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REVIEW ARTICLE

Targeted cancer therapy: interactions with other medicines

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Abstract Targeted therapy drugs, mainly those within the signal transduction inhibitors, are used more chronically than cytotoxic drugs and are metabolised by cytochrome P450 isozymes so patients are at high risk of having drug–drug interactions (DDI). Not only this, as the majority of them are given orally, new drug–drug interactions concerning gastrointestinal absorption can occur (e.g., with proton pump inhibitors). DDI can lead to changed systemic exposure, resulting in variations in drug response of the co-administered. In addition, concomitant ingestion of dietary supplements could also alter systemic exposure of drugs, thus leading to adverse drug reactions or loss of efficacy. In this review, we give an overview of the current existing data of known or suspected DDI between targeted therapy and other medicines. A review of package inserts was performed to identify drug–drug interactions for all targeted antineoplastic agents. Tertiary databases such as Lexicomp®, Drugs, Martindale, Facts and Comparisons®, and AHFS Drug Information were also referenced. This study covered 40 targeted antineoplastic agents (28 signal transduction inhibitors, 9 monoclonal antibodies and 3 other drugs, 2 monoclonal antibody conjugates and 1 fusion protein). Most of targeted therapy drugs are major CYP3A4 substrates with P-gp playing an important role in disposition too. Thus, there is a very common thread here that these agents will likely be sensitive victims to strong CYP3A4/P-gp inhibitors and inducers. It is essential that health care providers monitor patients for potential DDI to avoid a loss in efficacy or risk of greater toxicity from targeted therapy.

Keywords Drug–drug interactions · Pharmacology · Medication review · Molecular targeted therapy

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Introduction

Over the past few years, there has been a paradigm shift in cancer treatment from more unspecific agents (cytotoxic drugs) to target-based therapies with many of the newly approved anticancer agents against specific molecular targets. Targeted cancer therapies are drugs that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted drugs", "molecularly targeted therapies", "precision medicines", or similar names [1]. The two main groups of targeted therapy are monoclonal antibodies and the signal transduction inhibitors, being the tyrosine kinase inhibitors the most promising drugs nowadays [2].

Among these drugs, signal transduction inhibitors are used more chronically and are mainly metabolised by cytochrome P450 (CYP) isozymes so patients are at high risk of having drug–drug interactions (DDI). Not only this, as the majority of targeted therapy drugs are given orally, new drug–drug interactions concerning gastrointestinal absorption can occur (e.g., with proton pump inhibitors).

DDI can lead to changed systemic exposure, resulting in variations in drug response of the co-administered drugs [3]. In addition to co-administration of other drugs,

concomitant ingestion of dietary supplements could also alter systemic exposure of drugs, thus leading to adverse drug reactions or loss of efficacy. Furthermore, DDI may be associated with serious or even fatal events. In fact, DDI are estimated to account for approximately 4 % of deaths among patients with cancer [4].

In addition, DDI is an important issue among cancer population. It is commonly observed in these patients, as they often receive multiple medications concurrently. It was shown previously that patients who are taking multiple medications for the treatment of comorbid illnesses experience an increased incidence of drug interactions [5, 6]. However, the real incidence of DDI in cancer patients is unknown because the studies have evaluated it among patients with various medical conditions and different kind of anticancer drugs.

DDI can be classified into those that are pharmacokinetic and those that are pharmacodynamic [7]. 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 DDI concern is absorption (incomplete drug absorption is a risk of drug interaction) and metabolism by the cytochrome P450 isozymes. Pharmacodynamic interactions usually refer to alterations of pharmacological effects. The effect can be synergistic, additive, or antagonist.

Transporter-based interactions have been increasingly documented. Various reported interactions attributed earlier to other mechanisms of interaction, such as protein-displacement or enzyme inhibition/induction, may be due in part to the inhibition or induction of transport proteins, such as P-glycoprotein (P-gp), organic anion transporter (OAT), organic anion transporting polypeptide (OATP), organic cation transporter (OCT), multidrug resistance-associated proteins (MRP) and breast cancer resistant protein (BCRP).

One common misconception is that targeted therapy is safer and less toxic than intravenous chemotherapy. In fact, targeted therapy have specific toxicity profiles (some toxic effects are severe and even cause secondary tumours) that differ from those of cytotoxic drugs [8]. Furthermore, DDI are ubiquitous among the broad class of targeted therapies, which can contribute to enhanced treatment-related toxicities.

The biggest challenge today is to find out which DDI is a relevant one [9]. This question is still unanswered and great debate is growing in the literature [9, 10].

In this review, an overview of the current existing data of known or suspected DDI between targeted therapy and other medicines is given.

Methods

A review of package inserts was performed to identify drug–drug interactions for all targeted antineoplastic agents approved by the EMA. Additionally, tertiary databases such as Lexicomp® (www.lexi.com), Drugs (www.drugs.com), Martindale, Facts and Comparisons® (http://www.wolterskluwercdi.com/), and AHFS Drug Information were also referenced. Each medication was individually evaluated.

The definitions used by the FDA Drug Development and Drug Interactions department for regulatory procedures were assumed for purposes of this review. A drug was defined as an inducer or inhibitor (perpetrator) if the medication raised or lowered the plasma concentration of another medication (victim) that was metabolized by that enzyme. A drug was considered to be a strong inhibitor or inducer if its interactions caused change in the area under the plasma concentration–time profile (AUC) of a substrate by at least fivefold or changed the clearance of a medication higher than 80 %. A drug was classified as a moderate inhibitor or inducer if its interactions changed the AUC of a substrate by at least two- to fivefold or changed the clearance of a medication by 50–80 %. A drug was deemed to be a weak inhibitor or inducer if its interaction changed the AUC by 1.25- to 2-fold or changed the clearance of a medication by 20–50 % [11]. This categorization is applied in Table 2 using the following symbols: as the victim drug "*" indicating major substrate (as a victim drug) and "-" referring to minor substrate; and as the perpetrator drug, "+" representing weak inducer/inhibitor; "++" for moderate inducer/inhibitor; and "+++" designating strong inducer/inhibitor.

In addition, targeted therapy drugs were also analysed for interactions with acid suppressor medications such as proton-pump inhibitors, histamine 2-receptor antagonists and antiacids. Each agent was also evaluated for its effects on coumarin-containing products and for QTc interactions, defined as drug combinations with potential QTc-interval prolongation and/or torsades de pointes inducing properties. These interactions were categorized as yes, no or not studied.

All this research was summarized in a table and several recommendations were also included.

Results

Our review covered 40 targeted antineoplastic agents (28 signal transduction inhibitors, 9 monoclonal antibodies and 3 other drugs, two monoclonal antibody conjugates and one fusion protein—see Table 1 for more detailed information).

Table 1 Targeted cancer therapy included in the review

Drug	Mechanism of action	Molecular target	Type of cancer
Signal transduction inhibitors			
Afatinib	TKI	EGFR	Non-small cell lung cancer
Axitinib	TKI	VEGFR1-3 PDGFRα/β, c-KIT, FLT-3, CSF-1R, RET	Renal cell carcinoma
Bosutinib	TKI	BCR-ABL	Chronic myelogenous leukemia
Cabozantinib	TKI	c-MET-VEGFR1-3, TIE-2, Kit, RET, FL-3, TRKB, AXL	Medullary thyroid cancer
Cobimetinib	Serine/threonine kinase inhibitor	MEK	Metastatic melanoma with BRAF V600 mutation in combination with vemurafenib
Crizotinib	TKI	ALK	Non-small cell lung cancer
Dabrafenib	Serine/threonine kinase inhibitor	b-Raf	Metastatic melanoma with BRAF V600 mutation
Dasatinib	TKI	BCR-ABL, Src family, ephrin receptor, c-kit, PDGFR	Acute lymphoblastic leukemia Phi+
			Chronic myelogenous leukemia Phi+
Erlotinib	TKI	EGFR	Non-small cell lung cancer
			Pancreatic cancer
Everolimus	mTOR inhibitor	mTOR1	Breast cancer
			Pancreatic cancer
			Renal cell carcinoma
			Subependymal giant cell astrocytoma
Gefitinib	TKI	EGFR	Non-small cell lung cancer
Ibrutinib	TKI	Bruton's tyrosine kinase	Chronic lymphocytic leukaemia
			Mantle cell lymphoma
Imatinib	TKI	BCR-ABL, c-kit, PDGFR	Acute lymphoblastic leukemia Phi+
			Chronic eosinophilic leukemia or hypereosinophilic syndrome
			Chronic myelogenous leukemia
			Dermatofibrosarcoma protuberans
			Gastrointestinal stromal tumor (GIST)
			Myelodysplastic/myeloproliferative neoplasms
			Systemic mastocytosis
Lapatinib	TKI	HER2, EGFR	Breast cancer
Nilotinib	TKI	BCR-ABL, c-kit, PDGFR	Chronic myelogenous leukemia
Nintedanib	TKI	VEGFR 1-3, PDGFR, FGFR 1-3	Non-small cell lung cancer
Olaparib	PARP inhibitor	PARP1/2	Ovarian cancer
Pazopanib	TKI	VEGFR1/3, PDGFR, kit	Renal cell carcinoma
			Soft tissue sarcoma
Ponatinib	TKI	BCR-ABL	Acute lymphoblastic leukemia Phi+
			Chronic myelogenous leukemia Phi+
Regorafenib	TKI	VEGFR1-3, TIE2, c-kit, RET, BRAF, EGFR-1, PDFGR	Colorectal cancer
			GIST
Ruxolitinib	TKI	Janus Associated Kinases (JAK1,JAK2)	Myelofibrosis
			Polycythemia vera
Sorafenib	TKI	VEGFR1-2, PDGFRβ, Raf	Hepatocellular carcinoma
			Renal cell carcinoma
			Thyroid cancer
Sunitinib	TKI	VEGFR1-3, PDGFR,c-kit	GIST
			Pancreatic neuroendocrine cancer
			Renal cell cancer

Table 1 continued

Drug	Mechanism of action	Molecular target	Type of cancer
Temsirolimus	mTOR inhibitor	mTOR1	Renal cell carcinoma
Trametinib	Serine/threonine kinase inhibitor	MEK	Metastatic melanoma with BRAF V600 mutation in combination with dabrafenib
Vandetanib	TKI	VEGFR2, EGFR, RET	Medullary thyroid cancer
Vemurafenib	Serine/threonine kinase inhibitor	B-Raf	Metastatic melanoma with BRAF V600 mutation
Vismodegib	TKI	'Hedgegoh' signalling pathway, PTCH1, GLI1	Basal cell carcinoma
Monoclonal antibodies (MoAb)			
Alemtuzumab	MoAb	CD52	B cell chronic lymphocytic leukemia
Bevacizumab	MoAb	VEGF	Cervical
			Colorectal cancer
			Glioblastoma
			Non-small cell lung cancer
			Ovarian epithelial, fallopian tube, or primary peritoneal cancer
			Renal cell cancer
Brentuximab	MoAb	CD30	Anaplastic large cell lymphoma
			Hodgkin lymphoma
Cetuximab	MoAb	EGFR	Colorectal cancer
			Squamous cell carcinoma of the head and neck
Ofatumumab	MoAb	CD20	Chronic lymphocytic leukemia
Panitumumab	MoAb	EGFR	Colorectal cancer
Pertuzumab	MoAb	HER2	Breast cancer
Ramucirumab	MoAb	VEGFR2	Adenocarcinoma of the stomach or gastroesophageal junction
			Colorectal cancer
			Non-small cell lung cancer
Rituximab	MoAb	CD20	B-cell non-Hodgkin lymphoma
			Chronic lymphocytic leukemia
Trastuzumab	MoAb	HER2	Breast cancer
			Adenocarcinoma of the stomach or gastroesophageal junction
Others			
Aflibercept	Recombinant fusion protein	VEGF-A-B, PlGF	Colorectal cancer
Trastuzumab emtasine	MoAb conjugate	HER2	Breast cancer
T-DM1			

TKI tirosine kinase inhibitor, *ALK* anaplastic lymphoma kinase, *EGFR* epidermal growth factor receptor, *PARP* poly (ADP-ribose) polymerase, *PTCH1* patched homolog 1, *GLI1* glioma-associated protein 1

Signal transduction inhibitors ($n = 28$) (Table 2)

The CYP enzyme class was predominant for metabolisation of these drugs. The P-gp were also involved for 15 (53.6 %) medications. The majority of the medications analysed were substrates for multiple enzymes and/or transporters in their metabolism, the most prevalent combination of which was CYP enzymes plus P-gp.

Moreover, the addition of a targeted therapy agent to an anticoagulant may have variable effects on the international normalization ratio (INR). Approximately half of the signal transduction inhibitors ($n = 13$) affected the

Table 2 Drug-drug interactions

Targeted therapy drug	As the victim drug… Substrate	As the perpetrator…		Renal elimination interactions (% renal elimination)	DDI w/drugs affecting gastric acidity	Coumarin effects	Prolongs QTc	Specific recommendations
		Inhibits	Induces					
Afatinib	BCRP, P-gp	BCRP, P-gp	–	No (4 %)	Not studied	No	No	P-gp inducers/inhibitors: increase afatinib by 10 mg/reduce by 10 mg
Axitinib	CYP3A4*, 3A5*, 1A2-, 2C19-, UGT1A1-	CYP1A2-, 2C8-	–	No (23 % as inactive metabolites)	No	Possible	No	Strong CYP3A4 inh: decrease dose axitinib by 50 % Avoid strong CYP3A4 inducers Monitor INR
Bosutinib	CYP3A4*, P-gp	P-gp	–	No (3 %)	Yes	No	Yes	Avoid strong ind/inh CYP3A4 Avoid PPIs; if AntiH2 or antiacids, separate 2 h
Cabozantinib	CYP3A4*, CYP2C9-	P-gp	–	No (27 %)	Not studied	Not studied	Possible	Strong CYP3A4 ind/inh: increase/decrease cabozantinib dose by 40 mg (max dose 180 mg)
Cobimetinib	CYP3A4*, P-gp	CYP3A-, 2D6-	–	No (18 %)	Not studied	Not studied	Not known	Avoid strong ind CYP3A4 Strong CYP3A4 inh: reduce cobimetinib to 20 mg/daily
Crizotinib	CYP3A4*, P-gp,OATP1B1-, OATP1B3-	3A4 ++, P-gp, 2B6+++	–	No (2 %)	Possible	Not studied	Yes	Avoid strong ind/inh CYP3A4 PPIs, AntiH2 and antiacids may decrease bioavailability of crizotinib
Dabrafenib	CYP3A4*, 2C8*, P-gp, BCRP	BCRP++, OATP1B1-, OATP1B3-	CYP3A4++, 2B6, 2C8, 2C19, UDP	No (23 % as inactive metabolites)	Possible	Yes	Not studied	Decrease bioavailability of warfarin
Dasatinib	CYP3A4*	3A4+	–	No (4 %)	Yes	Possible	Yes	Avoid strong inducers CYP3A4 If strong CYP3A4 inhibitors: decrease dose of dasatinib to 20 mg or 40 mg (if 100 mg or 140 mg respectively) Avoid PPI or antiH2 Antiacids (separated 2 h) Monitor INR
Erlotinib	CYP3A4*, 1A2-	UGT1A1+++	–	No (8 %)	Yes	Yes	Not studied	Strong CYP3A4 ind/inh: increase/decrease dose of erlotinib by fractions of 50 mg (max dose 450 mg) Avoid PPI, separate antiH2 10 h after and 2 h before Monitor INR

Table 2 continued

Targeted therapy drug	As the victim drug… Substrate	As the perpetrator… Inhibits	As the perpetrator… Induces	Renal elimination interactions (% renal elimination)	DDI w/drugs affecting gastric acidity	Coumarin effects	Prolongs QTc	Specific recommendations
Everolimus	CYP3A4*, P-gp-	P-gp++	–	No (5 %)	Not studied	Not studied	No	Strong inh CYP3A4: decrease dose of everolimus to 2.5 mg Strong ind CYP3A4 increase everolimus in 5 mg increments (max dose 20 mg) Monitor with cyclosporine and other nephrotoxic agents
Gefitinib	CYP3A4*, 2D6*	BCRP, 2C19+, 2D6+	–	No (<4 %)	Yes	Yes	Not studied	Strong ind CYP3A4 consider gefitinib 500 mg/day PPI separate 12 h; antiH2 and antiacids separate 6 h Monitor INR
Ibrutinib	CYP3A4* 2D6-	P-gp+	–	No (<10 %)	Not studied	Yes	Not studied	Avoid strong ind/inh CYP3A4 Monitor INR
Imatinib	CYP,3A4*, 3A5*, 1A2-, 2C9-, 2D6-, 2C19-, P-gp-	CYP 3A4++, 3A5++, 2C9+, 2D6++, BCRP++, P-gp	–	No (13 %)	Not studied	Yes	Not studied	Strong ind CYP3A4, increase dose by 50 % imatinib Increased INR
Lapatinib	CYP 3A4*, P-gp	P-gp, 3A4+, 2C8++, BCRP	–	No (<2 %)	Not studied	No	Yes	Strong ind CYP3A4 increase lapatinib gradually up to 4500 mg Strong inh CYP3A4 decrease lapatinib to 500 mg
Nilotinib	CYP3A4*, P-gp	CYP3A4++, 2C9+, 2D6++, 2C8++, P-gp, UGT1A1	CYP2B6 ++, 2C8 ++, 2C9 ++	No (<1 %)	Yes	No	Yes	Avoid PPI Use separated antiH2 or antiacids 10 h after and 2 h before
Nintedanib	CYP3A4, P-gp	–	–	No (<1 %)	Not studied	Yes	No	Monitor INR
Olaparib	CYP 3A4*, P-gp	BCRP, OATP1B1, OCT1, OCT2, P-gp	–	No (44 % inactive metabolites)	Not studied	No	Not studied	Avoid strong CYP3A4 inducers Strong CYP3A4 inhibitors: decrease olaparib to 150 mg twice daily
Pazopanib	CYP3A4*, 1A2-, 2C8-, P-gp, BCRP	CYP2C8+, 2D6+, 3A4+, OATP1b1, UGT1A1	–	No (<4 %)	Yes	No	Yes	Avoid strong CYP3A4 inducers Strong inh CYP3A4 decrease pazopanib dose to 400 mg Avoid PPI, antiacids and antiH2
Ponatinib	CYP3A4-, 2C8-, 2D6-, P-gp-, BCRP-	P-gp, BCRP, BSEP	–	No (5 % aprox)	Possible	Not studied	No	Strong inh CYP3A4 : decrease ponatinib dose to 30 mg daily Avoid antiacids if possible
Regorafenib	CYP3A4*, UGT1A9	CYP2C8, 2C9, 2B6, 3A4, 2C19, UGT1A9, UGT1A1, BCRP, P-gp	–	No (19, 17 % as inactive metabolites)	No	Yes	No	Avoid strong ind/inh CYP3A4 Increase INR

Table 2 continued

Targeted therapy drug	As the victim drug… Substrate	As the perpetrator… Inhibits	As the perpetrator… Induces	Renal elimination interactions (% renal elimination)	DDI w/drugs affecting gastric acidity	Coumarin effects	Prolongs QTc	Specific recommendations
Ruxolitinib	CYP3A4*	–	–	No (74 % inactive metabolites)	No	Not studied	Yes	Strong CYP3A4 inhibitors: decrease ruxolitinib dose by 50 %; if platelets <100,000/mm3, avoid coadministration
Sorafenib	CYP3A4-, UGT1A9	CYP2B6++, 2C9++, 2C8+, UGT1A1, UGT1A9, BCRP, BSEP	–	No (19 %, as inactive metabolites)	No	Yes	Yes	Monitor INR
Sunitinib	CYP3A4*	BCRP, P-gp	–	No (16 %)	Not studied	Not studied	Yes	Strong inh CYP3A4 decrease sunitinib dose to 37.5 mg (GIST/RCC) or 25 mg (PNET) Strong ind CYP3A4 increase sunitinib to 87.5 mg (GIST/RCC) or 62.5 mg (PNET)
Temsirolimus	CYP3A4*, P-gp	CYP2D6+	–	No (<5 %)	N/A	Yes	No	Avoid strong inh CYP3A4 Increase risk of bleeding in the brain
Trametinib	–	CYP2C8+	CYP3A4+	No (<20 %)	Not studied	Not studied	Not studied	Not substrate of CYP, P-gp or BCRP
Vandetanib	CYP3A4*	P-gp, BCRP	–	No (25 % aprox)	No	Not studied	Yes	QTc: deaths reported, monitor closely electrolyte imbalance before initiation and ECG at baseline
Vemurafenib	CYP3A4*, P-gp, BCRP	CYP1A2++, 2D6+, P-gp, BCRP	CYP3A4+	No (<1 %)	No	Yes	Yes	Monitor INR
Vismodegib	CYP3A4-, 2C9-, P-gp	CYP2C8+, 2C9+, 2C19+, BCRP	–	No (4 %)	Possible	Possible	No	Altered pH may reduce bioavailability but not studied Monitor INR
Alemtuzumab	–	–	–	–	N/A	Not studied	Not studied	–
Bevacizumab	–	–	–	–	N/A	Not studied	Not studied	Increase cardiotoxicity with anthracyclines Increase toxicity of irinotecan (33 %) Avoid sunitinib (cases of MAHA)
Cetuximab	–	–	–	–	N/A	Not studied	Not studied	–
Ofatumumab	–	–	–	–	N/A	Not studied	Not studied	–
Panitumumab	–	–	–	–	N/A	Not studied	Not studied	–
Pertuzumab	–	–	–	–	N/A	Not studied	Not studied	–

Table 2 continued

Targeted therapy drug	As the victim drug…	As the perpetrator…		Renal elimination interactions (% renal elimination)	DDI w/drugs affecting gastric acidity	Coumarin effects	Prolongs QTc	Specific recommendations
	Substrate	Inhibits	Induces					
Ramucirumab	–	–	–	–	N/A	Not studied	Not studied	–
Rituximab	–	–	–	–	N/A	Not studied	Not studied	–
Trastuzumab	–	–	–	–	N/A	Not studied	Not studied	–
Aflibercept	–	–	–	–	N/A	Not studied	Not studied	–
Brentuximab	CYP3A4*, 3A5, P-gp, 2D6-	CYP3A4-	–	–	N/A	Not studied	Not studied	Monitor toxicity with strong inh/ind CYP3A4
Trastuzumab emtasine T-DM1	CYP3A4* (DM1), 3A5-	–	–	–	N/A	Not studied	Not studied	Delay treatments with ind/inh CYP3A4

* Major substrate, - minor substrate, + weak inducer/inhibitor, ++ moderate inducer/inhibitor, +++ strong inducer/inhibitor, *BCRP* breast cancer resistance protein, *BSEP* bile salt export pump, *DDI* drug-drug interaction, *GIST* GI stromal tumor, *MAHA* microangiopathic hemolytic anemia, *OATP* organic anion-transporting polypeptide, *P-gp* P-glycoprotein, *PNET* primitive neuroectodermal tumor, *RCC* renal cell carcinoma, *UGT* UDP uridine diphosphate glucuronosyltransferase

absorption of coumarin-derived anticoagulants, and prolongation of the QTc interval was significant in 12 agents. Additionally, any other DDI that had specific dose-modification recommendations available in the package insert or through tertiary databases were listed for 13 drugs. Finally, we also noted that acid suppression affected absorption rates for nine targeted therapy drugs.

Monoclonal antibodies and others ($n = 12$) (Table 2)

In general, several pathways have been described that may contribute to the metabolism of antibodies. All of these pathways involve the biodegradation of the antibody to smaller molecules, i.e., small peptides or aminoacids. Normally, no formal interaction studies with MoAb have been performed. As they are usually combined with other cytotoxic drugs, studies can be found regarding possible pharmacodynamic interactions between each agent. For example, cetuximab in combination with capecitabine and oxaliplatin (XELOX) the frequency of sever diarrhoea may be increased.

Two important exceptions (see Table 2) were found among antibody–drug conjugates brentuximab and trastuzumab emtasine. Both drugs are composed by a MoAb and covalently linked to another agent [antimicrotubule agent monomethyl aurastin E (MMAE) in case of brentuximab and a maytansine derivated called DM1 in case of trastuzumab emtasine]. These agents are released in vivo and are metabolized by CYP as described in Table 2.

Discussion

The major finding of this review is that most of targeted therapy drugs are major CYP3A4 substrates with P-gp playing an important role in disposition too. Thus, there is a very common thread here that these agents will likely be sensitive victims to strong CYP3A4/P-gp inhibitors and inducers. As a result, augmented or reduced exposure by variation of CYP activity might origin clinically significant toxic effects or ineffectiveness of treatment with targeted therapy drug. Specific recommendations concerning dose modifications of each drug or avoidance of concomitancy for such situations are described in Table 2. Physicians must be aware of the potential interactions of targeted therapy.

In general, MoAb are not implicated in DDI except antibody drug conjugates such as brentuximab or trastuzumab emtasine. Brentuximab is an antibody drug conjugate (ADC) in which approximately 4 molecules of MMAE are linked to a CD30-directed antibody molecule. In vivo data indicate a small amount of MMAE released

from the ADC is metabolized. In vitro data indicate that CYP3A4/5 is the primary metabolic pathway for MMAE. In an undefined study, rifampin, a strong CYP3A4 inducer, decreased the exposure to MMAE by approximately 46 %; ketoconazole, a strong CYP3A4 inhibitor, increased the exposure to MMAE by approximately 34 % (information from package insert).

However, the other group of targeted therapy, the signal transduction inhibitors, have a rather potential DDI with concomitant medication. There is a wide spectrum of recommendations on ways to manage DDI across this broad class of drugs. Although some DDI can be easily managed by an increase in monitoring using laboratory tests and patient tolerance, greater monitoring cannot mitigate the impact of others.

Remarkably, DDI with acid suppression therapy are still not fully understood neither clinical signification nor management. Manufacturers of several other oral chemotherapeutics recommend that avoidance of PPIs be considered. A good example can be erlotinib, while is generally recommended to avoid the concomitant administration with proton pump inhibitors, some recent studies find no relevant interaction between erlotinib and PPI [12, 13]. In a retrospective review of data from a randomized, placebo-controlled trial conducted in 485 patients with advanced or metastatic non-small cell lung cancer, the average erlotinib Cmin was not significantly different between users and non-users of acid suppression medications (including proton pump inhibitors (PPIs) or H-2 blockers) [13]. Progression-free and overall survival did not appear to be significantly altered by the use of acid suppressants. The retrospective nature of the study, uncontrolled use of acid suppressants throughout the study period, and lack of monitoring of adherence should also be considered. However, these results do raise questions about the clinical significance of this interaction. In a pharmacokinetic/pharmacodynamic/pharmacogenomic study involving Japanese patients with non-small cell lung cancer, erlotinib exposure was similar in patients receiving concurrent gastric acid suppressing medication ($n = 18$) compared to patients not receiving gastric acid suppressing therapy ($n = 38$) [14]. However, a recent pharmacokinetic study of 24 healthy volunteers, omeprazole decreased the erlotinib AUC and Cmax by 45 and 54 %, respectively. The AUC and Cmax of the active metabolite of erlotinib (OSI-420) also decreased by 55 and 60 %, respectively [15]. Interestingly, the same study found that coadministration of erlotinib 2 h after ranitidine (300 mg) decreased the AUC and Cmax of erlotinib by 33 and 54 %, respectively. The effect of ranitidine on erlotinib exposure was lessened using staggered administration times. Administration of erlotinib with ranitidine (150 mg twice daily) with the erlotinib dose given 10 h after the evening ranitidine dose and 2 h before the morning ranitidine dose, resulted in a decrease in the AUC and Cmax of erlotinib by 15 and 17 %, respectively [15].

The DDI between coumarin-derived anticoagulants and targeted therapy can potentially elevate INR, so, generally, they can be managed with increased monitoring of INR. Dabrafenib appears to be the only targeted therapy agent that may decrease bioavailability of warfarin.

Another important source of DDI are the complementary and alternative medicine.

In a systematic review of 890 pairs of herb-drug interactions, St. Johns wort was found to cause the majority of herb-drug interactions (147), followed by ginkgo (51) and kava kava (41). Warfarin (105) was identified as the drug most frequently involved, followed by insulin (41) and aspirin (36). Among drugs used in oncology, cases involving cyclosporine (16), heparin (14), and tamoxifen (11) have been reported [16].

Most targeted therapy drugs are eliminated by hepatic metabolism and excreted in faeces as metabolites or unchanged, with no significant contribution of renal clearance. Despite part of drug are eliminated by kidneys, this renal clearance is generally undertaken as inactive metabolites (see Table 2).

There are no guidelines or standards for determining clinical relevance of interactions via consistent systematic evaluation or classification [17]. One possible approach is to check medication for DDI by using DDI compendia. Nowadays, several commercial DDI compendia are available. It is advisable to consult more than just one DDI information reference source to ensure that is safe to use certain drugs concomitantly [17]. For example, two different compendia (Micromedex and www.drugs.com) were employed by van Leeuwen et al. to "maximize accuracy" of the medication review [18]. However, a recent systematic review on interactions between oral antineoplastic agents and concomitant medication was performed by using Micromedex and LexiComp handbook [19]. Moreover, studies have shown that major conflicts exist among drug compendia on DDI information such as severity and evidence ratings [20]. So, which compendia are more advisable? Currently there are no evidence supporting any of them respect the others. Several discrepancies were observed between the different compendia, some of them remarkable. Compendia use differing approaches to identify and evaluate evidence on DDI. It has been reported that the main factors that contributed to the observed discrepancies could be related to different sources of information and the different assumptions to extrapolated DDI of one drug to other drugs within the same class [20].

There are some limitations to the methodology followed in this article. The latest package inserts versions were analysed to identify DDI. Unfortunately, some of the drugs

commercially available for a substantial time do not have current studies for specific DDI. Second, certain DDI were not included in our analysis because of a pharmacodynamic interaction rather than a pharmacokinetic interaction. Therefore, it is important for health care professionals to evaluate pharmacodynamic interactions when prescribing oral chemotherapy. Lastly, the literature for anticancer drugs changes rapidly; the information in the tables provided in this article reflects the most current recommendations at the time data were collected. Therefore, it is crucial that health care providers actively review the most current data for DDI before any formal recommendations.

In conclusion, the patient population receiving targeted therapy is increasing rapidly, causing stark changes in the management and treatment of malignancies. It is essential that health care providers monitor patients for potential DDI to avoid a loss in efficacy or risk of greater toxicity from targeted therapy. Oncology pharmacists play an essential role in maintaining patient safety. To do this, a profound assessment not only of co-prescribed drugs, but also herbal supplements, lifestyle food and drinks (e.g., grapefruit juice), cardiac risk factors (QTc interval), and physical examination is needed. Moreover, it is highly recommendable a real collaboration between pharmacist, oncologists and haematologists, as well as other medical specialists to undertake a proper care of these patients.

Compliance with ethical standards

Informed consent Not applicable (not research involving human participants and/or animals).

Conflict of interest The authors declare that they have no conflict of interest.

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