mean $AUC_{0\text{-}12h}$ was only slightly higher (9%; range -10% up to +30%, P=.03) after erlotinib intake with cola.

Conclusions

Cola generated a clinically relevant and statistically significant increase in the bioavailability of erlotinib during esomeprazole treatment. In patients not taking a PPI, the effects of cola were marginal. These findings can be used to optimize the management of drug-drug interactions between PPIs and erlotinib.

INTRODUCTION

Erlotinib is an oral reversible tyrosine kinase inhibitor (TKI) of the epidermal growth factor receptor (EGFR) effective in non-small cell lung cancer (NSCLC). The advantage of the oral administration route of erlotinib causes a highly relevant new problem. The gastrointestinal absorption of erlotinib is a complex multifactorial process which is characterized by a poor and variable bioavailability, resulting in significant intra- and intersubject variability in exposure.[1] One of the most important factors that influences erlotinib absorption is intragastric pH.[2,3] Because of its weakly basic properties, erlotinib can be present in either the ionised and non-ionised form, depending on the intragastric pH. In case of an elevation in intragastric pH the equilibrium shifts towards the less soluble non-ionised erlotinib form and drug absorption will decrease. The concomitant use of acid reducing agents such as proton pump inhibitors (PPIs) therefore leads to a clinically significant drug-drug interaction (DDI) with erlotinib.[2-5] In a study with healthy volunteers, the concurrent use of the PPI omeprazole significantly reduced the AUC and C_{max} of erlotinib with 46% and 61% respectively.[6] As a result, the product label of erlotinib states that PPIs should not be taken concurrently with erlotinib. Recently, the concomitant use of erlotinib and acid suppressive agents was shown to be associated with decreased erlotinib efficacy in NSCLC patients.[5] Since a PPI is often indicated during erlotinib therapy, pharmacists and medical oncologists are confronted with challenges.[2,7]

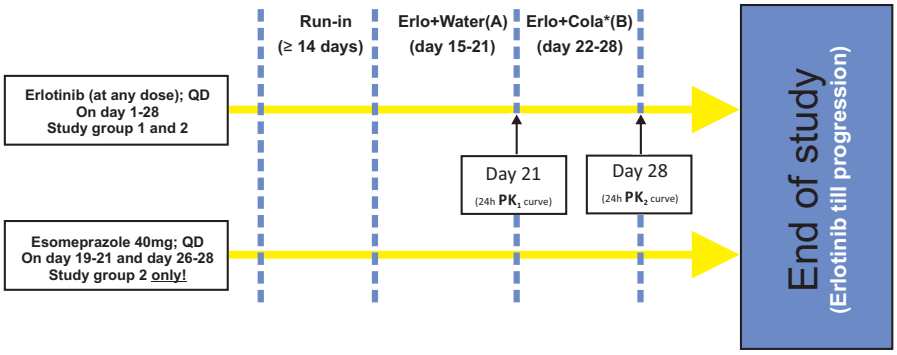
A solution for managing this DDI is not yet available. A practical way to by-pass the DDI between erlotinib and PPIs could potentially be to temporarily lower the stomach pH by taking erlotinib with an acidic beverage, such as cola. The classic form of this beverage has a pH of 2.5, leading to a temporary decrease of the stomach pH after intake. Other studies have shown that the absorption of weakly basic drugs, such as ketoconazole and itraconazole, was enhanced when taken concomitantly with Coca-Cola.[8,9] Due to similar physicochemical basic properties, we hypothesize that this positive effect could also be the case with erlotinib. In this study we therefore evaluated the impact of cola on the absorption of erlotinib (with and without esomeprazole) in patients with lung cancer.

METHODS

Study design and procedures

This is an open label, two-way, randomized, cross-over study in patients taking erlotinib for NSCLC. This study was performed at the Erasmus MC Cancer Institute in Rotterdam, the Netherlands, between March 2014 and June 2015. This study was approved by the medical ethics committee of the Erasmus Medical Center (MEC14-046) and was registered at www.trialregister.nl under number NTR4540.[10] A total of 28 patients on steady state erlotinib therapy were allocated to one of two study groups of 14 patients (study groups 1 and 2, see Figure 1). Study group 1 received erlotinib (Tarceva®; at any dose, day 1-14, at 10 AM) taken with 250 mL Coca-Cola Classic® or 250 mL water. Study group 2 received erlotinib (Tarceva®; day 1-14, at any dose, at 10 AM) and esomeprazole 40 mg (Nexium®; day 5-7 and 12-14, 7 AM) taken with 250 mL Coca-Cola Classic® or 250 mL water. After allocation to one of the study groups patients were randomized into 2 sequence arms (arm A and B, n=7). Sequence arm A first took erlotinib with water (for 7 days) followed by Coca-Cola Classic® (for 7 days). Arm B took Coca-Cola Classic® and water in the reversed order. On days 7 and 14, patients were admitted for 24-hours into the hospital for PK sampling (for study design, see Figure 1). Before signing informed consent, the use of interacting co-medication, (over-the-counter) OTC-drugs, herbal/ food supplements were collected in a structured anamnesis with the patient.

Figure 1: study design



PK= pharmacokinetic sampling day
Erlo= erlotinib
*Coca-Cola Classic®
Depending on sequence arms: A→B or B→A

Medication used by the patient was assessed for drug-drug interactions by using the drug-drug interaction software program Micromedex.[11] To ensure steady state concentrations, patients had to use erlotinib for a minimum of 14 days before entering the study. In study group 2, once daily 40 mg esomeprazole was given (for at least) 3 days before both PK-sampling days (3 hours before erlotinib intake) in order to achieve maximum elevation in intragastric pH.[12,13] Also patients who were using PPIs chronically before entering the study were allowed to participate into the study as long as they were willing to use esomeprazole 40 mg (Nexium®) for 3 consecutive days before both PK sampling days according to the protocol. Patients underwent an overnight fast before both PK days. On both PK-days, erlotinib was taken in the hospital. Since this was a study population of regular lung cancer patients with an indication for an EGFR TKI, erlotinib dose reductions due to toxicity were allowed. Patient compliance was assessed using a patient diary.

Eligibility

Eligibility criteria included patient age ≥ 18 years with histological or cytological confirmed diagnosis of lung cancer for which treatment with erlotinib monotherapy has been indicated, use of erlotinib monotherapy at any dose for at least 2 weeks prior to participation in the study, WHO Performance Status of 0 or 1 and no concurrent use of (OTC) medication or medication known to interact with either erlotinib or esomeprazole. Exclusion criteria included pregnant or lactating patients and a clear language barrier.

Pharmacokinetics

Blood samples for the analysis of erlotinib were collected prior to erlotinib dosing and 0.5h; 1h; 1.5h; 2h, 2.5h; 3h; 3.5h; 4h; 6h; 8h; 12h and 24h (13 samples/ hospitalization for all sequence arms) after erlotinib administration. Esomeprazole levels were not measured. At each time-point, blood samples were collected in 6 mL lithium heparin blood collection tubes. After collection, blood samples were processed to plasma (within 10 minutes by centrifugation for 10 minutes at 2,000 *g* at 4°C). Plasma was transferred into polypropylene tubes (1,8 mL Nunc vials), which was subsequently stored at T <-70°C until the time of analysis at the Laboratory of Translational Pharmacology (Josephine Nefkens Institute, Erasmus MC, Rotterdam, The Netherlands). Pharmacokinetic parameters of erlotinib were calculated using weighted non-compartmental analyses with WinNonlin 6.3 (Pharsight Corp., Mountain View, CA) and included area under the plasma-concentration time curves ($AUC_{0\text{-}12h}$), maximum concentration (C_{max}) and time to C_{max} (T_{max}).

Statistics

The primary objective was to determine the intra-patient differences in absorption (expressed by the $AUC_{0\text{-}12h}$ and C_{max}) after a 7 day period of concomitant treatment of erlotinib (with or without esomeprazole for 3 days) with Coca-Cola and 7 days of erlotinib with water, or *vice versa*. Each patient acted as his/her own control.

In this exploratory study, the primary endpoint was the relative difference (RD) between erlotinib AUC_{cola} and erlotinib AUC_{water}, calculated for each patient as: $RD = (AUC_{cola} - AUC_{water}) / AUC_{water}$. Coca-Cola was considered to have an impact on the erlotinib AUC when the absolute value of RD was at least 25% (i.e. less than or equal to -25%, or at least +25%).[14] Assuming an intra-individual standard deviation of the difference between AUC_{cola} and AUC_{water} of 30%, 14 evaluable patients per study group (= without or with esomeprazole) had to be included to obtain 80% power (2-sided significance level $\alpha = 0.05$) to detect this difference of 25% or more.[15]

In order to evaluate the impact of Coca-Cola on the AUC, i.e. compare AUC with Coca-Cola (AUC_{cola}) and AUC with water (AUC_{water}), we used the Stata-command 'pkcross', which was designed to analyze cross-over experiments [StataCorp. 2013. Stata: Release 13. Statistical Software. College Station, TX: StataCorp LP]. This command uses ANOVA models to analyze the data (please refer to Stata base reference manual, release 13, pages 1594-1602, for a detailed description). In this way possible period effects (first versus second `PK sampling period') and sequence effects (A → B versus B → A) were taken into account, assuming that no carryover effect exists. In case of a dose reduction (due to toxicity) PK data were normalized to a dose of 150 mg erlotinib. The *P*-value to indicate whether the mean AUC and mean C_{max} were significantly different after water *versus* after cola, was the *P*-value assigned to the treatment effect using the `pkcross' command. This was evaluated separately for patients who used esomeprazole, and for those who did not.

RESULTS

Patient characteristics

A total of 35 patients were enrolled of which 28 were evaluable, 14 in each study group. Seven patients were excluded from the study for varying reasons (i.e. the use of Diet Coca-Cola® (*n*=1), the use of generic brand esomeprazole instead of Nexium® (*n*=1), progression of disease prior to both PK sampling periods (*n*=2), impossibility to venipuncture (*n*=1)) and on patients own initiative (i.e. withdrawal of consent (*n*=2)). Baseline characteristics are shown in table 1. The majority of patients were male (61 %) and the median age was 63 years.

Table 1: subject characteristics at baseline

Characteristics	*N*	%
No of patients	28	100
Age (years)		
Median (range)	63 (39-77)	
Sex		
Female	11	39
Male	17	61
Race		
Caucasian	24	86
Asian	4	14
BMI (kg/m^2)		
Mean (range)	24,2 (19-31)	
Tobacco use		
Current (< 1 month)	2	7
None	26	93
ECOG-performance status		
0	15	54
1	13	46
Pre-treatment chemotherapy		
Yes	8	29
No	20	71
EGFR mutation		
Yes	14	50
No	10	36
Unknown	4	14
Dosage erlotinib		
50mg	1	4
100mg	4	14
150mg	23	82

Pharmacokinetics, safety and tolerability

In patients taking erlotinib and esomeprazole (study group 2, Table 2), the mean $AUC_{0\text{-}12h}$ was 39% higher (range -12% up to +136%; *P*=.004), while the mean C_{max} was 42% higher (range -4% up to +199%; *P*=.019) after cola, compared to water intake (Figure 2). In patients taking erlotinib without esomeprazole (study group 1, Table 3), the mean $AUC_{0\text{-}12h}$ was 9% higher (range -10% up to +30%; *P*=.03), while the mean C_{max} was comparable (0%; range -19% up to +18%; *P*= .62) after cola intake (Figure 2). Time to C_{max} (T_{max}) was not significantly altered in study group 1 (18%; range -60% to +194%, *P*=.75) and study group 2 (0%; range -20% to +52%, *P*=.99).

Table 2: summary of pharmacokinetic parameters study group 2 (Erlotinib + Esomeprazole + water vs. Coca-Cola)

Parameter	Erlo+Esom+Water (A)	Erlo+Esom+Coca-Cola (B)	Difference % (range)
Erlotinib dose*	150 (100-150)	150 (50-150)	
Erlotinib			
$AUC_{0\text{-}12h}$ (µg×h/ml), geometric mean (geometric mean CV%)	9.0 (19.9%)	11.8 (14.9%)	39% (-12% to +136%), *P*=.004
C_{max} (µg/ml), geometric mean (geometric mean CV%)	1.08 (152%)	1.43 (112%)	42% (-4% to +199%), *P*=.012

Erlo = erlotinib

Esom= esomeprazole 40 mg q.d

* Median (range)

** In case of a dose reduction (due to toxicity) PK data were normalized to a dose of 150 mg erlotinib

Table 3: Summary of pharmacokinetic parameters for study group 1 (Erlotinib+water vs. Coca-Cola)

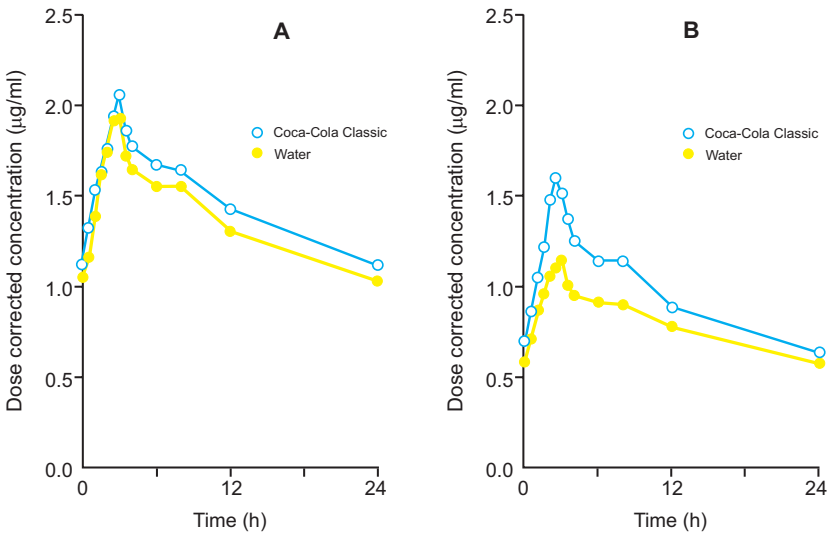
Parameter	Erlo + Water (A)	Erlo + Coca-Cola (B)	Difference % (range)
Erlotinib dose*	150 (50-150)	150 (50-150)	
Erlotinib**			
$AUC_{0\text{-}12h}$ (µg×h/ml), geometric mean (geometric mean CV%)	17.3 (8.5%)	18.6 (7.7%)	9% (-10% to 30%), *P*=.03
C_{max} (µg/ml), geometric mean (geometric CV%)	2.10 (68%)	2.09 (64%)	0% (-19% to +18%), *P*=.62

Erlo = erlotinib

* Median (range)

** In case of a dose reduction (due to toxicity) PK data were normalized to a dose of 150 mg erlotinib

Figure 2: pharmacokinetic profile



Mean dose corrected concentration vs. time profiles are shown for erlotinib alone administered with water or Coca-Cola Classic® (Treatment group A, n=14) and erlotinib + esomeprazole with water or Coca-Cola Classic® (Treatment group B, n=14)

Adverse events were generally mild and resolved without medical intervention. Erlotinib was well tolerated when administered with either cola or water (also in patients with known gastro-esophageal reflux disease). One subject in study group 1 developed grade 3 skin toxicity and hospital admission was required. After standard of care treatment the patient was discharged from hospital without sequela but showed progression during erlotinib therapy. In this patient the erlotinib was stopped and the patient was excluded from the study. Erlotinib treatment related AEs primarily affected the skin (e.g. grade 1 rash) and gastro-intestinal system (e.g. nausea, diarrhea). For details see table 4. There were no known deviations in the patients diaries concerning study adherence.

Table 4. Treatment related adverse events (AEs) during study period

	PPI (n=14)		Non-PPI (n=14)	
	Water	Cola	Water	Cola
Diarrhea*	2 (14%)	2 (14%)	3 (21%)	6 (43%)
Nausea*	1 (7%)	2 (14%)	1 (7%)	1 (7%)
Vomiting*	0	0	1 (7%)	0
Rash ¥**	9 (64%)	11 (79%)	9 (64%)	11 (79%)
Fatigue**	8 (57%)	8 (57%)	7 (50%)	7 (50%)

* All grade 1 according to CTC-AE version 4.03

** Grade 1 or 2 according to CTC-AE version 4.03

¥ One patient with grade 3 skin toxicity according to CTC-AE version 4.03

DISCUSSION

In this study, we showed that the use of cola significantly increases the mean exposure of erlotinib in patients using esomeprazole. This is most probably based on an increased solubility and absorption. Furthermore, in patients taking cola instead of water, the mean exposure to erlotinib also significantly increased, although this effect was clinically irrelevant. The observed pharmacokinetic parameters were comparable to previous reports.[6] Our study confirms that pH-dependent solubility plays a key role in erlotinib absorption and that a can (250 mL) of cola can enhance erlotinib absorption by temporarily lowering the intragastric pH.

Although H_2-antagonists (e.g. ranitidine) and antacids can substantially affect erlotinib bioavailability, esomeprazole (Nexium®; at regular dose; 40 mg q.d.) was used in our study as this is currently the most effective acid reducing agent on the market.[2,12,13] Furthermore, when using esomeprazole instead of other PPIs (e.g. pantoprazole), other factors such as inhibition of relevant drug-transporters which may also alter erlotinib pharmacokinetics (e.g. P-glycoprotein) can be ruled out.[16] To our knowledge, there are no other interactions (e.g. based on altered metabolism or clearance) between erlotinib and esomeprazole, besides those based on altered intragastric pH, that may alter erlotinib pharmacokinetics. A three day period before PK days was assumed to maximize the acid reducing effects, but also to minimize the period a patient was exposed to the unwanted drug-drug interaction between esomeprazole and erlotinib.[6,12,13]. This assumption was supported by the observation that there were no significant differences in $AUC_{0\text{-}12h}$ and C_{max} between patients taking esomeprazole for 3 days and on a continuous basis.

In this study, a large inter-patient variability in either AUCs and other pharmacokinetic parameters was observed. Several factors could explain this variability. Most probably, the absorption from the gut itself varies highly between patients. Adherence to the protocol during the study period (for instances by drinking of other (volumes of) acidic beverages or not taking erlotinib on an empty stomach) is unlikely to be the cause of variability, as the study protocol was explained thoroughly and patient diaries were heavily protocolled and checked by the investigators. More probable reasons are inter-patient differences in gastric emptying and gastrointestinal motility. Possibly, cola may not enhance absorption in all patients, as the gastric pH may also physiologically vary, as the effects may be lower if the gastric pH is lower in one patient compared to another.[1]

A limitation of this study is that we did not measure intragastric pH. As some patients might suffer from altered gastric acid secretion (e.g. achlorhydria or Zollinger-Ellison syndrome), large interpatient variations in intragastric pH can be expected. Because of the weak basic properties and an acid dissociation constant (i.e. the pH at which equilibrium is reached between the ionised and non-ionised form) near the stomach pH range of 1 to 4 (Erlotinib pK_a=5.4), intragastric pH shifts lead to a more significant shift towards the non-ionized (less soluble) form and subsequent lower bioavailability, compared to TKIs with a higher pK_a (e.g. sunitinib, afatinib[6]). This may partly explain the large variation seen in this study in erlotinib absorption. Measuring the intragastric pH per patient might give additional insights into the effect of cola intake on intragastric pH and subsequent absorption. Another limitation of this study is that it was not designed to explore effects of long term cola co-administration on the outcome of anti-cancer treatment with erlotinib. Since the study design was purely based on pharmacokinetic and chemical parameters (i.e. pH effect and subsequent erlotinib solubility and absorption) and the relative short time (i.e. 7 days) that patient were taking erlotinib with cola (instead of water), it did not allow us to evaluate the impact of cola on erlotinib efficacy. Therefore, the clinical impact of cola on erlotinib efficacy should be unraveled in further research.

In theory, in patients with elevated intragastric pH and subsequent impaired absorption (e.g. achlorhydria and gastrectomy), the use of cola may also increase bioavailability of erlotinib or other TKIs with a relatively low pK_a. Due to the nocturnal duodenogastric reflux peak during sleep, the intragastric pH is at night, on average, higher compared to morning stomach pH.[13] Many patients take a tyrosine kinase inhibitor *ante noctem*.[17] In theory, when a patient decides to take erlotinib *ante noctem*, cola could help increase bioavailability by temporarily lowering intragastric pH. The effect of cola on these subgroups should be further explored in future studies.

In clinical practice there is often a hard indication for the use of PPIs during erlotinib therapy (e.g. patient using corticosteroids and NSAIDs or with (recurrent) gastroesophageal reflux disease). On the other hand, physicians are faced with product label guidelines that advise to "avoid the combination" or to switch to less effective H_2A-antagonists or antacids (taken 2 hours after erlotinib).[6] When erlotinib and a PPI are given concomitantly, the AUC of erlotinib steeply decreases.[6] This suggests that lower bioavailability due to PPI use (up to 46% for erlotinib[6]) may deprive patients from optimal therapy.[5,18]

Thus, in case the combination between a PPI and erlotinib is inevitable, the pH lowering effects of cola may help physicians to optimize erlotinib therapy.

Although ingredients of cola, such as caffeine, may potentially interact with erlotinib pharmacokinetics, it is more likely that pH dependent solubility is the predominant factor in erlotinib absorption.[3,19] Erlotinib is a Biopharmaceutics Classification System (BCS)[20] class 2 drug, characterized by poor solubility but high intestinal permeability, which means that *in vivo* erlotinib bioavailability is predominantly limited by its solubility.[3,20] When dissolved, erlotinib is rapidly and extensively (>90%) absorbed across the intestinal membrane.[3]

Although cola can be associated with several disadvantages, such as dental corrosion and gastroesophageal irritation, it is (for most people) a palatable drink which is readily available worldwide. Furthermore, Coca-Cola Classic has the clear advantage of a substantial lower pH (pH~2,5) compared to other acidic beverages such as orange juice (pH~4), 7-Up (pH~3,5) and diet (cola) products (pH~3 to 4). In theory, drinks with higher pH might not be as effective in enhancing erlotinib absorption as Coca-Cola Classic. Additionally, although not studied, higher volumes of cola might acidify the stomach even more and erlotinib absorption could be further enhanced. However, in our study 250cc of cola was well tolerated and higher volumes might be less convenient for the patient (especially in the morning).

In conclusion, the use of cola provides a potential and easy to implement way to significantly improve erlotinib bioavailability, especially during concomitant use of esomeprazole. These findings can be used to optimize the management of the existing drug-drug interaction between erlotinib and PPIs. Potentially, effects of cola on erlotinib exposure may be extrapolated to other TKIs with a pH-dependent solubility (e.g. dasatinib, gefitinib and nilotinib) but this remains to be evaluated in further studies. And potentially also other acidic beverages (i.e. orange juice and other carbonated drinks) may have similar effects as cola. Also, this should be explored in future trials.

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Chapter 7

TYROSINE KINASE INHIBITORS AND PROTON PUMP INHIBITORS "REALLY INCOMPATIBLE?"

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Submitted

INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have rapidly become an established factor in daily oncology practice.[1] They have been shown to be effective in a wide variety of solid and hematologic malignancies. At present, there are 25 TKIs approved by the FDA.[2] Many new TKIs are under investigation, and indications for existing TKIs are rapidly expanding.[2] Use of the oral administration route of TKIs offers logistic flexibility and is convenient for the patient.[3] Despite these advantages, the oral route of administration also causes a highly relevant new problem. TKIs are generally characterized by a poor and variable bioavailability, resulting in significant between-patient variability in plasma levels and exposure. This variability is the result of an interplay of factors, including tissue permeability, membrane transport and enzymatic metabolism.[4] Most importantly, acid-inhibitory drugs, like proton pump inhibitors (PPIs), increase the intragastric pH, which decreases the solubility and thereby the biological availability of most TKIs and was shown to be associated with decreased TKI efficacy.[5]

Although PPIs are extensively used during anti-cancer treatment, there is still much controversy on how to manage drug-drug interactions (DDIs) between TKIs and PPIs.[6, 7] For some TKIs, the effect of a PPI on absorption from the gut is thoroughly investigated and specific guidelines for the management of such DDIs are provided in the product label.[2] For most others, only basic pre-clinical pharmacokinetic or *in vitro* chemical studies (e.g. on pH dependent solubility) have been executed and specific guidelines for the management of these DDIs are not provided. Since cancer patients on TKI therapy are often 'poly-pharmacy' patients and may heavily rely on drugs such as vitamin K antagonists, non-steroid anti-inflammatory drugs (NSAIDs), and corticosteroids, they are at risk for gastro-intestinal reflux disease or peptic ulcer disease. Therefore, for many cancer patients there is a solid indication for gastro-protection or treatment of gastro-intestinal symptoms with PPIs during treatment.[8, 9] Indecisive guidelines (predominately given in the product label)[2] such as 'screen for toxicity' or 'avoid combination' still pose prescribers for a dilemma whether or not to continue the combined treatment in individual patients.[1]

UNRAVELLING THE DRUG-DRUG INTERACTION BETWEEN TKIs AND PPIs

To appreciate the background of the DDIs between TKIs and PPIs, theoretical pharmacokinetic and pharmacodynamic principles and known pharmacokinetic DDI studies have to be considered.

TKI absorption and intragastric pH

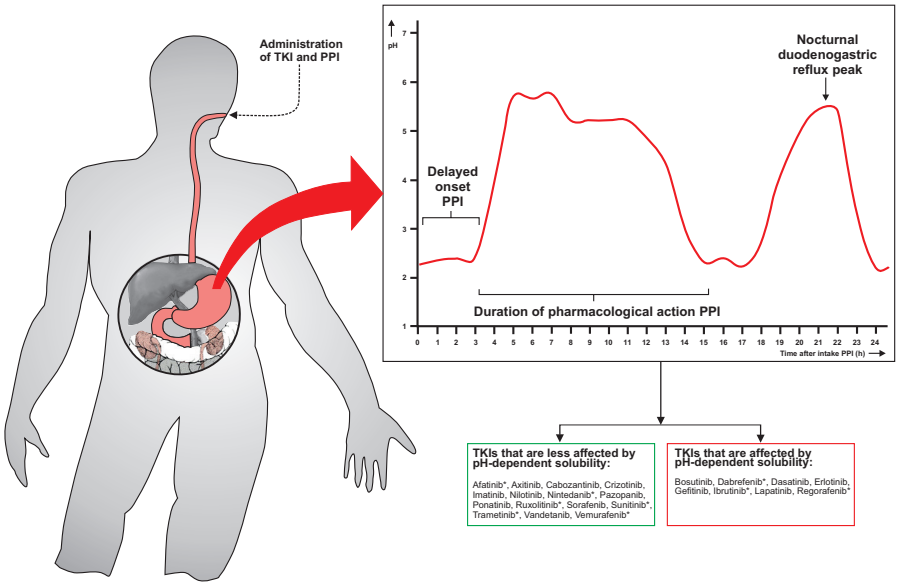
Although the absorption of TKIs may be influenced by many factors, the major determinant in TKI absorption is the pH-dependent solubility.[1, 10] Crucial physiological factors that affect pH dependent solubility and TKI absorption, are intragastric pH and the dissociation constant pK_a. Since TKIs are weakly basic, there is an equilibrium between the ionized and non-ionized form that is dependent on intragastric pH and the pK_a of the TKI. At normal acidic intragastric pH (pH range 1 to 2), the equilibrium shifts to the ionized form. Since the ionized form has better solubility, TKI absorption from the gastro-intestinal tract is optimal at low intragastric pH. However, when the intragastric pH is elevated (e.g. due to concurrent PPI use), the balance shifts towards the non-ionized form of the drug and solubility and bioavailability may decrease significantly. Another important factor determining the absorption rate is the pK_a as this is the pH at which there is an equilibrium between the ionized and non-ionized form. TKIs with a pK_a near the pH range of the stomach (pH 1-4; e.g. erlotinib, dasatinib) are usually more affected by intragastric pH than TKIs with a higher pK_a (e.g. imatinib and afatinib) because of a larger shift towards the less soluble non-ionized drug form with higher pH.[1, 11] Consequently, TKIs with a pK_a near 4 to 5 typically show an intragastric pH dependent solubility and therefore are more prone to clinically relevant drug-drug interactions with PPIs.[1]

PPI pharmacodynamics

Besides TKI bioavailability, the pharmacodynamic profile of PPIs is important to consider for management of DDIs between TKIs and PPIs. PPIs are highly effective acid inhibitory agents and are registered in a once daily dose for the majority of their indications. Although this dosing strategy is usually effective in controlling gastro-oesophageal reflux disease, PPIs do not elevate the intragastric pH over the full 24-hour range (see figure 1).[12-15] There are two important explanations for this 24-hour variation in acid suppression: *i*) the delayed onset of the pharmacological effect of PPIs and *ii*) the duration of pharmacological action.[15, 16]

For most PPIs, the acid-inhibitory effects (defined by an intragastric pH above 4)[17, 18] will only be reached 3 to 4 hours after intake.[15, 16] This delayed onset of action is caused predominantly by the use of enteric coated tablets or capsules. Since PPIs are easily protonated, they are unstable at low (intragastric) pH and therefore a coating is indicated. Polymer coatings are stable at low intragastric pH, but break down easily at higher intestinal pH. As a result, the PPI is protected against degradation in the stomach and arrives intact in the duodenum where absorption takes place. The resulting delay of acid-inhibitory effects after administration amounts up to an average of 3-4 hours (figure 1).

Figure 1: schematic 24-hours Intragastric pH curve with enteric coated PPI q.d.



Schematic 24-hours intragastric pH curve during PPI use (enteric coated, q.d.) with delayed onset of action (3-4 hours), duration of action (12-14 hours with q.d. PPI use) and the nocturnal duodenogastric reflux peak (obtained by the supine position during sleep). Figure was derived with permission from Hunfeld et al.[15]

* Based on "*In vitro*" pre-clinical studies only; TKI=Tyrosine Kinase Inhibitor, PPI=proton pump inhibitor, q.d.=once daily

Although most PPIs are characterized by a short half-life ($t_{½}$) of approximately 1 to 2 hours, the pharmacodynamic effects on intragastric pH last much longer, because of its irreversible covalent binding to the proton pumps. After 2 to 3 days of daily use a steady state in acid inhibition is reached.[12, 19] Meanwhile, new proton pumps are generated *in vivo* on a continuous basis, and subsequently gastric acid will be secreted from these new pumps, compensating the elevated pH.[15] As a consequence, the intragastric pH will start to decrease again and drops to pH values < 4 within 12-14 hours after PPI administration (figure 1).[15] On the other hand, during nighttime, physiological duodenogastric reflux occurs as a result of the supine position during sleep. As a result, there is an elevation in intragastric pH during nighttime which sharply returns to baseline after getting out of bed (**figure 1**).[15] Furthermore, a substantial proportion of patients above 80 years of age suffer from achlorhydria; a state in which the production of hydrochloric acid in the stomach is low or absent and the intragastric pH is substantially elevated.[20] Both nighttime duodenogastric reflux and achlorhydria in older patients may profoundly alter TKI bioavailability. Of note, in serious gastro-oesophageal reflux disease, physicians may prescribe a PPI in a twice daily dose. In contrast to a once daily dose, more frequent (and often higher) dosing of PPIs (e.g. twice daily dose or continuous dosing) leads to a greater and more constant elevation of intragastric pH above a pH of 4 over the full 24-hours range.[9]

Available drug-drug interaction studies and study design

As mentioned above, the intragastric pH is not elevated over the full 24-hours range during PPI therapy. Therefore, outcomes of drug-drug interaction studies between a PPI and a TKI are highly dependent on the study design, and especially the time of intake for both TKI and PPI. Two types of studies can be distinguished: *i*) the TKI and PPI are administered concomitantly and *ii*) the TKI is administered 2 to 3 hours after the intake of the PPI. There are strengths and limitations for both types of study designs.

When the drugs are taken concomitantly and if the observed effect is low/nihil, this may indicate that there is indeed no interaction between the two drugs, but it may also well be that a DDI would have been observed if the PPI would have been taken at another moment in time[2, 21]. As mentioned before, when the TKI and PPI are administered concomitantly, there is the 3-4 hour window after PPI intake in which the TKI absorption will not be significantly affected by the PPI, potentially leading to a false perception that no DDI occurs. For some TKIs (e.g. axitinib and nilotinib)[2], the question remains if an alternative time schedule of

PPI to TKI intake would lead to an increase or decrease of the TKI absorption, as this is unfortunately studied rarely. Therefore, if no clinically relevant effect is seen in studies while these drugs are taken at the same time, the subsequently drawn conclusion that "TKI and PPI may be used concomitantly" should –in our opinion– be replaced by "TKI and PPI *must* be used concomitantly", to guarantee a safe use.

When a TKI is administered a few hours after a PPI, the intragastric pH is almost certainly elevated. When no pH dependent solubility is expected a study setup where the TKI is administered a few hours after the PPI might be the best study setup to completely rule out an absorption based DDI as was shown for cabozantinib.[22]

MANAGEMENT OF TKI-PPI DRUG INTERACTIONS

There is often a hard indication for the concomitant use of TKIs and PPIs. In clinical practice however, it is often advised to avoid the combination or to switch to less effective acid suppressive drugs such as antacids and H_2-antagonists (e.g. ranitidine).[12] As a result, the patient is often deprived from optimal therapy for gastro esophageal reflux disease. In addition, H_2-antagonists and antacids may also compromise the TKI bioavailability leading to an inadequate antitumor effect.[1, 2]

For several TKIs approved by the FDA the effect on bioavailability has only been studied *in vitro* whereas pH dependent solubility and TKI absorption *in vivo* is often multifactorial.[4] In this case, only preclinical *in vitro* data on chemical pH dependent solubility may not predict the true *in vivo* effects on bioavailability (e.g. afatinib)[2] of a concomitantly used PPIs. If it is stated (e.g. in the assessment report of the FDA)[2] that there is no significant DDI between a certain TKI and PPI this should, in our opinion, be confirmed in an adequately designed *in vivo* pharmacokinetic drug-drug interaction study.

There is a lot of discussion whether TKIs and PPIs are really incompatible. For instance, there is the interesting suggestion by Ter Heine *et al.* that when the PPI dose (in this case pantoprazole) is relatively low, erlotinib can be used concomitantly. However, this recommendation is based on a study performed in a single patient and solid pharmacokinetic data provided in the FDA assessment report stated otherwise (mentioning a 46% and 61% decrease in erlotinib AUC and C_{max} respectively).[2, 23] Although many pharmacokinetic DDI studies have

already been conducted and published in either an FDA assessment report or scientific literature, a clear advice on the management of the DDI between PPIs and TKIs is rarely given. Studies on alternative time schedules of PPI to TKI intake to completely rule out a DDI are also scarcely available, and drawn conclusions on the management (e.g. can be used concomitantly) may not always be 100% solid.

Due to the nocturnal duodenogastric reflux peak, intragastric pH is elevated during sleep. On theoretical grounds (and regardless of PPI use) the bioavailability of TKIs is not optimal when taken *ante noctem* and should be avoided and product label recommendations to administer the TKI in the evening should be avoided (e.g. pazopanib)[2]. Furthermore patients --especially those of 80 years and older-- on TKI therapy might suffer from achlorhydria with a suboptimal absorption as a result.[20] More research is needed to investigate TKI bioavailability during nighttime sleep and achlorhydria.

When using pantoprazole instead of other PPIs, TKI pharmacokinetics may be altered through inhibition of drug transporters such as P-glycoprotein (P-gp).[24] Since many TKIs are substrates for P-gp (e.g. erlotinib and lapatinib) physicians should prescribe pantoprazole with great caution or switch to other PPIs, such as omeprazole, during TKI therapy. Moreover, for these TKIs, results obtained from drug interaction studies with omeprazole may not be extrapolated directly to pantoprazole. More research is needed to explore the clinical significance of the DDI between pantoprazole and TKIs.

We recently showed that the intake of erlotinib with an acidic beverage (cola) enhanced the bioavailability by almost 40% in patients also taking esomeprazole.[25] Through temporarily lowering the intragastric pH by administering the TKI with cola the DDI between TKIs and PPIs can be bypassed (partly). Especially, when there is a hard indication for twice daily use of a PPI (and subsequent continuous 24-hours intragastric pH elevation), in our opinion, cola may be a simple and practical solution to manage the DDI between TKIs and PPIs.

When all pharmacological characteristics and data of either TKIs and PPIs are considered, a balanced, practical and safe advice on how to manage this drug combination can be given. Since the intragastric pH is not elevated over the whole 24-hour range as shown in figure 1, a target period of low intragastric pH can be used to safely administer the TKI.

In conclusion, to properly manage the DDIs between TKIs and PPIs, a twice daily PPI dose must first be brought back to a once daily regimen, whereas the PPI must be given in an enteric coated formulation. If the TKI is administered in the morning, a couple of hours prior to intake of the PPI, the enteric coating of the PPI will provide a target period of low intragastric pH during which TKIs with a pH dependent solubility can pass through a stomach with sufficiently low pH. More research on alternative timing schedules of PPI to TKI intake, achlorhydria and nighttime TKI absorption is necessary as this will provide further insights into the effects of elevated intragastric pH on TKI bioavailability.

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Chapter 8

GENERAL DISCUSSION AND SUMMARY

8

GENERAL DISCUSSION AND SUMMARY

Although cancer is a significant and leading public health burden among men and women worldwide, treatment options are rapidly evolving. Among these, the use of anticancer drugs is still the cornerstone in the treatment of most forms of cancer. However, the significant progress in the development of novel (targeted) anticancer drugs is also associated with many challenges as was described in detail **chapter 1**.

Since most anticancer drugs have narrow therapeutic windows it is important to "get the dose right" in order to optimize drug exposure and minimalize resistance and toxicity. To accomplish this there is a shifting paradigm towards individualized therapy. Along with other factors, the use of comedication and the subsequent risk for DDIs is one of the key factors influencing systemic drug exposure in cancer patients. DDIs can be divided in two groups: "pharmacokinetic" and "pharmacodynamic" drug interaction. When pharmacokinetic and/or pharmacodynamic parameters are modified by the concomitant use of comedication, systemic exposure and effect of the anticancer drug might be affected and may lead to unpredictable effect and toxicity of the therapy. This thesis investigated the occurrence and clinical relevance of DDIs during anticancer therapy and specific recommendations to guide clinicians through the process of managing DDIs in daily clinical practice were given.

Traditionally, the pharmacological focus of conventional anticancer drugs have been on targeting DNA processing and cell division. Although these anticancer drugs can be very effective, their lack of selectivity usually leads to serious toxicity which may limit their use. In order to improve efficacy and diminish adverse events of cancer treatment, more specific targets have been identified the past decade. One of the most promising groups in 'targeted therapy' are the TKIs. All TKIs are administered orally which significantly improves patient quality of life. Although TKIs have advantages over traditional chemotherapy, there are new challenges that arise. The oral route of administration, the fact the TKIs are given on a continuous daily basis and are predominately metabolized through CYP enzymes makes them highly prone to DDI. Therefore, in **chapter 2**, literature about DDIs in TKIs therapy was reviewed. The main goal of this review was to give the treating clinician a comprehensive overview of the most important DDIs during TKI therapy: *i*)TKIs and acid reducing agents, *ii*) CYP-inhibitors/inducers during TKI therapy and *iii*) QT_c interactions. Acid reducing drugs like PPIs can profoundly influence the bioavailability and

CYP inhibitors/inducers can significantly affect the exposure of TKIs; clinical intervention is often needed. Although rare, QT_c-interval prolonging DDIs can have fatal consequences and must be accounted for. To improve the safe use of TKIs in clinical oncology practice, a profound assessment of co-prescribed drugs is needed. In order to achieve this, clinicians should collaborate closely with (hospital)pharmacist and general practitioners. In addition, more pharmacokinetic and pharmacodynamic research is needed on DDIs in TKI therapy to provide a profound basis for medication review. And last but not least, in case of a suspected DDI, where pharmacokinetic data are not available, physicians and pharmacists must weigh "pros" and "cons" and, if possible, extrapolate available pharmacological data to an individual patient.

In **chapter 3 and chapter 4**, a retrospective study was done to provide an overview of the prevalence of potential DDIs in either intravenous and oral anticancer therapy, respectively.

In this analysis, we detected a high prevalence of PDDIs with 46% to 58% of all patients being exposed to at least one potential DDI. More importantly, these potential DDIs were not just theoretically relevant. 16% to 34% of all patients had at least one potential DDI that may have caused harmful side effects and would require intervention or intensive monitoring. Coumarines, quinolones, anti-epileptics, opoids and hydrochlorothiazide were frequently involved in a DDI. The majority of DDIs concerned central nervous system depression interactions (risk of falling), DDIs that can cause gastrointestinal toxicity (e.g. NSAIDs and corticosteroids) and prolongation of QT_c interval. With the increasing numbers of new oral anticancer agents that become available, the risk for DDIs will consequently increase.

Due to the retrospective design, a major limitation of this study is that it did not investigate the clinical impact of the potential DDIs. Although the clinical relevance was not established in these two studies, we can still conclude that potential DDIs are common in cancer patients and screening for potential interactions should take place routinely during anticancer therapy. However, the clinical relevance of DDIs remains to be assessed in further research.

In **chapter 5**, a prospective study was performed to assess the prevalence of DDIs leading to actual clinical interventions during cancer therapy. This study served as a sequel to chapter 3 and chapter 4 and the clear desire the investigate the clinical relevance of DDIs in cancer patients. In this study we included

302 patients and resulted in a clinical intervention already executed by the (hemato)oncologist in 39 patients (13%), while an additional intervention was proposed by a clinical pharmacologist in 42 patients (14%). Coumarins and GI-interactions (especially the combination of corticosteroids with NSAIDs) were frequently involved in an intervention, as were combinations of drugs that are known to cause QT_c-interval prolongation and DDIs between TKIs and acid reducing agents (e.g. PPIs).

This study shows that clinical interventions on DDIs are frequently required among patients using anticancer therapy. The collaboration with a clinical pharmacologist almost doubled the number of clinical interventions due to DDIs. Structured screening for clinically relevant DDIs, by clinicians (oncologists and clinical pharmacologists), should take place before the start and during anticancer treatment. To create a solid base for medication review and, by this, to identify and prevent potentially harmful DDIs all drugs prescribed by oncologists, general practitioners, and other healthcare professionals should be documented electronically, including patient's medical status, in one national! computer-based patient record.

Although the DDI between TKIs and PPIs was frequently seen in the prospective study addressed in chapter 5, there are still no clear recommendations on how to manage DDIs between TKIs and PPIs. Since pH dependent solubility seems to be the key factor that influences TKI absorption, we evaluated the impact of cola on the exposure of erlotinib (during PPI use) in patients with lung cancer in **chapter 6**. In this randomized cross-over pharmacokinetic trial twenty-eight evaluable patients were included in the analysis. In the patients taking erlotinib concomitant with a PPI with cola, the mean $AUC_{0\text{-}12h}$ increased with 39% (range -12% up to +136%; P=.004). Apparently, cola generated a clinically relevant and statistically significant increase in the bioavailability of erlotinib during PPI treatment. These findings provide a practical solution to manage the DDI between erlotinib and PPIs. Potentially, effects of cola on erlotinib exposure may be extrapolated to other TKIs.

On the other hand, when all pharmacological characteristics of either TKIs and PPIs are considered, a practical advice purely based on pharmacological principles can be given to manage this drug combination. In **chapter 7**, we discussed the pharmacological profile of either TKIs and PPIs and provided another solid way to manage this DDI in clinical practice. Since the intragastric pH is not elevated over the full 24-hour range, a target time-window of

low intragastric pH can be used to safely administer the TKI. If the TKI is administered in the morning, a couple of hours prior to intake of the PPI, the enteric coating of the PPI will provide a target time-window during which TKIs with a pH dependent solubility can pass through the stomach with sufficiently low pH. By application of this dosing interval, the absorption of the TKI is not compromised by the PPI.

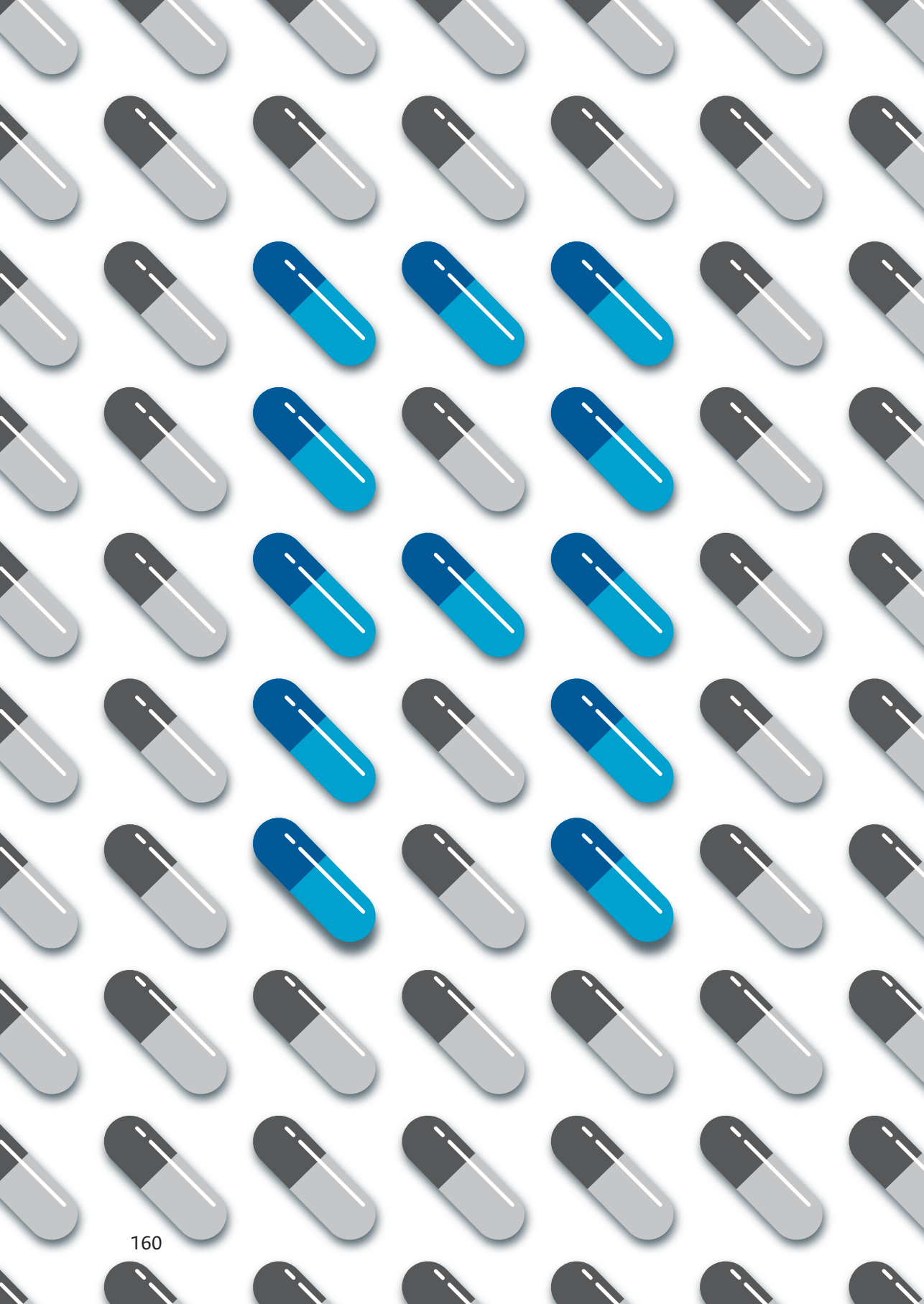
Strangely, the effect of a PPI on TKI pharmacokinetics is not investigated for all TKIs in the pre-registration phase. The effect of PPIs on TKIs absorption should always be investigated in an "*in vivo*" pharmacokinetic study. More research is also needed into the effects of the nighttime duodenogastric reflux pH peak (as a result of the supine position during sleep) on TKI bioavailability taken "*ante noctem"*.

Finally, in order to individualize drug therapy, DDIs are to be reckoned with in cancer patients. Clinicians should collaborate in order to identify and manage DDIs in clinical practice. For this, one national computer-based patient record is needed.

In this prospective study only adult cancer patients were included. Paediatric cancer patient were beyond the scope of this thesis. However, in childhood cancer the currently prescribed drugs have a high DDI potential. On the other hand, the number of co-medications used concomitantly with anticancer drugs will probably be lower than in adults cancer patients. Further prospective research is needed to fully explore the prevalence and clinical relevance of DDIs in childhood cancer. In the Erasmus University Medical Centre, a prospective clinical trial such as this is currently ongoing.

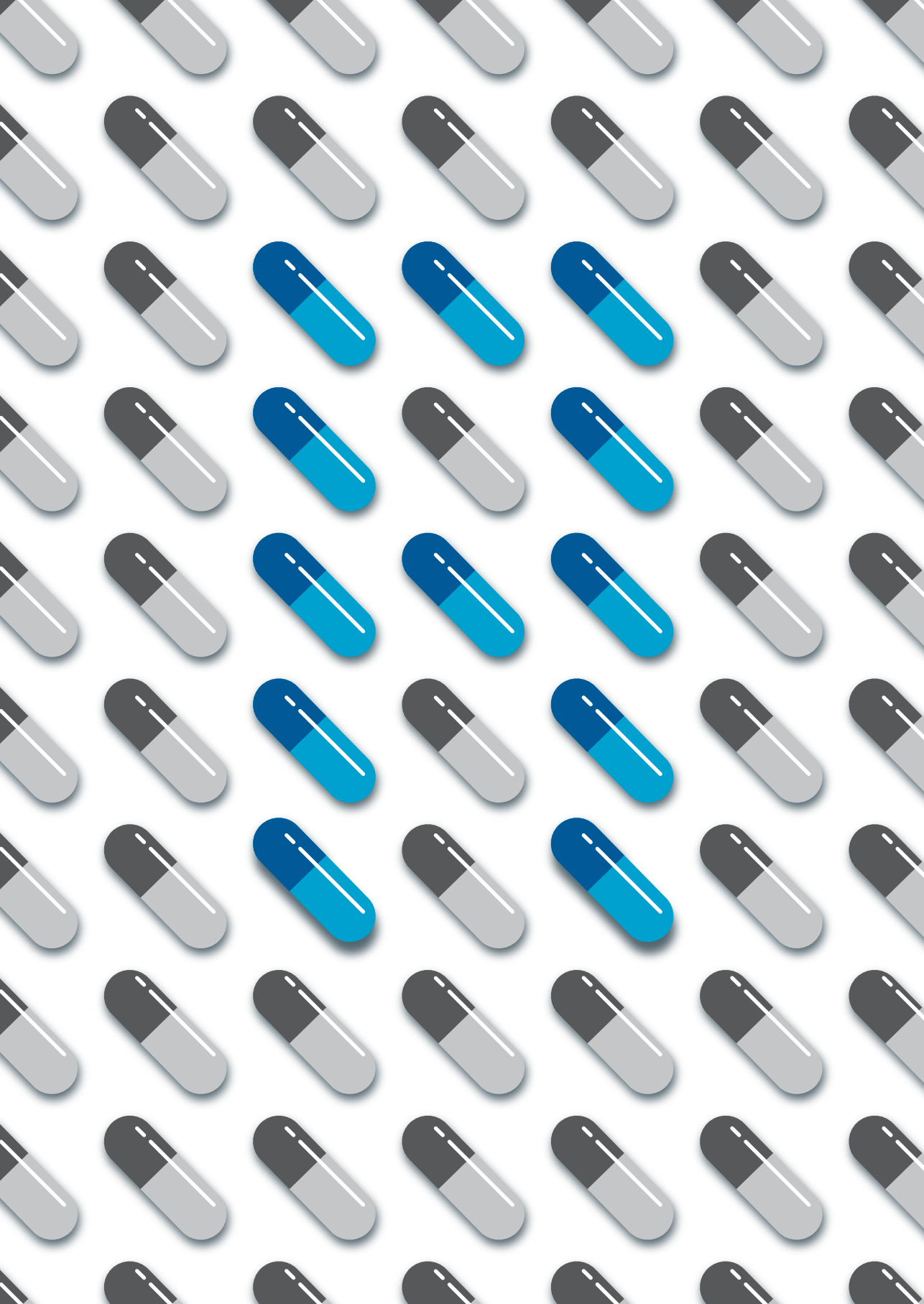
Evidently, more research is needed on the effects of co-medication on anticancer drugs to explore the true interaction potential of anticancer drugs. For instance, the interaction potential of drug transporter, such as OCTs and OATPs, and their role on increasing or reducing toxicity and pharmacological effect needs to be further explored.

This pharmacological research should always lead to a clear and practical recommendation that can readily be used in clinical practice. If no pharmacological data are available, healthcare professionals should collaborate and use common medical and pharmacological principles to extrapolate known data, in order to provide practical recommendations to manage a certain DDI to individualize and optimize anticancer therapy.



Apendices 1

DISCUSSIE EN SAMENVATTING



DISCUSSIE EN SAMENVATTING

Hoewel de nieuwe en innovatieve behandelopties voor de behandeling van kanker elkaar in snel tempo opvolgen is kanker nog steeds een van de meest voorkomende doodsoorzaken bij zowel mannen en vrouwen wereldwijd. Hierbij vormt, ondanks alle nieuwe ontwikkelingen, de behandeling met antikanker geneesmiddelen nog altijd de hoeksteen van de antikanker therapie tegen de meeste vormen van kanker. De belangrijke vooruitgang in behandelopties heeft echter ook zijn keerzijde. Vooral de ontwikkelingen van de nieuwe (meer selectieve) antikanker geneesmiddelen worden geassocieerd met vele nieuwe uitdagingen en problemen. Deze zijn uitvoerig beschreven in **hoofdstuk 1.**

Aangezien de meeste antikanker geneesmiddelen een smalle therapeutische breedte hebben (ze veroorzaken bij een te hoge blootstelling bijwerkingen, terwijl deze middelen bij een te lage blootstelling niet werkzaam zijn) is het van groot belang om "de juiste dosis" te verkrijgen. Dit om de blootstelling aan het geneesmiddel te optimaliseren en de resistentie en bijwerkingen te beperken. Om dit te bereiken is er steeds meer een verschuiving van één identieke dosis voor alle patiënten, naar de meer geïndividualiseerde antikanker behandeling (de zogenaamde "therapie op maat").

Samen met een aantal andere factoren (zoals voedsel, genetische- en fysiologische factoren) is het gebruik van comedicatie en het daaropvolgende risico op geneesmiddelwisselwerkingen één van de belangrijkste factoren die de blootstelling aan antikanker geneesmiddel kan beïnvloeden (zie ook figuur 1). Geneesmiddel wisselwerkingen kunnen worden onderverdeeld in twee groepen: de zogenaamde "farmacokinetische" en de "farmacodynamische" geneesmiddel wisselwerkingen.

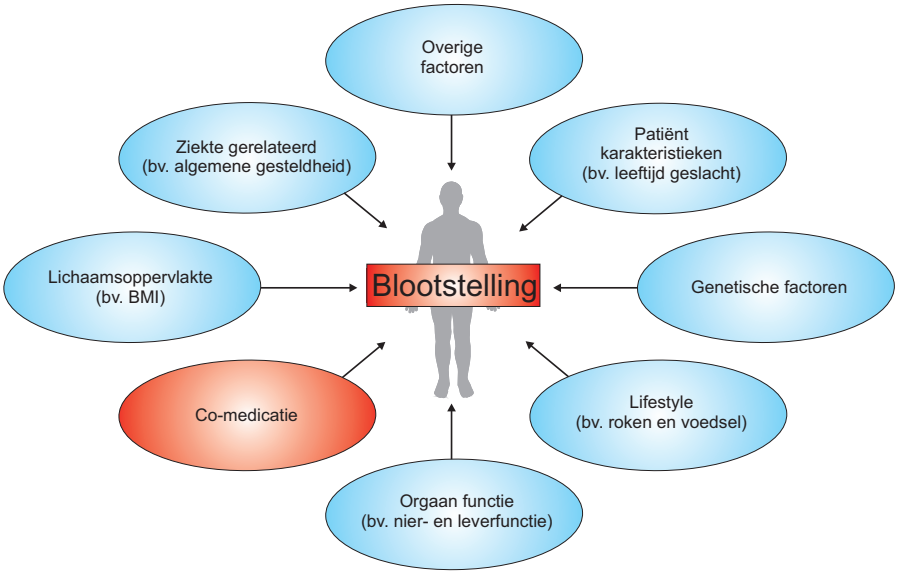
Wanneer farmacokinetische en/of farmacodynamische parameters worden gewijzigd door het gelijktijdig gebruik van comedicatie kan de blootstelling aan het antikanker geneesmiddel worden beïnvloed. Dit kan bij de patiënt weer leiden tot een verlies van werking dan wel tot meer bijwerkingen. In dit proefschrift wordt het voorkomen en de klinische relevantie van geneesmiddel wisselwerkingen bij kankerpatiënten onderzocht. Verder worden er, waar mogelijk, specifieke aanbevelingen gegeven voor artsen en apothekers voor het identificeren en afhandelen van geneesmiddel wisselwerkingen in de dagelijkse klinische praktijk.

In de traditionele antikanker therapie ligt de focus van werkzaamheid vooral bij het verstoren van processen in het genetisch materiaal (DNA). Hoewel deze antikankergeneesmiddelen zeer effectief zijn, leiden ze door gebrek aan selectiviteit doorgaans tot ernstige bijwerkingen (toxiciteit). Deze toxiciteit kan zelfs zo ernstig zijn dat ze het gebruik van deze middelen kunnen beperken. Om het effect en bijwerkingenprofiel van antikanker geneesmiddelen te optimaliseren verschuift de geneesmiddelontwikkeling de laatste decennia steeds meer naar geneesmiddelen die (zeer) specifiek de kankercel aanvallen (en niet tegelijkertijd andere snel delende cellen zoals traditionele chemotherapie dat doet). Deze gerichte anti-kanker behandeling waarbij (in theorie) alleen de kankercel wordt aangevallen noemen we "targeted therapie".

Eén van de meest veelbelovende groepen geneesmiddelen die valt binnen de groep van "targeted therapie" zijn de Tyrosine Kinase Inhibitors (TKI's). Het grote voordeel van het gebruik van TKI's is dat ze in tegenstelling tot traditionele chemotherapie oraal (in tabletvorm) ingenomen kunnen worden. Dit verbetert het gebruiksgemak en de kwaliteit van leven voor de patiënt tijdens de behandeling met antikanker geneesmiddelen. Hoewel TKIs voordelen hebben boven traditionele chemotherapie, zijn er ook vele nieuwe uitdagingen. De orale route (inname via de mond in plaats van een infuus) en het gebruik op continue basis (in plaats van een wekelijkse of 3-wekelijkse toediening) maakt dat deze geneesmiddelen zeer gevoelig zijn voor wisselwerkingen. Daarnaast worden TKI's in de lever omgezet in afbraakprodukten door enzymen genaamd 'cytochromen' (of CYPs). Om deze reden hebben we in **hoofdstuk 2** een literatuur-onderzoek gedaan om deze wisselwerkingen goed in kaart te kunnen brengen. Het belangrijkste doel van dit review-artikel was om de behandelend arts een overzicht te geven van de belangrijkste wisselwerkingen en tevens praktische adviezen hoe met deze wisselwerkingen om te kunnen gaan. In het review lag de focus voornamelijk op de drie belangrijkste wisselwerkingen, namelijk: i) TKIs en maagzuurremmers, ii) CYP-remmers / inductoren (= aanjagers) tijdens TKI therapie en iii) een combinatie van geneesmiddelen die tot een levensbedreigende vertraging van het hartritme kunnen leiden (het zogenaamde QT_c-interval).

Maagzuurremmers zoals proton pomp remmers (bijvoorbeeld omeprazol en pantoprazol) kunnen een belangrijke negatieve invloed hebben op de opname van TKIs vanuit de darm, terwijl door het remmen van (CYP) enzymen in de lever (door CYP-remmers en CYP- inductoren) de TKI spiegel in het bloed aanzienlijk omhoog of naar beneden kan gaan. Bij bovenstaande geneesmiddel

Figuur 1: De belangrijkste factoren die de bloedspiegel (blootstelling) van antikanker geneesmiddelen kunnen beinvloeden



wisselwerkingen is een klinische interventie (bijvoorbeeld dosis aanpassing, stoppen van geneesmiddel e.d.) door een arts of apotheker vaak nodig. Hoewel zeldzaam, kunnen wisselwerkingen betreffende het (teveel) vertragen van het hartritme fatale gevolgen hebben. Omdat de gevolgen van deze wisselwerking zo ernstig kunnen zijn moeten clinici hiermee rekening mee houden. Om het veilig gebruik van TKIs te borgen in de klinische praktijk, moet een actueel medicatieoverzicht met alle medicatie die de patiënt op dat moment gebruikt beoordeeld worden (inclusief kruiden geneesmiddelen e.d.). Om dit te bereiken moeten clinici nauw samenwerken met (ziekenhuis) apothekers en huisartsen. Ook moet er meer onderzoek gedaan worden naar andere wisselwerkingen die mogelijk van invloed kunnen zijn op de bloedspiegel van TKIs. En “last but not least”, als er een vermoeden is van een geneesmiddel wisselwerking en er zijn geen farmacologische gegevens beschikbaar, dan moeten artsen en apothekers de krachten bundelen en ‘voors’ en ‘tegens’ tegen elkaar afwegen. Indien mogelijk, moeten ze bestaande gegevens extrapoleren om tot een goed advies te komen voor die individuele patiënt op dat moment.

In **hoofdstuk 3 en hoofdstuk 4**, zijn retrospectieve studies uitgevoerd om een overzicht te krijgen van de prevalentie van geneesmiddel wisselwerkingen in zowel intraveneuze en orale anti-kanker therapie, respectievelijk. Een retrospectieve studies (of terugkijkend onderzoek) betekent dat je in de tijd terug kijkt en in dit geval nagaat hoeveel geneesmiddel wisselwerkingen er reeds hebben plaatsgevonden door middel van onderzoek in de medische status van de patiënt (oftewel: de blik is terug in de tijd gericht).

In deze analyse hebben we een hoge prevalentie van wisselwerkingen gezien, met 46% tot 58% van alle patiënten die werden blootgesteld aan ten minste één geneesmiddel wisselwerking. Wat van belang was, was dat deze wisselwerkingen niet alleen theoretisch van aard waren. In 16% tot 34% van alle patiënten zagen we tenminste één wisselwerking die mogelijk schadelijke bijwerkingen zou kunnen veroorzaken. Hierbij zou een klinische interventie of intensieve monitoring op zijn plaats zijn. Bloedverdunners, sommige antibiotica , anti-epileptica, opiaten en een middel tegen hoge bloedruk waren vaak betrokken bij een wisselwerking. De meerderheid van de betrokken wisselwerkingen had betrekking op een verhoogd dempend effect (van de combinatie van geneesmiddelen) op het centrale zenuwstelsel (met sufheid en het gevaar van vallen en (heup)fracturen tot gevolg). Verder werden veel wisselwerkingen gezien die een extra kans op maagschade (bv pijnstillers uit de groep van de NSAID's) en een mogelijk levensbedreigende vertraging van het hartritme (het zogenaamde QT_c-interval) tot gevolg hebben. Met het toenemende aantal nieuwe orale antikanker middelen dat beschikbaar komt, zoals de bovengenoemde TKIs, die ook in toenemende mate in combinatie worden gegeven, wordt het risico op wisselwerkingen steeds groter.

Door het retrospectieve karakter van de studie, waarbij wordt teruggekeken naar reeds gedocumenteerde gegevens, is een belangrijke beperking van deze twee studies dat de klinische gevolgen (bijvoorbeeld bijwerkingen of ineffectiviteit van een bepaald antikanker geneesmiddel) niet onderzocht zijn. Hoewel er niet gekeken is naar de klinische relevantie in deze twee studies, kunnen we toch concluderen dat geneesmiddel combinaties die mogelijk kunnen leiden tot een wisselwerking vaak voorkomen bij patiënten met kanker. Routinematige screening voor mogelijke wisselwerkingen moet dus plaatsvinden tijdens de behandeling van kanker. De klinische relevantie van geneesmiddel wisselwerkingen moet echter worden onderzocht in toekomstig onderzoek.

In **hoofdstuk 5** is een prospectieve studie uitgevoerd, waarbij juist nieuwe gegevens worden verzameld, om het vóórkomen van geneesmiddel wisselwerkingen die leiden tot een daadwerkelijke klinische interventie tijdens de behandeling van kanker te beoordelen.

Studie patiënten worden bij een prospectieve studie gevolgd in de toekomst (oftewel: de blik is in de tijd vooruit gericht).

Deze studie diende als een vervolg op de onderzoeken beschreven in hoofdstuk 3 en hoofdstuk 4 en de daar omschreven specifieke wens om de klinische relevantie van wisselwerkingen bij patiënten met kanker te onderzoeken. In deze studie, waarin 302 patiënten werden geïncludeerd, bleek dat een klinische interventie door de behandelend (hemato)oncoloog werd uitgevoerd bij 39 patiënten (13%), terwijl een additionele interventie werd gedaan door een klinisch farmacoloog bij nog eens 42 patiënten (14%). Bloedverdunners en de combinatie van corticosteroïden met NSAIDs (door een verhoogde kans op maagschade) waren vaak betrokken bij een wisselwerking die leidde tot een interventie. Verder werden wisselwerkingen die een additionele verlenging van het QT_c-interval gaven en wisselwerking waarbij TKIs en maagzuurremmers (proton pomp remmers) betrokken waren frequent gezien.

Deze studie toont aan dat er vrij vaak een klinische interventie op basis van een geneesmiddel wisselwerking vereist is bij patiënten die antikanker therapie ondergaan. Verder heeft de samenwerking tussen clinici en een klinisch farmacoloog geleid tot een verdubbeling van het aantal klinische interventies als gevolg van een geneesmiddel wisselwerking. Gestructureerde screening voor klinisch relevante geneesmiddel wisselwerkingen, door clinici (oncologen en klinisch farmacologen), zou routinematig moeten plaatsvinden vóór aanvang en tijdens de antikanker behandeling. Om tot een effectieve medicatiebewaking te komen, moet er eerst een solide basis zijn waarin een actueel overzicht van alle medicijnen (inclusief kruiden en zelfzorg geneesmiddelen) voorhanden is. Oncologen, huisartsen en andere beroepsbeoefenaren in de gezondheidszorg zouden, idealiter, alle medische gegevens en voorgeschreven geneesmiddel moeten vastleggen in één **landelijk** elektronisch medicatie dossier.

Daar de wisselwerking tussen TKIs en maagzuurremmers vaak werd waargenomen in de studie beschreven in hoofdstuk 5, zijn er nog geen duidelijke aanbevelingen voor de omgang met deze wisselwerking in de klinische praktijk. Aangezien zuurgraad (pH)-afhankelijke oplosbaarheid de “achilleshiel” lijkt bij

de opname van TKI's in het bloed, onderzochten we de invloed van de inname van erlotinib met cola (ten opzichte van water) op de blootstelling van erlotinib, met en zonder maagzuurremmer, bij longkanker patienten in **hoofdstuk 6**. In deze gerandomiseerde farmacokinetische cross-over studie werden 28 evalueerbare patiënten geïncludeerd in de analyse. Bij de patiënten die hun erlotinib gelijktijdig met een maagzuurremmer namen met cola lag de bloedspiegel gemiddeld 39% hoger ten opzichte van de inname met water. Hiermee heeft de inname met cola geleid tot een klinisch relevante verhoging van de opname van erlotinib tijdens het gebruik van maagzuurremmers. Deze bevindingen bieden een praktische oplossing voor het omzeilen van de wisselwerking tussen erlotinib en maagzuurremmers. Mogelijk kan het "cola-effect" op erlotinib worden doorgetrokken naar andere TKI's of andere zure dranken.

Anderzijds, wanneer alle farmacologische eigenschappen van zowel TKIs en maagzuurremmers worden beschouwd, dan kan een praktisch advies louter gebaseerd op farmacologische principes toereikend zijn om deze geneesmiddel wisselwerking af te handelen. In **hoofdstuk 7**, hebben we het farmacologisch profiel van zowel TKI's als de maagzuurremmers uitvoerig beschouwd en hebben we op basis van deze gegevens getracht een praktische manier te vinden om deze geneesmiddel wisselwerking af te handelen in de klinische praktijk. Aangezien bij éénmaal daags gebruik van maagzuurremmers de maag pH niet gedurende de volledige 24-uur verhoogd is, is het mogelijk om het tijdsvenster van (relatieve) lage pH in de maag te gebruiken om de TKI veilig in te nemen. Als men de TKI in de ochtend een paar uur voor de maagzuurremmer inneemt, zal de maagsap resistente coating (een coating die het geneesmiddel beschermt tegen de negatieve invloed van maagzuur) van de maagzuuremmer een tijdvenster creëren (maagzuurremmers werken pas na een paar uur) waarin de TKI bij voldoende lage pH op kan lossen en op normale wijze opgenomen kan worden in het bloed. Bij toepassing van deze gespreide inname, wordt de absorptie van de TKI niet negatief beïnvloed door de maagzuurremmer.

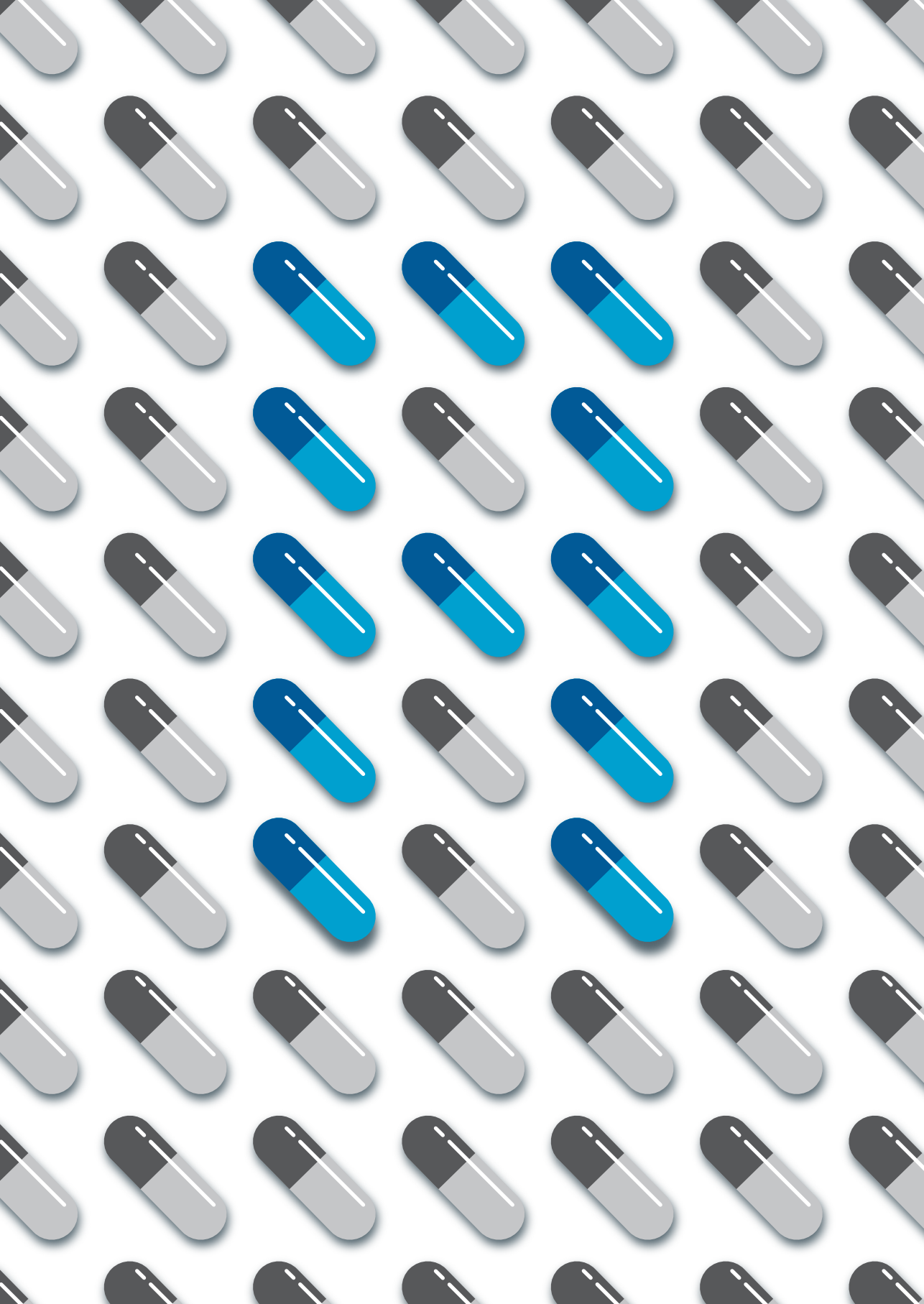
Vreemd genoeg wordt het effect van maagzuurremmers op TKI absorptie en blootstelling lang niet altijd onderzocht tijdens de ontwikkelingsfase van het geneesmiddel. Aangezien maagzuurremmers een klinisch relevant effect kunnen hebben op TKI absorptie en blootstelling zou deze wisselwerking naar onze mening altijd onderzocht moeten worden in een farmacokinetische onderzoek "in proefpersonen". Tevens is er meer onderzoek nodig naar de effecten van de nachtelijke reflux van darmsappen in de maag (mede als gevolg van de rugligging tijdens de slaap), de hiermee verhoogde pH in de maag en het effect

op de absorptie van TKI's wanneer deze ingenomen worden voor de slaap.
Tot slot, wanneer men de medicamenteuze behandeling van kanker wil individualiseren, dan zijn geneesmiddel wisselwerkingen een zeer belangrijke factor om rekening mee te houden. Artsen en andere zorgverleners moeten samenwerken om wisselwerkingen te identificeren en af te handelen in de klinische praktijk. Eén nationaal elektronisch patiëntendossier zou hier bij kunnen helpen.

In de onderzoeken beschreven in dit proefschrift zijn alleen volwassen kankerpatiënten geïncludeerd. Kinderen met kanker vielen buiten het bestek van dit proefschrift. Echter, de antikanker geneesmiddelen die bij kinderen worden voorgeschreven geven ook een hoge kans op wisselwerkingen met andere geneesmiddelen. Meer onderzoek is nodig om de prevalentie en klinische relevantie van wisselwerkingen bij kinderkanker volledig in kaart te brengen.

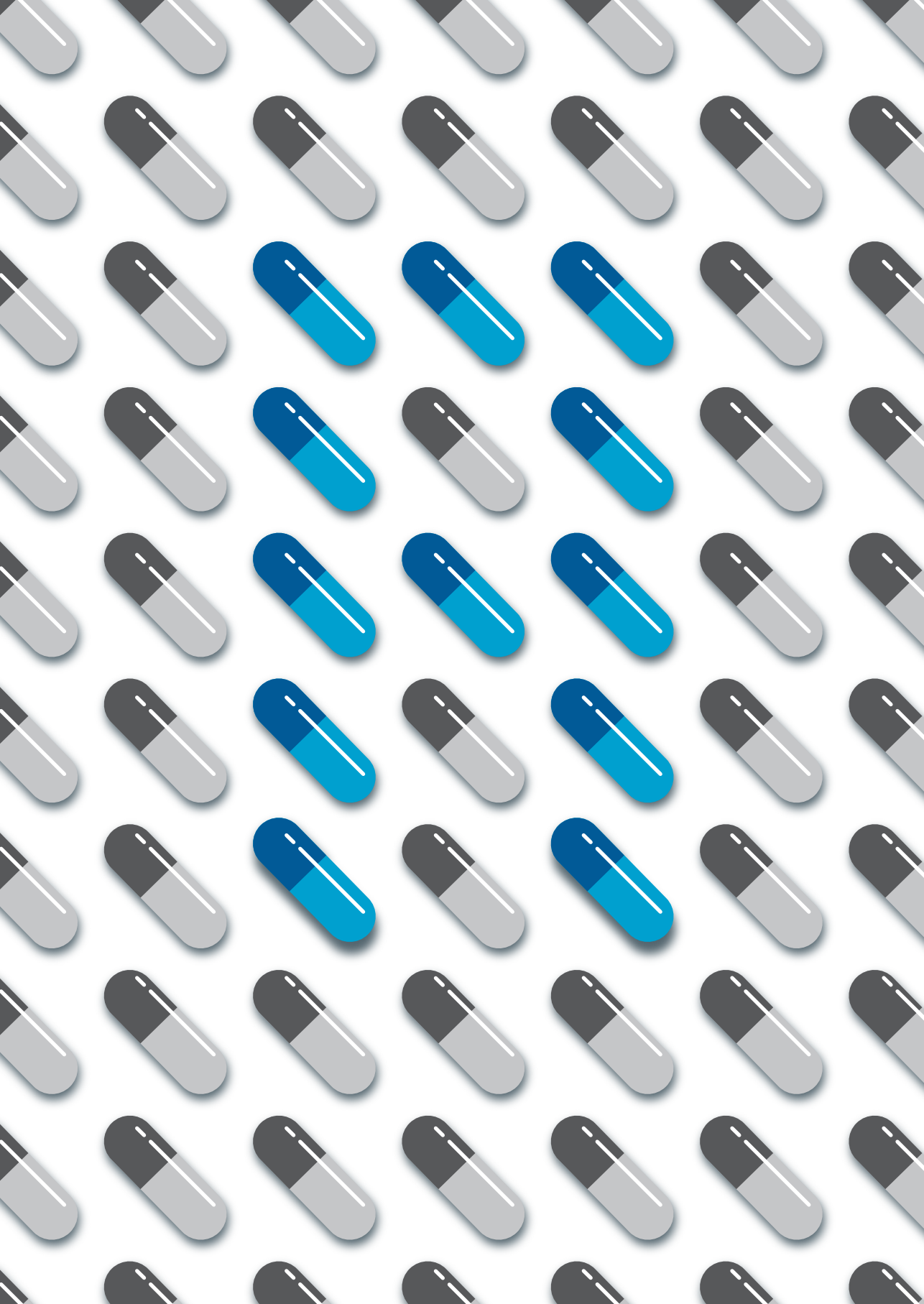
Ondanks het vele onderzoek dat reeds is gedaan is nog altijd meer onderzoek naar de effecten van gelijktijdig gebruik van comedicatie op antikanker geneesmiddelen noodzakelijk om het ware interactie potentieel van geneesmiddelen tegen kanker in kaart te brengen.

Deze farmacologisch onderzoeken naar wisselwerkingen moeten altijd leiden tot een duidelijk en praktisch advies dat gemakkelijk in de klinische praktijk uitgevoerd kan worden. Als er geen farmacologische gegevens beschikbaar zijn aangaande een bepaalde wisselwerking, dan moeten beroepsbeoefenaren in de gezondheidszorg samenwerken en gebruik maken van elkaars kennis. Als er geen gegevens beschikbaar zijn in de literatuur dan moeten artsen en apothekers in staat kunnen zijn hun kennis van farmacokinetiek en -dynamiek te gebruiken om bestaande gegevens te extrapoleren alvorens tot een praktische aanbeveling voor het afhandelen van een bepaalde wisselwerking te komen. Uiteindelijk moet dit leiden tot een meer geïndividualiseerde antikanker therapie met optimaal effect en zo min mogelijk bijwerkingen.



Apendices 2

DANKWOORD



Gezien het feit dat het dankwoord in een proefschrift meestal als eerste gelezen wordt maak ik van deze gelegenheid dankbaar gebruik om een aantal mensen die mij dierbaar zijn en die mij hebben geholpen bij het tot stand komen van dit proefschrift te bedanken.

Lieve Pa en Ma, allereerst wil ik jullie bedanken. Zonder jullie onvoorwaardelijke liefde en steun was ik nooit zover gekomen! Nog steeds kan ik altijd op jullie rekenen en voelt de Kerkweg als een warm nest. Ik bewonder ook jullie grote toewijding als grootouders. Katootje en Roelien boffen maar! Lieve Pa, jij bent in 1980 gepromoveerd en ik nu 26 jaar later ook. Het staat me nog goed bij dat ik vroeger met je meeging naar het Hersen Instituut. Ik kan me de geïmmuniseerde geit Betsie, het coupes snijden met Romeo en Bart, of gewoon met jou door een microscoop kijken nog goed herinneren. Wellicht onbedoeld en onbewust is daar mijn eerste interesse voor de wetenschap geboren. Lieve Ma, zonder jouw engelen geduld en hulp bij het eindeloze repeteren van SO's en proefwerken Duits en Nederlands had ik wellicht nooit hier gestaan. Ook je goede adviezen op "keypoints" in mijn leven hebben mij de goede kant opgestuurd. Ik ben je hier heel dankbaar voor.

Prof. Dr. Mathijssen, beste Ron, wat heb ik veel te danken aan jou! Met jouw ervaring en grenzeloze energie haal je elke keer weer het maximale uit jouw mensen. Altijd kon ik op je bouwen en dat 24/7! Tot laat op de avond, in de weekenden en zelfs tijdens de vakantie konden we praten over de leuke maar soms ook minder leuke dingen van het onderzoek. Onze eerste ontmoeting voelde een beetje als "serendipity". We kenden elkaar eigenlijk al, ik jou o.a. van jouw St. Janskruid paper en jij mij omdat je mijn eerste artikel had gereviewed (Ann Oncol. 2011), maar toch hadden we elkaar nog nooit in levende lijve ontmoet. Door de jaren heen zijn we ook echt maatjes geworden en ik kijk uit naar de komende jaren waar we hopelijk samen nog veel hoogtepunten kunnen beleven! Ik zeg; "consolideren en doorpakken", op naar interactiestudies 2.0!

Prof. Dr. van Gelder, beste Teun, in 2012 was jij de eerste die potentie in mij zag en het mogelijk maakte met mijn promotie te starten. Op belangrijke momenten in de afgelopen jaren was je er om mijn promotie in de juiste richting bij te stellen. Ook kon ik altijd bij je terecht voor een praatje of advies en een goed luisterend oor. Meer dan iedereen, was je ook de stille kracht achter dit proefschrift. Altijd wist je de scherpe randjes van bijvoorbeeld een van onze artikelen af te halen waardoor het stuk naar een hoger niveau getrokken werd. Zichtbaar kon je genieten van de succesjes die we de afgelopen jaren hebben behaald, dat kon ik altijd erg waarderen. Ik hoop dat we de komende jaren binnen het samenwerkingsverband tussen apotheek en oncologie nog veel zullen samenwerken!

Dr. Jansman, beste Frank, ik kende je al vanuit mijn periode in Maastricht waar het fundament gelegd werd voor dit proefschrift. Ook al zat je op afstand, met al jouw enthousiasme stond jij altijd klaar om mee te denken en dingen op te pakken. Zo hebben we samen het voortouw genomen bij het schrijven van het review en de eerste studie naar wisselwerkingen in de oncologie. De bezoekjes aan het Deventer Ziekenhuis zullen mij bij blijven. Als copromotor was jij altijd de manager in ons promotieteam. Hierbij benadrukte je vaak dat promoveren ook vooral managen en (soms tegen beter weten in) doorwerken is. Samen nemen we nu zitting in de “Werkgroep Interacties Oncologie”; ik hoop dat we deze samenwerking in de toekomst verder zullen uitbouwen.

Prof. Dr. Sonneveld, Prof. Dr. Gelderblom en Prof. Dr. Beijnen, bedankt voor het zitting nemen in de kleine commissie en voor de snelle beoordeling van het manuscript. Het lijkt weinig, maar een goedgekeurd manuscript is de laatste stap naar de verdediging. Het heeft meer impact dan sommige denken.

Prof. dr. Aerts, beste Joachim, de afgelopen jaren is de samenwerking tussen de afdelingen oncologie en long-oncologie sterk geïntensiveerd. Zeker met de Cola-studie hebben we veelvuldig samengewerkt. Ik heb onze samenwerking tot nu toe als zeer prettig ervaren en hoop dat we in de toekomst nog veel mooie ideeën kunnen uitwerken. Veel dank voor het zitting nemen in mijn grote commissie.

Prof. dr. de Wit en Prof. dr. Smit, hartelijk dank voor uw deelname in mijn grote commissie.

Beste Inge, Mei en Peter, bedankt voor alle hulp bij de Cola-studie. Zonder jullie zou het lab stuurloos zijn. Dank voor het doormeten van alle samples, het maken van figuren, meewerken aan analyses, en "last but not least" alle gezelligheid.

Dr. Eechoute, beste Karel, we kennen elkaar nog niet zo heel lang maar ik kan je gezelschap en de daarmee gemoeide gitzwarte (Belgische…?) humor zeer waarderen, ik hoop dat je in de toekomst kiest voor de academie en dat we kunnen blijven samenwerken!

Beste Stijn, vanaf april zijn we beide postdoc op het lab, ik hoop dat we samen met Ron het lab de komende jaren kunnen uitbreiden. Consolideren en doorpakken toch?

Beste mede OIO genoten, Sander, Jacqueline, Lisette, Annemiek, Femke en Bodine, dank voor alle hulp en steun die ik van jullie heb mogen ontvangen. We vormen inmiddels een heel hecht en gezellig team waar iedereen hard werkt maar ook veel voor elkaar over heeft. Ik heb intens genoten van onze OIO besprekingen, journal clubs, vele borrels in Café Arie, de Ballentent en de skivakantie in Oberau! Sander, door de jaren heen hebben we vele mooie momenten meegemaakt, ik kan je humor en "no stress" houding waarderen. Succes met de opleiding tot internist volgend jaar. Jacqueline, altijd recht door zee en niet op je mondje gevallen. Ook jij, veel succes met de opleiding tot reumatoloog. Lisette, jij was altijd de theoreticus van ons allen, ik heb veelvuldig bij je aangeklopt tijdens het opzetten van de Cola-studie. Veel succes met je nieuwe baan in Den Haag. Annemiek, ook al hebben we elkaar niet vaak getroffen was jij altijd de stille kracht in de OIO kamer, ik heb zeer veel respect voor het promotie traject wat je doorloopt. Succes komende jaar met promoveren, afstuderen en jouw eventuele nieuwe baan als medicus. Femke, je bent er pas net, maar nu al een vaste waarde binnen ons team, je werklust werkt aanstekelijk en je gezelligheid ook. De komende jaren zullen we bij de aantal studies intensief gaan samenwerken. Ik kijk hier echt naar uit! Beste Bodine, welkom in het team, succes de komende jaren!

Beste studenten, Daniel, Femke, Ingeborg, Foad, Koen, Nikki, Emma en Anne, ik ben jullie zeer dankbaar voor alle hulp en inzet die jullie hebben getoond. Zonder jullie "handjes" op de werkvloer was dit niet gelukt. Daniël, jij was mijn eerste student, jouw werklust (en het vroege opstaan….) heeft een diepe indruk op mij achter gelaten. Ingeborg en Foad, tijdens de prospectieve studie, hebben

jullie vele patiënten geïncludeerd, het gaat jullie goed in de farmacie. Nikki en Koen, “het dreamteam”, tegelijkertijd waren jullie mijn steun en toeverlaat tijdens de Cola-studie. Emma, jij was de opvolger van het dreamteam, dat heb je met verve gedaan en dat heeft mede geleid tot een prachtige JCO paper. Anne, ondanks dat ik niet je directe begeleider was hebben we veel contact gehad. Dank voor je inzet, gezelligheid en leuk dat je bij ons was, ik hoop je in de toekomst nog tegen te komen. Femke, Koen en Emma, wat leuk dat jullie hebben gekozen voor een vervolg in de oncologie en verbonden blijven aan ons lab.

Beste Nicole, dank voor alle steun tijdens mijn promotie en daarbuiten. Ik kan jou motto “alles komt altijd goed” zeer waarderen. Mede door jouw promotie en aanvullingen is het laatste opinie artikel tot stand gekomen. Ik hoop de komende jaren, als maatje in de kliniek, nog veel met je samen te werken!

Beste Prof. dr. Sleijfer, beste Stefan, dank voor de steun het afgelopen jaar en de mogelijkheid om als klinische ziekenhuisapotheker op de afdeling Interne Oncologie aan de slag te mogen. Ik kijk echt uit naar de komende jaren!

Beste oud collega’s uit Maastricht UMC en het Radboud MC, dank voor de hulp en steun die ik van jullie heb gekregen tijdens de eerste studie. Ellen, David en Cees, dank voor de mogelijkheid om onderzoek te doen. Rogier, Thomas, we treffen elkaar binnenkort weer op de racefiets!

Beste Leni, Diane, en Bimla, jullie zijn een prachtig stel. Leni, dank voor de hulp tijdens mijn promotie. Diane, wat leuk dat je mee was op de skivakantie! En Bimla, jouw catering tijdens de kerstborrel is fenomenaal.

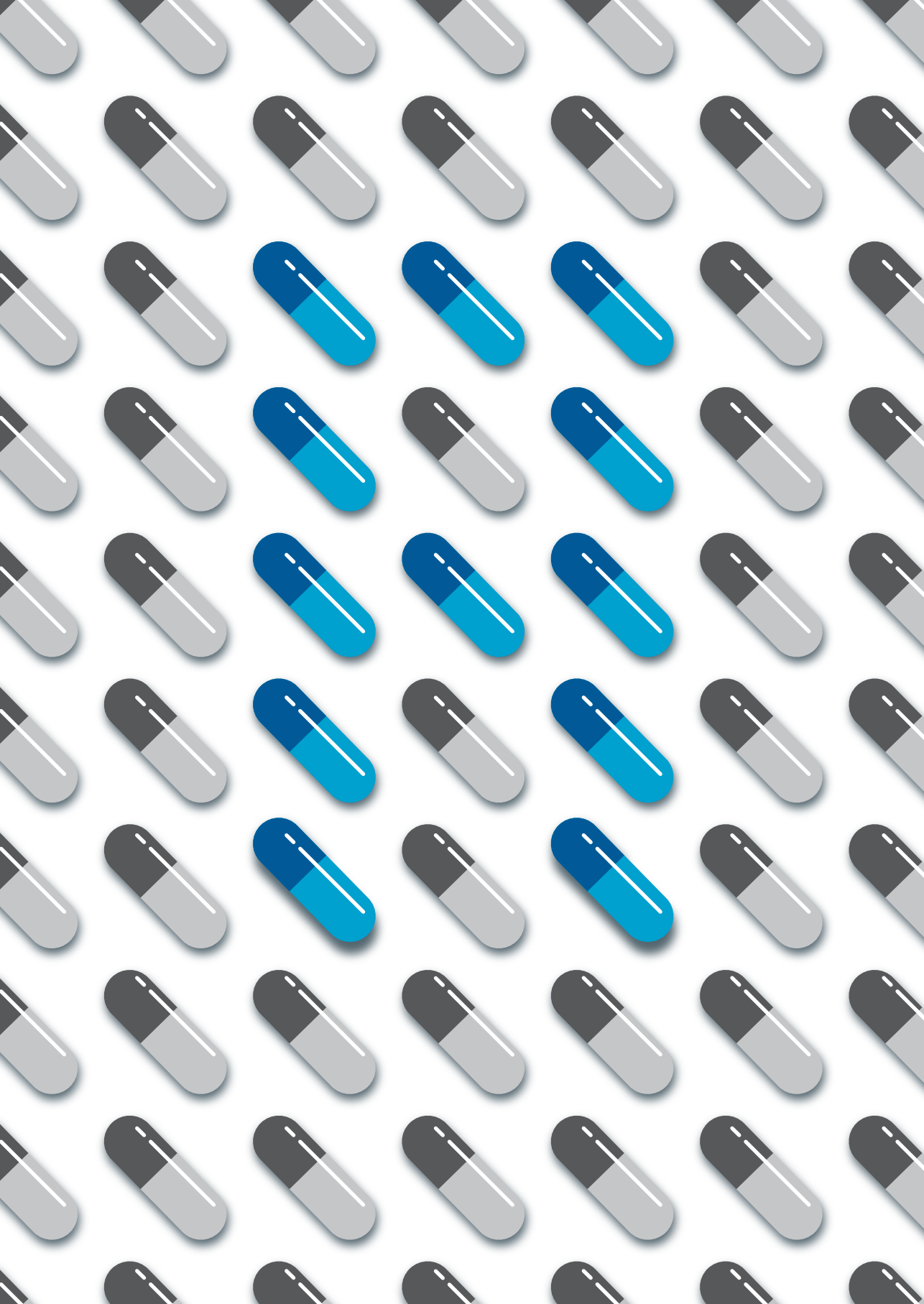
Lieve Aris en Sietse, Lia en Annemarie, wat gezellig dat we zo dicht bij elkaar wonen. In zware tijden waren jullie er voor mij en Marije. In goede tijden is het altijd gezellig! Dank daarvoor!

Clubgenoten, kegelclubgenoten, fietsmannen, familie, buren, andere vrienden en kennissen, jullie brengen veel gezelligheid en plezier in mijn leven. Ik kan me geen leven voorstellen zonder jullie.

Beste paranimfen, Nes en Pa, wat leuk dat jullie mijn paranimfen willen zijn! Nes, we kennen elkaar al sinds dag één van de KMT. Als clubgenoot, huisgenoot, getuige en ceremoniemeester op elkaars huwelijk hebben we al heel veel meegemaakt. Prachtig dat jij mij nu bijstaat bij mijn promotie. Pa, 26 jaar later promoveer ik, wat fantastisch dat je erbij kan zijn en dat je me bijstaat!

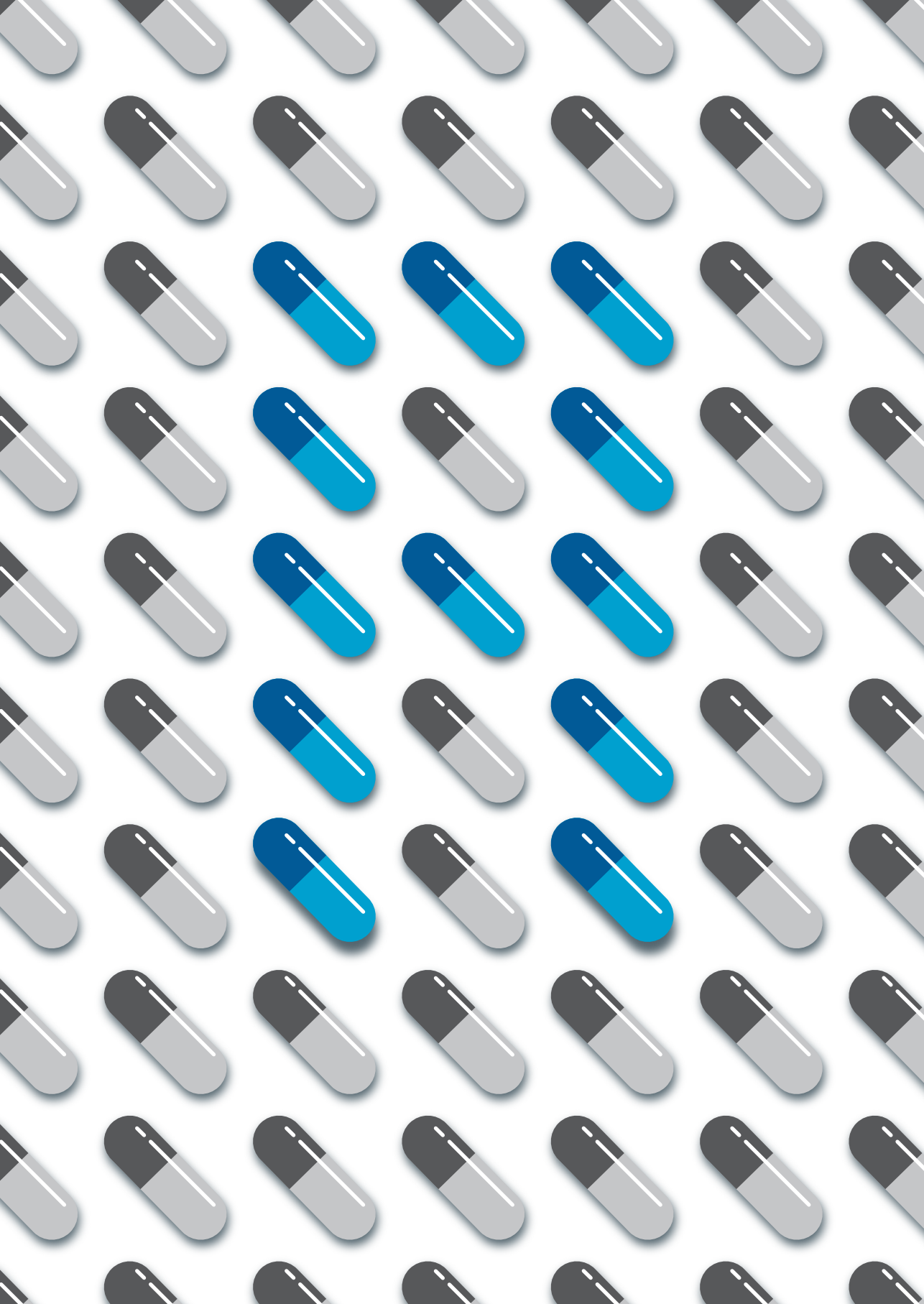
Lieve Marije, toen ik je voor het eerst zag was ik op slag verliefd. Tijdens mijn promotie stond je altijd aan mijn zijde! Jij brengt balans in mijn leven en dankzij jouw onvoorwaardelijke steun en liefde waren de tegenslagen minder zwaar. Jij hebt mij geleerd dat liefde niet zonder elkaar kunnen is, ik hou heel veel van je!

Lieve Kato en Roelien, jullie zijn mijn engeltjes. Elke dag als ik thuis kom vliegen jullie in mijn armen, wat is dat een groot geluk! Wat ben ik trots op jullie en wat doen jullie het goed. Lieve kleine Jet, ik mis je elke dag.



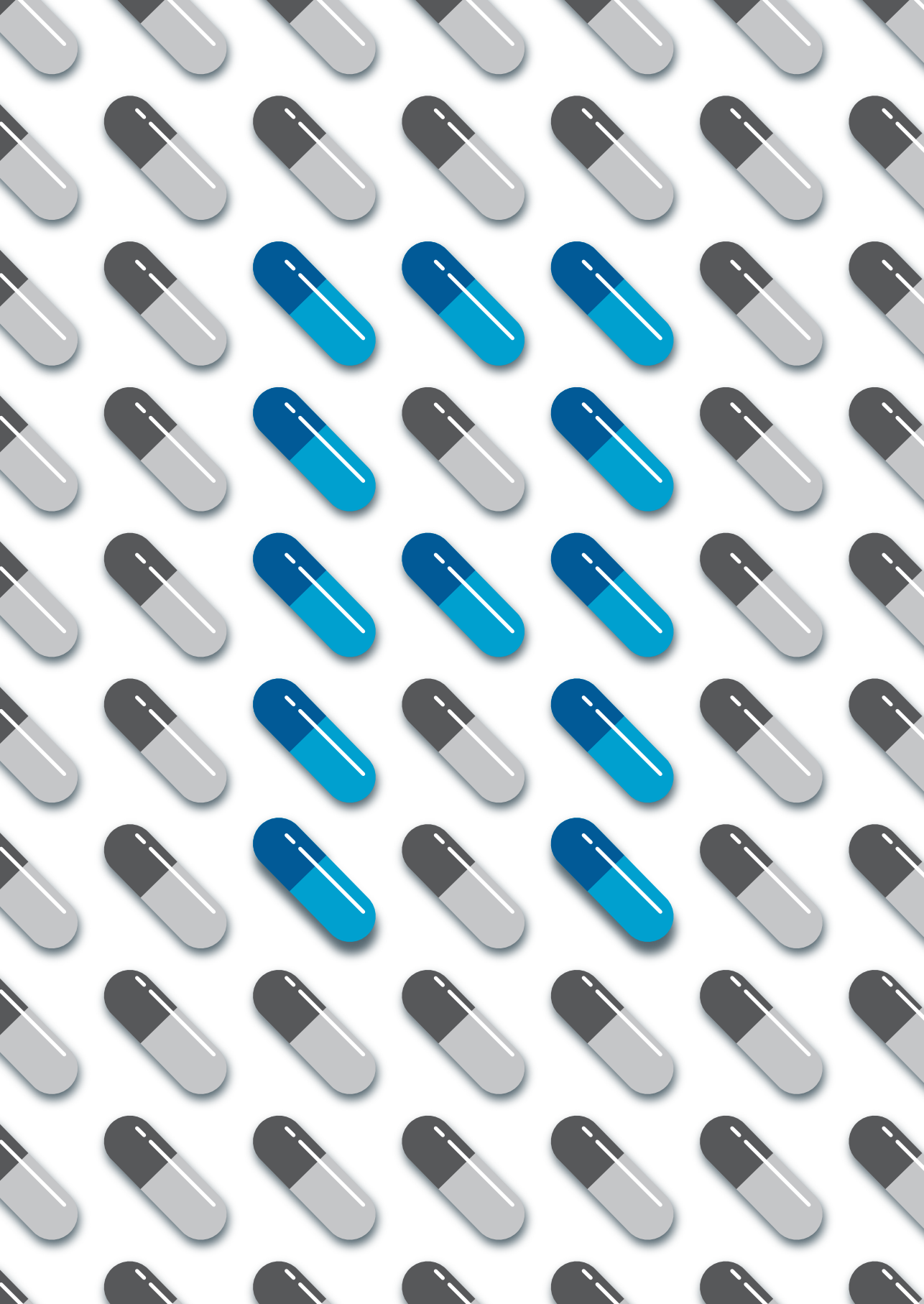
Apendices 3

CURRICULUM VITAE



CURRICULUM VITAE

Roelof van Leeuwen werd op 2 mei 1978 geboren te Maarssen. In 1998 heeft hij zijn VWO diploma behaald aan College de Klop te Utrecht. Tijdens zijn middelbare schooltijd heeft hij een 'summer-student' onderzoeksstage gelopen aan de University of Massachusetts, Worcester, VS. Aansluitend is hij gestart met de studie Farmacie aan de Universiteit Utrecht. Tijdens zijn studie heeft hij een stage van 6 maanden gevolgd aan de Edinburgh University, Clinical Pharmacology Unit, Edinburgh, Schotland onder leiding van Prof. David Webb. In mei 2004 heeft hij zijn apothekers diploma gehaald. In hetzelfde jaar is hij als assistent niet in opleiding gestart in het Westfriesgasthuis te Hoorn waarna gestart kon worden met de opleiding tot ziekenhuisapotheker te Zaans Medisch Centrum te Zaandam en VU medisch centrum te Amsterdam. Na het behalen van de opleiding is hij als ziekenhuisapotheker-onderzoeker gaan werken in de apotheek affiliatie Maastricht UMC en Radboud UMC. Onder leiding van prof. dr. Cees Neef en prof. dr. David Burger is Roelof tevens met onderzoek gestart. Januari 2012 is Roelof als ziekenhuisapotheker aangesteld in het Erasmus MC te Rotterdam waar hij het promotieonderzoek zoals beschreven in dit proefschrift is gestart bij de ziekenhuisapotheek en het laboratorium Translationele Farmacologie van de afdeling interne oncologie, onder begeleiding van prof. dr. T. van Gelder, prof. dr. A.H.J. Mathijssen en Dr. F.G.A. Jansman. Momenteel heeft Roelof een aanstelling bij zowel de ziekenhuisapotheek als de afdeling interne oncologie.



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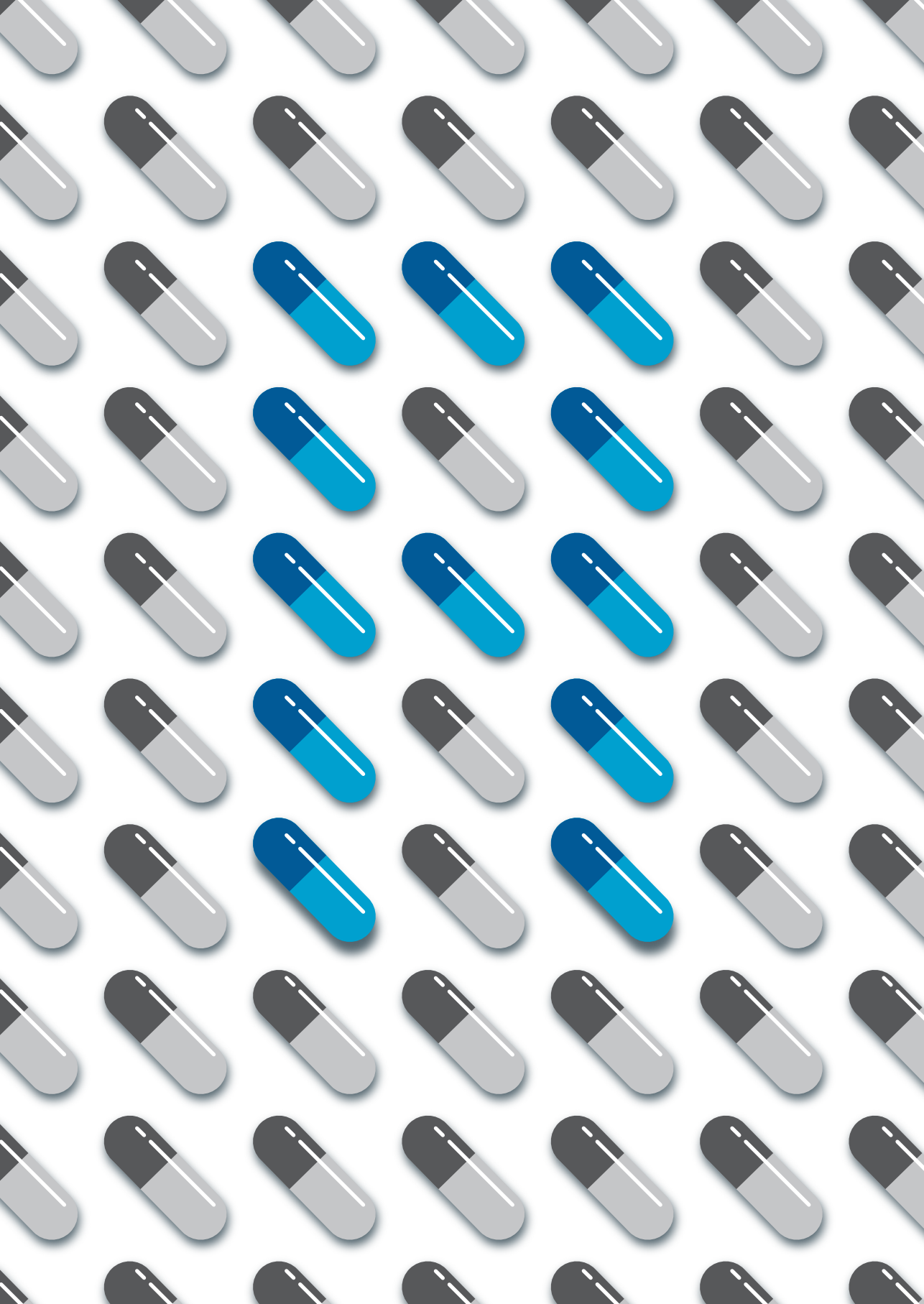
PUBLICATIONS



In the field of this thesis

Van Leeuwen RWF, Swart EL, Boom FA, Schuitenmaker MS, Hugtenburg JG. Potential drug interactions and duplicate prescriptions among ambulatory cancer patients: a prevalence study using an advanced screening method.
BMC Cancer. 2010 Dec 13;10:679

Van Leeuwen RWF, Swart EL, Boven E, Boom FA, Schuitenmaker MS, Hugtenburg JG
Potential drug interactions in cancer therapy: a prevalence study using an advanced screening method.
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Van Leeuwen RWF, Brundel D, Neef C, van Gelder T, Mathijssen RHJ, Burger DM, Jansman FGA. Potential drug-drug interactions in cancer patients treated with oral anti-cancer drugs.
Br J Cancer. 2013 Mar 19;108(5):1071-8

Van Leeuwen RWF, van Gelder T, Mathijssen RHJ, Jansman FGA. Drug-drug interactions with tyrosine kinase inhibitors: a clinical perspective (review).
Lancet Oncol. 2014 Jul;15(8):e315-26

Van Leeuwen RWF, van Gelder T, Mathijssen RHJ, Jansman FGA. Drug interactions between tyrosine-kinase inhibitors and acid suppressive agents: more than meets the eye-Authors' reply. (Letter).
Lancet Oncol. 2014 Oct;15(11):e470-1

Van Leeuwen RWF, Jansman FGA, van den Bemt PMLA, de Man F, Piran F, Vincenten I, Jager A, Rijneveld AW, Brugma JD, Mathijssen RHJ, van Gelder T. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions.
Ann Oncol. 2015 May;26(5):992-7

Van Leeuwen RWF, Mathijssen RH, Jansman FG, van Gelder T. Reply to the letter to the editor 'potential clinical relevant drug-drug interactions: comparison between different compendia, do we have a validated method?' by Conde-Estévez et al. (Letter)
Ann Oncol. 2015 Jun;26(6):1272-3

Van Leeuwen RWF, Peric R, Hussaarts KGAM, Kienhuis E, IJzerman NS, De Bruijn P, Van der Leest C, Codrington H, Kloover JS, Van der Holt B, Aerts JG, Van Gelder T, Mathijssen RHJ. Influence of the Acidic Beverage Cola on the Absorption of Erlotinib in Patients With Non–Small-Cell Lung Cancer
J Clin Oncol. 2016; Feb 8. [Epub ahead of print]

Gelderblom H, Claus-Henning K, Launay-Vacher V, Van Leeuwen RWF. Drug-drug interactions associated with kinase inhibitors: highlighting a new resource for oncologists and clinical pharmacists. (Letter)
Ann Oncol. 2016 Jan 19 [epub ahead of print]

Van Leeuwen RWF, Jansman FGA, Hunfeld NG, Peric R, Reyners AKL, Imholz ALT, Brouwers JRBJ, Aerts JG, Van Gelder T, Mathijssen RHJ. Tyrosine Kinase Inhibitors and proton pump inhibitors, really incompatible?
Submitted

In other fields

Ten Tusscher BL, Beishuizen A, Girbes AR, Swart EL, Van Leeuwen RWF. Intravenous fat emulsion therapy for intentional propafenone intoxication (Case report).
Clin Toxicol (Phila). 2011 Aug;49(7):701

Boone NW, Van Leeuwen RWF. Tissue plasminogen activator (tPA) in the management of predominantly hemorrhagic age-related macular degeneration, milligram/milliliter or microgram/milliliter? (Letter)
Clin Ophthalmol. 2012;6:145

Van Leeuwen RWF, De Vries F. Use of hormonal contraceptives and risk of HIV-1 transmission. (Letter)
Lancet Infect Dis. 2012 Jul;12(7):508-9

Abdulla A, Van Leeuwen RWF, De Vries Schultink AH, Koch BC. Stability of colistimethate sodium in a disposable elastomeric infusion device.
Int J Pharm. 2015 May 30;486(1-2):367-9

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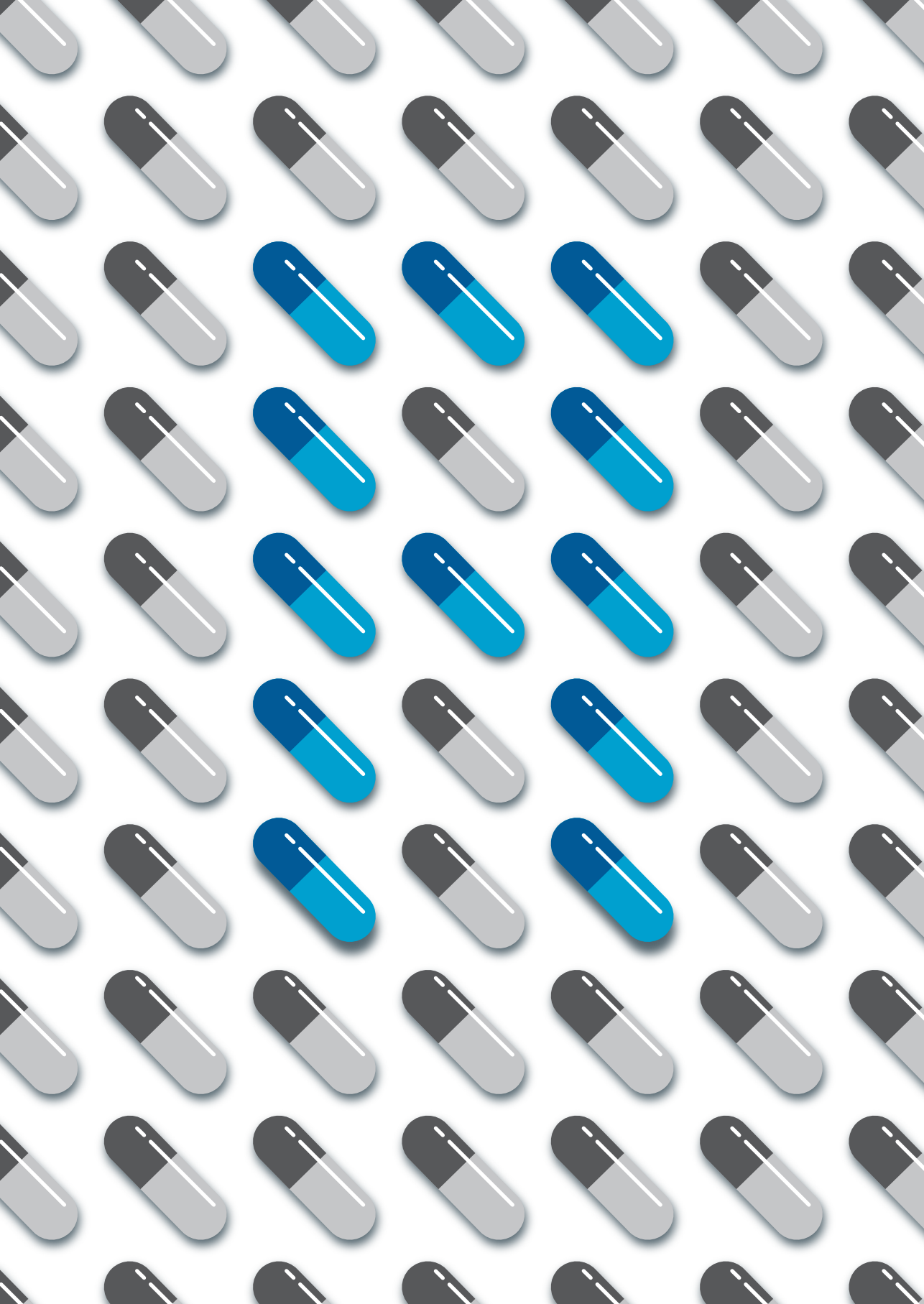

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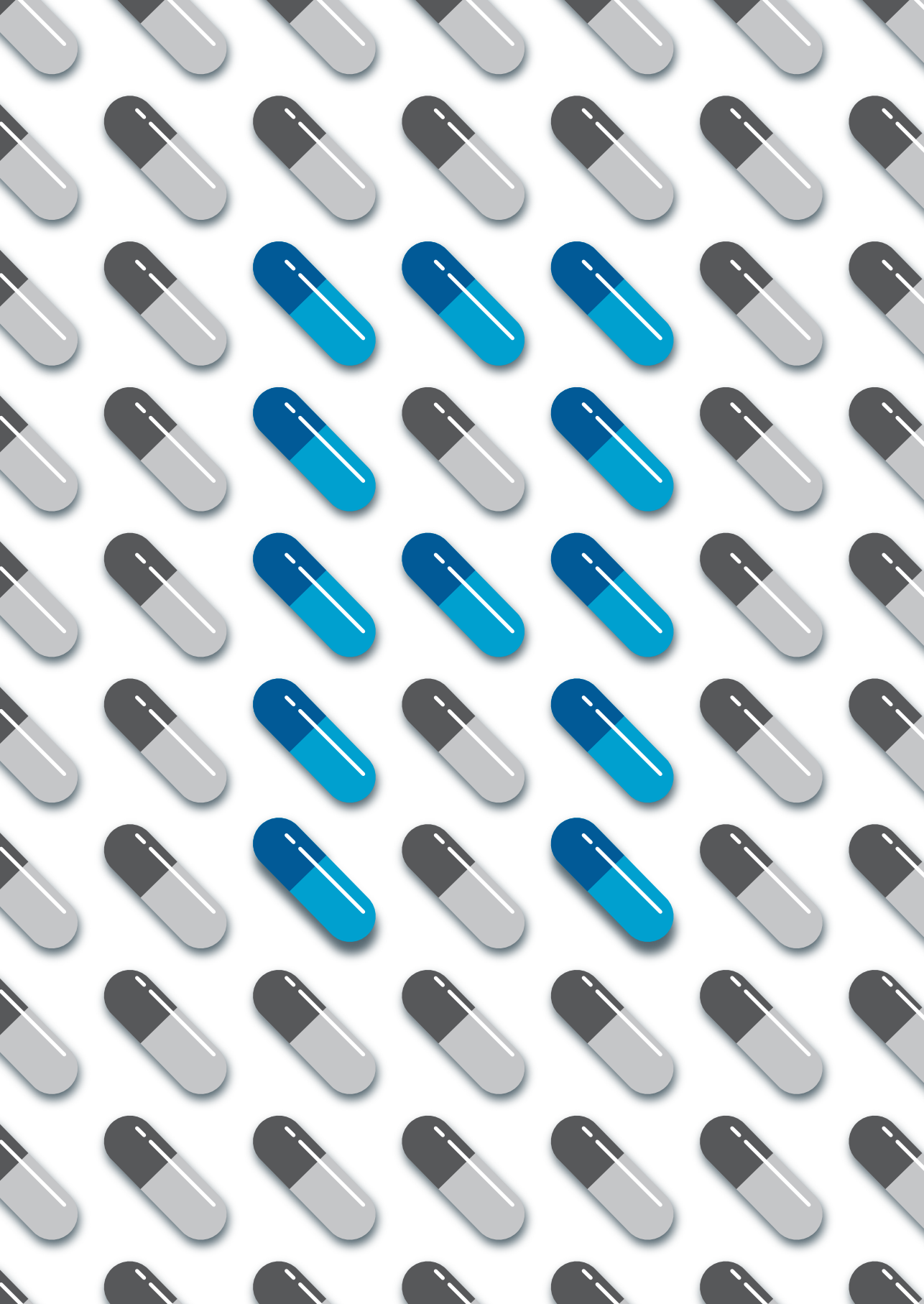
PORTFOLIO



PhD PORTFOLIO

Name PhD student:	Roelof Wouter Frederik van Leeuwen
Erasmus Departments:	Clinical Pharmacy Medical Oncology
PhD period:	2012-2016
Promotor:	Prof. T. van Gelder Prof. A.H.J. Mathijssen
Co-promotor:	Dr. F.G.A. Jansman

1. PhD training		
	Year	**Workload (ECTS)**
General courses		
BROK course (Erasmus MC)	2013	1
Integrity in Research	2014	1
Training Open Clinica	2014	0,4
Specific courses (e.g. Research school, Medical Training)		
Basic Cancer course NVVO, Ellecom	2010	2
PUOZ Anticoagulation medicine	2014	1
PUOZ hemato-oncology day	2015	1
Seminars and workshops		
Clinical Pharmacology meeting	2012-2016	2
PhD- meeting Personalized Medicine	2012-2016	2
Others	2012-2016	2
Presentations		
ESMO 2012, Vienna, poster presentation	2012	1
ESMO 2014, Madrid, poster presentation	2014	1
ESMO 2015, Vienna, poster presentation	2015	1
NVKF&B Scientific Meeting (oral presentations)	2013	1
Figon Dutch Medicine Days, poster presentation	2014	1
Figon Dutch Medicine Days, poster presentation	2015	1
Research Meeting Medical Oncology, oral presentations	2014	0,5
Daniel den Hoed Dag, 2014	2014	0,5
PUOZ course Hemato-oncology, oral presentation	2015	0,5
Others (eg. Hematology day, Nursing congress)	2012-2016	2
(International) conferences		
European Society for Medical Oncology (ESMO), Vienna	2012	1
European Society for Medical Oncology (ESMO), Madrid	2014	1
European Society for Medical Oncology (ESMO), Vienna	2015	1
Figon Dutch Medicine Days	2014	0,4
Figon Dutch Medicine Days	2015	0,4
ASCO annual meeting 2013, Chicago	2013	1
ASCO annual meeting 2014, Chicago	2014	1
ASCO annual meeting 2015, Chicago	2015	1
Other		
MOLMED day, Erasmus MC	2014	0,2
Research Meeting Medical Oncology	2012-2016	0,4
NVKF&B scientific meeting	2013-2014	0,6

2. Teaching activities		
	Year	**Workload (ECTS)**
Lecturing		
Education medical students	2012-2016	2
PhD- meeting Personalized Medicine	2012-2016	1
Clinical Pharmacology meeting	2012-2016	1
Clinical Research Meeting (dept Medical Oncology)	2012-2016	1
Clinical Lessons nurses (hemato-)oncology	2012-2016	1
ESMO e-learning on Drug-Drug Interactions in oncology	2015	1
Supervising Master's thesis		
Daniel Brundel	2012	1
Femke de Man	2013	1
Ingeborg Vincenten	2013	1
Foad Piran	2013	1
Koen Hussaarts	2014	1
Nikki IJzerman	2014	1
Emma Kienhuis	2014	1
Committee work		
Special Interest Group Hematology, NVZA/KNMP	2013-2016	1
Management of drug interaction in Oncology Committee, NVZA/KNMP	2015-2016	0,5

Notes