Gastrointestinal toxicities of novel agents in cancer therapy

Amani Asnacios[a], Sylvie Naveau[a,b,c], Gabriel Perlemuter[a,b,c]

[a] *AP-HP, Hôpital Antoine Béclère, Service d'hépato-gastroentérologie, Clamart, F-92140, France*
[b] *INSERM, U764, Institut Fédératif de Recherche 13, Clamart, F-92140, France*
[c] *Univ Paris-Sud, Faculté de médecine Paris-Sud, Clamart, F-92140, France*

Introduction

Cancer is the second cause of death in Western countries and its incidence continues to increase. There has also been increase in the elderly population of patients with a good performance status for whom a proposition of specific cancer treatment should be made.

For the last 10 years, there has been a revolution with regards to the development of novel agents refered to as "targeted therapy". Indeed, the better understanding of mechanisms of oncogenesis has led to the development of new anti-cancer molecules, and many agents have been developed recently with different sites of action.

However, these drugs can be responsible for gastrointestinal side effects, and particularly diarrhoea and hepatotoxicity that can potentially limit their use. We will describe herein pathophysiology, incidence, clinical features and treatment of digestive and liver toxicities for targeted therapies approved for clinical practice. In this article, we will use the National Cancer Institute (NCI) grading system (Table 1). Table 2 summarizes incidence of diarrhoea, indications of approved targeted therapy and the molecular targets.

Incidence, clinical pattern and pathophysiology of diarrhoea

Anti-epidermal growth factor receptor (EGFR) therapies

Two different anti-EGFR targeting strategies are currently available: monoclonal antibodies that target the extracellular domain of the receptor, inhibiting dimerisation and subsequent signal transduction, and small molecule inhibitors of the intracellular phosphotyrosine kinase domain [1]. Monoclonal antibodies are approved for the treatment of metastatic colorectal cancer (mCRC) (cetuximab, panitumumab), and for the treatment of head and neck cancer in the case of cetuximab; the tyrosine kinase inhibitors (TKIs) are used for the treatment of non-small cell lung cancer (NSCLC) (gefitinib, erlotinib) and for pancreatic cancer in the case of erlotinib.

Table 1
Common terminology criteria for adverse events (NCI-CTCAE)

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	None	Increase <4 stools/d over pre-treatment	Increase 4–6 stools/day over pre-treatment	Increase >7 stools/day or incontinence; or need for parenteral support for dehydration	Physiologic consequences requiring intensive care; or haemodynamic collapse
AST and ALT	None	<2.5 ULN	>2.5–5 ULN	5–20 ULN	>20 ULN
Bilirubin	None	<1.5 ULN	>1.5–3 ULN	>3–10 ULN	>10 ULN
Lipase	None	>1–1.5 ULN	>1.5–2 ULN	>2–5 ULN	>5 ULN
Pancreatitis	None	–	–	abdominal pain with pancreatic enzyme elevation	Complicated by shock (acute circulatory failure)
Haemorrhage/bleeding without grade 3 or 4 thrombocytopenia	None	Mild without transfusion	–	Requiring transfusion	Catastrophic bleeding requiring major non-elective intervention

Table 2
Incidence of diarrhoea from approved targeted therapies

Molecule	Incidence of diarrhoea (%)		Adm	Target	Disease	Reference(s)
	All grades	Grade 3/4				
Erlotinib	54	6	O	EGFR	NSCLC, Pancreatic cancer	[2]
Gefitinib	40–60	6.8	O	EGFR	NSCLC	[3]
Cetuximab	28 + irinotecan: 72%	2 22	IV	EGFR	Colorectal cancer Head and neck cancer	[4,5]
Panitumumab	21	1/0	IV	EGFR	Colorectal cancer	[6]
Trastuzumab	7	0	IV	HER2	Breast cancer	[7]
Lapatinib	51	<10/<1	O	EGFR/ HER2	Breast cancer	[8]
Imatinib	45	1–5	O	BCR-Abl, Kit, PDGFR	CML, GIST	[9,10]
Sunitinib	20	3/0	O	BCR-Abl, Kit, PDGFR	CML, GIST, renal carcinoma	[11]
Nilotinib	10	2	O	BCR-Abl, Kit, PDGFR	CML	[12]
Dasatinib	25–50	2–6	O	Abl, Kit, PDGFR	CML, acute lymphoblastic leukaemia	[13]
Sorafenib	39–55	8/0	O	RAF, VEGFR, PDGFR	Renal carcinoma, hepatocellular carcinoma	[14–16]
Bevacizumab	<10	0	IV	VEGF-A	mCRC, breast cancer, renal carcinoma, NSCLC	[17,18]
Bortezomib	34–40	4–8/0	IV	Proteasome inhibitor	Multiple myeloma	[19]
Temsirolimus	27	1	IV	mTOR	Renal carcinoma	[20]

Adm: administration; O: orally; IV: intravenously; CML: chronic myelogenous leukaemia; GIST: gastrointestinal stromal tumour; NSCLC: non-small cell lung cancer.

Diarrhoea occurs in about 20–28% of patients undergoing anti-EGFR monoclonal antibody therapy but is rarely severe: 1–2% of grade 3–4. The incidence and severity of diarrhoea is higher with EGFR-TKIs than with anti-EGFR monoclonal antibodies, which have an incidence of 50–60% including 5% grade 3–4; diarrhoea is a dose limiting toxicity for TKIs [21,22].

Diarrhoea related to erlotinib led to significantly more dose-treatment reduction in comparison with placebo (observed in 5% vs. 1% of patients, respectively) in a phase III trial with NSCLC patients [23]. Diarrhoea appears frequently within the first 2 weeks after treatment initiation [22]. Contrary to skin rash, which is correlated to drug steady state concentration, diarrhoea appears correlated with dose and not with plasma concentrations [24], suggesting a direct effect of erlotinib on the gastrointestinal tract. This hypothesis is also supported by the fact that oral small molecule-TKIs are more frequently associated with diarrhoea than monoclonal antibodies administered intravenously. It is interesting to note that EGFR is widely expressed in the normal colic mucosa in which it regulates both chloride secretion and sodium absorption by colonocytes [25–28]. Therefore, EGFR inhibition can subsequently lead to secretory diarrhoea.

Epidermal growth factor (EGF) is also described to be involved in the maintenance of mucosal integrity, the stimulation of mucin production and the enhancement of prostaglandin synthesis [29]. Inhibition of EGFR might therefore lead to digestive lesions.

Some clinical characteristics were described to be associated with the response to anti-EGFR TKIs in patients with NSCLC: adenocarcinoma, women, Asian ethnicity, and never-smoker status [3,30,31]. Diarrhoea related to drug toxicity was also correlated in some studies with a clinical benefit and/or was a predictive factor of tumour response to TKI [31]. Moreover, several molecular features of the tumour such as activating EGFR mutation [32,33] or K-ras mutation [1,34] were shown to be predictive factors of response or non-response to treatment, respectively.

Somatic EGFR mutations in tumour cells are significantly associated with response to gefitinib for NSCLC; however they are not associated with the incidence or the severity of drug toxicities including diarrhoea [33].

EGFR intron 1 polymorphism mediates response to EGFR inhibitors and is associated with skin toxicity [35]. Cells with a lower number of CA single sequence repeats in the intron 1 (CA-SSR 1) of EGFR have a higher expression of EGFR protein and are more sensitive to the inhibitory effects of erlotinib. Correlation between CA-SSR1 polymorphism and diarrhoea has not been explored. Nevertheless, as CA-SSR1 is a germinal polymorphism, we can hypothetise

that patients showing this polymorphism may have an overexpression of EGFR in the gastrointestinal tract.

The –216G/T and –191C/A polymorphisms in the EGFR promoter lead to a higher expression of EGFR gene. These polymorphisms were associated with a grade $\geqslant$2 diarrhoea, in a prospective study of 80 patients [24], suggesting a direct role of the EGFR in the mechanism of diarrhoea. A polymorphism of the drug transporter ABCG2 and of the CYP3A4 and CYP3A5 genes may modify the pharmacokinetics and therefore the toxicities of the drug; the 141K-ABCG2 polymorphism is associated with a lower expression and activity of ABCG2, and consequently a higher accumulation of both gefitinib and erlotinib [36]. This 141K-ABCG2 polymorphism is correlated with the incidence of diarrhoea in patients treated with gefitinib [37]. However, in another study, there was a correlation between ABCG2 polymorphisms and erlotinib pharmacokinectics parameters but not with diarrhoea. In this study, CYP 3A5*3G polymorphism, leading to a lower expression of CYP3A5 and drug accumulation, was marginally associated with any grade diarrhoea [24].

Anti-HER2 (ErbB2) therapies

Trastuzumab (Herceptin®) is a monoclonal antibody directed against HER2. Trastuzumab is rarely associated with diarrhoea, with a total incidence of 7% versus <1% in patients without treatment and without any grade 3–4 toxicity [7].

Lapatinib is a dual anti-EGFR and anti HER2 TKI (Tyverb® in France, Tykerb® in US) approved for the treatment of metastatic breast cancer overexpressing HER2 in association with capecitabine. Crown [8] pooled the results of eleven clinical trials (phase I, II and III) concerning patients with metastatic breast cancer treated with lapatinib to analyse diarrhoea. Lapatinib was given at doses ranging from 1000 to 1500 mg/day as monotherapy ($n = 926$), or in combination with either capecitabine ($n = 198$) or a taxane ($n = 687$). Overall, diarrhoea occurred in 55% of lapatinib-treated patients versus 24% of controls. All grade diarrhoea occurred in 51% of patients treated with lapatinib alone, 65% in association with capecitabine and 48% in association with taxane. Most diarrhoea was grade 1–2; grade 3 occurred in 9% of patients versus 4% in non-lapatinib treated patients and grade 4 in less than 1% (in both groups).

Forty percent of patients treated with lapatinib experienced the first episode of diarrhoea within 6 days after drug introduction for a median duration was of 7–9 days. Diarrhoea led to treatment discontinuation in 2% of cases.

In a phase I trial of lapatinib, 42% of the 67 patients experienced grade 1–2 diarrhoea while there were no grade 4 incidents [38]. Diarrhoea was dose related and not associated with serum concentration, again suggesting a direct effect on gastrointestinal mucosa. This could be due to the potential effect of lapatinib on EGFR in normal mucosa but may also be due to an effect on ErbB2 in colic mucosa. Indeed, ErbB2 and ErbB3 receptors mediates inhibition of calcium-54ependent chloride secretion in colonic epithelial cells [39] and ErbB2 is involved in maintenance of the enteric nervous system [40,41].

Multi-targeted kinase inhibitors

Imatinib (Gleevec® or Glivec®). This orally bioavailable TKI and is associated with diarrhoea in about 40% of patients; diarrhoea is rarely severe, with less than 5% of patients experiencing grade 3–4 diarrhoea [9,10,42]. Diarrhoea is related to drug dose [28]. In gastrointestinal stromal tumour (GIST), independent risk factors for diarrhoea were high imatinib dose, female sex and the primary site of gastrointestinal disease [43]. The mechanism remains unknown, but one hypothesis is the inhibition of the colonic pace-maker cell (Cajal cells) which are c-Kit positive [28,44].

Sunitinib (Sutent®) Diarrhoea is observed in about 20% of treated patients including 3% with grade 3 but no grade 4 diarrhoea [11].

Sorafenib (Nexavar®) was initially developed as a serine/threonine kinase inhibitor of raf-1. It also inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), c-KIT and Fms-like tyrosine kinase-3 (Flt-3). It is approved for the treatment of renal carcinoma [14] and hepatocellular carcinoma [15]. In a phase III trial including 602 patients comparing sorafenib with placebo for advanced hepatocellular carcinoma, the main adverse effect was diarrhoea which occurred in 39% of patients versus 11% in the placebo arm. Diarrhoea was generally mild, with 8% grade 3 and no grade 4. Diarrhoea was the most frequent adverse event that led to dose reduction (8% of cases) [15]: diarrhoea often occurs within the first week of administration and appeared to be dose dependent [28]. Interestingly, diarrhoea together with skin toxicity were significantly associated with increased time to progression in a pooled analysis of sorafenib in solid tumours [45].

Nilotinib (Tasigna®) is a multi-target (BCR-Abl, KIT, PDGFR) TKI approved for the treatment of imatinib-refractory or intolerant Philadelphia Chromosome-positive chronic myeloid leukaemia (CML) patients. In a phase I trial, no grade 3–4 diarrhoea occurred [12]. In a phase II trial, nilotinib-related diarrhoea was observed in less than 10% patients with only 1% grade 3–4 [46].

Dasatinib (Sprycel®) caused all grades of diarrhoea in about 50% of patients, including 6% of grade 3–4. However, diarrhoea was not a dose-limiting toxicity [13].

Anti-angiogenic therapies

The oral TKIs **sunitinib** and **sorafenib** have been described above.

The anti-vascular endothelial growth factor (VEGF) monoclonal anti-body, **bevacizumab** is approved for the treatment of metastatic CRC, breast carcinoma, renal cancer and NSCLC. In a phase I safety trial, moderate diarrhoea occurred in only 12% of patients with no grade 3 or 4 diarrhoea [17]. The association with chemotherapy did not lead to a significant increase of incidence or severity of diarrhoea [18,47].

Others

Temsirolimus (Torisel®) frequently causes diarrhoea in a phase III trial, occurring in 27% of patients with less than 1% of patients experiencing grade 3–4 diarrhoea. In an animal model, a high dose of rapamycin was responsible for a reduced intestinal surface area leading to a malabsorption of lipids [48].

Bortezomib (Velcade®) is a proteasome inhibitor used to treat multiple myeloma. Incidence of all grade diarrhoea was about 30–40% in phase II/III trials of bortezomib alone or in combination with chemotherapy; grade 3 diarrhoea occurred in 4–8% of patients, but no patient developed grade 4 diarrhoea [19,49].

Diarrhoea is reported as watery, with no bleeding, and associated with mild to moderate abdominal pain and cramps. Symptoms occur within the first 12–18 h after infusion initiation, and lasts for 1–2 days [28].

Management of diarrhoea in patients undergoing targeted therapy

As described above, little is known about the precise mechanisms of diarrhoea. Therefore, treatment remains empirical. It is important to exclude another cause of diarrhoea to avoid inappropriate treatment discontinuation. Medical anamnesis should check for laxative treatment, a concomitant intake of treatment promoting diarrhoea, such as magnesium-containing anti-acids, false diarrhoea of constipated patients or a past history of gastrointestinal tract surgery (at risk of swarm). If necessary, particularly in the case of antibiotics administration within the last 3 months, a stool examination should be carried out to look for *Clostridium* or another infection [44].

Patients should be informed about the risk of diarrhoea due to targeted therapy and given hygienic and dietetic advice, such as the increase of fluid intake and a fibre-poor diet.

In most patients, diarrhoea resolves with conventional approaches, without dose modification [8]. It can be useful to rapidly start loperamide treatment with the classic administration of two 2 mg tablets after the first occurrence of diarrhoea followed by one tablet after consecutive episodes every 4 h [11,28,50]. Such a prescription should be systematically given to patients undergoing targeted therapy.

In a minority of patients (<5% of cases), but particularly with orally administered small molecules, dose modification or treatment discontinuation is necessary [15,43]. The combination of cholestyramine and loperamide treatment can be efficient [28].

Octreotide acetate and long-acting formulations have been shown to be effective in the control of chemotherapy-induced diarrhoea [51,52]. However, no trial has confirmed efficacy of octreotide in diarrhoea related to targeted therapy. If diarrhoea does not respond to limited intervariations, a dose of 0.5 mg subcutaneously (s.c.) of octreotide acetate every 8 h for 48–96 h may be recommended when diarrhoea is resistant to loperamide. Octreotide should be discontinued within 24 hours after the resolution of diarrhoea [51].

Budesonide is a topically active steroid with high activity in inflammatory bowel disease. Budesonide is administered orally and has a 90% first pass effect in the liver leading to a low systemic availability. It was shown to be efficient in chemotherapy-related diarrhoea if there was no response to loperamide [44]. There is no available trial studying its effect in case of loperamide-resistant diarrhoea induced by targeted therapy.

In a minority of patients, diarrhoea is severe (responsible for dehydration, renal insufficiency or electrolyte imbalances or associated with fever and/or grade 3–4 neutropenia). In such patients, there is a need for hospitalisation for evaluation, intravenous fluid administration and electrolyte correction and/or antibiotics. Treatment with targeted agents must be

discontinued. If necessary, treatment might be reintroduced at lower doses after recovery and under medical supervision.

Gastrointestinal bleeding, gastrointestinal perforation and wound-healing problems

Bleeding is a recognised side effect of anti-angiogenesic therapy and in a phase II trial, haemorrhage was identified as a possible side-effect of bevacizumab treatment [53]. However, a phase III randomized trial enrolling 813 patients with previously untreated mCRC showed that grade 3–4 bleeding from any cause was similar in the two groups of patients irrespective of bevacizumab administration. Nevertheless, all three cases of grade 4 bleeding were in the irinotecan–5-fluorouracil–leucovorin (IFL) + bevacizumab group [18]. This was confirmed in another phase III trial including 462 patients with metastatic breast cancer; there was no grade 4 haemorrhage and no significant differences for serious bleeding between patients given bevacizumab or not [47].

In a phase III trial including 842 patients with advanced NSCLC, there was a significant increase of grade 3–5 all-cause bleeding in the case of addition of bevacizumab to paclitaxel and carboplatin (0.7% versus 4.4%). However, bleeding was due to an increase in haemoptysis and not to gastrointestinal bleeding [54], suggesting that bleeding is related to the tumour itself.

Grade-3 digestive ulceration with bleeding within the radiotherapy field has also been reported [55]. No mechanism was proposed and it was concluded that bevacizumab is generally safe in this population. Acute gastrointestinal toxicity now seems to be lower than previously reported and is easily manageable.

The oral anti-VEGFR-TKI sorafenib was not associated with digestive haemorrhage or variceal bleeding in cirrhotic patients treated for hepatocellular carcinoma in a randomised trial versus placebo which included 602 patients [15].

Imatinib, at a high dose of 800 mg/d was responsible for digestive haemorrhage-related death in four patients which represented approximately 45% of possible drug-related deaths [56]. Pathophysiology is unknown.

Gastrointestinal perforation was observed in six patients (1.5%) included in the IFL+ bevacizumab arm of a phase III randomised trial of first-line treatment in mCRC [18]. Colon surgery within the previous 2 months in two patients and peptic-ulcer disease in one patient were factors of gastrointestinal perforation. Of the six patients with a perforation, three had a confirmed complete or partial response to IFL+ bevacizumab. Incidence of gastrointestinal perforation is higher in case of untreated primary colic cancer [28].

Bevacizumab is also associated with **wound-healing complications** in about 2–4.5% of patients who had surgery after treatment initiation [29,54]. A period of 5–6 weeks free from bevacizumab treatment is recommended before and after surgery to avoid bleeding and wound-healing complications.

Targeted therapy and hepatic toxicity

Kit and PDGFR inhibitors

Imatinib

In clinical trials, severe hepatotoxicity occurs in less than 5% of patients [57–60]. Hepatotoxicity is the second major cause of dose reduction or treatment discontinuation.

To date, a total of 24 case reports of severe hepatitis-induced by imatinib have been published [58,61–77]. Among them, five were fatal [58,62,72,73,77]. Seventy-four percent of patients with liver toxicity were women with a median age of 57 years (range 18–79 years). Imatinib was administered for CML in 87% of cases (two patients had GIST and one was treated for polycythemia vera). Median delay between treatment initiation and liver injury was 22 weeks (range 1.7–104 weeks). Fifty percent of patients showed non-specific symptoms such as asthenia or anorexia. In these cases, aminotransferase levels were higher than 10-fold the upper limit of normal (ULN) [74]. Toxicity was attributed to imatinib after elimination of other causes (e.g. viral, immune, haemochromatosis, vascular liver or biliary injury) and in some cases by its recurrence after re-administration of imatinib [63,65,70,71]. After treatment discontinuation, evolution was often benign with normalisation of liver tests in 7 weeks (range 2–20 weeks). However, fatal liver injury occurred in five patients; two of these patients were concomitantly treated by acetaminophen (one patient took less than 1 g per day after the beginning of symptoms) and one patient had a hepatitis B virus infection but without evidence of recurrence [77]. Liver pathology (on explanted liver or sample) was available for 14 patients. In most patients, lesions showed necrotic hepatitis associated with a non-specific inflammatory infiltrate; patients with fulminant hepatitis had a massive viral hepatitis-like necrosis compatible with an inflammatory idiosyncratic mechanism [63,64,71]. In other patients, eosinophils were found in the

inflammatory infiltrate [76]; interface hepatitis and bridging necrosis similar to that observed in auto-immune hepatitis and suggestive of an immuno-allergic mechanism has also been described [69]. In one case, massive hepatocellular necrosis was associated with micro-thrombi in hepatic vessels suggesting that liver injury was related to an increase of the pro-thrombotic potential of the polycythemia vera [62].

Little is known about the mechanisms of liver toxicity but imatinib is metabolised by cytochrome P450. Therefore, an increase in toxic metabolites is possible in cases where there is use of enzymatic inducers (like alcohol [66] or roxythromycin [63]). An idiosyncratic mechanism was therefore largely evocated. However, an immuno-allergic mechanism was probable in at least three patients, with the presence of hypersensitivity manifestations such as eosinophilia, cytopenia [61,67,76], presence of eosinophils at liver pathology, and presence of auto-antibodies in serum: antinuclear, anti-cytosol 1 with an increase of gamma-globulin [66,69].

Liver tests and prothrombin time should be performed before initiation of imatinib and then weekly or twice a month in the first month and then monthly thereafter or in case of symptoms. Treatment has to be withdrawn in cases of grade-3 hepatotoxicity. Some authors have re-introduced imatinib at slowly increasing doses together with prednisone without recurrence of liver injury [67,70,74,78]. Among them, some patients experienced recurrence of liver toxicity when imatinib was re-introduced before steroid administration. One should be cautious in case of use of enzymatic inducers; the patient should be informed to avoid excess alcohol and auto-medication. Of note, there is a risk of a decreased concentration of the drug if enzymatic inhibitors are used.

Sunitinib

Sunitinib hepatotoxicity is not clear. In clinical trials, hepatotoxicity was reported in less than 1% of patients: two patients died with liver injury but had hepatic metastasis. Liver samples were not available rendering the evaluation of the mechanism and the relationship with the drug difficult. Mueller and colleagues reported a case of fatal fulminant hepatitis after 5 months of treatment in a 75-year old woman with metastatic renal cancer [79]. The use of the Naranjo adverse drug reaction probability scale [80] indicated a possible relationship between sunitinib and hepatotoxicity.

It is important to note the possibility of a drug-drug interaction with letrozole; both treatments undergo hepatic metabolism by cytochrome P450 isoenzyme 3A4; however, neither agent appears to be a strong inhibitor of this isoenzyme.

Given the lack of formal recommendations for hepatic monitoring during sunitinib therapy and pharmacokinetic similarities with imatinib, baseline and monthly monitoring of liver tests is a reasonable recommendation [79]. Association with enzymatic inhibitors must be used with caution.

No cross-over toxicity was reported in case of treatment with sunitinib after imatinib-induced hepatotoxicity [71].

Anti-EGFR tyrosine kinase inhibitors therapies

Gefitinib

In four phase I trials with gefitinib, hepatotoxicity was a dose limiting toxicity as was diarrhoea [22, 81–83]. In the IDEAL 1 trial [3], 2% of patients experienced grade 3–4 hepatotoxicity that needed treatment discontinuation. Ho and colleagues reported a case of severe cytolytic hepatitis with gefitinib [84]. This toxicity was dose-54ependent. Moreover, maximum concentration (Cmax) and area under the curve (AUC) depend on the number of consecutive days of gefitinib administration [22]. Therefore, Seki and colleagues [81] administered a classical dose of 250 mg but spaced it by 5 days in two patients with a tumour response but with grade-3 cytolytic hepatitis. While initial re-challenge was impossible when given daily, they did not observe any recurrence of cytolysis with this spaced schedule and obtained objective response or disease stabilisation in these two patients.

Erlotinib

In clinical trials, dose-limiting toxicities were related to diarrhoea, skin rash or fatigue, but not to hepatotoxicity. A maximum of grade-2 liver toxicity was observed in fewer than 4% of patients. A case of a grade-3 aminotransferase level increment in a patient treated by erlotinib monotherapy for pancreatic carcinoma was also reported [85]. Of note, erlotinib is metabolised by the cytochrome pathway.

Anti-HER2 therapies

To date, **trastuzumab-induced hepatotoxicity has not been reported in any trial. However,** a case report concerning a 54-year old woman with grade-4 hepatotoxicity related to trastuzumab has been reported [86]. The mechanism of hepatic injury is unclear.

CP-724,714 a reversible, highly selective oral HER-2-TKI was accompanied, in a phase I trial, by

Table 3
Recommendations of tests according to treatment

	Liver tests			Lipase if abdominal pain
	W0	W1 to W4	Every M	
Imatinib	+	+	+	
Sunitinib	+		+	+
Lapatinib	+		+	
Sorafenib				+
Nilotinib				+

W: week; M: Month

a dose-limiting hepatotoxicity in nearly 30% of the patients; 10% of patients had grade 3 hepatotoxicity [87]. The cytolytic and cholestatic toxicities were drug-related and prohibited further dose escalation beyond the 250 mg dose. Patients were better able to tolerate the 250 mg thrice daily dosing but unable to tolerate higher doses (400 mg twice daily), suggesting that peak levels rather than cumulative exposure determine the observed liver toxicity.

Lapatinib

Lapatinib hepatotoxicity is rare and reversible. In the GlaxoSmithKline's worldwide safety database 39 cases of hepatotoxicity were identified. Among them, 38.5% were receiving lapatinib monotherapy [88]. The majority of cases were from clinical trials, which yielded a crude incidence of 0.4% for hepatobiliary events in the entire lapatinib programme while seven cases of hepatotoxicity were from other sources. There have been 13 reports of death due to liver-related events. However, due to these patients' medical conditions and underlying cancer, it is difficult to ascertain lapatinib's role. It is advised to monitor liver function before initiating treatment and monthly thereafter or as clinically indicated. Lapatinib should be discontinued and not restarted in patients with severe changes in liver function. Caution should be taken in cases involving the use of CYP3A4 inducers.

Anti-VEGF monoclonal antibody bevacizumab

No significant hepatotoxicity was reported in a phase I trial with bevacizumab [17]. A possible case of bevacizumab-related sclerosing cholangitis in a 65-year old Caucasian patient has been reported [89]. The patient received 2 months of bevacizumab as neo-adjuvant therapy before liver resection for two synchronous liver metastases of colon cancer. A liver biopsy performed in the third postoperative week when the bilirubin reached a plateau showed cholestatic hepatitis with marked ductopenia with segmental neutrophilic cholangitis but mainly fibrous cholangitis and periductal fibrosis. Obstructive arteriopathy and venopathy were found in many small portal vessels suggestive of organisation of occlusive thrombi. The resected liver specimen showed a mild cholestatic pattern with focal periductal fibrosis and small peribiliary arterial and portal thrombosis [89].

A possible mechanism involves a decrease of endothelial cell repair capacity related to VEGF inhibition [89].

Of note, in a retrospective study with 105 patients, bevacizumab appeared to improve pathologic response and to protect against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases [90]. Oxaliplatin is indeed known to be responsible for sinusoidal obstruction syndrome (SOS) [91,92].

In conclusion, little is known about the mechanisms of hepatotoxicity due to targeted agents and management is often empirical. One should be cautious with the use of enzymatic inducers or inhibitors together with agents metabolised by the cytochrome pathway (e.g. imatinib, gefitinib, erlotinib). Hepatic function tests should be performed regularly (Table 3). In case of liver dysfunction, other aetiologies should be ruled out and the use of the adverse drug reaction probability scale will help to evaluate the relationship between drug and hepatotoxicity. A declaration to the pharmacovigilance agency should be made.

Some authors have proposed the reintroduction of imatinib together with corticosteroids; others suggest to modify the schema of treatment administration.

Elevation of pancreatic enzymes

Elevation of lipase can be observed with the small oral multi-targeted therapies sorafenib, sunitinib and nilotinib. Lipase increase or pancreatitis is rarely described with anti-EGFR, or anti-VEGF monoclonal

antibodies. It occurs in less than 5% of patients treated by the combination of **erlotinib** and gemcitabine for pancreatic cancer. Lipase increase has not been reported in patients treated by erlotinib alone in NSCLC [2]. In a trial studying **bevacizumab** together with cyclophosphamide in 15 heavily pre-treated patients with recurrent ovarian cancer, one patient presented grade-3 pancreatitis [93].

In a non-randomised trial studying **sunitinib** in 106 patients with renal cell carcinoma, an increase of lipase without clinical symptoms was observed in 28% of cases [11].

In phase I/II studies, a grade 3 lipase increase was observed in 18% of patients receiving **nilotinib**. Treatment was discontinued in one patient for pancreatitis; of note, this patient had a past history of pancreatitis [12,46].

In a non-randomised phase II trial investigating **sorafenib** in 129 patients with advanced renal cell carcinoma, an increase in lipase was the most frequent any-grade drug-related adverse event with an incidence of 56%. Although 30% of patients had grade 3/4 elevated lipase, no patient developed clinical pancreatitis [94]. However, in a phase I trial, among 69 patients with advanced refractory tumours treated with **sorafenib**, three patients (4%) experienced grade-3 pancreatitis. Pancreatitis occurred in the 3–6 weeks after treatment introduction and did not appear to be dose-54ependent. Patients recovered after discontinuing treatment within 2 weeks [16].

In a randomised trial comparing **sorafenib** versus placebo in hepatocellular carcinoma, there was no significant difference between the two groups for all grade increase of lipase and also for grade 3–4 [15].

The mechanism underlying this lipase increase is unknown; no sign suggesting an immuno-allergic mechanism, such as hyper-eosinophilia, was reported. An ischaemia of the pancreas was hypothesised [95].

In conclusion, elevated lipase is frequently observed with sunitinib, nilotinib and sorafenib, but it is rarely associated with clinical pancreatitis. Lipase increase is not dose-dependent and the pathophysiology is unknown. It is important to search for pancreatitis in patients with abdominal pain undergoing these treatments (Table 3). Caution should be taken in case of a past medical history of pancreatitis.

Conclusion

Novel agents are revolutionising the treatment of cancer. Several toxic effects are associated with these new drugs including gastrointestinal adverse effects. These effects must be considered with caution as they can lead to a poor compliance, a decrease of drug intake and even discontinuation of treatment leading to compromised cancer control. Investigations are warranted to determine the precise pathophysiologic mechanisms of these side effects to improve efficacy and tolerance of treatment. Knowledge of these mechanisms may also lead to an adaptation of drug dosage to the individual patient.

Conflict of interest statement

None declared.

References

1 Linardou H, Dahabreh IJ, Kanaloupiti D, et al. Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. *Lancet Oncol* 2008;**9**:962–72.

2 Cohen MH, Johnson JR, Chen YF, et al. FDA drug approval summary: erlotinib (Tarceva) tablets. *Oncologist* 2005;**10**:461–6.

3 Fukuoka M, Yano S, Giaccone G, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol* 2003;**21**:2237–46.

4 Hanna N, Lilenbaum R, Ansari R, et al. Phase II trial of cetuximab in patients with previously treated non-small-cell lung cancer. *J Clin Oncol* 2006;**24**:5253–8.

5 Saltz LB, Meropol NJ, Loehrer PJ, Sr., et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 2004;**22**:1201–8.

6 Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007;**25**:1658–64.

7 Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1659–72.

8 Crown JP, Burris HA, 3rd, Boyle F, et al. Pooled analysis of diarrhea events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat* 2008;**112**:317–25.

9 Guilhot F. Indications for imatinib mesylate therapy and clinical management. *Oncologist* 2004;**9**:271–81.

10 Dagher R, Cohen M, Williams G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. *Clin Cancer Res* 2002;**8**:3034–8.

11 Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *Jama* 2006;**295**:2516–24.

12 Kantarjian H, Giles F, Wunderle L, et al. Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL. *N Engl J Med* 2006;**354**:2542–51.

13 Guilhot F, Apperley J, Kim DW, et al. Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase. *Blood* 2007;**109**:4143–50.

14 Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;**356**:125–34.
15 Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378–90.
16 Strumberg D, Richly H, Hilger RA, et al. Phase I clinical and pharmacokinetic study of the Novel Raf kinase and vascular endothelial growth factor receptor inhibitor BAY 43-9006 in patients with advanced refractory solid tumors. *J Clin Oncol* 2005;**23**:965–72.
17 Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. *J Clin Oncol* 2001;**19**:843–50.
18 Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;**350**:2335–42.
19 Fanucchi MP, Fossella FV, Belt R, et al. Randomized phase II study of bortezomib alone and bortezomib in combination with docetaxel in previously treated advanced non-small-cell lung cancer. *J Clin Oncol* 2006;**24**:5025–33.
20 Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;**356**:2271–81.
21 Hidalgo M, Siu LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol* 2001;**19**:3267–79.
22 Nakagawa K, Tamura T, Negoro S, et al. Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. *Ann Oncol* 2003;**14**:922–30.
23 Shepherd FA, Rodrigues Pereira J, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;**353**: 123–32.
24 Rudin CM, Liu W, Desai A, et al. Pharmacogenomic and pharmacokinetic determinants of erlotinib toxicity. *J Clin Oncol* 2008;**26**:1119–27.
25 Uribe JM, Gelbmann CM, Traynor-Kaplan AE, et al. Epidermal growth factor inhibits Ca(2+)-dependent Cl^- transport in T84 human colonic epithelial cells. *Am J Physiol* 1996;**271**:C914–22.
26 Uribe JM, Keely SJ, Traynor-Kaplan AE, et al. Phosphatidylinositol 3-kinase mediates the inhibitory effect of epidermal growth factor on calcium-dependent chloride secretion. *J Biol Chem* 1996;**271**:26588–95.
27 McCole DF, Barrett KE. Decoding epithelial signals: critical role for the epidermal growth factor receptor in controlling intestinal transport function. *Acta Physiol (Oxf)* 2009;**195**:149–59.
28 Loriot Y, Perlemuter G, Malka D, et al. Drug insight: gastrointestinal and hepatic adverse effects of molecular-targeted agents in cancer therapy. *Nat Clin Pract Oncol* 2008;**5**:268–78.
29 Widakowich C, de Castro G, Jr., de Azambuja E, et al. Review: side effects of approved molecular targeted therapies in solid cancers. *Oncologist* 2007;**12**:1443–55.
30 Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer – molecular and clinical predictors of outcome. *N Engl J Med* 2005;**353**:133–44.
31 Thomas SK, Fossella FV, Liu D, et al. Asian ethnicity as a predictor of response in patients with non-small-cell lung cancer treated with gefitinib on an expanded access program. *Clin Lung Cancer* 2006;**7**:326–31.
32 Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004; **350**:2129–39.
33 Fujiwara Y, Kiura K, Toyooka S, et al. Relationship between epidermal growth factor receptor gene mutations and the severity of adverse events by gefitinib in patients with advanced non-small cell lung cancer. *Lung Cancer* 2006;**52**:99–103.
34 Lievre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res* 2006;**66**:3992–5.
35 Amador ML, Oppenheimer D, Perea S, et al. An epidermal growth factor receptor intron 1 polymorphism mediates response to epidermal growth factor receptor inhibitors. *Cancer Res* 2004; **64**:9139–43.
36 Li J, Cusatis G, Brahmer J, et al. Association of variant ABCG2 and the pharmacokinetics of epidermal growth factor receptor tyrosine kinase inhibitors in cancer patients. *Cancer Biol Ther* 2007;**6**:432–8.
37 Cusatis G, Gregorc V, Li J, Spreafico A, et al. Pharmacogenetics of ABCG2 and adverse reactions to gefitinib. *J Natl Cancer Inst* 2006;**98**:1739–42.
38 Burris HA, 3rd, Hurwitz HI, Dees EC, et al. Phase I safety, pharmacokinetics, and clinical activity study of lapatinib (GW572016), a reversible dual inhibitor of epidermal growth factor receptor tyrosine kinases, in heavily pretreated patients with metastatic carcinomas. *J Clin Oncol* 2005;**23**:5305–13.
39 Keely SJ, Barrett KE. ErbB2 and ErbB3 receptors mediate inhibition of calcium-dependent chloride secretion in colonic epithelial cells. *J Biol Chem* 1999;**274**:33449–54.
40 Crone SA, Negro A, Trumpp A, et al. Colonic epithelial expression of ErbB2 is required for postnatal maintenance of the enteric nervous system. *Neuron* 2003;**37**:29–40.
41 Al-Dasooqi N, Bowen JM, Gibson RJ, et al. Trastuzumab induces gastrointestinal side effects in HER2-overexpressing breast cancer patients. *Invest New Drugs* 2009;**27**:173–8.
42 Demetri GD, Titton RL, Ryan DP, et al. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 32-2004. A 68-year-old man with a large retroperitoneal mass. *N Engl J Med* 2004;**351**:1779–87.
43 Van Glabbeke M, Verweij J, Casali PG, et al. Predicting toxicities for patients with advanced gastrointestinal stromal tumours treated with imatinib: a study of the European Organisation for Research and Treatment of Cancer, the Italian Sarcoma Group, and the Australasian Gastro-Intestinal Trials Group (EORTC-ISG-AGITG). *Eur J Cancer* 2006;**42**:2277–85.
44 Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage* 2008;**36**:413–23.
45 Strumberg D, Awada A, Hirte H, et al. Pooled safety analysis of BAY 43-9006 (sorafenib) monotherapy in patients with advanced solid tumours: Is rash associated with treatment outcome? *Eur J Cancer* 2006;**42**:548–56.
46 le Coutre P, Ottmann OG, Giles F, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated-phase chronic myelogenous leukemia. *Blood* 2008;**111**:1834–9.
47 Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 2005;**23**:792–9.

48 Dias VC, Madsen KL, Mulder KE, et al. Oral administration of rapamycin and cyclosporine differentially alter intestinal function in rabbits. *Dig Dis Sci* 1998;**43**:2227–36.

49 Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol* 2007;**25**:3892–901.

50 Papandreou CN, Logothetis CJ. Bortezomib as a potential treatment for prostate cancer. *Cancer Res* 2004;**64**:5036–43.

51 Barbounis V, Koumakis G, Vassilomanolakis M, et al. Control of irinotecan-induced diarrhea by octreotide after loperamide failure. *Support Care Cancer* 2001;**9**:258–60.

52 Rosenoff S. Resolution of refractory chemotherapy-induced diarrhea (CID) with octreotide long-acting formulation in cancer patients: 11 case studies. *Support Care Cancer* 2004;**12**:561–70.

53 Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003;**21**:60–5.

54 Elez E, Macarulla T, Tabernero J. Handling side-effects of targeted therapies: safety of targeted therapies in solid tumours. *Ann Oncol* 2008;**19** Suppl 7:vii146–52.

55 Keefe DM, Gibson RJ. Mucosal injury from targeted anti-cancer therapy. *Support Care Cancer* 2007;**15**:483–90.

56 Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol* 2008;**26**:620–5.

57 Cohen MH, Williams G, Johnson JR, et al. Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia. *Clin Cancer Res* 2002;**8**:935–42.

58 Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002;**99**:1928–37.

59 O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003;**348**:994–1004.

60 Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002;**347**:472–80.

61 Ohyashiki K, Kuriyama Y, Nakajima A, et al. Imatinib mesylate-induced hepato-toxicity in chronic myeloid leukemia demonstrated focal necrosis resembling acute viral hepatitis. *Leukemia* 2002;**16**:2160–1.

62 Lin NU, Sarantopoulos S, Stone JR, et al. Fatal hepatic necrosis following imatinib mesylate therapy. *Blood* 2003;**102**:3455–6.

63 James C, Trouette H, Marit G, et al. Histological features of acute hepatitis after imatinib mesylate treatment. *Leukemia* 2003;**17**: 978–9.

64 Kikuchi S, Muroi K, Takahashi S, et al. Severe hepatitis and complete molecular response caused by imatinib mesylate: possible association of its serum concentration with clinical outcomes. *Leuk Lymphoma* 2004;**45**:2349–51.

65 Rocca P, El Jastimi S, Troncy J, et al. [Imatinib mesylate-induced acute cytolytic hepatitis]. *Gastroenterol Clin Biol* 2004;**28**:918–9.

66 Ayoub WS, Geller SA, Tran T, et al. Imatinib (Gleevec)-induced hepatotoxicity. *J Clin Gastroenterol* 2005;**39**:75–7.

67 Ikuta K, Torimoto Y, Jimbo J, et al. Severe hepatic injury caused by imatinib mesylate administered for the treatment of chronic myeloid leukemia and the efficacy of prednisolone for its management. *Int J Hematol* 2005;**82**:343–6.

68 Yamazaki R, Okamoto S, Chen CK, et al. Successful management of liver injury caused by imatinib mesylate in a patient with previously untreated chronic myelogenous leukemia in the chronic phase. *Leuk Lymphoma* 2006;**47**:1427–30.

69 Dhalluin-Venier V, Besson C, Dimet S, et al. Imatinib mesylate-induced acute hepatitis with autoimmune features. *Eur J Gastroenterol Hepatol* 2006;**18**:1235–7.

70 Ferrero D, Pogliani EM, Rege-Cambrin G, et al. Corticosteroids can reverse severe imatinib-induced hepatotoxicity. *Haematologica* 2006;**91**:ECR27.

71 Pariente A, Etcharry F, Cales V, et al. Imatinib mesylate-induced acute hepatitis in a patient treated for gastrointestinal stromal tumour. *Eur J Gastroenterol Hepatol* 2006;**18**:785–7.

72 Cross TJ, Bagot C, Portmann B, et al. Imatinib mesylate as a cause of acute liver failure. *Am J Hematol* 2006;**81**:189–92.

73 Ridruejo E, Cacchione R, Villamil AG, et al. Imatinib-induced fatal acute liver failure. *World J Gastroenterol* 2007;**13**:6608–11.

74 Fuster F, Medina L, Vallansot R, et al. [Imatinib-induced toxic hepatitis: description of two cases and review of the literature]. *Gastroenterol Hepatol* 2007;**30**:525–30.

75 Mindikoglu AL, Regev A, Bejarano PA, et al. Imatinib mesylate (gleevec) hepatotoxicity. *Dig Dis Sci* 2007;**52**:598–601.

76 Kong JH, Yoo SH, Lee KE, et al. Early imatinib-mesylate-induced hepatotoxicity in chronic myelogenous leukaemia. *Acta Haematol* 2007;**118**:205–8.

77 Thia TJ, Tan HH, Chuah TH, et al. Imatinib mesylate-related fatal acute hepatic failure in a patient with chronic myeloid leukaemia and chronic hepatitis B infection. *Singapore Med J* 2008;**49**:e86–9.

78 Yamazaki R, Aisa Y, Mori T, et al. Administration of imatinib mesylate in patients with chronic myeloid leukemia with short bowel. *Leuk Lymphoma* 2009;**50**:670–2.

79 Mueller EW, Rockey ML, Rashkin MC. Sunitinib-related fulminant hepatic failure: case report and review of the literature. *Pharmacotherapy* 2008;**28**:1066–70.

80 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–45.

81 Seki N, Uematsu K, Shibakuki R, et al. Promising new treatment schedule for gefitinib responders after severe hepatotoxicity with daily administration. *J Clin Oncol* 2006;**24**:3213–4; author reply 3214–5.

82 Ranson M, Hammond LA, Ferry D, et al. ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. *J Clin Oncol* 2002;**20**:2240–50.

83 Baselga J, Rischin D, Ranson M, et al. Phase I safety, pharmacokinetic, and pharmacodynamic trial of ZD1839, a selective oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with five selected solid tumor types. *J Clin Oncol* 2002;**20**:4292–302.

84 Ho C, Davis J, Anderson F, et al. Side effects related to cancer treatment: CASE 1. Hepatitis following treatment with gefitinib. *J Clin Oncol* 2005;**23**:8531–3.

85 Ramanarayanan J, Scarpace SL. Acute drug induced hepatitis due to erlotinib. *Jop* 2007;**8**:39–43.

86 Srinivasan S, Parsa V, Liu CY, et al. Trastuzumab-induced hepatotoxicity. *Ann Pharmacother* 2008;**42**:1497–501.

87 Munster PN, Britten CD, Mita M, et al. First study of the safety, tolerability, and pharmacokinetics of CP-724,714 in patients with advanced malignant solid HER2-expressing tumors. *Clin Cancer Res* 2007;**13**:1238–45.
88 http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/DHCPL/2008.html.
89 Delis S, Triantopoulou C, Bakoyiannis A, et al. Sclerosing cholangitis in the era of target chemotherapy: a possible anti-VEGF effect. *Dig Liver Dis* 2009;**41**:72–7.
90 Ribero D, Wang H, Donadon M, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. *Cancer* 2007;**110**:2761–7.
91 DeLeve LD, Shulman HM, McDonald GB. Toxic injury to hepatic sinusoids: sinusoidal obstruction syndrome (veno-occlusive disease). *Semin Liver Dis* 2002;**22**:27–42.
92 Aloia T, Sebagh M, Plasse M, et al. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol* 2006;**24**:4983–90.
93 Chura JC, Van Iseghem K, Downs LS, Jr., et al. Bevacizumab plus cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer. *Gynecol Oncol* 2007;**107**:326–30.
94 Akaza H, Tsukamoto T, Murai M, et al. Phase II study to investigate the efficacy, safety, and pharmacokinetics of sorafenib in Japanese patients with advanced renal cell carcinoma. *Jpn J Clin Oncol* 2007;**37**:755–62.
95 Amar S, Wu KJ, Tan WW. Sorafenib-induced pancreatitis. *Mayo Clin Proc* 2007;**82**:521.