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REVIEW ARTICLE

Hepatotoxicity of Tyrosine Kinase Inhibitors: Clinical and Regulatory Perspectives

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Abstract The introduction of small-molecule tyrosine kinase inhibitors (TKIs) in clinical oncology has transformed the treatment of certain forms of cancers. As of 31 March 2013, 18 such agents have been approved by the US Food and Drug Administration (FDA), 15 of these also by the European Medicines Agency (EMA), and a large number of others are in development or under regulatory review. Unexpectedly, however, their use has been found to be associated with serious toxic effects on a number of vital organs including the liver. Drug-induced hepatotoxicity has resulted in withdrawal from the market of many widely used drugs and is a major public health issue that continues to concern all the stakeholders. This review focuses on hepatotoxic potential of TKIs. The majority of TKIs approved to date are reported to induce hepatic injury. Five of these (lapatinib, pazopanib, ponatinib, regorafenib and sunitinib) are sufficiently potent in this respect as to require a boxed label warning. Onset of TKI-induced hepatotoxicity is usually within the first 2 months of initiating treatment, but may be delayed, and is usually reversible. Fatality from TKI-induced hepatotoxicity is uncommon compared to hepatotoxic drugs in other classes but may lead to long-term consequences such as cirrhosis. Patients should be carefully monitored for TKI-induced hepatotoxicity, the management of which requires individually tailored reappraisal of the risk/benefit. The risk is usually manageable by dose adjustment or a switch to a suitable alternative TKI. Confirmation of TKI-induced hepatotoxicity can present challenges in the presence of hepatic metastasis and potential drug interactions. Its diagnosis in a patient with TKI-sensitive cancer requires great care if therapy with the TKI suspected to be causal is to be modified or interrupted as a result. Post-marketing experience with drugs such as imatinib, lapatinib and sorafenib suggests that the hepatotoxic safety of all the TKIs requires diligent surveillance.

1 Introduction

Phosphorylation of proteins by protein kinases is an important activating mechanism in the communication of signals within a cell and regulation of cellular activity and function [1, 2]. It is estimated that the activity of up to 30 % of all the human proteins may be modified by these kinases. Activation of proteins by these kinases is known to regulate the majority of cellular biochemical pathways involved in the transduction of extracellular signals and thereby regulate cellular responses including differentiation, proliferation and survival. Thus, each kinase functions as an "on" switch. These kinases can also be overexpressed or become mutated and get stuck in the "on" position, resulting in unregulated growth of the cell, an essential step in oncogenesis. Not surprisingly, the past decade has witnessed the approval of a number of small-molecule tyrosine kinase inhibitors (TKIs) for the treatment of a variety of cancers. As of 31 March 2013, a total of 18 antineoplastic TKIs have been approved by the US Food and Drug Administration (FDA), 15 of which have also been

The views expressed in this paper are those of the authors and do not necessarily reflect the views or opinions of their affiliates, any regulatory authorities or any of their advisory bodies.

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approved by the European Medicines Agency (EMA). In a study comparing three groups of antineoplastic agents, the clinical benefit derived from recently approved antineoplastic drugs was found to be greater for targeted anticancer agents than for chemotherapeutic agents [3].

While these agents are generally well tolerated, clinical experience has highlighted their unexpected association with serious toxic effects on the heart, lungs, liver, kidneys, thyroid, skin, blood coagulation, gastrointestinal tract and the nervous system. This adverse safety profile is not altogether too surprising since tyrosine kinases are widely distributed throughout the body with specific functional roles in different organs. We have previously reviewed 16 TKIs with regard to their cardiovascular safety and on-target toxicities that could serve as biomarkers of their efficacy [4, 5]. Since then, the FDA has approved two more antineoplastic TKIs (cabozantinib and ponatinib).

The majority of the approved TKIs are all relatively new. Nine of the 18 TKIs have been approved as recently as the last 24 months. Given the nature of their indications, the pre-approval database is necessarily limited, with many approved on an expedited basis. At present, the post-marketing experience is also very limited. Following a detailed analysis of the adverse drug reactions of targeted anticancer agents from their reporting in pivotal randomized clinical trials and subsequently updated drug labels, Seruga et al. [6] concluded that many rare but serious and potentially fatal adverse drug reactions associated with these agents are not reported in clinical trials. Whereas patients in pre-approval clinical trials are carefully selected, treatment of less selected patients in routine oncologic practice may increase the likelihood of toxicity and lower the probability of benefit [7].

Hepatotoxicity is one of the serious class-related safety issues signalled in pre-approval clinical trials with TKIs and is now gradually being reported relatively more frequently following their wider clinical use. The purpose of this review is to summarize the currently available information on the hepatotoxic potential of approved TKIs and challenges involved in the diagnosis of TKI-induced hepatic injury. We acknowledge that at present, the data are sparse and often incomplete but we perceive a need to bring together the available information to increase the awareness of the prescribing physicians to this potential risk. For the purpose of this review, we chose to categorise a TKI as hepatotoxic if the FDA label included a warning *and* required patients to be monitored for their liver function tests (LFT).

Before discussing the hepatotoxicity of TKIs specifically, it may be helpful to summarize the regulatory concerns on drug-induced liver injury (DILI) generally, and the consequential drug attrition rates. Since clinical oncologists are heavily involved in clinical trials of TKIs, it may also be helpful to increase their understanding of how the regulatory authorities approach the assessment of hepatotoxicity.

2 Impact and Prediction of Drug-Induced Hepatotoxicity

Drug-induced hepatotoxicity does not appear to have any unique clinical or histological signature and can mimic, clinically and histologically, almost every naturally occurring liver disease in man. Most cases of drug-induced structural hepatotoxicity can be either acute or chronic, involving histological features of hepatocellular damage, cholestasis and/or steatosis. Often, the pathological spectrum is mixed with predominance of a particular histological type. Combined data from two large studies suggest that hepatocellular necrosis accounts for about 55 %, cholestasis 25 % and mixed form 20 % of drug-induced hepatotoxicity [8, 9]. The same drug may induce different types of injury in different individuals [10]. The major mechanisms underpinning drug-induced hepatotoxicity are based on the production of reactive metabolites generated by phase I oxidation reactions, immunological and/or alterations in mitochondrial function. Mitochondrial dysfunction is believed to have a central role in induction of liver injury. For a more detailed discussion on the mechanisms of DILI, the reader is referred to other reviews [11–18].

A large number of drugs have been withdrawn from the market because of their hepatotoxicity. Indeed, this toxicity is the leading cause of drug withdrawals. Two analyses suggest that in relative terms, drug-induced hepatotoxicity is assuming greater significance. In one analysis of 131 safety-related drug withdrawals in three European Union (EU) countries and the USA during the period 1961 to December 1992, 23 (17.6 %) drugs were withdrawn as a result of hepatotoxicity [19]. A more recent analysis of 38 drugs withdrawn from the market between 1990 and 2006 revealed that 14 (37 %) were withdrawn as a result of hepatotoxicity [20]. Review of these drugs has also identified certain features that are potentially associated with hepatotoxicity. These include chirality (e.g. dilevalol and bufenadrine), genetic factors (isoniazid and perhexiline), dose schedules (benoxaprofen), drug interactions (valproic acid), duration of therapy (bromfenac), drug formulations (sustained release formulation of nicotinic acid), induction of autoimmunity (ticrynafen), female gender (virtually all hepatotoxic drugs) and general drug hypersensitivity [10, 21]. A recent genome-wide association study has also revealed that flucloxacillin-induced hepatitis is strongly associated with *HLA-B*5701* (odds ratio of 80.6; 95 % CI 22.8–284.9) [22].

Novel drugs, TKIs included, are often perceived to be not only more effective but also safer. Unfortunately,

clinical experience shows that this is rarely the case. Ticrynafen, a novel uricosuric diuretic also known as tienilic acid that was approved for use in hypertension in 1979, had to be withdrawn in 1980 after having been implicated as the cause of serious hepatic injury [23]. Benoxaprofen was also a novel non-steroidal anti-inflammatory drug that was approved in 1980 but had to be withdrawn from the market in 1982 following reports of fatal cholestatic jaundice. More recently, troglitazone was introduced in 1997 as an oral hypoglycaemic drug that was the first in a new chemical class of compounds with a novel mechanism of action. An ever increasing number of reports of serious hepatotoxicity led to its withdrawal from the UK market in December 1997, within just 2 months of its introduction, and worldwide by March 2000. The interval to onset of severe liver injury varied widely, ranging from as early as 4 days after commencing the drug to more than 2 years of its continuous use. The onset and progression of injury even in delayed-onset cases was rapid as evidenced by normal LFT within the previous 1 month [24, 25]. Troglitazone also highlighted inadequate monitoring of patients for LFT despite regulatory warnings and recommendations [24].

Regulatory authorities have reacted to this serious iatrogenic hazard by promulgating guidelines on its earlier detection and mitigation clinically through risk management [26–29]. These authorities emphasize that since the risk of serious drug-induced hepatotoxicity is in the range of at most 1 per 10,000, it would be rare to find even a single case of serious hepatic injury even if several thousand subjects were studied and consider adequate nonclinical animal testing during drug development to be essential in early detection of the hepatotoxic potential of drugs. The frequency of asymptomatic rises in serum hepatic transaminases per se in pre-approval data sets does not correlate well with the frequency of symptomatic liver injury that may follow in the post-marketing period [10]. Therefore, regulatory authorities and drug developers have relied principally on Hy's law or rule [30], named after the late Professor Hyman Joseph Zimmerman, to predict post-approval risk of serious hepatotoxicity and for making recommendations on whether, following on-treatment LFT abnormalities, treatment with the suspect drug should be continued, discontinued or its dose reduced.

According to Hy's rule that is based on extensive clinical experience, a significant risk of severe hepatotoxicity is associated with medications which cause an injury [elevation in alanine aminotransferase (ALT)] *together with* a reduction in hepatic function (the synthesis and transportation of bilirubin). Thus, a case that meets the Hy's rule criteria is defined as a patient with concurrent elevation in ALT greater than three times the ULN (upper limit of normal) and total bilirubin greater than twice the ULN with no evidence of biliary obstruction (e.g. elevation of alkaline phosphatase) or of other causes that can reasonably explain these elevations in ALT and bilirubin.

When the above criteria for acute liver failure are considered to have been met, Hy's rule predicts a mortality rate that can exceed 10 %, the mortality rate depending on the drug. Registry studies from Sweden and Spain have confirmed the validity of Hy's rule by demonstrating a mortality rate of 9–12 % in consecutive DILI patients [8, 9]. Occurrence of pre-approval cases (even 2–3) that meet Hy's rule criteria has been associated with, and has often predicted, potential for significant post-marketing serious liver injuries. Thus, Hy's rule calls for enhanced vigilance of the patient concerned since the stopping rules imply that if the drug is discontinued before a patient crosses the threshold of hepatotoxic irreversibility, then potentially fatal acute liver failure can be prevented. Although the exact level of ALT elevation that signals the risk of developing potentially fatal acute liver failure is not known with any certainty, an eightfold rise from a normal baseline is generally considered to represent the threshold below which DILI may be reversible for most drugs causing hepatocellular injury [31]. Nevertheless, depending on the nature of the indication for using a particular drug, the prescribing information of many drugs often recommends that the drug be stopped if ALT levels exceed three times the ULN.

3 Tyrosine Kinase Inhibitors and Hepatotoxicity

During the development of TKIs, hepatotoxicity has sometimes been severe enough to be a dose-limiting toxicity or to require termination of the drug from further development [32, 33]. In a study of 40 patients treated with foretinib in eight dose cohorts, dose-limiting toxicities included grade 3 elevations in aspartate aminotransferase (AST) [32]. The development of CP-724,714, an EGFR inhibitor, was discontinued because of its hepatotoxic potential [33]. In a study of 30 female patients with advanced malignant solid HER2-expressing tumours treated with CP-724,714, dosing at potentially clinically effective doses was not feasible as a result of reversible, cholestatic liver dysfunction. Treatment-related adverse events included hyperbilirubinaemia (27 %) and elevated transaminases (30 %). Grade 3 elevation of ALT was observed in 3 of the 11 patients before potentially clinically effective doses could be achieved [34].

3.1 Incidence and Severity

In pre-approval clinical trials of TKIs, taken as a whole class, hepatotoxicity has manifested itself as low-grade

increases in ALT and/or AST in about 25–35 % of the patients and as high-grade increases in serum transaminases in about 2 % of the patients. As shown in Table 1, the incidences of both all-grade and high-grade increases vary widely between agents and the potential for serious hepatotoxicity with lapatinib, pazopanib, ponatinib, regorafenib and sunitinib is believed to be sufficiently high as to require a boxed label warning. There have been a few reports of hepatic failure with some TKIs and in general, fatalities from TKI-induced hepatotoxicity are rare, reported so far with crizotinib, imatinib, lapatinib, pazopanib, ponatinib, regorafenib and sunitinib. A comprehensive meta-analysis of 12 published studies suggested that there is a significant overall increase in the odds of developing high-grade (grade 3 or above) hepatotoxicity with the use of TKIs compared to the control arms [35]. In another study of EGFR-treated patients with normal LFT at baseline, the incidence rate of new elevations of ALT greater than three times the ULN was 6.2 % and of the combination end point (of AST or ALT greater than three times the ULN *and* bilirubin greater than twice the ULN *and* alkaline phosphatase less than twice the ULN) (Hy's rule cases), the incidence rate was 0.4 % [36].

3.2 Interval to Onset

In the majority of cases, the time to onset of increased ALT and AST is 2–8 weeks of initiating therapy (Table 1). Exceptionally, however, it may be delayed as in a few cases following treatment with imatinib, pazopanib and sunitinib. Hepatotoxicity with lapatinib may occur days to several months (median 7 weeks), while that associated with pazopanib within the first 18 weeks, after initiation of treatment. The median time to onset of ALT or AST elevation following ponatinib was 46 days (range 1–334 days).

3.3 Histopathology

Although hepatotoxicity associated with the TKIs is not uncommon, there is remarkably poor documentation of its histological features. Much of the available information relates to imatinib-induced hepatotoxicity since it has been the longest in clinical use. These reports suggest that hepatocellular necrosis is by far the most frequent form of TKI-induced liver injury. Table 2 summarizes the key reports that we have been able to locate on liver histology of patients with TKI-induced hepatotoxicity. In cases where a biopsy result is not available, the profile of LFT abnormalities also suggests hepatic necrosis. However, other forms of hepatic damage such as cholestasis can occur [33]. In some cases, the damage ultimately leads to hepatic cirrhosis. We discuss below some features of hepatotoxicity induced by some TKIs.

In a patient who developed imatinib-induced hepatotoxicity after 6 months' treatment, liver function slowly improved over the following weeks and a repeat liver biopsy showed severely reduced liver parenchyma and massive ductular proliferation. Subsequently, although the liver function progressively improved, the patient developed portal hypertension. A year later, another liver biopsy revealed post-necrotic hepatic cirrhosis [37]. Although hepatocellular necrosis is a typical feature of hepatotoxicity following imatinib, mild cholestasis has also been reported in one of the seven cases reviewed by Ridruejo et al. [38]. Interestingly, Kong et al. [39] reported a patient with dominant cholestatic damage with only mild hepatocellular damage in a patient following imatinib therapy. Pariente et al. [40] reported a patient with gastrointestinal stromal tumour (GIST) in whom treatment with imatinib was re-initiated twice after laboratory tests normalized. During both re-challenges, including one with only 2.5 % of the recommended therapeutic dose, liver toxicity reappeared [40]. The patient was subsequently treated with sunitinib without any liver toxicity. A review of 20 published cases shows that despite discontinuation of imatinib, hepatic damage can be progressive [41]. Tonyali et al. [42] reported a 53-year-old woman with advanced GIST who developed hepatotoxicity while receiving imatinib for 10 weeks. Despite discontinuing imatinib immediately, the patient developed hepatic encephalopathy, jaundice, and coagulopathy a week later. Her LFT normalized after a 9-week period of prednisolone treatment.

Although biopsy-documented severe centrilobular necrosis with moderate-to-severe steatosis has been reported in a patient receiving sunitinib, a conclusion on the association of these changes to sunitinib is complicated by the fact that the patient was also taking acetaminophen (also known as paracetamol) and levothyroxine [43]. A review of the regulatory documents revealed that hepatic necrosis and lymphocyte infiltration characterized biopsy-proven hepatotoxicity induced by regorafenib, pazopanib and ponatinib [44, 45].

3.4 Mechanisms of TKI-Induced Hepatotoxicity

As far as the TKIs are concerned, a class effect based on inhibition of a specific tyrosine kinase is unlikely because pharmacologically diverse TKIs are known to be hepatotoxic. Neither is there any evidence that hepatotoxicity of these drugs may be related to a particular chemical class. For example, lapatinib is an anilinoquinazoline, pazopanib is an aminopyrimidine and regorafenib is a pyridylcarboxamide while sunitinib is a pyrrolylcarboxamide. Furthermore, as discussed below, patients who develop hepatotoxicity on gefitinib are able to tolerate erlotinib, although both the drugs have a 4-anilinoquinazoline structure and inhibit EGFR-mediated pathways.

Table 1 Laboratory and clinical data on hepatic injury induced by TKIs

Drug	Major indication(s) approved	Incidence of ALT/AST elevations (%)[a]		Latency to onset of hepatic injury	Cases of hepatitis or hepatic failure?	Fatal cases of hepatic failure?
		All grades	Grade 3–4			
TKIs whose FDA labels require monitoring of liver function during their clinical use						
Axitinib	Renal cell carcinoma	22	<1	No information	No	No
Bosutinib	Chronic myeloid leukaemia	20	4–9	Median 30–33 days	Yes	No
Crizotinib	Non-small cell lung cancer	57	6	Within first 2 months	Yes	Yes
Erlotinib	Non-small cell lung cancer	35–45[b]	10–14[b]	Within 2–4 weeks	Yes	No
	Pancreatic cancer					
Gefitinib	Non-small cell lung cancer	10–24	5–6	Within first 2 months	Yes	No
Imatinib	Chronic myeloid leukaemia	6–12	3–6	Reported to be 12–77 days	Yes	Yes
	Acute lymphoblastic leukaemia					
	Hypereosinophilic syndrome					
	Myelodysplasia or proliferation					
	Gastrointestinal stromal tumour					
Lapatinib	HER2-positive breast cancer	37–53[b]	2–6[b]	Days to several months after initiation of treatment	Yes[c]	Yes
				Median 49 days		
Nilotinib	Chronic myeloid leukaemia	35–62	1–4	No information	Yes	No
Pazopanib	Renal cell carcinoma	46–53	7–12	Within first 18 weeks	Yes[c]	Yes
	Soft tissue sarcoma					
Ponatinib	Chronic myeloid leukaemia	56	8	Within 1 week	Yes[c]	Yes
	Acute lymphoblastic leukaemia					
Regorafenib	Colorectal cancer	45–65	6	2–6 weeks	Yes[c]	Yes
Sunitinib	Gastrointestinal stromal tumour	40–60	2–5	Reported to be 4 weeks in one case and 9 weeks in another	Yes[c]	Yes
	Renal cell carcinoma					
	Pancreatic neuroendocrine tumours					
Vemurafenib	Melanoma with BRAF mutation(s)	35–38	3	Median 3–6 weeks	Yes	No
TKIs whose FDA labels do not require monitoring of liver function during their clinical use						
Cabozantinib	Medullary thyroid cancer	86	3–6	No information	No	No
Dasatinib	Chronic myeloid leukaemia	50	1–9	No information	No	No
	Acute lymphoblastic leukaemia					
Ruxolitinib	Myelofibrosis	18	0	No information	No	No

Table 1 continued

Drug	Major indication(s) approved	Incidence of ALT/AST elevations (%)[a]		Latency to onset of hepatic injury	Cases of hepatitis or hepatic failure?	Fatal cases of hepatic failure?
		All grades	Grade 3–4			
Sorafenib	Renal cell carcinoma Hepatocellular carcinoma	21–25	2	No information	No	No
Vandetanib	Medullary thyroid cancer	51	2	No information	No	No

AST aspartate transaminase, *ALT* alanine transaminase

[a] Values shown are best estimates computed from pre-approval EU [44] and US [45] regulatory reviews and labels of the TKI concerned from data across a number of trials and indications when appropriate. These values have not been adjusted for changes in placebo treatment arms

[b] When used in combination with conventional chemotherapy

[c] FDA labels of these TKIs carry a boxed warning concerning their hepatotoxic potential [45]

Table 2 Histological characteristics of TKI-induced hepatotoxicity

TKI	Predominant histological features in liver biopsies	Reference
Pazopanib	Hepatocellular necrosis	[45]
Ponatinib	Hepatocellular necrosis	[45]
Regorafenib	Hepatocyte necrosis and lymphocyte infiltration	[45]
Imatinib	Hepatocellular necrosis	[37]
	Hepatocellular necrosis	[42]
	Hepatocellular necrosis	[96]
	Hepatocellular necrosis	[97]
	Hepatocellular necrosis	[98]
	Acute hepatitis cytolysis with mild cholestasis	[99]
	Focal hepatocellular necrosis with mild infiltration of lymphocytes around necrosis	[100]
	Cholestatic hepatitis	[39]
Erlotinib	Hepatocellular necrosis with marked portal inflammation and ductular proliferation	[101]
Gefitinib	Active necrosis against a background of chronic hepatitis and increased fibrosis	[102]
Sorafenib	Hepatocellular necrosis	[60]
	Hepatocellular necrosis	[61]
	Features of immune-mediated hepatitis	[62]
Sunitinib	Hepatocellular necrosis	[43]

Takeda et al. [46] suggested an immune mechanism for gefitinib-induced hepatic injury in one case on the basis of (a) a positive drug lymphocyte stimulation test for gefitinib and (b) a much shorter latency to onset of the third and the fourth episodes of ALT elevations, developing immediately after resumption of a few tablets of gefitinib. However, the lymphocyte stimulation test is not reliable enough for diagnosing immunologically mediated drug-induced hepatitis and an immunologically-mediated mechanism is not consistent with the reported safety of lower doses of gefitinib in a number of cases with gefitinib-induced hepatotoxicity [47, 48]. Lim et al. [49] reported a patient in whom the dose of gefitinib had to be reduced to 250 mg to be taken every other day as a result of hepatotoxicity at higher doses, and it could be continued safely and beneficially for 17 months. In contrast, results from a study that sought to identify gene variants associated with lapatinib-induced ALT elevation and hepatobiliary adverse events support a role for immune mechanisms in lapatinib-induced hepatotoxicity [50]. In this study, *DQA1*02:01* allele carriage was present in 71 % of ALT cases and in 21 % of controls ($p < 0.001$; odds ratio 9.0; 95 % CI 3.2–27.4). As a predictor of risk of liver safety in ALT cases versus controls, *DQA1*02:01* had negative and positive predictive values of 0.97 (95 % CI 0.95–0.99) and 0.17 (95 % CI 0.10–0.26), respectively [50].

Gefitinib and erlotinib are both metabolized primarily by CYP3A4 but CYP1A1 also plays a major role in the metabolism of erlotinib and CYP2D6 provides a significant alternative pathway for the elimination of gefitinib. Kijima et al. [48] investigated whether a decreased CYP2D6 activity might at least partially account for gefitinib-induced hepatotoxicity. The *CYP2D6* genotypes of the three patients with gefitinib-induced hepatotoxicity studied were *1/*10, *10/*10 and *1/*5, suggesting altered gefitinib metabolism. These investigators suggested that *CYP2D6* genotype might be more closely associated with gefitinib-induced hepatotoxicity in patients with low activity, compared to those with high activity, of CYP3A4 and CYP1A1. However, a large case-control study by Suzumura et al. [51] did not find any association between

reduced CYP2D6 activity and an increased risk of any adverse events in either the gefitinib or the erlotinib cohort. Interestingly, Suzumura et al. [52] recently reported that the frequency of skin rash is significantly higher in gefitinib-treated patients with reduced CYP2D6 activity compared to those with normal CYP2D6 activity, although available evidence does not suggest an association between either total or unbound gefitinib steady-state plasma trough concentrations and the development of skin rash [53].

CP-724,714 was discontinued from further development because of its potential for hepatocellular injury and hepatobiliary cholestasis [33]. Subsequent studies in established human hepatocyte models and in vitro transporter systems suggested that CP-724,714 was directly cytotoxic with mitochondria identified as a target organelle for its hepatic toxicity. These studies also found that it inhibited hepatic efflux transporters, resulting in hepatic accumulation of the drug and bile constituents. It therefore appears that two distinctly separate mechanisms led to hepatotoxicity due to CP-724,714—hepatocellular injury and hepatobiliary cholestasis [33]. Further investigations are needed to determine whether this may also apply to other TKIs.

Importantly, however, more recent studies with acetaminophen have provided valuable insights into the potential role of intracellular signal transduction in the mechanisms of drug-induced hepatotoxicity. Herein we summarize some of the key features of the highly complex mechanisms involved. During acetaminophen-induced liver injury, VEGF and its receptors are upregulated, and treatment with a VEGFR2 inhibitor has been shown to impair hepatocyte proliferation following acetaminophen exposure [54]. Furthermore, hepatic tissue repair, including the reconstitution of hepatic microvasculature, plays a critical role in determining the final outcome of acetaminophen hepatotoxicity [55]. In acetaminophen-induced liver injury, hepatocyte death requires the sustained activation of c-Jun kinase (JNK), a kinase important in mediating apoptotic and necrotic cell death. Inhibition of JNK using chemical inhibitors or knocking down JNK can prevent hepatocyte death even in the presence of extensive glutathione depletion, covalent binding, and oxidative stress [56]. Acetaminophen-induced liver injury is an accepted model of drug-induced hepatotoxicity and whether these findings can be extrapolated to TKIs remains to be investigated. Protein tyrosine phosphatase 1B (PTP1B) dephosphorylates and inactivates EGFR, PDGFR and HGFR among other tyrosine kinase receptors and its deficiency (resulting in a shift of these receptors to activated state) has been reported to accelerate hepatic regeneration [57]. Signal transduction pathways activated/inhibited during oxidative stress reportedly play a key role in drug-induced liver injury and overall, many signalling pathways are important in regulating drug-induced liver injury [58]. Given these complex interactions of tyrosine kinase signalling cascades with hepatocyte integrity, it may not altogether be too surprising if TKIs are associated with hepatotoxicity, albeit with varying degrees of potency.

3.5 Requirements for Monitoring Patients

The prescribing information of TKIs perceived to be hepatotoxic recommends baseline and periodic monitoring LFT in patients (Table 3). Patients with abnormal LFT should be monitored more frequently, as often as weekly if necessary. Depending on the severity or persistence of the abnormalities, it is recommended to withhold dosing, reduce dosing or permanently discontinue the TKI concerned. Permanent discontinuation may become necessary but this poses a dilemma if the tumour is responsive to the TKI concerned. This requires that the diagnosis of TKI-induced hepatic injury be established with care and reasonable certainty.

3.6 Post-Marketing Experiences

Although the FDA label of sorafenib does not include a warning or a requirement to monitor patients for their LFT, post-marketing experience suggests that it is probably hepatotoxic. Its use in hepatocellular carcinoma complicates interpretation of LFT. Sorafenib was first approved in 2005 but liver failure associated with its use was first described much later in a patient with thyroid cancer who developed elevated LFT 8 weeks after starting the treatment. Despite discontinuing sorafenib, hepatic function worsened with a fatal outcome secondary to hepatic failure [59]. Since then, other reports of sorafenib-induced hepatotoxicity have continued to appear [60–65]. In a Periodic Safety Update Report (#6) submitted by the sponsor to the Committee for Medicinal Products for Human Use (CHMP), it was noted that cumulatively, 6 adverse events of hepatitis and 31 events of hepatic failure had been reported. Eight of these were potentially consistent with drug-induced hepatitis. Consequently, in August 2010, the prescribing information for sorafenib in the EU was amended to include its potential for hepatotoxicity [66]. Lapatinib was first approved by the FDA in March 2007. The contents of the initially approved label did not signal any review concern regarding its hepatotoxic potential [45]. However, following clinical experience over the next few months, the FDA approved in July 2008 a revised label with a boxed warning on its hepatotoxicity [45].

3.7 Diagnostic and Therapeutic Dilemmas

Although Hy's rule is very helpful in making therapeutic decisions in most settings, its application in cancer patients taking TKIs poses significant challenges since (a) TKIs that

Table 3 Summary of FDA recommendations on liver function tests monitoring [45][a]

Drug	Monitoring recommendations
Axitinib	Monitor ALT, AST and bilirubin before initiation of, and periodically throughout, treatment with axitinib
Bosutinib	Monitor liver enzymes at least monthly for the first 3 months and as needed. Withhold, reduce dose or discontinue bosutinib depending on the changes observed. In cases meeting Hy's rule, discontinue bosutinib permanently
Crizotinib	Monitor monthly and as clinically indicated with more frequent testing in patients with grade 2–4 elevations. Temporarily suspend, reduce dose of or suspend crizotinib as indicated. In cases meeting Hy's rule, discontinue crizotinib permanently
Erlotinib	Periodic liver function testing is recommended. In the setting of worsening liver function tests, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. Erlotinib dosing should be interrupted or discontinued if total bilirubin is >3 × ULN and/or transaminases are >5 × ULN in the setting of normal pretreatment values
Gefitinib	Periodic liver function testing should be considered. Discontinuation of gefitinib should be considered if changes are severe
Imatinib	Monitor liver function before initiation of treatment and monthly thereafter or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or reduction of the dose of imatinib depending on the severity
Lapatinib	Monitor liver function tests before initiation of treatment, every 4–6 weeks during treatment, and as clinically indicated. Discontinue and do not restart lapatinib if a patient experiences severe changes in liver function tests
Nilotinib	Hepatic function tests should be checked monthly or as clinically indicated. If changes are grade 3 or greater, withhold nilotinib and monitor liver function tests. Resume nilotinib at reduced dose when changes return to grade 1 severity or less
Pazopanib	Monitor serum liver tests before initiation of treatment with pazopanib and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period. Patients with isolated ALT elevations between 3 × ULN and 8 × ULN may be continued on pazopanib with weekly monitoring of liver function until ALT return to grade 1 or baseline. Patients with isolated ALT elevations of >8 × ULN should have pazopanib interrupted until they return to grade 1 or baseline. In cases meeting Hy's rule, pazopanib should be permanently discontinued. Patients should be monitored until resolution
Ponatinib	Monitor liver function tests at baseline, at least monthly or as clinically indicated. Interrupt, reduce or discontinue ponatinib as clinically indicated. Discontinue ponatinib in cases meeting Hy's rule
Regorafenib	Obtain liver function tests before initiation of regorafenib and monitor at least every 2 weeks during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to <3 × ULN or baseline. Temporarily hold and then reduce or permanently discontinue regorafenib depending on the severity and persistence of hepatotoxicity. Discontinue ponatinib in cases meeting Hy's rule
Sunitinib	Monitor liver function tests before initiation of treatment, during each cycle of treatment, and as clinically indicated. Sunitinib should be interrupted for grade 3 or 4 drug-related hepatic adverse events and discontinued if there is no resolution. Do not restart sunitinib if patients subsequently experience severe changes in liver function tests or have other signs and symptoms of liver failure
Vemurafenib	Monitor liver function tests before initiation of treatment and monthly during treatment, or as clinically indicated. Laboratory abnormalities should be managed with dose reduction, treatment interruption, or treatment discontinuation

AST aspartate transaminase, *ALT* alanine transaminase, *ULN* upper limit of normal

[a] Physicians should check the latest labels for detailed recommendations on dose modifications in patients with hepatic injury

inhibit UDP-glucuronosyltransferase isoform 1A1 (UGT1A1) impair elimination of bilirubin, with a resulting increase in unconjugated bilirubin and (b) elevated serum transaminases are frequent in the presence of liver metastasis. The combination of these two factors in a patient may well mimic the criteria articulated in Hy's rule.

Both pazopanib and regorafenib inhibit UGT1A1 and carry a boxed hepatotoxicity warning. Pazopanib has been shown to give rise to isolated mild hyperbilirubinaemia that is usually irrelevant clinically [67]. In one of the pazopanib studies submitted to the FDA, grade 2–4 hyperbilirubinaemia was present in 16 % of patients receiving pazopanib and 4 % receiving placebo. Given the increased incidence of elevations in ALT and bilirubin with pazopanib, the database was examined for cases that would meet the definition of Hy's rule and after screening the pazopanib monotherapy population ($N = 990$), only four cases (0.4 %) that met the Hy's rule criteria were identified [45].

Liver metastasis, frequently present in patients with cancers, often complicates the interpretation of the results of LFT and biopsy may be the only way to confirm hepatotoxicity [68]. For example, the frequencies of AST or ALT greater than three times the ULN in regorafenib-treated patients were 17 % in patients with metastasis and 6 % in those without metastasis. The corresponding rates for patients on placebo were 16 % and 1 %, respectively. In contrast, the frequencies of increase in ALT in pazopanib-treated patients were 54 % in the presence of metastasis and 62 % without metastasis. Thus, it is important to establish drug-induced hepatic injury with certainty before reducing the dose of, or discontinuing, a potentially beneficial drug.

Furthermore, it may also be difficult to evaluate whether hepatotoxicity is the result of another co-administered drug, either directly or indirectly through a drug interaction. TKIs are intended to be a chronic therapy in patients who often have co-morbidities or are in receipt of co-medications. Given their pharmacokinetic properties [4] and ability to interact with drug transporters [69], TKIs are susceptible to many drug–drug and drug–disease interactions. Data on the interaction potential of three TKIs (imatinib, dasatinib and nilotinib) illustrate the scope of the interaction potential of TKIs generally [70]. Lapatinib is indicated to be administered with capecitabine or letrozole. According to the FDA label, the incidences of all grades of rise in ALT were 37 % in patients receiving it in combination with capecitabine and 33 % in those receiving capecitabine alone and the incidences on lapatinib/letrozole combination and letrozole monotherapy were 46 % and 35 %, respectively. A grade 3 increase was more frequent when lapatinib was combined with capecitabine (2 % versus 1 %) and letrozole (5 % versus 1 %).

Acetaminophen is frequently used for the relief of mild to moderate pain by patients with cancers. It is eliminated mainly by glucuronidation. Isoforms UGT1A1, UGT1A6, UGT1A9 and UGT2B15 have been identified as the principal isoforms responsible for acetaminophen glucuronidation over its clinically relevant concentration range [71, 72]. When the glucuronidation pathway is impaired or saturated, an alternative CYP2E1-mediated pathway generates a highly reactive hepatotoxic intermediate, *N*-acetyl-*p*-benzoquinone-imine, NAPQI [73, 74]. Thus, when acetaminophen glucuronidation is impaired, the risk of acetaminophen hepatotoxicity is higher [75]. Erlotinib, nilotinib, pazopanib, sorafenib and regorafenib have the potential to inhibit UGT1A1 whereas gefitinib [76, 77], sorafenib and regorafenib have the potential to inhibit UGT1A9. The characteristic cascade of events that gives rise to acetaminophen-induced hepatotoxicity is its enhanced metabolic activation by CYP2E1 (and possibly CYP3A4) to NAPQI, covalent binding of NAPQI to proteins, glutathione depletion, and hepatic necrosis. Studies by Laine et al. [78] have also suggested that CYP3A4 is the major CYP enzyme form catalysing acetaminophen oxidation to NAPQI in human liver but the significance of this is unclear at present.

Both the European prescribing information [79] and the FDA label [80] for imatinib suggest that caution should be exercised when using high doses of imatinib and acetaminophen concomitantly. The data, however, are conflicting. In animal models, an increase in irreversible hepatotoxicity was observed when both drugs were co-administered [81]. Ridruejo et al. [38] described a patient treated with imatinib who experienced exacerbations of hepatic toxicity upon co-administration with acetaminophen. However, in a clinical study in Korean patients, the pharmacokinetics of acetaminophen and its major metabolites in the presence of imatinib were similar to those of the control conditions and the combination was well tolerated [82].

In the pazopanib data set submitted to the FDA, one patient fulfilling Hy's rule criteria had taken both acetaminophen as needed (approximately 1,600 mg daily) and pazopanib prior to the first elevation in ALT to greater than three times the ULN and total bilirubin to greater than twice the ULN. The high levels returned to normal after both the drugs were discontinued. The patient with acute liver failure with fatal outcome reported by Weise et al. [43] was also taking acetaminophen (and levothyroxine) concurrently with sunitinib. Paradoxically, however, it has been demonstrated that whereas high dose of sunitinib with acetaminophen potentiates hepatotoxicity, low doses are protective [83, 84]. From the foregoing, it seems likely that the true scale of hepatotoxic interaction between the TKIs and acetaminophen is at present unknown since a large number of drugs inhibit CYP3A4, the principal enzyme that metabolizes almost all the TKIs.

3.8 Re-Challenge and Cross-Reactivity

Available evidence strongly suggests a lack of cross-reactivity between the TKIs even when they are known to be active at the same tyrosine kinase or belong to the same chemical class. Effectively, this eliminates hepatotoxicity as an on-target toxicity related to inhibition of the target tyrosine kinase pathway. Spataro [37] was able to introduce nilotinib in the treatment of a patient who had developed imatinib-induced hepatotoxicity. A successful switch to sunitinib in a patient who developed imatinib-induced hepatotoxicity, confirmed by two re-challenges, has already been referred to earlier [40]. Lack of cross-reactivity is better illustrated by erlotinib and gefitinib. Liver dysfunction has been reported to be significantly more frequent in Japanese patients receiving gefitinib than erlotinib. The odds ratio of developing liver dysfunction following gefitinib versus erlotinib treatment was determined to be 3.30 (95 % CI 1.59–7.22) [51]. As a result, it is more often necessary to discontinue gefitinib than erlotinib because of hepatotoxicity.

3.8.1 Switch from Gefitinib to Erlotinib

Ohashi et al. [85] retrospectively assessed the occurrence of liver toxicity in eight patients with non-small cell lung cancer who were switched to treatment with erlotinib following severe gefitinib-induced liver injury. Severe liver injury recurred in only one of these eight patients while receiving erlotinib and treatment with erlotinib in this case was discontinued because of the onset of skin rash and liver

injury. After liver function was restored, erlotinib was resumed at a lower dose but nonetheless severe liver injury recurred. Ku et al. [86] reported two patients who developed grade 2–3 hepatotoxicity starting between 4 and 6 weeks after initiation of gefitinib. This effect peaked between 10 and 20 weeks. One of the patients experienced recurrence of hepatotoxicity when re-challenged with gefitinib. Both patients were able to tolerate erlotinib without the development of hepatotoxicity. Nagano et al. [87] also reported a patient who was treated with gefitinib for 6 weeks when he developed substantially elevated hepatic enzyme levels, requiring the discontinuation of gefitinib. Gefitinib was reintroduced with an intermittent treatment schedule after the transaminase levels normalized, but these rose again, and the cancer progressed. Gefitinib was eventually replaced with erlotinib without any signs of liver toxicity and with stable disease for 7 weeks. Kitade et al. [88] have also reported a successful switch to erlotinib in a patient who developed hepatotoxicity following 6 months of treatment with gefitinib. She continued the therapy with erlotinib for 3 years, during which her disease stabilized without hepatotoxicity or any further complications. Takeda et al. [89] reported two patients with hepatotoxicity due to gefitinib who were also successfully changed to erlotinib without any evidence of recurrence of hepatic injury.

3.8.2 Switch from Erlotinib to Gefitinib

Takeda et al. [89], Nakatomi et al. [90] and Kunimasa et al. [91] each reported one patient who had developed hepatotoxicity due to erlotinib and were switched successfully to gefitinib.

In the context of lack of cross-reactivity, it is also worth noting that there are also a few reports of successful treatment with erlotinib after gefitinib-induced severe interstitial lung disease [89, 92–94] and vice versa [95].

4 Conclusions

TKIs are associated with potentially fatal hepatotoxicity that is usually reversible on dose reduction or discontinuation of the TKI concerned. Despite an adverse overall safety profile which negatively impacts on their clinical risk/benefit, their toxicity profile has not proved to be a barrier to their regulatory approval because they are effective, often highly so, in treating life-threatening conditions for which there are limited treatment options, if any. Since some of these toxic effects are on-target effects related to the primary pharmacological activity of TKIs and are therefore linked intricately with their efficacy, these targeted agents that lead to improvements in efficacy also increase treatment-related morbidity and mortality.

There is at present no evidence to suggest that TKI-induced hepatotoxicity is an on-target effect linked to its efficacy and therefore its appearance calls for adjustment of therapy when it is severe enough. However, its diagnosis can be very challenging in the presence of co-morbidities (such as liver metastasis) and co-medications (with potentially hepatotoxic drug interactions). Therefore, whenever possible, hepatotoxic co-medications or drugs that are inhibitors of TKI elimination should be avoided.

Before therapy with an otherwise effective TKI is altered, the diagnosis of drug-induced hepatic injury must be established with reasonable certainty in order to optimize safety and efficacy in an individual patient.

TKIs need careful post-marketing surveillance for their hepatotoxic safety. Experience with drugs such as imatinib, lapatinib and sorafenib suggests that as the TKIs are used more widely, with expanding indications for each, their post-marketing safety profile and risk/benefit assessment may require regular re-assessment. It is troubling to know that cases meeting Hy's rule have been identified in TKI clinical trials of relatively small sample sizes. This may well signal a potential for substantial post-marketing hepatic morbidity. It is therefore critical that patients are monitored carefully. In order to better assess the hepatic safety of these agents in terms of frequency, severity and outcomes, it may be that all cases should be better documented and reported to a central registry. As discussed earlier, troglitazone has highlighted the risks of inadequate patient monitoring. Although it is uncertain whether regular monitoring of LFT ultimately translates into better outcomes, prudence dictates appropriate monitoring of patients treated with TKIs for evidence of liver injury and appropriate management of these patients. Provided the patients are carefully monitored and correctly managed, there seems no obvious reason why it should not be possible to achieve anticancer efficacy and optimize risk/benefit at an individual patient level.

Conflict of Interest The authors have no conflicts of interest that are directly relevant to the content of this review and have not received any financial support for writing it. RRS was formerly a Senior Clinical Assessor at the Medicines and Healthcare products Regulatory Agency (MHRA), London, UK. JM is the Chief Cardiac Consultant to eResearchTechnology Inc (eRT), Philadelphia, PA, USA which provides cardiac safety services to drug development companies. Both RRS and JM now provide expert consultancy services on development of new drugs to a number of pharmaceutical companies. DRS is a first-year house officer at a district general hospital and has no consultancy relationships.

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