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Review article**Multikinase inhibitor-induced liver injury in patients with cancer: a review for clinicians**

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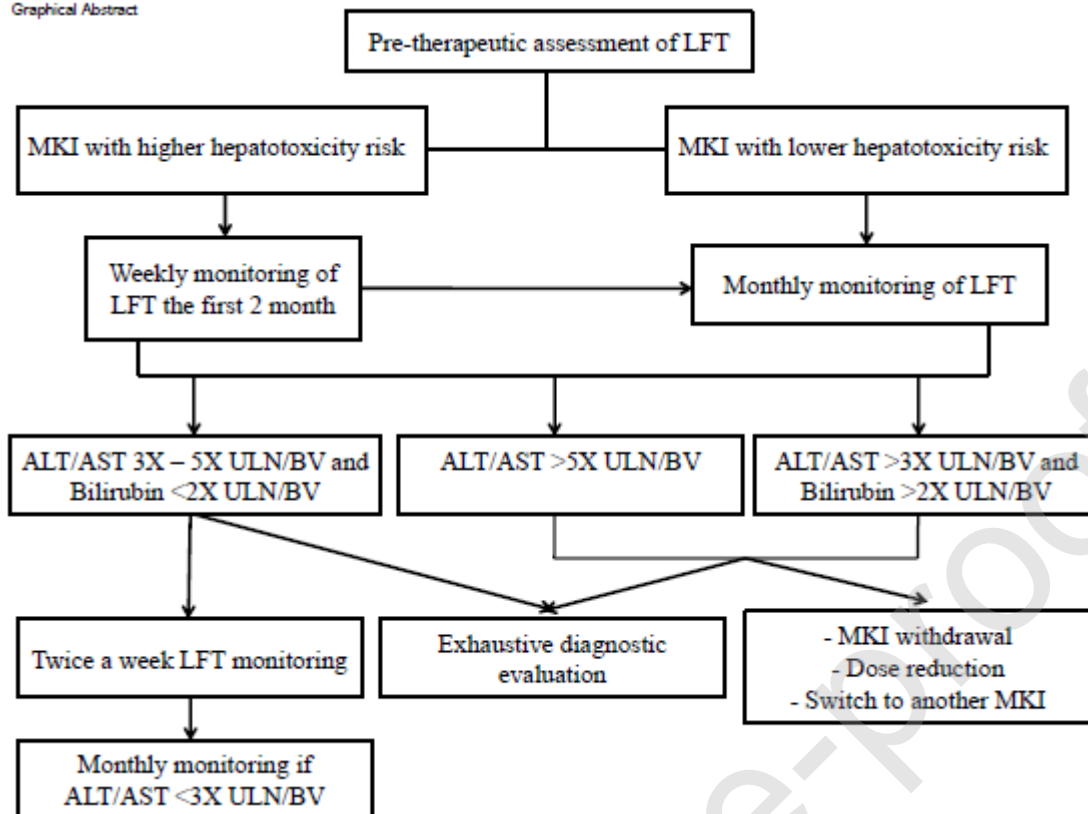
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Graphical abstract

Graphical Abstract



Abstract

Background. Multikinase inhibitors (MKI) are targeted molecular agents that have revolutionized cancer management. However, there is a paucity of data concerning MKI-related liver injury risk and clinical guidelines for the management of liver toxicity in patients receiving MKI for cancer are scarce.

Design. We conducted a PubMed search of articles in English published from January 2000 to December 2018 related to hepatotoxicity of the 29 FDA-approved MKIs at doses used in clinical practice. The search terms were the international non-proprietary name of each agent

cross-referenced with «hepatotoxicity», «hepatitis», «hepatic adverse event», or «liver failure», and «phase II clinical trial», «phase III clinical trial», or «case report».

Results. Following this search, 140 relevant studies and 99 case reports were considered. Although asymptomatic elevation of aminotransferase levels has been frequently observed in MKI clinical trials, clinically significant hepatotoxicity is a rare event. In most cases, the interval between treatment initiation and the onset of liver injury is between one week and two months. Liver toxicity is often hepatocellular and less frequently mixed. Life-threatening MKI-induced hepatic injury has been described, involving fulminant liver failure or death. Starting from existing data, a description of MKI-related liver events, grading of hepatotoxicity risk, and recommendations for management are also given for various MKI molecules.

Conclusion. All MKIs can potentially cause liver injury, which is sometimes irreversible. As there is still no strategy available to prevent MKI-related hepatotoxicity, early detection remains crucial. The surveillance of liver function during treatment may help in the early detection of hepatotoxicity. Furthermore, the exclusion of potential causes of hepatic injury is essential to avoid unnecessary MKI withdrawal.

Keywords: multikinase inhibitor, drug-induced liver injury, hepatotoxicity.

1. Introduction

Drug induced liver injury (DILI) is the fourth most common cause of liver damage in Western countries and the most frequent reason for market withdrawal of a drug [1, 2]. The incidence of DILI is between 1 per 10,000 and 1 per 100,000 patient-years, but is expected to rise in the context of increasing drug availability and prescription [3]. DILI is traditionally

classified as intrinsic (or direct) or idiosyncratic. Intrinsic DILI, related to drug accumulation, is dose dependent and therefore predictable, occurring in a high proportion of exposed individuals. Idiosyncratic DILI is generally not dose related and is unpredictable based on dose or the pharmacological properties of the molecule [4]. DILI caused by most drugs is idiosyncratic. Although the pathogenesis is largely unknown, idiosyncratic DILI is probably the consequence of interactions between host susceptibility, environmental factors, and the pharmacological properties of the drug [5].

The definition of DILI includes one of the following thresholds: ALT \geq 5X ULN (upper limit of normal), ALT \geq 3X ULN associated with bilirubin \geq 2X ULN, or alkaline phosphatase \geq 2X ULN in the absence of bone pathology [6]. For patients with abnormal liver function (LF) before initiation of the culprit drug, ULN is replaced by the mean baseline values prior to DILI onset. In the absence of specific tests for DILI, the diagnosis relies on circumstantial evidence and the exclusion of other causes of liver damage [7].

The emergence of innovative therapies, such as targeted molecular agents, has revolutionized the management of cancer. Among these molecules, multi-kinase inhibitors (MKIs) block phosphorylation cascades involved in tumour proliferation, survival, motility, angiogenesis, and evasion from the immune response [8]. Their targeted action theoretically decreases the risk of adverse events. Nevertheless, MKI use has been associated with serious toxic effects, such as skin toxicity, cardiotoxicity, and hepatotoxicity (idiosyncratic DILI) [9-11]. However, there is a paucity of data concerning MKI-related hepatotoxicity risk and clinical guidelines for the management of liver toxicity in patients receiving MKIs for cancer are scarce. Early diagnosis of DILI is essential, as the continuation of treatment could cause acute liver failure, associated with a 60 to 80% mortality rate in the absence of liver transplantation [12]. On the other hand, an erroneous diagnosis of DILI may lead to unnecessary drug withdrawal, which may affect the prognosis of patients with cancer. We therefore performed an exhaustive

review of the published data on hepatic adverse events and DILI related to MKI use and discuss the issue of hepatotoxicity during MKI treatment for cancer.

Journal Pre-proof

2. Methods

We conducted a PubMed search of articles in English published from January 2000 to December 2018 related to hepatic toxicity of the 30 FDA-approved MKI at doses used in clinical practice: alectinib, afatinib, axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, crizotinib, dabrafenib, dacomitinib, dasatinib, erlotinib, gefitinib, ibrutinib, imatinib, lapatinib, lenvatinib, osimertinib, nilotinib, nintedanib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, trametinib, vandetanib, vemurafenib, everolimus, and temsirolimus. The search terms were international non-proprietary name of each agent cross-referenced with «hepatotoxicity», «hepatitis», «hepatic adverse event», or «liver failure», and «phase II clinical trial», «phase III clinical trial», or «case report». The results of the literature search are presented in Figure 1. Clinical trials reporting hepatic adverse events occurring under treatment and including 20 or more patients (except for bosutinib, for which the threshold was fixed at 10 patients due to a lack of data) were retained. Case reports describing DILI were considered suitable for review by author consensus based on the exclusion of other causes of liver injury and the use of validated scales for the assessment drug imputability. If necessary, drug imputability was reassessed by the authors based on information provided in the manuscripts. Phase I clinical trials were excluded, as we aimed to review hepatotoxicity associated with therapeutic doses.

The potential for causing hepatotoxicity was assessed for each agent on the basis of five criteria: published cases of DILI, published cases of DILI leading to death, ALT or AST > 3X ULN (upper limit of normal) associated with bilirubin \geq 2X ULN (Hy's law) in clinical trials, published clinical trials describing cases of DILI with acute liver failure, and hepatotoxicity demonstrated by published experimental studies. Based on these criteria, the hepatotoxicity risk of MKI was estimated to be low (absence of Hy's law criteria, absence of DILI with acute liver failure in clinical trials, absence of published cases of DILI), moderate (published cases of DILI without reported death), or high (published cases of DILI with reported death or Hy's law

criteria and DILI with acute liver failure in clinical trials). The isolated elevation of aminotransferases was not considered, as its incidence poorly correlates with the incidence of severe liver injury.

3. Results

We first present the existing data on the epidemiology of MKI-related hepatotoxicity, starting from that obtained in clinical trials. We then detail the clinical-biological presentation and diagnostic strategy of DILI associated with MKI use. We also present data concerning the physiopathology of liver events.

3.1 Epidemiology

In most clinical trials, patients are excluded when baseline aminotransferase levels are $> 2.5X$ ULN in the absence of hepatic metastases or $> 5X$ ULN if hepatic metastases are present or the baseline bilirubin level is $> 1.5X$ ULN [13]. However, baseline LF test (LFT) values are often unknown in case-reports or not mentioned in clinical trials. In this context, even grade 3 to 4 elevations in aminotransferase levels reported in clinical trials are difficult to interpret as DILI in the absence of baseline values. Severe hepatic events (grade 3-4), defined as aminotransferase levels $> 5X$ ULN, have been detected in 0 to 29% of patients treated with MKI in clinical trials (Table 1). The heterogeneity between publications on the incidence of increases in aminotransferase levels is high, even for the same agent. For example, severe hepatic events have been described in 4 to 19% of patients treated with bosutinib and in 1 to 11% of those receiving gefitinib (Table 1). In clinical trials, cases of defined DILI have been mentioned for alectinib, afatinib, bosutinib, ceritinib, cobimetinib, crizotinib, gefitinib, imatinib, lenvatinib, osimertinib, pazopanib, ponatinib, regorafenib, sorafenib, sunitinib, and vemurafenib [11, 14-29]. Nevertheless, no description of the clinical features was offered.

Based on preregistration clinical trials, we estimate the prevalence of hepatotoxicity with liver failure to be 0.2 to 0.5% of treated patients for molecules such as afatinib, ceritinib, crizotinib, lenvatinib, and regorafenib [11, 16, 18, 26, 30]. No case reports of DILI have been published or reported for clinical trials of axitinib, cabozantinib, dabrafenib, dacomitinib, nilotinib, trametinib, vandetanib, or temsirolimus. The only hepatotoxicity event potentially related to these agents reported in clinical trials is mostly transient increased aminotransferase levels. It should be mentioned that surveillance of patients included in clinical trials is strictly regulated. Therefore, abnormal LFT are picked up early enough such that they do not often progress to serious toxicity that needs to be reported. These data may not translate in real-life settings where hepatotoxicity events are identified later and treated patients can be much sicker at baseline than in clinical trials.

3.2 Clinical presentation and laboratory tests

The clinical and biological presentation of DILI related to MKI use has only been described in case reports. MKI-induced liver injury includes various biological and clinical presentations, ranging from isolated abnormalities in LFT values to nonspecific symptoms, such as anorexia, asthenia, nausea, abdominal pain, arthralgia, and rash and more specific symptoms, such as jaundice, progressive liver failure with the loss of hepatocellular function, hepatic encephalopathy, and death. In most cases, patients are completely asymptomatic, and the increased aminotransferase level revealed by routine blood tests is the only element that raises a suspicion of MKI-related hepatotoxicity.

Limited data are available from MKI clinical trials. When provided, the latency of hepatotoxicity varies between the first cycle of treatment for crizotinib [18, 31-36] and several months for molecules such as bosutinib [37-42], and imatinib [20, 40, 43, 44], with most cases occurring during the first two months of treatment (Table 2). Significant liver toxicity generally consists of an increase in aminotransferase levels $> 5X$ ULN, but baseline values are not

reported. Nevertheless, associated hyperbilirubinemia (Hy's law) has been described for alectinib, bosutinib, ceritinib, cobimetinib, crizotinib, gefitinib, imatinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib, and the vandetanib-ipilimumab association [14-22, 27, 28, 30, 45-48].

A more detailed description of MKI-related hepatotoxicity is provided by case reports (Table 2). Latency varies between one week for erlotinib [49-51], sorafenib [52], regorafenib [53], and more than six months for gefitinib [54, 55], dasatinib [56], ibrutinib [57], imatinib [58, 59], nintedanib [60], and sunitinib [61]. DILI related to MKI use is hepatocellular (elevated aminotransferase levels with either no or a small increase in alkaline phosphatase levels), but cases of mixed DILI (elevation of both aminotransferase and alkaline phosphatase levels) have been published for dasatinib [56], imatinib [62], pazopanib [63], sorafenib [52], everolimus [64], and vemurafenib [65]. Elevated bilirubin levels meeting Hy's law criteria (hepatocellular type injury seen concurrently with bilirubin > 2X ULN) has been reported for crizotinib (2 cases - death) [35, 66], erlotinib (3 cases - death) [50, 67, 68], ibrutinib (2 cases - recovery) [57, 69], imatinib (5 cases - 1 death) [70-74], lapatinib (1 case - recovery) [75], pazopanib (2 cases - recovery) [76], regorafenib (5 cases - 2 deaths) [53, 77], sorafenib (3 cases - 1 death) [78-80], sunitinib (2 cases - death) [61, 81], and the vemurafenib-ipilimumab association (2 cases - recovery) [48] (Table 2).

3.3 Histological features

Liver biopsy performed in three published cases of erlotinib or gefitinib-induced hepatotoxicity revealed elements of an immuno-allergic (hypersensitivity) mechanism: active hepatitis with portal inflammation (lymphocyte, plasma cell, and neutrophil infiltration) and bridging necrosis [68, 82, 83]. The liver histology for imatinib-induced hepatic injury has been described in 12 case reports [62, 71, 74, 84-92]. Bridging necrosis (mainly centrilobular) associated with portal inflammatory infiltrates containing lymphocytes, plasma cells, and many

eosinophils was found, suggesting a hypersensitivity mechanism. In cases of mixed DILI, histological cholestasis was present. Bridging fibrosis and acute viral hepatitis-like histological features (focal necrosis, with lymphocyte infiltration surrounding the necrotic zones and sinusoids) have been described in two cases of imatinib-induced hepatotoxicity [62, 74, 84, 86]. Histological features suggesting hypersensitivity DILI (bridging necrosis, hepatocellular dropout surrounding the centrilobular areas, and portal eosinophil infiltration) have been reported in one case of lapatinib-induced hepatotoxicity [75]. For ibrutinib- and pazopanib-induced liver injury, histology shows cholestatic hepatitis with eosinophil infiltration within the portal tracts [63, 69]. Cholestatic hepatitis in association with granulomatous inflammation and eosinophil infiltrate has been described in a case of vemurafenib-related DILI [65]. Histological lesions compatible with metabolic (centrilobular hepatic necrosis with confluent destruction of acinar zone 3 and scarce inflammation) or immuno-allergic DILI (bridging necrosis with portal lymphocyte and plasma cell infiltration) have been described in eight cases of hepatotoxicity to regorafenib, sorafenib, and osimertinib [46, 77-80, 93, 94]. The only case report of sunitinib-induced hepatotoxicity with available liver biopsy showed liver invasion by cancerous cells and thus the histological features may not be related to DILI [61]. In a recently reported case of alectinib-induced hepatitis, liver biopsy showed bridging necrosis with an inflammatory infiltrate containing lymphocytes, macrophages, and plasma cells [95].

3.4 Imputability assessment

MKI-associated liver injury can mimic almost all known causes of hepatic disease (viral hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis, metabolic diseases, biliary tract obstruction, hepatic ischemia, vascular obstruction, and sepsis) and is consequently diagnosed by ruling out all other possible causes [96]. Imputability assessment of MKI-related DILI is not detailed in clinical trials. In case reports, the RUCAM

(Roussel Uclaf Causality Assessment Method) causality assessment score has been used and diagnostic tests discussed.

The RUCAM score is the most widely used method for assessing causality in hepatotoxicity induced by various drugs and includes several criteria, such as [97] event chronology, description of the first clinical signs, results of LFTs after drug withdrawal (a 50% decrease of liver enzyme levels following withdrawal of the suspected culprit drug is highly suggestive of DILI) or drug re-challenge (recurrence of LFT abnormalities), concomitant medication (including self-medication, phytotherapy products, and illicit drugs), other potential causes, previous case reports of DILI, nature of the drug, drug dosage, and alcohol consumption. Deliberate or inadvertent drug re-challenge resulting in a deterioration of LF provides the strongest evidence for drug imputability. Positive drug re-challenge has been described for crizotinib (4 cases) [36, 98], erlotinib (2 cases) [68, 99], gefitinib (6 cases) [82, 83, 100-102], imatinib (10 cases), osimertinib (1 case), pazopanib (2 cases) [103], and regorafenib (1 case) [104] (table 2).

3.5 Management and outcome

In case reports, MKI-related toxicity has typically consisted of an increase in aminotransferase levels with either no or a slight increase in alkaline phosphatase levels that spontaneously normalize within 10 days to five months from drug withdrawal in three quarters of cases (Table 2). Glucocorticoids (20-40 mg/day) were necessary in addition to drug discontinuation in case reports of DILI related to imatinib [74], pazopanib [103], and the vemurafenib-ipilimumab combination [48]. Nevertheless, a fatal evolution despite drug withdrawal was reported for crizotinib [35, 66], erlotinib [49, 50, 67, 68], imatinib [58, 72], pazopanib [63], regorafenib [46, 77], sorafenib [80], and sunitinib [61, 81, 105]. Two cases of cirrhosis were reported after 18 and 24 months of imatinib treatment [74, 106]. No other cause of liver disease was found in these patients.

In case reports of crizotinib-related DILI, LFT abnormalities returned despite drug reintroduction at a lower dose (250 mg daily versus 250 mg twice daily) but completely disappeared following drug withdrawal [36]. Successful reintroduction at a reduced dose has been reported in clinical trials [18, 33, 107]. LFT abnormalities recurred upon restarting the drug in two case reports of erlotinib-related DILI, with a fatal evolution in one case [68, 99]. DILI also recurred after gefitinib or regorafenib re-challenge in case reports with concurrent corticoid administration [83] or dose reduction [82, 104]. Nevertheless, the reintroduction of gefitinib was possible for one patient one year later [102]. For imatinib- and pazopanib-related DILI, LFT abnormalities reappeared upon restarting the drug, but successful reintroduction was reported when combined with prednisone in seven [85, 108, 109] and two case reports [103], respectively. In the only case report describing osimertinib-related DILI with a positive re-challenge, the drug could be restarted following oral desensitization, without the recurrence of LFT abnormalities [110].

Cross-toxicity has not been described for MKIs and the switch to erlotinib [54, 101] or afatinib [51, 82, 111] appears to be a safe option for patients developing gefitinib-associated DILI (Table 2). Furthermore, patients developing erlotinib-related DILI were switched to gefitinib without DILI recurrence [99, 112]. The dabrafenib/trametinib combination was also successfully introduced to a patient developing vemurafenib-induced severe liver injury [113].

In clinical trials, liver toxicity related to MKI agents is often transient and non-severe. For bosutinib, LFT values returned to normal for half of patients without drug withdrawal [42]. Nevertheless, fatal cases of MKI-related hepatotoxicity have been reported for crizotinib (1 case) [18], gefitinib (1 case) [22], imatinib (1 case) [20], lenvatinib (3 cases) [114, 115], pazopanib (2 cases) [116], sorafenib (7 cases) [117-120], and sunitinib (9 cases) [121, 122].

3.6 Pathophysiology of MKI-induced hepatotoxicity

The risk of MKI-induced liver injury is likely determined by drug properties, including the generation of toxic reactive metabolites, host factors, and interactions between the two [123]. Most MKIs are metabolized by the cytochrome P450 (CYP450) pathway. Thus, variations in CYP450 isoenzyme activity may critically influence the development of DILI by modifying the level of exposure to the reactive metabolites and/or altering the disposition of the MKI molecule. Gefitinib is metabolized in the liver by CYP3A4, CYP2D6, CYP3A5, and CYP1A1. It has been suggested that CYP2D6 is specifically used as an alternative pathway for gefitinib metabolism [124]. CYP2D6 deficiency may therefore favour gefitinib-induced liver injury in patients taking CYP3A4-inhibitory drugs [124]. Lapatinib undergoes extensive metabolism by CYP3A4 and CYP3A5, generating reactive metabolites that may covalently modify cellular proteins, potentially leading to immune-mediated DILI [125, 126]. Furthermore, the presence of the human leukocyte antigen (HLA)-DQA1*02:01 allele was shown to be associated with a higher risk of lapatinib-induced liver injury in woman with advanced breast cancer [126]. It was also shown that HLA-B*57:01 carriage confers a risk of aminotransferase elevation in patients receiving pazopanib [76]. The hepatotoxicity of lapatinib and pazopanib may therefore be attributed to the interaction between CYP450 polymorphisms and host immune status. Despite a low risk of liver toxicity risk when given as a monotherapy, the vemurafenib-ipilimumab combination was shown to be associated with hepatotoxicity in 60% of patients in a phase 1 clinical trial [48]. Ipilimumab is an immune checkpoint inhibitor that swings the balance towards immune stimulation and may therefore favour an immunological DILI to vemurafenib.

A recent study showed that erlotinib-induced hepatocyte apoptosis *in vitro* is mediated by mitochondrial damage [127]. Regorafenib can also induce hepatocyte necrosis *in vitro* at clinically relevant concentrations by uncoupling liver mitochondrial respiration and inducing

autophagy [128]. Furthermore, imatinib, lapatinib, and sunitinib increase the production of reactive oxygen species, impair cellular oxygen consumption, alter glycolysis, and induce apoptosis in human hepatoma HepG2 cells [129]. Overall, these experimental data suggest that mitochondrial injury is a possible mechanism for hepatotoxicity related to MKI use. Consistent with this assumption, various MKIs that induce metabolic-idiosyncratic hepatotoxicity, such as gefitinib, sunitinib, and sorafenib, are able to impair mitochondrial function in isolated rodent liver mitochondria at clinically relevant concentrations [130, 131].

The adenosine triphosphate-binding cassette transporters ABCG2 and ABCB1 are involved in the efflux of xenobiotics from hepatocytes into the bile. It was recently shown that concomitant use of anti-acid-secreting agents, such as H₂ antagonists and proton-pump inhibitors, is associated with an increased risk of gefitinib-induced liver toxicity [132]. Gefitinib is known to be a substrate of ABCG2 and ABCB1 expressed in hepatocytes [133]. Thus, inhibition of ABCG2 and ABCB1 by proton-pump inhibitors and H₂ antagonists, respectively, may theoretically increase the concentration of gefitinib in the liver, contributing to hepatotoxicity.

Sorafenib and regorafenib are metabolized primarily by oxidative metabolism in the liver via the CYP3A4 pathway and glucuronidation mediated by the uridine diphosphate-glucuronosyl-transferase 1A (UGT1A) 9 pathway [134]. Both drugs potently inhibit UGT1A 9 and 1, contributing to the hyperbilirubinemia observed in patients treated with sorafenib and regorafenib [135].

The results for individual MKI agents are summarized in Table 2 [11, 14, 18, 23, 33-36, 42, 46, 47, 49-56, 58, 59, 61-64, 66-68, 70-92, 94, 98, 99, 101, 102, 105, 106, 109, 111, 112, 114, 115, 124, 132, 136-165].

4 Discussion

Data on DILI from MKI drugs are scarce and there are no recent reviews addressing MKI-related hepatic events. Nevertheless, clinical trials suggest that all MKI agents are associated with a risk of hepatotoxicity, defined as an increase in aminotransferase levels, with or without an increase in bilirubin levels. For certain MKI agents, such as bosutinib, the resolution of LFT abnormalities is observed without drug discontinuation or dose reduction. Such hepatic tolerance to drug toxicity has already been described for isoniazide [166], tacrine [167], and agomelatine [168]: these drugs can initially induce an increase in aminotransferase levels that is thereafter reversible, despite the continuation of treatment. Such an "adaptive phenomenon", which is not synonymous with DILI, is probably underestimated, as drug-induced elevation of aminotransferase levels generally results in treatment withdrawal. Overall, the molecules for which the frequency of severe aminotransferase abnormalities ($> 5X$ ULN), Hy's low criteria, and DILI appears to be the highest are crizotinib, erlotinib, gefitinib, imatinib, lenvatinib, pazopanib, regorafenib, sorafenib, sunitinib and vemurafenib-ipilimumab association (table 1 and 2). Those with apparently lower risks are axitinib, cabozantinib, dabrafenib, dacomitinib, dasatinib, nilotinib, ponatinib, trametinib, vandetanib, everolimus, and temsirolimus (Tables 1 and 2) [14, 18, 31-45, 47, 48, 57, 69, 93, 95, 110, 117-122, 136-142, 155, 169-254] [255-257].

The detection of DILI during pre-marketing clinical trials is a difficult challenge due to the lack of good predictive biomarkers and the small number of patients treated relative to the frequency of DILI. The FDA has proposed indicators of the potential to cause severe hepatotoxicity to guide drug development research: elevation of aminotransferase values to $> 3X$ ULN, with reference to a placebo; any marked elevation of aminotransferases to $> 5X$ ULN in the treatment group, without a corresponding increase in the placebo group; or one or more cases of bilirubin titres increasing to $> 2X$ ULN associated with aminotransferase levels of $>$

3X ULN (Hy's law), with no other explanation [258]. The presence of at least one of these criteria may indicate a significant risk of hepatic toxicity and cases of severe DILI can be expected in post-marketing settings. Of note, the definition of hepatic event severity in clinical trials involving MKI drugs is based on the Common Terminology Criteria for Adverse Events (CTCAE), developed by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI) [259]. According to these criteria, the elevation of aminotransferase > 5X ULN is defined as a severe hepatic event. However, it should be mentioned that asymptomatic increases in aminotransferase levels without jaundice cannot be considered as severe hepatotoxicity. A more reliable scale for grading the severity of liver injury related to drug use was proposed by the Drug-Induced Liver Injury Network (DILIN) [260]. In the DILIN scale, the severity of hepatic events is based on the presence of jaundice, signs of hepatic or other organ failure, the necessity of hospitalization, and death. The presence of these severity criteria is not required in the CTCAE definition. Therefore, the use of the CTCAE criteria in MKI clinical trials may overestimate the severity of MKI-induced hepatotoxicity. It should also be mentioned that LFT abnormalities do not necessarily reflect drug-related toxicity in MKI treated patients. Liver metastases are present in up to 50% of patients in clinical trials and may induce LFT abnormalities. Therefore, LFT perturbations should be interpreted with caution to avoid inappropriate MKI withdrawal. Routine LFT (ALT, AST, PAL, bilirubin) are not specific biomarkers of DILI. Nevertheless, ALT and AST specifically indicate hepatocyte damage and are still the gold standard that should be used to monitor patients [261]. Studies of various individual gene polymorphisms may allow the identification of more reliable indicators of the risk of MKI-related DILI for use in the future. Of note, pre-existing chronic liver disease does not appear to favour MKI-induced hepatotoxicity, but once it develops, DILI may have devastating consequences for patients with a reduced baseline hepatic reserve.

Drug-drug interactions should be considered. Thus, it would be advisable to avoid co-prescriptions that may target or inhibit the same CYP450 pathway in patients treated with MKI. Immuno-allergic mechanisms may play a role, as suggested by the association between lapatinib and pazopanib-induced liver injury and HLA-DQA1*02:01 and HLA-B*57:01 carriage, respectively. Nevertheless, the clinical relevance of CYP450 pathway and HLA typing of MKI-treated patients has not been proven. DILI related to MKI use is idiosyncratic and generally considered to be dose independent. However, crizotinib and nintedanib were successfully reintroduced at lower doses in most patients who developed hepatotoxicity (Table 2).

The strengths of this review include the exhaustive analysis of published cases of MKI-related DILI and the evaluation of LFT abnormalities described in clinical trials.

The main limitation of this review is related to publication biases that must be considered in the analysis of the literature. Any analysis involving case reports is subject to an inherent bias toward the publication of more severe MKI-related hepatic toxicity. Furthermore, the number of reported cases of DILI is inevitably higher for the most frequently used MKI agents, which may tend to falsely indicate a higher hepatotoxicity risk. Finally, alternative causes of liver injury are incompletely ruled out in a considerable number of clinical trials and case reports.

4.1 Recommendations for clinical practice

Early detection followed by prompt drug withdrawal can prevent hepatic failure and partially explains the low rate of clinically-significant hepatic adverse events in MKI clinical trials. Furthermore, a correct diagnosis of DILI is essential to avoid inappropriate therapy discontinuation. Therefore, LFT assessment at baseline can provide an estimation of the reference values, identify any underlying liver injury, and help in the interpretation of LFT abnormalities during MKI treatment. Of note, hepatitis B virus (HBV) reactivation has been

described during treatment with certain MKI molecules, such as everolimus, temsirolimus, imatinib, sunitinib, sorafenib, erlotinib, and afatinib [262, 263]. This adverse event may progress to severe hepatitis and have a mortality rate as high as 11%, despite antiviral treatment [262]. Furthermore, MKI withdrawal is required irrespective of HBV reactivation severity. Therefore, the European Association for the Study of the Liver recommends that all candidates for chemotherapy should be screened for HBsAg and anti-HBc antibody before initiation of treatment [264]. Once HBsAg detected, prophylactic antiviral therapy may reduce the risk of HBV reactivation and prevent chemotherapy disruption. HBV reactivation during chemotherapy was previously reviewed [262].

The utility of regular LFT monitoring to prevent clinically-significant hepatic adverse events is difficult to evaluate in practice due to the very low incidence of DILI. However, LFT monitoring is a valuable tool for the early detection of drug-related hepatotoxicity until more specific markers of DILI are available [265]. According to clinical trials and case reports, most cases of MKI-related DILI occur during the first two months of exposure. Therefore, weekly monitoring of LFT should be performed for the first two months when using a MKI with a greater risk of hepatotoxicity (Table 2; Figure 2). LFT assessment may then be continued on a monthly basis. For MKIs with an apparently lower liver toxicity risk (Table 2; Figure 2), monthly monitoring of LFT is reasonable. In patients with long-term exposure to imatinib, non-invasive evaluation of hepatic fibrosis by transient elastometry once a year may be useful, due to the risk of developing cirrhosis (table 2) [74, 106]. Nevertheless, there is only a weak level of evidence to support this strategy.

The cut-offs for LFTs for MKI withdrawal are difficult to define, especially for patients with a hepatic extension of disease. MKI treatment should be promptly discontinued if serum aminotransferase levels are $> 5X$ ULN or if the criteria for Hy's law are present. In cases of moderate aminotransferase elevation $< 5X$ ULN, LFT monitoring should be performed twice a

week and MKI treatment may be continued. For patients with high baseline aminotransferase levels, the MKI should be discontinued if serum aminotransferase levels reach > 5 times the baseline value. Of note, MKIs that inhibit UGT1A 1 (sorafenib and regorafenib) impair the elimination of bilirubin, with a resulting increase in unconjugated bilirubin levels, mimicking the criteria for Hy's law.

Permanent drug withdrawal may become necessary, but this poses a dilemma if the tumour is responsive to the MKI concerned. Exhaustive investigations should therefore be performed to exclude other potential causes of liver injury and confirm the diagnosis of MKI-related DILI, including serological tests for hepatotropic viruses (hepatitis A, B, C, and E viruses, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus), autoantibody tests, iron and copper levels, and abdominal ultrasonography. A recent study showed that immune-mediated DILI related to immune-checkpoint inhibitor use has specific histologic characteristics such as granulomatous hepatitis [266]. Furthermore, the severity of histological lesions guided patient management (those with severe lesions benefited of corticosteroid administration while those with mild lesions spontaneously improved) supporting the necessity of liver biopsy for this indication. For MKI-related DILI, liver histology does not reveal any specific lesions and is therefore not mandatory for diagnosis. Nevertheless, liver biopsy is useful if autoimmune hepatitis is suspected [265]. Liver biopsy may also be considered if LFT worsens or fails to resolve after drug withdrawal to exclude alternative diagnoses, notably the hepatic extension of cancer. Hepatitis E virus (HEV) infection is not considered in the differential diagnosis of DILI in most published cases of MKI-induced liver damage. However, HEV infection has been shown to be the cause of liver injury in 3 to 7% of cases initially adjudicated as DILI [267, 268]. Of note, patients with cancer are immunocompromised and might not mount a good antibody response. Furthermore, false positive HEV serology can occur in autoimmune hepatitis and Epstein-Barr infection [269]. Both anti-HEV IgM and HEV-RNA

testing should therefore be performed in all cases of suspected MKI-induced hepatotoxicity, particularly if the clinical features are compatible with acute viral hepatitis.

The surveillance of LF (ALT, alkaline phosphatase, and bilirubin) is essential until normalization or a return to baseline values. In most cases, LF improves after drug discontinuation, but hepatic injury may sometimes persist for several months. For cases with immuno-allergic characteristics, oral prednisone initiated at a daily dose of 25 to 30 mg and gradually tapered over 2 to 8 months may be an option if LFT abnormalities fail to resolve or worsen following drug discontinuation [48, 74, 103]. Once LFT values return to baseline, patients should be considered for treatment with another MKI molecule due to the lack of cross-hepatotoxicity between different MKI drugs (Table 2). In the absence of an alternative anticancer treatment, a re-challenge may be performed under strict surveillance of LF due to the risk of hepatic failure [18, 33, 99, 102, 107]. Concomitant administration of corticoids at a daily dose of 0.5 mg/kg may be an option for patients for whom imatinib or pazopanib re-challenge is attempted [85, 103, 108, 109]. Future studies are required to determine whether N-acetylcysteine is an efficient preventive or curative treatment for MKI-induced hepatotoxicity [270]. Figure 2 proposes an algorithm for the management of patients with suspected MKI-induced liver toxicity.

4.2 Conclusions

All MKI molecules may potentially cause liver damage, which is sometimes irreversible. As there is still no strategy available to prevent MKI-related hepatotoxicity, early detection remains crucial. Surveillance of LF during treatment may help in the early detection of hepatic adverse events. It is essential that potential causes of hepatic injury be excluded to avoid unnecessary MKI withdrawal.

Authorship contributions

Camille Houron and Marie Danielou performed research studies, analysed the data and wrote the manuscript. Olivier Mir contributed to the research studies and data analysis. Bernard Fromenty contributed to the data analysis. Gabriel Perlemuter and Cosmin Sebastian Voican contributed to the research design, research studies, data analysis, writing the manuscript and supervision of the study.

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Conflict of interest statement

Olivier Mir acted as consultant for Eli-Lilly, Janssen, Lundbeck, Pfizer, Roche, Servier, Vifor Pharma; as a speaker for Eli-Lilly, Roche, Servier, Medscape and PrimeOncology; and owns stock options from Amplitude Surgical, Transgene and Ipsen. Gabriel Perlemuter received travel funds from Janssen and Gilead; consulting fees from Bayer, Biocodex, Roche, Gilead, Pierre Fabre, and Servier; and royalties from Elsevier-Masson, Solar, Flammation/Versilio, and John Libbey Eurotext. Camille Houron, Marie Danielou, Bernard Fromenty and Cosmin Sebastian Voican declare that they have no competing interests.

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Table 1. Hepatotoxicity of MKI agents in clinical trials.

Drug	Incidence of LFT abnormalities - all grades (%)	Grade 3-4 LFT abnormalities (%)	Outcome	References
afatinib	20-50	1-2		[136, 137]
alectinib	10-50	1-4		[14, 138]
axitinib	2-42	1-8		[169-174]
bosutinib	14-58	4-19		[37-42]
cabozantinib	16-97	2-8		[139, 140]
ceritinib	25-35	11-21		[31]
cobimetinib	24-70	6-12		[141, 142]
crizotinib	13-40	2-16		[18, 31-36]
dabrafenib	11-42	0-4		[143, 144]
dacomitinib	0-20	0-2		[253, 256, 257]
dasatinib	3-16	0-9	Death reported for crizotinib (1 case)	[175-179]
erlotinib	2-85	0-12	gefitinib (1 case)	[180-192]
gefitinib	6-87	1-11	imatinib (1 case)	[22, 193-198]
ibrutinib	0-14	0-3	lenvatinib (3 cases)	[145, 146]
imatinib	1-35	1-3	pazopanib (2 cases), sorafenib (7 cases) and sunitinib (9 cases).	[20, 40, 43, 44]
lapatinib	26-41	8-14		[199, 200]
lenvatinib	12-14	3-5		[30, 114, 115]
nilotinib	0-70	4-9		[201]
nintedanib	5-59	1-9		[147-149]
osimertinib	4-6	1	No information available for the other molecules.	[23, 150]
pazopanib	8-68	1-20		[24, 45, 202-219]
ponatinib	3-12	2-4		[220]
regorafenib	7-92	5-11		[221-225]
sorafenib	3-44	0-29		[117-120, 226-234]
sunitinib	9-67	0-8		[28, 121, 122, 235-239]
trametinib	10-44	0-5		[151-153]
vandetanib	3-51	2-5		[11, 154]
vemurafenib	11-38	0-6		[47, 155]
everolimus	5-87	0-6		[239-247]
temsirolimus	4-56	0-7		[248-251]

Abbreviations: MKI, multikinase inhibitor, LFT, liver function tests

Table 2. Hepatotoxicity of MKI in case reports.

MKI agent	Type of hepatic lesion	Mechanism	Latency	Outcome	Liver Biopsy	Other	Risk of liver injury	References
alectinib	Hepatocellular	Metabolic	5 months	Recovery: 1 case No deaths reported	Severe active hepatitis with bridging necrosis	Successful reintroduction at the same dose after LFT normalisation Hepatitis E infection not ruled out	moderate	[95]
bosutinib	Hepatocellular	Immuno-allergic	Within 4 months	Recovery: 1 case No deaths reported	-	Hy's law cases Recovery without drug withdrawal for half of patients (clinical trials)	moderate	[42]
crizotinib	Hepatocellular	Metabolic; immuno-allergic	10 days - 2 months	Recovery: 3 cases Death: 3 cases	-	Positive re-challenge: 4 cases Successful reintroduction at reduced dose in most cases (clinical trials)	high	[18, 33-36, 66, 98]
dasatinib	Mixed	Metabolic	7 months	Recovery: 1 case No deaths reported	-	-	moderate	[56]
erlotinib	Hepatocellular	Immuno-allergic	2 - 37 days	Recovery: 5 cases Death: 6 cases	Severe active hepatitis with bridging necrosis	Successful switch to gefitinib: 2 cases Positive re-challenge: 2 cases Other possible causes incompletely ruled out	high	[49-51, 67, 68, 82, 99, 111, 112, 156-158]
everolimus	Mixed	Metabolic	3 months	Recovery: 1 case No deaths reported	Patchy sinusoidal dilatation, portal eosinophils	-	low	[64]

gefitinib	Hepatocellular	Metabolic; immuno- allergic	22 - 392 days	Recovery: 19 cases No deaths reported	Hepatocyte necrosis and increased fibrosis	Successful switch to erlotinib or afatinib: 15 cases Positive lymphocyte stimulation test: 1 case Positive re-challenge: 6 cases	high	[54, 55, 83, 100- 102, 124, 132, 159- 161]
ibrutinib	Hepatocellular	Metabolic	2 – 36 weeks	Recovery: 2 cases No deaths reported	Centrilobular (zone 3) hepatocyte injury and mixed inflammatory cell infiltrate, canalicular cholestasis	-	moderate	[57, 69]
imatinib	Hepatocellular; mixed	Immuno- allergic	12 - 504 days	Recovery: 22 cases Cirrhosis: 1 case LT: 2 cases Death: 2 cases	Centrilobular (zone 3) hepatocyte necrosis and inflammatory infiltrate, fibrous scars Autoimmune hepatitis- like lesions (bridging necrosis, lymphoplasmacytic infiltrate)	Positive re-challenge: 10 cases Corticotherapy allowed imatinib reintroduction and/or LFT recovery: 11 cases Successful switch to dasatinib: 2 case	high	[58, 59, 62, 70-74, 84-92, 106, 108, 109, 162-165],
lapatinib	Hepatocellular	Immuno- allergic	25 days	Recovery: 1 case No deaths reported	Bridging necrosis, eosinophil infiltrate	-	moderate	[75]
nintedanib	Hepatocellular	Metabolic	8 months	Recovery: 1 case No deaths reported	-	Low body surface area is a risk factor for aminotransferase elevation during treatment Successful reintroduction at reduced dose	moderate	[60, 255]
osimertinib	Hepatocellular	Immuno- allergic	15 days - 1 month	Recovery: 3 cases No deaths reported	Pericentral necrosis	Positive re-challenge: 1 case	moderate	[93, 110, 252]

Successful reintroduction after oral desensitization: 2 cases
Possible causes incompletely ruled out

pazopanib	Hepatocellular; mixed	Immuno-allergic	14 - 28 days	Recovery: 3 cases Death: 3 cases (2 cases in clinical trials)	Inflammatory infiltrate in periportal areas with eosinophilia, mild centrilobular cholestasis	Positive re-challenge: 2 cases Corticotherapy allowed pazopanib reintroduction: 2 cases	high	[63, 76, 103]
regorafenib	Hepatocellular	Metabolic; immuno-allergic	5 days - 4 months	Recovery: 5 cases Death: 2 cases	Centrilobular hepatic necrosis with confluent destruction of acinar zone 3	Possible drug-induced autoimmune hepatitis Positive re-challenge: 1 case	high	[46, 53, 77, 94, 104]
sorafenib	Hepatocellular; mixed	Metabolic; immuno-allergic	8 days - 2 months	Recovery: 4 cases Death: 1 case	Hepatocyte necrosis with lymphocyte infiltrate	-	high	[52, 78-80]
sunitinib	Hepatocellular	Metabolic	21 - 252 days	Death: 3 cases	Centrilobular necrosis	-	high	[61, 81, 105]
vemurafenib	Mixed	Immuno-allergic	6 weeks	Recovery: 1 case No deaths reported	Granulomatous inflammation and eosinophil infiltrate, centrilobular (zone 3) canalicular cholestasis	Successful switch to dabrafenib: 1 case	moderate	[65]
vemurafenib-ipilimumab combination	Hepatocellular	Immuno-allergic	2-5 weeks	Recovery: 6 cases No deaths reported	-	Corticotherapy allowed LFT recovery: 5 cases Hy's law cases	high	[48]

Abbreviations: MKI: multi-kinase inhibitor, LFT: liver function tests

Figure 1. Results of the literature search.

Figure 1

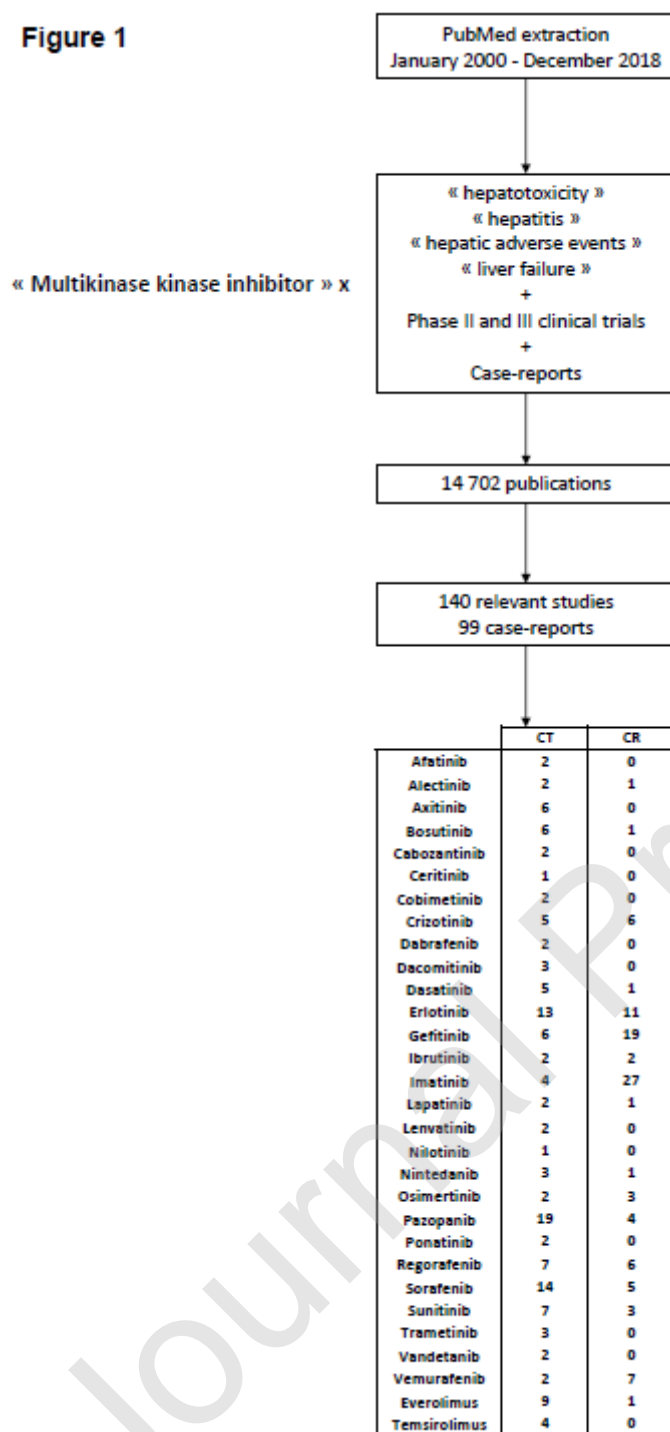


Figure 2. Management of patients with suspected MKI-induced liver toxicity.

Abreviations: LFT: liver function tests, MKI: multi-kinase inhibitor, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ULN: upper limit of normal, BV: baseline value

