

Drug Insight: gastrointestinal and hepatic adverse effects of molecular-targeted agents in cancer therapy

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SUMMARY

Recent advances in the understanding of molecular mechanisms of cancer have led to the development of novel compounds that target specific cancer pathways. These drugs encompass monoclonal antibodies and tyrosine and non-tyrosine kinase inhibitors, and have been approved by the FDA and the European Medicines Agency, among others, for cancer treatment. These agents are associated with several toxic effects including potentially unacceptable gastrointestinal adverse effects. Diarrhea and hepatotoxicity, the most common adverse events experienced with these treatments, can frequently lead to treatment discontinuation and consequently decreased cancer control. We review the incidence and clinical patterns of the gastrointestinal and hepatic toxic effects induced by the main molecular-targeted therapies and propose some hypotheses for the causes of each adverse event.

KEYWORDS diarrhea, hepatotoxicity, molecular-targeted therapies, pancreatitis

REVIEW CRITERIA

The information for this Review was compiled by searching the PubMed and MEDLINE databases for articles published until 1 April 2007. Electronic early-release publications were included. Only articles published in English were considered. The search terms used included each molecular target compound listed in Table 1 in association with the following: “diarrhea”, “hepatotoxicity”, “hepatic dysfunction”, “pancreatitis”, “lipasemia”, “intestinal perforation”, “intestinal bleeding” and “clinical management”. Abstracts from the American Society of Clinical Oncology Annual Meetings (1998–2006) were also identified by use of the same search terms.

CME

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the clinical presentation of diarrhea caused by molecular targeted therapy.
- 2 Specify a recommended treatment for diarrhea caused by molecular targeted therapy.
- 3 Describe hepatitis associated with molecular targeted therapy.
- 4 Identify the pathophysiology and clinical management of elevated pancreatic enzymes associated with molecular targeted therapy.

Competing interests

JC Soria declared associations with the following companies: Eli Lilly, Roche, Sanofi-Aventis and Wyeth. D Malka declared associations with the following companies: Merck, Pfizer, Roche, Sanofi-Aventis and Serono. See the article online for full details of the relationships. The other authors and the journal editor L Hutchinson declared no competing interests. The CME questions author CP Vega declared that he has served as an advisor or consultant to Novartis, Inc.

INTRODUCTION

A seismic shift has rocked the foundations of oncology over the past few years, with groundbreaking advances in our understanding of cancer cell biology. The development of a tumor can be the result of one or several of the following alterations in cell physiology: growth signal self-sufficiency, insensitivity to growth-inhibitory signals, evasion of apoptosis, an unlimited replicative potential, sustained angiogenesis, tissue invasion, and metastasis.¹ New treatments that target the different pathways that regulate these processes have been developed. Agents that block

a specific molecular target have proved beneficial in the treatment of several tumor types and are now widely used. These agents include monoclonal antibodies as well as oral, small-molecule kinase inhibitors. Unfortunately, these compounds also exert activity on normal cells that express the molecular target, thus giving rise to adverse effects. The spectrum of adverse events is broad and includes gastrointestinal toxic effects, which require careful clinical management. There are several reasons why understanding liver and gastrointestinal adverse effects is important. Firstly, side effects that are unacceptable to the patient might lead to discontinuation of targeted therapy. Secondly, the need for further oral treatment to manage gastrointestinal adverse effects might alter patient compliance with the targeted treatment. Thirdly, iatrogenic alterations in gastrointestinal and/or liver physiology can alter the pharmacokinetics and pharmacodynamics of oral targeted agents, which differ in their properties from monoclonal antibody-based targeted therapies, and of other cancer drugs given concomitantly. Fourthly, hepatic or gastrointestinal adverse effects could provide insights into the mechanisms of toxicity and efficacy of targeted agents, and into the physiology of the liver and gastrointestinal tract. In addition, the large growth in the spectrum of targeted agents and in the number of patients treated by these agents is likely to considerably increase the frequency of such adverse effects. Finally, the cutaneous adverse effects of some targeted agents (e.g. EGFR inhibitors), and hepatic or gastrointestinal adverse effects might be surrogate markers of treatment efficacy. This Review reports on the clinical gastrointestinal and hepatic adverse events associated with molecular-targeted cancer treatments, and discusses the potential mechanisms that cause these toxic effects (Table 1).

DIARRHEA

Incidence

Diarrhea can be a major cause of treatment discontinuation and of decreased drug efficacy because it represents a dose-limiting toxic event. The incidence of drug-induced diarrhea observed in phase I–III studies of some molecular-targeted cancer drugs is summarized in Table 2. In a large BR.21 phase III trial that compared erlotinib treatment with placebo in patients with non-small-cell lung cancer (NSCLC), diarrhea was observed in 55% of patients receiving erlotinib, compared with 19% of patients in the placebo arm. Grade 3–5

diarrhea was seen in 6% of patients in the erlotinib arm and in fewer than 1% in the placebo arm.² Diarrhea was the reason for dose reduction of erlotinib in 5% of cases and for treatment discontinuation in 6% of patients. The Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL 1) trial was designed to evaluate the EGFR inhibitor gefitinib in patients with NSCLC. In this trial, 24% of patients received 250 mg/day of gefitinib and 43% received 500 mg/day; both groups took anti-diarrheal compounds.³

Some reports have suggested a correlation between the occurrence of toxic effects, especially skin adverse events, and overall survival.^{4,5} The presence of polymorphisms affecting intron 1 of *EGFR* correlated with the degree of skin toxic events (e.g. acneiform rash) and the response to anti-EGFR-based therapies.⁶ A retrospective analysis of patients with advanced NSCLC assessed whether there was a potential correlation between *EGFR* mutations and the severity of adverse events including diarrhea following treatment with gefitinib. No correlation between *EGFR* mutation status and severity and frequency of diarrhea was noted.⁷ Diarrhea caused by gefitinib treatment is associated with improvement of cancer symptoms. Diarrhea was reported to be an independent predictor of response to treatment in multivariate analysis, and this adverse effect could be a marker of clinical benefit.⁸ Furthermore, an analysis of four phase I trials showed that patients who experienced diarrhea when treated with sorafenib had a significantly increased time to progression compared with patients who did not experience such toxic effects.⁹

Clinical pattern of toxicity

Diarrhea is defined as an increase of more than 300 g/day in stool weight. Therefore, an increase in the number of stools or a decrease in the stool consistency characterizes diarrhea. In general, molecular-targeted agents in cancer therapy induce a similar clinical pattern of diarrhea. Oral compounds induce chronic diarrhea (i.e. a few days after treatment initiation) that can persist throughout treatment. The median time to onset of the first symptoms of diarrhea with sorafenib treatment is generally short, and occurs within the first week after initiation of treatment. Most of these diarrhea episodes are moderate in severity (i.e. grade 1 or grade 2).¹⁰ Generally, there is a marked increase in diarrhea at higher sorafenib dose levels compared with lower sorafenib dose levels, raising the possibility of a toxic dose-dependent effect of

Table 1 Molecular-targeted therapies discussed in this Review and their targets.

Drug	Development phase	Main area of development	Class of agent	Molecular target
Erlotinib (Tarceva [®] , OSI Pharmaceuticals, Inc., Melville, NY)	Approved	Non-small-cell lung cancer	Kinase inhibitor	HER1
Gefitinib (Iressa [®] , AstraZeneca, London, UK)	Phase III	Non-small-cell lung cancer	Kinase inhibitor	HER1
Cetuximab (Erbix [®] , ImClone Systems Incorporated, New York, NY)	Approved	Colorectal and head and neck cancer	Monoclonal antibody	HER1
Pertuzumab (Omnitry [®] , Genentech Inc.)	Phase II	Breast cancer	Monoclonal antibody	HER2
Lapatinib (Tykerb [®] , GlaxoSmithKline, Carrigaline, Ireland)	Approved for MBC HER2 ⁺ ; Phase III	Breast, prostate, and esophageal cancer	Kinase inhibitor	HER1 and HER2
HKI 272 (Wyeth Pharmaceuticals)	Phase II	Non-small-cell lung cancer	Kinase inhibitor	HER1 and HER2
Trastuzumab (Herceptin [®] , Genentech, Inc., South San Francisco, CA)	Approved	Breast cancer	Monoclonal antibody	HER2
Sorafenib (Nexavar [®] , Bayer Aktiengesellschaft, Leverkusen-Bayerwerk, Germany)	Approved	Renal cell carcinoma	Kinase inhibitor	VEGFR3, RAF, PDGFR β
Sunitinib (Sutent [®] , Pharmacia and Upjohn Company, Morris Plains, NJ)	Approved; Phase III	Renal cell carcinoma and GIST resistant to imatinib	Kinase inhibitor	VEGFR3, RAF, PDGFR β
Vatalanib (PTK 787, Novartis Pharmaceuticals, East Hanover, NJ)	Phase II	Prostate and pancreatic cancer	Kinase inhibitor	VEGFR1–3, PDGFR β
Bevacizumab (Avastin [®] , Genentech, Inc.)	Approved; Phase III	Lung, breast, and colorectal cancer	Monoclonal antibody	VEGF
Everolimus (Certican [®] , Novartis AG Aktiengesellschaft, Basel, Switzerland)	Phase II	Lung, breast, and colorectal cancer	Kinase inhibitor	mTOR
Temsirolimus (CCI-779; Torisel [®] , Wyeth, Madison, NJ)	Phase III	Lymphoma, breast cancer, melanoma, lung cancer, and renal cell carcinoma	Kinase inhibitor	mTOR
Imatinib (Gleevec [®] , Novartis)	Approved	GIST and chronic myelogenous leukemia	Kinase inhibitor	BCR–ABL, KIT, PDGFR α
Nilotinib (Tasigna [®] , Novartis)	Phase III	Chronic myelogenous leukemia	Kinase inhibitor	BCR–ABL
Tipifarnib (Zarnestra [®] , Johnson & Johnson, New Brunswick, NJ)	Phase III	Leukemia and breast cancer	Kinase inhibitor	Farnesyltransferase
Alvocidib (flavopiridol)	Phase II	Leukemia and pancreatic cancer	Kinase inhibitor	Cyclin-dependent kinase
Gemtuzumab (Mylotarg [®] , Wyeth Pharmaceuticals)	Approved	Acute myeloid leukemia	Monoclonal antibody	CD33
Bortezomib (Velcade [®] , Millenium Pharmaceuticals, Inc., Cambridge, MA)	Approved	Multiple myeloma	Proteasome inhibitor	Proteasomes

Abbreviations: GIST, gastrointestinal stromal tumors; HER, human epidermal growth factor receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

the drug. Diarrhea usually resolves within a few days after cessation of treatment with sorafenib.

Diarrhea is often observed during the first treatment cycle with oral anti-EGFR tyrosine

kinase inhibitor compounds.¹¹ The median time to the first diarrhea episode is nearly 14 days, but the time of onset can vary widely. Diarrhea episodes are usually moderate and are generally

well controlled with dose reduction and with administration of loperamide.¹²

Imatinib is a tyrosine kinase inhibitor that targets platelet-derived growth factor receptor, KIT, and the BCR–ABL oncoprotein. Clinical studies of imatinib have shown that incidence of diarrhea is related to drug dose.^{13,14} As found with other molecular-targeted compounds, diarrhea can be managed by discontinuation of therapy or by use of antidiarrheal drugs. In patients with gastrointestinal stromal tumors, independent risk factors for diarrhea were high imatinib dose, female sex, and the primary site of gastrointestinal disease.¹³ The experimental cyclin-dependent kinase inhibitor flavopiridol causes watery diarrhea, which has a peak incidence on day three of infusion.¹⁵ In general, diarrhea is not associated with abdominal pain, but if untreated, it can lead to dehydration. Analysis of stools has shown some features of secretory diarrhea with a high content of sodium and chloride and with no presence of mucus, blood, leukocytes or *Clostridium difficile* toxins.¹⁶ Histopathological findings do not show microscopic damage to the bowel mucosa.¹⁶

The proteasome inhibitor bortezomib frequently induces watery diarrhea with no bleeding, but treatment with this drug is often associated with abdominal pain and cramps. The abdominal symptoms seen with bortezomib are mild to moderate, dose-dependent and time-dependent, start within 12–18 hours after infusion initiation, and last for 1–2 days. Loperamide is an effective anti-diarrheal treatment even after a high dose (i.e. higher than recommended in phase II and III trials) of bortezomib.^{17,18} The experimental drugs tipifarnib and lonafarnib are farnesyl transferase inhibitors that induce secretory diarrhea on the third day of treatment, without causing steatorrhea, tenesmus or bloody stools. No abnormalities are present on abdominal examination. As with other treatments, diarrhea also resolves with drug cessation or loperamide therapy.

Few histopathological findings are available in this context of diarrhea induced by targeted therapies. In a phase I trial, microscopic analysis of tissue treated with the pan-EGFR tyrosine kinase inhibitor HKI-272 revealed mild duodenal mucosal gland dilatation and degeneration, and mild edema and slight villus atrophy in the small intestine.¹⁹ Some molecular-targeted agents can be used in combination with cytotoxic compounds. The safety of such combination

Table 2 Incidence of drug-induced diarrhea in phase I–III studies of molecular-targeted cancer drugs.

Drug	Incidence of diarrhea (%)	Reference
Erlotinib	55 (6% grade 3–5) 68 (12% grade 3–4) ^a	Shepherd <i>et al.</i> (2005) ² Herbst <i>et al.</i> (2005) ⁶⁵
Gefitinib	40–60 (8% grade 2) 58 (3% grade 3–4) ^a	Fukuoka <i>et al.</i> (2003) ³ Herbst <i>et al.</i> (2004) ⁶⁶
Lapatinib	40 (10% grade 3) 60 (13% grade 3–4)	Burrhis <i>et al.</i> (2005) ²⁴ Geyer <i>et al.</i> (2006) ⁶⁷
HKI-272	84	Wong <i>et al.</i> (2006) ¹⁹
Sorafenib	33 (24% grade 2–3)	Escudier <i>et al.</i> (2005) ¹⁰
Sunitinib	20 (grade 2–3)	Motzer <i>et al.</i> (2006) ¹¹
Imatinib	45	Demetri <i>et al.</i> (2002) ¹⁴
Flavopiridol	50	Liu <i>et al.</i> (2004) ¹⁵
Bortezomib	32 (8% grade 3–4) 29 (9% grade 3–4)	Fanucchi <i>et al.</i> (2003) ³⁴

^aDrug used in combination with cytotoxic chemotherapy.

regimens is often similar to that expected on the basis of the known diarrhea associated with molecular-targeted agents and conventional compounds; therefore, combination therapy can lead to an additive toxicity. Hence, these associations might result in dose reduction or treatment discontinuation.

Management

Diarrhea induced by inhibitors that target the EGFR pathway can be managed easily by reducing the dose of the oral compound, which rapidly lowers the incidence and severity of diarrhea. Rarely does treatment have to be interrupted. Other induced causes of diarrhea, such as the use of laxatives, stool softeners, antacids or antibiotics, a fiber-rich diet, infection, partial intestinal obstruction or fecal impaction, surgery and radiation toxicity should be excluded. Loperamide is a useful treatment that can decrease intestinal motility. For example, HKI-272 can increase the incidence and severity of diarrhea, and we recommend starting loperamide treatment immediately after the first occurrence of diarrhea by administering two 2 mg tablets followed by one tablet every 2 hours, as recommended with CPT-11.¹² Octreotide, a somatostatin analog, has been shown to reduce intestinal secretion induced by neuroendocrine tumors. Some data indicate that octreotide is efficacious at reducing bolus fluorouracil and leucovorin (IFL)-induced diarrhea.²⁰ At present, such data are not available for diarrhea induced by molecular-targeted agents.

Table 3 Mechanisms of diarrhea caused by targeted therapies.

Drug	Mechanism
Anti-EGFR	Secretory mechanisms by inhibiting EGFR effects on chloride secretion
Anti-VEGFR	Direct damage of intestinal mucosa
mTOR inhibitor	Microflora alteration Malabsorption
Flavopiridol	Secretory mechanisms by inhibiting EGFR effects on chloride secretion Potentiate secretagog Direct damage of intestinal mucosa Alteration of Cajal cells via c-KIT inhibition
Bortezomib	Autonomic nerve dysfunction
Imatinib	Alteration of Cajal cells Direct damage of intestinal mucosa

Abbreviations: mTOR, mammalian target of rapamycin; VEGFR, vascular endothelial growth factor receptor.

The same management approach can be applied to diarrhea induced by other tyrosine kinase inhibitors. The combined treatment of loperamide and colestyramine can reduce flavopiridol-induced diarrhea.¹⁶ In a phase I trial of flavopiridol, a combination of colestyramine three times per day and loperamide administered during the first week of cancer treatment was the most-effective regimen; however, this regimen is poorly tolerated.^{16,21}

Pathophysiology of diarrhea induced by targeted therapies

The pathophysiological mechanism of drug-induced diarrhea remains unclear (Table 3). A plausible explanation can be derived from the occurrence of secretory diarrhea, which results from excessive chloride secretion and deficient sodium absorption. In the normal colon, sodium absorption and chloride secretion are stimulated directly by intracellular messengers such as cyclic AMP and intracellular calcium. EGFR is frequently overexpressed in gastrointestinal normal mucosa. There is evidence that EGFR is a negative regulator of chloride secretion.²² Some studies have reported that EGF decreases chloride secretion in T84 human colonic intestinal epithelial cells via a mechanism that involves protein kinase C (PKC) and phosphatidylinositol 3-kinase (PI3K).²³ EGFR inhibitors could, therefore, increase chloride secretion by blocking this regulation loop and thereby inducing secretory diarrhea. Furthermore, flavopiridol has a minimal independent effect on chloride secretion,

but it increases secretion induced by calcium-dependent agonists and can reverse the inhibitory effect of EGF on chloride secretion. Interestingly, flavopiridol can potentiate the chloride secretory response to taurodeoxycholate, a bile acid that is a calcium-dependent chloride secretagog, in T84 cells. These findings may explain how colestyramine was able to reduce diarrhea in other studies by reducing bile acid in the intestine.^{16,24} Flavopiridol and other similar compounds could, therefore, potentiate natural secretagogues and induce secretory diarrhea.²⁵

A burning question is why compounds that target HER2 do not induce diarrhea as frequently as EGFR inhibitors do. Some preclinical data show that HER2 is involved in the inhibitory effect of EGF on epithelial chloride secretion because it enables formation of the EGFR/HER2 heterodimer.²⁶ Authors of a recent study have suggested that inhibition of EGFR/EGFR homodimer signaling, rather than of EGFR/HER2 heterodimer signaling, may be the key molecular event determining the different dermatological toxic effects observed between EGFR-targeted and HER2-targeted therapies.²⁷ Such data are not available for intestinal and colonic cells but this might be a possible explanation. This concept also applies to the tyrosine kinase inhibitor lapatinib, which targets both HER2 and EGFR, for which 10% grade III diarrhea was noted compared with a lower amount for the HER2-targeted agent trastuzumab.²⁴ A further theory is that diarrhea could be induced through direct damage to the normal mucosa, which could be the reason for decreased absorption of water, electrolytes or other compounds such as lipids. Several facts favor this hypothesis. First, diarrhea occurs more frequently with oral compounds than with monoclonal antibodies, suggesting that there is a direct effect on the digestive mucosa or that the tyrosine kinases targeted by these drugs are blocked. Second, diarrhea increases as the dose levels of oral kinase inhibitors increase, whereas there is no association between diarrhea and erlotinib dose.²⁸ The pharmacokinetics of erlotinib in a large patient population with solid tumors was assessed. No correlation was observed between plasmatic exposure and diarrhea, whereas frequency of diarrhea is known to be dose related.²⁸ These results suggest direct damage from erlotinib. Such data are not available for other tyrosine kinase inhibitors. Third, preclinical histopathological results showed that atrophy of the mucosal villi of the small intestine

leads to malabsorption during treatment with mammalian target of rapamycin (mTOR) inhibitors. Sirolimus, an immunosuppressive agent and inhibitor of mTOR, alters intestinal function in rabbits by decreasing jejunal uptake of certain fatty acids and by inducing intestinal atrophy.²⁹ Fourth, systemic glucuronidation of flavopiridol, which can decrease luminal exposure to the drug, is inversely associated with the risk of developing diarrhea. Diarrhea developed in 91% of patients with a poor glucuronidase function because of intestinal exposure to toxic levels of flavopiridol, whereas 73% of patients with extensive glucuronidation function did not develop diarrhea.³⁰ Colestyramine, which binds to flavopiridol, can alleviate the symptoms of diarrhea and prevent toxic effects on the intestinal mucosa. These results might also be seen with oral kinase inhibitors such as erlotinib or sorafenib, which undergo hepatic glucuronidation.³¹

Another mechanism that is involved in the onset of diarrhea is a change in normal intestinal microflora. Native microflora have a key role in absorption of several proteins and prevent pathological bacteria from settling in the gastrointestinal tract. Some compounds can induce diarrhea by changing these natural microflora. CCI-779 (temsirolimus), an mTOR inhibitor with immunosuppressive properties, might cause fecal alterations with mucoid feces and colitis, secondary to an immunosuppressive or an antimicrobial effect, leading to altered microbial flora in the bowel.

Alleviation of increased bowel movements has been observed with loperamide, suggesting that dysmotility could be responsible for inducing diarrhea. Intestinal cells responsible for colonic motor function (i.e. Cajal cells) could be a target of several compounds. These cells are positive for KIT expression, which explains why imatinib or flavopiridol can induce diarrhea.³² Loss of Cajal cells, however, generally results in colonic inertia and not diarrhea.³³ Moreover, several compounds may alter the serum level of hormones, such as vasoactive intestinal peptide or thyroid stimulating hormone, that are involved in intestinal motility; however, no specific data on these functions are available. Bortezomib treatment is associated with diarrhea,³⁴ which might be related to neuropathy. Indeed, neurotoxicity and some cardiovascular toxic effects including hypotension and hypertension have been observed with bortezomib. Thus, a possible explanation for bortezomib-induced diarrhea could be intestinal autonomic nerve dysfunction.¹⁷

Another surprising mechanism has been suggested by a non-randomized study, which showed that low-dose aspirin was able to reduce gefitinib-induced adverse events including diarrhea by inhibiting platelet activation.³⁵ There was a marked increase following aspirin administration in some platelet-related factors such as thromboxane A₂ in patients treated with gefitinib. Thromboxane A₂ is an endogenous secretagogue of chloride secretion in the distal colon.³⁶ It is possible, therefore, that gefitinib could induce diarrhea by increasing some inflammatory mediators as a secondary response to activation of cell immunity. Further studies are warranted to confirm this hypothesis.

In summary, these data show that, despite the high prevalence and unpleasant consequences of diarrhea in cancer treatment, many investigations are still required to increase our understanding of the pathophysiological mechanisms involved and to improve treatment. These further investigations include pre-treatment and post-treatment biopsies in humans, absorption tests, fecal studies, and animal model studies.

HEPATOTOXICITY

Hepatotoxicity is the second common cause of discontinuation of treatment with imatinib. Studying the hepatotoxicity of this kinase inhibitor could shed light on hepatic physiology related to adverse effects from cancer therapies. For example, hepatocyte-specific deficiency of *Pten* in mice resulted in steatohepatitis, indicating that *Pten* is a key regulator of hepatocyte metabolism.³⁷ Hepatic adverse effects, such as asymptomatic elevations of transaminases, are examples of other common toxic events associated with molecular-targeted therapies (Table 4). Some compounds also increase γ -glutamyl transpeptidase or bilirubin levels, which reflects enzyme induction. Indeed, an interaction with hepatic membrane transporters might alter the absorption of unconjugated bilirubin, or the expression or function of ATP-binding cassette transporters such as multi-drug resistance-associated protein 2 (MRP2), which is responsible for the excretion of bilirubin glucuronide into the bile. In rats, flavopiridol glucuronides are potential substrates of MRP2 and inhibit biliary excretion of bilirubin, which explains the increased conjugated hyperbilirubinemia associated with flavopiridol in 15% of cases.³⁸ By contrast, MRP2 mRNA levels do not seem to be affected by prolonged treatment with imatinib.³⁹ *In vitro* metabolism data show that sorafenib and erlotinib

Table 4 Incidence and clinical pattern of drug-induced hepatotoxicity.

Drug	Incidence of hepatotoxicity (%)	Clinical pattern of hepatotoxicity	Histological features	Physiopathology
Erlotinib or gefitinib	11 (2% grade 2–3)	Cytolytic hepatitis Isolated hyperbilirubinemia	Chronic hepatitis with active necrosis	Direct action (targeting of hepatocytes that overexpress EGFR) UGT1A1 (UD11) inhibition
Imatinib	10 (4% grade 3)	Cytolytic hepatitis	Hepatic necrosis; sometimes mild cholestasis; no granuloma or fatty infiltration	Hypersensitivity Metabolic reaction
Gemtuzumab	2 16 (grade 3–4) 25 (grade 3–4)	Portal hypertension Cytolytic hepatitis Hyperbilirubinemia	Sinusoidal obstruction syndrome	Exposure to unconjugated calicheamicin in the circulation Non-specific uptake of the antibody–calicheamicin complex by Kupffer cells Receptor-mediated uptake of the antibody–calicheamicin complex through CD33 expression

inhibit the phase II conjugation pathway UGT1A1 (UD11) enzymes, which are involved in bilirubin conjugation; this inhibition explains the rise in unconjugated bilirubin sometimes observed with these agents.²⁸ The bile salt export pump mediates canalicular secretion of bile salts. It is possible that several compounds might inhibit trafficking of the bile salt export pump from the Golgi to the canalicular membrane. This reduced trafficking might occur by inhibition of the extracellular signal-regulated kinase and p38 mitogen-activated protein kinase downstream of EGFR activation, given that EGFR is overexpressed at baseline in normal hepatocytes.⁴⁰

Severe hepatitis has been described with the use of imatinib and gemtuzumab ozogamicin (Mylotarg®, Wyeth, Madison, NJ). In patients with either gastrointestinal stromal tumors or chronic myelogenous leukemia treated with imatinib, grade 3 increases in serum aspartate aminotransferase and alanine aminotransferase levels occurred in 4% of cases, particularly in patients with advanced-phase disease or with infiltration of leukemic cells into the liver.⁴¹ Rising transaminase levels are often observed within the first 3 months of imatinib treatment but can occur much later, even after 1 year of therapy. When imatinib is stopped, abnormalities often resolve within 3 weeks and enzyme elevation often occurs after several months. Several severe cases of hepatitis following imatinib therapy have been observed.^{42,43} Histological findings of acute liver failure with imatinib demonstrate cytolytic hepatitis with necrosis, and sometimes mild cholestasis with portal and lobular inflammation.⁴¹ A similar pattern of viral hepatitis with lymphocyte infiltration around the necrotic lesions has been reported.⁴⁴ Severe cytolytic hepatitis with

gefitinib has also been noted.⁴⁵ Gemtuzumab ozogamicin is a monoclonal antibody conjugated to calicheamicin, which is the cytotoxic antitumor compound that targets the CD33 surface antigen in acute myeloid leukemia. This compound has been reported to induce portal hypertension, in 0.9% of patients, although higher incidences have been observed in cases when hematopoietic stem-cell transplantation was performed before or after infusion of gemtuzumab ozogamicin. Liver biopsy samples show possible sinusoidal fibrosis and hepatocyte necrosis.⁴⁶

Mechanisms involved in severe hepatotoxicity, including high aminotransferase levels, mild or severe cholestasis, and hepatic failure, are not well understood (Table 4). Most molecular-targeted cancer agents are metabolized in the liver via the cytochrome pathway. Drug-induced stress can give rise to an increase in heat-shock proteins, ensuring spontaneous normalization of liver abnormalities, which suggests a direct toxic effect. In addition, the geldanamycin analog 17-(allylamino)-17-demethoxygeldanamycin (17-AAG), which targets heat shock protein 90, can lead to hepatotoxicity (mainly liver transaminase elevation) in 30% of cases.⁴⁷ It has been suggested that there is a link between hepatotoxicity and serum concentrations of drugs, such as imatinib.⁴⁸ Moreover, the severity of toxic effects can be increased when imatinib is taken with a CYP3A4 inhibitor such as roxithromycin.⁴⁹

Hypersensitivity reactions with immune-mediated drug reactions could be involved in hepatic adverse effects. Imatinib has been reported to induce autoimmune hepatitis.⁵⁰ Imatinib could worsen an underlying prothrombotic status by damaging endothelial cells, especially in the liver. Indeed, there have been reports of fatal necrosis

caused by imatinib in patients with polycythemia; liver biopsy samples showed evidence of fibrin thrombi in hepatic veins, but microscopic emboli were also detected in the lungs.⁵¹ Hepatotoxicity associated with gemtuzumab ozogamicin can be explained by sinusoidal obstruction syndrome, the mechanism of which probably involves targeting of CD33⁺ cells in the sinusoids of the liver, activation of stellate cells, damage to sinusoidal endothelial cells, sinusoidal vasoconstriction, and ischemic hepatocyte necrosis.⁵²

Management

The management of hepatotoxicity must be adapted to each patient according to the severity and impact on the patient of this adverse effect, while the mechanisms of hepatotoxicity must also be considered. The mechanisms of hepatic toxic events are largely unknown; therefore, management is often empiric. Other causes of liver disease can be established by use of ultrasound or CT scanning and by screening for viral hepatitis and elevated serum ferritin and alpha-1-antitrypsin levels. A liver biopsy can be performed, if indicated. Liver function must be carefully monitored, particularly in instances of abnormal liver function tests (LFTs) before initiation of treatment. For example, some authors recommend LFTs before treatment with imatinib, then weekly during the first month and at least monthly thereafter, because of the reported risk of fatal hepatitis with imatinib.⁵³

In current practice, imatinib therapy is interrupted when patients exhibit hepatotoxicity of grade 3 or 4 transaminase elevation (i.e. greater than fivefold the upper limit of normal). When abnormalities return to grade 1 or less, imatinib can be reintroduced at a reduced dose. If the liver toxic effects do not recur within 6–12 weeks, the initial dose can be re-escalated, accompanied by close monitoring by use of LFTs. For recurrent grade 3 toxicity, guidelines recommend discontinuation of imatinib.⁵³ In instances of grade 2 hepatotoxicity, imatinib can be continued but the dose should be lowered according to the clinical situation.

A rise in bilirubin levels induced by erlotinib or gefitinib might not reflect the pathological situation, and consequently these compounds can be continued safely in this instance. Indeed, high bilirubin levels reflect a concentration-dependent effect of erlotinib on metabolism; high erlotinib concentrations result in high bilirubin concentrations.²⁸ We would recommend discontinuation

of these compounds when grade 3 or 4 toxicity occurs. Clinicians should be aware of drug–drug interactions, especially with CYP3A4 and CYP3A5 inducers and drugs metabolized by CYP3A4 and CYP3A5 (e.g. imatinib, gefitinib and erlotinib).^{54,55} CYP3A4 and CYP3A5 inducers can increase plasma levels of targeted therapies or drugs combined with such therapy and give rise to hepatotoxicity. By contrast, sorafenib can be coadministered with inducers or inhibitors of CYP3A4 without altering the drug's biodistribution, even though this compound is metabolized by CYP3A4.³¹ Patients taking molecular-targeted cancer drugs should avoid a further hepatotoxic compound such as alcohol or paracetamol. One patient experienced fatal hepatic dysfunction while on imatinib and high-dose paracetamol.⁵⁶ The cause of the interaction between the two compounds is unknown. Other patients have received the combination without hepatic dysfunction;⁵⁷ however, all patients on these therapies should be monitored carefully. Less-toxic medications should replace nonessential hepatotoxins whenever possible.

Few data are available on the influence of hepatic impairment when targeted therapies are used. In patients with hepatocellular carcinoma and mild or moderate hepatic dysfunction (Child–Pugh class A or B, respectively), plasma sorafenib levels were not different in patients with mild hepatic impairment compared to those with moderate impairment.⁵⁸ Some case reports mention the safe administration of imatinib in patients with impaired liver function who have received 4 months of the therapy. No pharmacokinetic data are available for patients with Child–Pugh C because patients with severely impaired liver function are excluded from clinical trials. Moreover, no efficient method is available to prevent hepatotoxicity. Coadministration of steroids and gefitinib to patients who have experienced previous hepatic reactions has led to hepatotoxicity. By contrast, steroids were able to resolve imatinib-induced hepatic toxic effects in a few patients.⁵⁹

Elevation of pancreatic enzymes

Elevation of pancreatic enzymes (i.e. hyperlipasemia and hyperamylasemia) is not common with conventional chemotherapy. Sorafenib and sunitinib can induce hyperlipasemia and hyperamylasemia. These abnormalities are not observed with the anti-VEGF monoclonal antibody bevacizumab, anti-EGFR therapies or

other oral antiangiogenic compounds. Thus, it is unknown whether these abnormalities result from the combined inhibition of vascular endothelial growth factor receptor (VEGFR), platelet derived growth factor receptor (PDGFR) and FMS-like tyrosine kinase 3 (FLT3).

Elevated pancreatic enzyme levels are of grade 1 or 2 in most patients treated with sorafenib, but severe cases of enzyme elevation (grade 3–4) have been observed in 21% of patients treated with sunitinib.⁶⁰ This pancreatic toxic effect does not seem to be dose-dependent, and it occurs mainly within the first weeks of therapy. No medical intervention is required, and withdrawal of the compound can resolve pancreatic enzyme abnormalities within 2 weeks. Generally, patients do not experience any abdominal pain. Liver function test results are usually normal for patients treated with sorafenib, and liver ultrasonography does not reveal evidence of any bile duct dilatation in these patients. Furthermore, abdominal CT scans do not detect any abnormalities in pancreas morphology.⁶¹ These abnormalities often resolve even if treatment is not discontinued. Similarly, sunitinib can be safely continued in patients with asymptomatic pancreatic enzyme elevations. A study has shown that, when used at the recommended dose, nilotinib caused grade 3 or 4 elevation hyperlipasemia in 28% of patients, although imatinib did not induce this pancreatic adverse effect.⁶²

The physiopathology of elevated pancreatic enzymes in patients undergoing these cancer treatments is unknown. Elevation of pancreatic enzymes might be an immunoallergic reaction or a marker of the drug bioactivity. It is not clear whether these effects are caused by pancreatitis. According to guidelines, abdominal pain and lipase elevation threefold above the upper limit of normal are required for the diagnosis of pancreatitis. Hypereosinophilia is not observed concomitantly with hyperlipasemia, and there are no biological markers for this effect. Thus, isolated elevation of lipase does not seem to be a good criterion for diagnosis of pancreatitis, and other causes of pancreatitis should be excluded. Management of this adverse effect is not well established, and whether the molecular-targeted drug may be continued or not has not been confirmed. We recommend that treatment could be pursued in patients with grade 1 or 2 hyperlipasemia elevation without clinical signs of pancreatitis. If grade 3 or 4 lipasemia elevation occurs (above twofold the upper limit

of normal), treatment with imatinib must be discontinued until the serum level of enzymes returns to grade 1.

Intestinal bleeding and perforation

Several cases of gastrointestinal perforation have been reported in patients treated with bevacizumab and chemotherapy. The Bevacizumab Regimens Investigation of Treatment Effects and Safety (BRiTE) registry reported gastrointestinal perforation in 1.7% of 1,987 patients with metastatic colorectal cancer.⁶³ The clinical pattern and severity of perforation seen was variable, ranging from asymptomatic to fatal perforations. Most gastrointestinal perforations occurred within the first 3 months after initiation of treatment. The incidence of perforations was greatest in cases of an intact primary tumor or a recent history of sigmoidoscopy or colonoscopy. On the other hand, long-term use of nonsteroidal anti-inflammatory compounds or a history of peptic ulcer disease or diverticulosis were not associated with a high risk of gastrointestinal perforation. A rapid response to molecular-targeted cancer drugs could be associated with toxic effects and necrosis as evidenced by perforation.¹⁴ It has also been suggested that treatment with bevacizumab following radiation of the pelvis might increase the risk of ischemic bowel damage.⁶⁴ At present, no preclinical or prospective trial data have confirmed this hypothesis. Consequently, patients should be monitored carefully for symptoms of gastrointestinal perforation, and bevacizumab should be discontinued in patients who experience such adverse effects.

CONCLUSIONS

Understanding the critical roles that pathways have in tumor cellular processes has led to the development of new compounds that target specific pathways. Several toxic effects are associated with these new drugs, including gastrointestinal adverse effects. These adverse effects need to be considered carefully because they can lead to the discontinuation of oral treatment and subsequently compromise cancer control. Further investigations are warranted to elucidate the pathophysiology of these harmful effects, especially that of diarrhea. Indeed, one issue is to determine how to combine these targeted molecular therapies in order to inhibit multiple signaling pathways without increasing toxic effects. A better understanding of these mechanisms can lead to improved molecular-targeted treatment and enable unacceptable toxic effects to be avoided.

KEY POINTS

- Gastrointestinal and hepatic adverse effects are common features of molecular-targeted therapies
- Limited data are available regarding the pathophysiology of such toxicities
- Pathophysiological mechanisms of diarrhea mainly involve secretory diarrhea, and direct blockage of tyrosine kinases present in the intestinal epithelium
- Pharmacokinetic interactions are often involved in hepatic toxicity
- Hepatic and gastrointestinal adverse effects might provide insights into the mechanisms of action of molecular-targeted agents and, more widely, into the physiology of the liver and the gastrointestinal tract

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Competing interests

JC Soria declared associations with the following companies: Eli Lilly, Roche, Sanofi-Aventis and Wyeth. D Malka declared associations with the following companies: Merck, Pfizer, Roche, Sanofi-Aventis and Serono. See the article online for full details of the relationships. The other authors declared no competing interests.

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