86050.docx

WORD COUNT 5761
TIME SUBMITTED 07-AUG-2023 11:33AM
PAPER ID 101804325

Name of Journal: *World Journal of Hepatology*
Manuscript NO: 86050
Manuscript Type: MINIREVIEWS

Liver toxicity of targeted anticancer therapies in myeloproliferative neoplasms

Liver toxicity and myeloproliferative neoplasms treatment

Abstract
Because of its central role in metabolism, the liver is susceptible to the deleterious effects of ingested medications (drugs, herbs, and nutritional supplements) that can affect all types of hepatic cells. Drug-induced liver injury (DILI) comprises a range of unexpected reactions that occur after exposure to any type of medication. Even if the majority of cases consist of mild, temporary, elevations in liver enzyme markers, DILI can manifest, in some patients, as acute liver failure and represents a significant cause of liver disease and, in some instances, of attributable mortality. Herein, we briefly overview available data on DILI induced by targeted anticancer agents in the management of classical myeloproliferative neoplasms: chronic myeloid leukemia, polycythemia vera, essential thrombocythemia and myelofibrosis.

Key Words: Myeloproliferative neoplasms; Chronic myeloid leukemia; Myelofibrosis; Polycythemia vera; Essential thrombocythemia; Hepatotoxicity; Drug-induced liver injury

Purwar S, Fatima A, Bhattacharyya H, Simhachalam Kutikuppala LV, Cozma MA, Găman MA. Liver toxicity of targeted anticancer therapies in myeloproliferative neoplasms. *World J Hepatol* 2023; In press

Core Tip: Targeted anticancer therapy can cause liver toxicity in patients diagnosed with myeloproliferative neoplasms. Although most cases of drug-induced liver injury are self-limiting and/or resolve with the use of hepatoprotective agents, treatment interruption may be warranted in some instances.

INTRODUCTION

Brief overview of myeloproliferative neoplasms (MPNs)

Haematopoietic stem cells have the property of pluripotency and capacity of self-renewal giving rise to either myeloid or lymphoid cell lines which differentiate into mature blood cells. Overproduction of terminal myeloid cell lines in the bone marrow due to certain mutations in hematopoietic stem cells gives rise to a group of disorders known as myeloproliferative neoplasms (MPNs). MPNs are broadly classified Philadelphia-positive MPNs, i.e., chronic myeloid leukemia (CML), classical Philadelphia-negative MPNs, i.e., polycythemia vera (PV), primary myelofibrosis (PMF) and essential thrombocythemia (ET), and non-classical Philadelphia-negative MPNs which include chronic neutrophilic leukemia, chronic eosinophilic leukemia-not otherwise specified and MPN-unclassifiable (MPN-U) [1, 2].

Epidemiology of MPNs

There has been an increase in the incidence rate of CML while its age-standardized incidence rate decreased to 0.84 per 100,000 individuals in 2019 as compared to 0.96 in 1990. In addition, a slight elevation in the incidence of CML cases has been detected in males *vs* females [3]. According to a systematic review of 20 studies from Europe, North America, Asia and Australia which assessed the incidence rate of PV, the annual pooled incidence rate was 0.84 per 100,000 individuals. There was no significant difference in the crude annual incidence between males and females [4]. Ten studies from Europe and North America reported the annual pooled incidence rate to be 1.03 per 100,000 inhabitants with higher pooled annual incidences in males *vs* females [4]. PMF has the lowest incidence among classical Philadelphia-negative MPNs with an annual pooled

incidence of 0.47 per 100,000 subjects and higher incidence in males rather than females [4].

CML is characterized by a reciprocal translocation between chromosomes 22 and 9, respectively, which results in the fusion of the Abelson Murine Leukemia (ABL1) gene with the Breakpoint Cluster Region (BCR) gene. This generates a chimeric protein with constitutively active tyrosine kinase activity which promotes cell growth and signaling through various downstream pathways [5]. The World Health Organization (WHO) has divided the progression of CML into 2 phases primarily based on blast cells counts in the peripheral blood or bone marrow: chronic phase and blast phase (≥20% myeloid blast cells in the bone marrow or peripheral blood or elevated numbers of lymphoid blast cells in the bone marrow or peripheral blood or evidence of extramedullary proliferation of blast cells) with the majority of the patients presenting in the chronic phase [6].

Nowadays there has been an increase in the life expectancy of CML subjects, relatively similar to the one of the general population. This improvement is attributed to the fact that most newly diagnosed cases of CML occur in the chronic phase of the disease and due to the availability of new and effective therapies [7].

Classical Philadelphia-negative MPNs include PV which primarily involves excess proliferation of red blood cells, ET with thrombocytosis in the peripheral blood and overactive megakaryocytes in the bone marrow and PMF which involves fibrosis of the bone marrow and other diagnostic criteria. The pathogenesis of classical Philadelphia-negative MPNs requires constitutive activation of the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway due to mutations in a variety of genes out of which JAK2V617F gain of function mutation is the most frequent, being present in >95% cases of PV and >50% cases of PMF and ET [8, 9]. Remaining cases of PV are linked to JAK2 exon 12 mutations while majority of the remaining cases of PMF and ET have detectable MPL or CALR mutations [10]. Both ET and PV have relatively favorable prognosis with ET carrying the best prognosis whereas PMF carries the worst prognosis [11].

DRUG INDUCED LIVER INJURY (DILI): BRIEF OVERVIEW

Because of its central role in metabolism, the liver is susceptible to the deleterious effects of ingested medications (drugs, herbs, and nutritional supplements) that can affect all types of hepatic cells [12, 13]. Drug-induced liver injury (DILI) comprises a range of unexpected reactions that occur after exposure to any type of medication. Even if the majority of cases consist of mild, temporary elevations in liver enzyme markers, DILI can manifest in some patients as acute liver failure (ALF). Thus, DILI may emerge as a significant cause of liver disease and, in some instances, lead to increased mortality rates in subjects who experience it [14, 15, 16].

Its pathogenesis is complex and not fully understood and can vary greatly between different individuals and based on the drugs that cause liver injury, explaining the wide range of phenotypic traits in terms of clinical presentation and severity [17]. DILI is the result of a combination of genetic, non-hereditary, and environmental variables, and is typically attributed to an allergic immune response [18].

The potential multiple clinical presentations and the lack of specific biomarkers or biochemical tests makes the diagnosis often difficult and delayed. Consequently, DILI must always be taken into account in patients who are prescribed medications and exhibit unexplained liver injury [17, 19]. Moreover, DILI represents the leading cause for drug withdrawal from the marketplace and can lead to changes in drug costs and challenges regarding medication availability [20].

The pathophysiology of DILI is a complex, multistep process that involves both direct injury and different inflammatory responses, induced by either the drug itself, by its metabolites or by the immune system. It implies a combination of various host-related, environmental and drug-related factors. If ALF does not occur, patients usually fully recover after an episode of DILI if the responsible medication is halted [12, 18, 21].

Among the main pathophysiological processes involved in the pathogenesis of DILI, one must highlight oxidative stress, interference with bile acids' transportation, alteration of mitochondrial biogenesis and triggering of innate immune responses, necrosis or even apoptosis [15, 18].

Liver toxicity can be categorized as direct, indirect or idiosyncratic based on the underlying mechanism of action of the chemical compound that leads to DILI: Direct hepatotoxicity is caused by agents which cause direct harm to the liver. This type of injury is common, predictable, dose-dependent, and has a short latency period (1 to 5 days). It causes elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations, induces minimal or no symptoms, is associated with normal total bilirubin levels and usually disappears once the drug is stopped or the dose is lowered [22, 23].

Indirect hepatotoxicity represents "a condition caused by the medication's actions rather than from its inherent hepatotoxic effects or immunogenicity". This best translates to "what the drug does rather than what the drug is" and can either mean induction of a new liver condition or an exacerbation of a preexisting condition, *e.g.*, induction of immune-mediated hepatitis, reactivation of viral hepatitis or progression of fatty liver disease [12, 22].

Idiosyncratic hepatotoxicity is caused by agents that have no direct hepatotoxic effect. It is an unpredictable condition, less common (<1 of every 10,000 exposed individuals), it is not dose-related, has a longer latency period (up to several weeks) and a more variable clinical presentation [12, 22, 24].

A rapid diagnosis of DILI is crucial since one of the primary treatment interventions for hepatotoxicity is drug withdrawal. Moreover, establishing a DILI diagnosis can aid in the prevention of further adverse reactions through regulatory decisions, such as prescription warnings or even the removal of pharmaceuticals from the market [12, 13, 25].

In most cases, diagnosis of DILI is one of exclusion, since there is no specific test available for this entity. One must eliminate other causes of liver injury, *e.g.*, infectious hepatitis, acute alcoholic hepatitis or ischaemic hepatitis. Suspicion of DILI arises from the discovery of alterations in usually ordered liver tests, i.e., AST, ALT, total and direct bilirubin levels, serum albumin, alkaline phosphatase (ALP) or international normalized ratio [13].

Clinical manifestations, such as fatigue, nausea, malaise, right upper quadrant pain,

pruritus, and jaundice are non-specific and commonly encountered in a wide variety of acute and chronic liver diseases. Liver imaging (abdominal ultrasonography, magnetic resonance cholangiography or computed tomography) is usually used to exclude the presence of biliary obstruction and focal lesions. Liver biopsy is done in less than half of suspected cases, usually in instances where the evolution of liver injury is not reversed after a suspected medication has been discontinued [22, 26]. There are over 18 different histological aspects of DILI proposed until now all of which associate to different extents inflammation of hepatocytes, bile accumulation, ductopenia, steatohepatitis, macro- and microvesicular fatty depositions in the liver, pigment deposition, fibrosis or vascular congestion and obliteration [12, 19]. DILI can also be classified based on its biochemical pattern based on ALT and ALP levels. A pattern of hepatocellular damage is defined by an "elevation in ALT greater than 2 to 5 times the upper limit of normal (ULN) and/or by an ALT/ALP ratio also greater than 5". A pattern of cholestatic damage is defined by an "elevation in ALP greater than 3 times the ULN and/or an ALT/ALP ratio less than 2". A pattern of mixed hepatocellular/cholestatic damage is defined by "an increase in ALT greater than 2 to 5 times the ULN and an increase in ALP greater than 3 times the ULN and/or an ALT/ALP ratio between 2 and 5". These patterns have been proposed by the "American Association for the Study of Liver Diseases" (AASLD) and are summarized in Table 1 [18, 27, 28]. Management. While in some patients DILI can spontaneously resolve without the need for active treatment, in most cases, the hallmark of DILI treatment is the withdrawal of the offending drug. Clinical and biochemical alterations are expected to improve over the next several days or weeks. Since patients who develop jaundice are more likely to progress to ALF, these subjects usually require strict monitoring and probably hospitalization, particularly if DILI exhibits a hepatocellular phenotype. Treatment of DILI is usually supportive, with no other specific medications showing any significant use. However, there many agents used for supportive purpose, *e.g.*, corticosteroids (empirically used by many clinicians), cholestyramine (administered to patients with acute liver injury caused by leflunomide), carnitine (an antidote for valproate-induced

liver injury) or N- acetylcysteine (an antidote for acetaminophen toxicity), silymarin, L-arginine, L-ornithine L-aspartate and/or vitamin E [13, 29, 30, 31, 32]. Prognosis. DILI typically resolves after discontinuation of the incriminated drug and/or administration of hepatoprotective agents. However, in rare cases, DILI may progress to ALF, with clinical features such as jaundice, ascites, encephalopathy, coagulopathy and a mortality rate of 60% to 90% without liver transplantation [14, 17]. Different scoring systems for predicting prognosis of DILI have been proposed. The most validated and the one still used by The Food and Drug Administration (FDA) to this day during the drug development process to identify pharmacological agents that can potentially induce severe liver injury is the "Hy's law", developed by Hyman Zimmerman in the 1960s, according to which 10% of the patients who develop jaundice will develop ALF. Other scores for predicting severity in DILI are the Model for End-Stage Liver Disease (MELD) score, King's college criteria (KCC) score and Acute Liver Failure Study Group (ALFSG) index [12, 13, 19]. Older age, higher drug dosages, presence of liver disorders or cardiovascular comorbidities, African American ethnicity and female sex have all been linked to an elevated risk of DILI and to more severe forms, but there is little empiric data available to support that these variables are indeed risk factors for DILI or have an impact on its prognosis [33].

MAIN THERAPEUTIC AGENTS USED IN MPNS

The development of tyrosine kinase inhibitors (TKIs) following the discovery of the BCR-ABL chimeric gene has drastically improved the success rate of CML treatment. TKIs have improved the 10-year survival rate from 20% to 80-90% [34]. Commonly used TKIs for the treatment of chronic phase CML involve first generation TKIs, *e.g.*, imatinib, second generation TKIs, i.e., dasatinib, nilotinib and bosutinib, and third generation TKIs, i.e., ponatinib. Imatinib was the first TKI to be approved by the FDA [35]. It was the IRIS trial that first showed the high effectiveness of imatinib to increase the survival rate of newly diagnosed CML patients as compared to interferon alpha plus cytarabine [34]. It is

a fairly safe drug as long as close monitoring of subjects is performed. Second generation TKIs exhibit rapid molecular responses and have been used in cases of resistance/intolerance to imatinib [36].

The discovery of the involvement of the JAK/STAT pathway in the pathogenesis of classical Philadelphia-negative MPNs paved the way for development of TKIs inhibiting the JAK/STAT pathway. Ruxolitinib was the first targeted drug developed that inhibits both JAK1 and JAK2 and is approved for use in intermediate and high-risk myelofibrosis (MF) based on the COMFORT trials, and in cases of PV resistant or intolerant to hydroxyurea based on the RESPONSE trial [37].

Fedratinib is another TKI inhibiting JAK2 and FMS-like tyrosine kinase 3 (FLT3) and approved for the treatment of intermediate or high-risk PMF or secondary MF (SMF). Diarrhea, nausea and anemia are common side effects associated with this therapy. Renal function, liver enzymes, lipase and amylase may require frequent monitoring during the treatment [38].

Momelotinib is a recently FDA-approved JAK1/JAK2 inhibitor which antagonizes the activin A receptor type 1 (ACVR1). It is used in the treatment of patients with MF with moderate/severe anemia [14]. It is similar to ruxolitinib but with the added advantage of improving anemia [12]. Most common side effects associated with it are diarrhea, peripheral neuropathy, dizziness, nausea and thrombocytopenia[39].

In high-risk patients suffering from PV and ET, cytoreductive therapy with hydroxyurea and interferon alpha are first line choices employed to reduce the rate of thrombotic events. Hydroxyurea is a potent ribonucleotide reductase inhibitor causing inhibition of DNA synthesis and cell death [40].

Interferons, especially pegylated interferon α (peg-IFNα) and ropeg interferons, are used nowadays as effective alternatives to cytoreduction with hydroxyurea in patients with ET and PV. Studies have reported a decrease in the JAK2V617F allele burden following prescription of interferon-based therapy which does not occur with the use of hydroxyurea. Interferon is also used along with ruxolitinib in patients of low to

intermediate risk MF. Peg-IFNα and ropeg interferons are associated with a lower rate of adverse effects *vs* standard interferons α used in the past [41].

EPIDEMIOLOGY OF DILI IN PATIENTS DIAGNOSED WITH MPNS

DILI is mainly characterized by an increase in liver enzymes' concentrations due to damage induced to hepatocytes. Hepatotoxicity in CML subjects who are on TKI therapy presents as low-grade elevation of ALT and/or AST levels in about 25-35% of cases and high-grade elevation in about 2% of patients. Use of newer generation TKIs, *e.g.*, bosutinib, nilotinib and ponatinib, has been associated with higher risks of liver toxicity [42].

In the 5-year follow-up of the phase 3 DASISION (Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) trial which compared the two aforementioned pharmacological agents, DILI was a rare event, and therapy discontinuation was only required in the subgroup who received 400 mg of imatinib daily due to increases in ALT or AST concentrations (n = 1 each out of 258 individuals) and in one cases for toxic hepatitis (n = 1), however, no subjects (n = 0 out of 258 individuals) discontinued treatment with 100 mg of daily dasatinib due to DILI [43].

In the ENESTnd trial which compared the daily administration of 400 mg nilotinib (n = 277 patients) and 300 mg nilotinib (n = 279 patients) to each other and to 400 mg imatinib (n = 280 patients) for the management of newly diagnosed CML, the investigators pointed out multiple cases of liver toxicity. Elevations in total bilirubin (n = 171, 62% *vs* n = 149, 53% *vs* n = 27, 10%), ALT (n = 203, 73% *vs* n = 186, 66% *vs* n = 57, 20%) and AST (n = 134, 48% *vs* n = 112, 40% *vs* n = 65, 23%) concentrations were more likely to occurs in the 400 mg nilotinib and 300 mg nilotinib *vs* 400 imatinib group, respectively, whereas an increase in alkaline phosphatase (n = 76, 27% *vs* n = 59, 21% *vs* n = 92, 33%) values was more common in patients who received imatinib. However, grade 3/4 adverse events were rare and occurred predominantly in individuals who were prescribed nilotinib 400 mg or 300 mg *vs* imatinib 400 mg; All grades elevations occurred in total bilirubin (n = 21, 8% *vs* n = 10, 4% *vs* n = 1, <1%), ALT (n = 25, 9% *vs* n = 11, 4% *vs* n = 7, <2%) and AST

(*n* = 8, 3% *vs n* = 4, 1% *vs n* = 3, 1%) values, respectively, whereas a grade 3/4 increase in alkaline phosphatase only occurred in 1 case (<1%) of imatinib-treated patients [44].

The NOVEL trial evaluated the safety and efficacy of nilotinib in 85 subjects suffering from imatinib intolerant/resistant-CML. Their findings revealed that non-hematological adverse events occurring in correlation with the use of nilotinib manifested as elevations in ALT (*n* = 18, 21.2%), bilirubin (*n* = 12, 14.1%) and/or AST (*n* = 7, 8.2%) values, respectively, however grade 3/4 were rare and only 2 and 1 patients, respectively, experienced grade 3/4 rises in AST (2.4%) and/or ALT (1.2%) concentrations. In NOVEL, one patient with imatinib-induced liver toxicity required a switch of therapy to nilotinib with subsequent resolution of DILI. Serious adverse events related to DILI manifested as jaundice and chronic hepatitis [45].

In the BYOND trial which explored the benefits of 500 mg once daily of bosutinib for CML individuals (*n* = 163 subjects) who exhibited resistance and/or intolerance to other TKIs, DILI manifested only as elevations in AST (all grades *n* = 32, 19.6%) and/or ALT concentrations (all grades *n* = 42, 25.8%). However, grade 3/4 increases in ALT (*n* = 23, 14.1%) and/or AST (*n* = 7; 4.3%) were not common [46].

In the clinical trial which evaluated the benefits of bosutinib prescription in 119 CML subjects who failed to achieve satisfactory responses to imatinib and dasatinib and/or nilotinib, an increase in AST/ALT values was noted in 16% of cases (13% classified as therapy-related), with only 6% of grade 3 adverse events and none serious/grade 4 side effects being noted. Elevations in these biochemical markers manifested early after drug initiation (approximately 81 days) and lasted for about 29 days. DILI was successfully managed with dose interruptions, reductions and/or use of hepatoprotective agents in 6, 5 and 1 case(s) of CML, respectively. Grade 3/4 DILI was more likely to be seen in CML individuals who received imatinib in the first 6 mo following CML diagnosis and in subjects who exhibited elevated basophil counts [47].

Data from the CML registry in Belgium suggest that ponatinib-induced DILI cases are rare. In the 33 CML subjects who received ponatinib, liver toxicity was rare and occurred

in <10% of treated individuals: hepatocellular injury, hepatitis and cholestasis were noted in 1 case each [48].

In the PEARL study which evaluated the safety and efficacy of ponatinib in CML subjects who experienced failure to 2 or more TKIs, grade 1/2 non-hematological adverse events (including DILI) were highlighted in 19 (40%) of the 48 CML individuals enrolled. No liver-related grade 3/4 side events were noticed by the investigators [49].

Asciminib is a recently introduced TKI for the management of CML, including T315I-mutated cases. This pharmacological agent inhibits the BCR-ABL1 protein in an allosteric manner, leading to an inactive conformation of its target. In a phase 1 trial of asciminib in heavily pretreated CML individuals, this novel medication lead to elevation in ALT (*n* = 16, 10.7%; grade 3/4 *n* = 4, 2.7%), AST (*n* = 15, 10%; grade 3/4 *n* = 3, 2%) or gamma-glutamyltransferase (*n* = 12, 8%; grade 3/4 *n* = 3, 2%) concentrations, however, grade 3/4 Liver-related adverse events occurred in <3% of asciminib-treated subjects [50].

In the STAMP trial that investigated 40 mg of asciminib twice daily *vs* 500 mg of bosutinib once daily in individuals diagnosed with CML with ≥2 previous TKI therapies, DILI was more frequently noticed in the bosutinib group, i.e., 27.6% (*n* = 21) and 21.1% (*n* = 16) of subjects experienced elevations in ALT and AST concentrations, respectively, *vs* 3.8% (*n* = 6) each in the asciminib group. Grade 3/4 adverse effects were more likely to present in bosutinib-prescribed subjects (14.5%, *n* = 11 for ALT; 6.6% *n* = 5 for AST) *vs* asciminib-treated subjects (3.8%, *n* = 6 for ALT and AST each). Treatment discontinuation was required in bosutinib-prescribed CML cases due to significant increases in ALT concentrations [51].

Ruxolitinib seems a safe option in terms of liver toxicity. Based on the findings of a double-blind, placebo controlled trial assessing ruxolitinib in the management of MF classified as intermediate-2 or high-risk, DILI was not mentioned amongst the most common adverse (experienced by at least 10% of the 155 enrolled subjects) caused by the aforementioned pharmacological agent [52].

Ruxolitinib was associated with an increase in ALT concentrations in around 6% of MF patients and with high-grade elevations in only 1% of the individuals enrolled in the JUMP trial [53].

In the RuxoBeat trial which investigated the benefits of ruxolitinib therapy in newly-diagnosed PV, 7 of 28 treated subjects (25%) experienced changes in biochemical markers, including DILI, however, only 3 cases of grade 3 adverse events were reported out of which 2 consisted of elevations in AST/ALT concentrations and required reduction of the prescribed dose. However, no patient necessitated interruption of ruxolitinib [54].

Similarly, the results of the assessment conducted by Vannnucchi *et al* only pointed out minor changes in ALT/AST values following ruxolitinib administration in individuals diagnosed with PV [55].

The EXPAND trial assessed the safety and efficacy of ruxolitinib in individuals with MF and thrombocyte counts between 50000/mmc and 100000/mmc. In this investigation, a total of 5 cases of elevations in bilirubin values were noticed: 1 of the 18 patients who had platelets <75000/mmc but >50000/mmc and 4 of the 20 patients who had platelets <100000/mmc but >75000/mmc. However, of these, only two grade 3 or more increases in bilirubin levels were highlighted, all of which were reported in patients with thrombocyte counts <100000/mmc but >75000/mmc [56].

In a clinical trial which explored the co-administration of ruxolitinib and interferon alpha-2 for management of PV and MF, grade 1/2 Liver-related adverse events, i.e., an increase in AST and lactate dehydrogenase (LDH) values were noted in 7 (14%) and 17 (34%) of the 50 patients receiving therapy, with no cases of grade 3-4 side effects occurring in neither subjects with PV nor MF [57].

In the JAKARTA trial which compared fedratinib *vs* placebo, elevations of liver enzymes were detected in 40-60% of the subjects, however, ≥3 grade elevations in these serum markers were not common. In JAKARTA, 96 subjects were assigned to receive 400 mg of fedratinib daily, 97 to receive 500 mg/day of the same drug, whereas 95 individuals received placebo pills. All grades elevations in ALT (fedratinib 400 mg: 53%; fedratinib 500 mg: 46%; placebo: 17%) and AST (fedratinib 400 mg: 60%; fedratinib 500 mg: 48%;

placebo: 29%) concentrations were frequently detected in the fedratinib subgroups *vs* placebo, whereas bilirubin levels were more likely to increase in the placebo group (fedratinib 400 mg: 31%; fedratinib 500 mg: 28%; placebo: 40%) [58]. However, grade 3-4 increases in ALT values were only noted in 3% of the fedratinib 400 mg and 500 mg subgroups each *vs* 0% in placebo, grade 3-4 increases in AST values were only noted in 2% of the fedratinib 400 mg and 500 mg subgroups each *vs* 1% in placebo, whereas grade 3-4 elevations in bilirubin concentrations occurred in 2% of the placebo and fedratinib 400 mg subgroups and in 1% of the fedratinib 500 mg subgroup, respectively [58].

Momelotinib therapy in MF was also associated with cases of liver toxicity, i.e., grade 3-4 increases in ALT concentrations in 4% of patients and in AST and ALP concentrations in 2% of patients each [59]. Grade 1-2 increases in AST (21%), ALT (19%) and bilirubin (13%) concentrations were also detected [59]. In an integrated assessment of momelotinib based on data derived from phase 3 randomized clinical trials, Verstovsek *et al* also highlighted that of the 725 individuals with MF who received the drug, 9 subjects (1.2%) experienced notable elevations in ALT values which required dose interruption/reduction or momelotinib discontinuation [60]. When momelotinib was tested for PV and/or ET, the investigators did not report cases of liver toxicity in either cohort [61].

Ropeg interferons are relatively safer drugs than previously used interferons in terms of liver toxicity. When pegylated interferon alfa-2a was tested in the management of PV (n = 40) and ET (n = 39), grade 3 increases in liver function tests were reported in 5% (n = 2) and 8% (n = 3) of the PV and ET subgroups, respectively. No grade 4 side effects were reported [62]. In a trial exploring the safety and benefits of pegylated interferon alpha-2b in PV and ET, elevations in liver enzymes were among the most frequent non-hematological side effects. In total, 2 subjects required pegylated interferon alpha-2b discontinuation due to elevations in AST and ALT values [63].

DILI IN MPNS

Data on risk factors for DILI in patients living with MPNs are scarce, however, several assessments have identified potential risk factors linked with an increased risk of imatinib/TKI-induced hepatotoxicity, namely [64, 65, 66]:

use of proton pump inhibitors (3.8 fold increased risk): imatinib is both a substrate and an inhibitor of the ABCG2 which is a drug efflux pump expressed on various body tissues, including the liver. Thus, the inhibition of this pump leads to increased drug concentrations in liver cells, thus increasing the risk of hepatotoxicity. Moreover, proton pump inhibitors are hepatotoxic on their own.

presence of liver disease or HBV carrier state (8 fold elevated risk): imatinib is metabolized by the liver; therefore, liver impairment or HBV carrier state may increase its plasma levels due to ineffective drug metabolism.

drug dose >400 mg (2.3 fold increased risk): higher plasma levels of imatinib can enhance the risk of liver toxicity

body weight of <55 kg (2.2 fold increased risk): the dose of imatinib is chosen based on the phase of the disease and not based on body surface area

concomitant use of acetaminophen: acetaminophen itself is hepatotoxic

use of alcohol: alcohol acts as a cytochrome oxidase enzyme inducer, thereby increasing the levels of toxic metabolites

use of hepatotoxic drugs

The relative risk of DILI seems, however, higher with the prescription of 2nd & 3rd generation TKIs compared to 1st generation pharmacological agents (imatinib) [67]. The average duration from drug initiation to DILI development with the use of TKIs was of 2-6 mo, whereas with the use of ruxolitinib it was of 1-6 mo [68, 69]. In most cases, the diagnosis of DILI was established after the virology panel results for hepatitis B, HIV, CMV or EBV infections came in negative. Autoimmune antibody testing, abdominal ultrasound, liver biopsy and toxicology screening (alcohol, illicit drugs, acetaminophen) were also performed in conjunction with liver function tests to exclude other causes of liver injury [70, 71]. Liver biopsy is usually not preferred to provide diagnostic information

regarding liver injury but it is considered for the staging of fibrosis [72]. In some instances, genetic testing for hereditary conditions, such as hemochromatosis or Wilson's disease, might be required [73]. Pharmacogenomics assessments for mutations/polymorphisms in HLA genes, drug metabolizing enzymes, ABC and/or SLC transporters, might also be required to understand why certain individuals develop DILI [74].

However, investigations on DILI in subjects with MPNs remain scarce and the pathogenesis of DILI induced by targeted anticancer agents warrants further consideration in future studies. For example, researchers could focus on studying the impact of oxidative stress, immunity and bile acids metabolism on the onset of DILI in individuals with MPNs.

DILI remains a diagnosis of exclusion. The recommended biochemical criteria for DILI are the following [72, 73] :

ALT values ≥ 5 ULN

AST values ≥ 3 ULN

ALP values ≥ 2 ULN

total bilirubin ≥ 2 ULN

A common tool used for the diagnosis of DILI is the Roussel Uclaf Causality Assessment Method (RUCAM). It is based on 7 factors, including onset of reaction, clinical response after withdrawal or continuation of drug, response to readministration, temporal relationship, risk factors, concomitant drug use and absence of any non-drug etiologies [75].

Management of DILI in MPNs. In the majority of cases, discontinuation of the drug in individuals with clinically established hepatotoxicity and/or administration of hepatoprotective agents have been found to normalize liver enzymes in a few weeks. In cases of severe liver injury, resolution has been achieved by treatment with high-dose steroids for a few weeks. For example, imatinib therapy can be resumed with dose reductions or with the use of low doses of steroids if hepatotoxicity occurs [76]. The

European LeukemiaNet (ELN) has established guidelines for management of TKI-induced liver injury [77] (Figure 1).

Since CML patients often require lifelong treatment, Lopina *et al* have suggested a novel score-based decision algorithm (Table 2) for restarting TKIs after acute imatinib-induced liver injury and for the choice of 2nd generation TKIs [78]. The score takes into account:

the grade of hepatotoxic reaction

the grade of response to the use of imatinib, i.e., presence of early molecular response (EMR) to imatinib therapy at 3 mo (3-month BCR-ABL1 ≤10% according to the international scale) (not applicable if imatinib treatment was prescribed for <3 mo)

the grade of response to the use of imatinib, i.e., presence of EMR to imatinib therapy at 6 mo (6-month BCR-ABL1 <1% according to the international scale) (not applicable if hepatotoxicity developed in <6 mo of imatinib therapy)

the presence of a liver offender (concomitant use of another drug that probably caused drug interactions)

12

the presence of viral hepatitis reactivation identified by polymerase chain reaction.

The approach to restart imatinib can be based on the score listed above [78] as follows:

score = 0 points: withdraw the drug and switch to 2nd generationTKIs

score = 1 point: it is preferred to withdraw imatinib if the patient requires treatment for >6 mo

score ≥ 2 points: restart imatinib after resolution of DILI

The choice of a 2nd generation TKI is based on the presence of comorbidities and/or of BCR-ABL1 kinase domain mutations [78].

Other cases of DILI in CML patients require special considerations. For example, reactivation of hepatitis B infection often undergoes spontaneous resolution but treatment with antiviral agents (tenofovir and entecavir) is sometimes needed. Moreover, liver transplantation has been found to be successful in imatinib-induced fulminant liver failure [70].

In patients who develop hepatotoxicity while on ruxolitinib, abrupt drug discontinuation is to be avoided as it can lead to potentially fatal withdrawal symptoms. Therefore, dose

reduction is done over time. Douglas *et al* recommend liver biopsy for adaptive management in patients with evidence of hepatocellular damage potentially caused by the use of ruxolitinib [79].

Prevention of DILI in MPNs. The relatively limited number of particular treatments and antidotes that are presently available restricts the medical therapy of acute DILI. The primary therapeutic strategy for DILI remains stopping the alleged harmful substance [80]. When N-acetyl cysteine (NAC) is given within 4 to 16 h after an acute acetaminophen overdose, hepatotoxicity is effectively avoided. NAC is less helpful for acute liver failure caused by non-acetaminophen drugs [81]. First-line prevention measures include avoiding the use of some potentially hepatotoxic medications in patients with underlying chronic liver disease or who have been identified as having a genetic or other risk factor for developing DILI. Other measures include monitoring ALT, AST and other liver-associated enzymes (ALP, bilirubin *etc.*) to detect hepatotoxicity for particular medications early on. In some developed countries, limiting the availability of potentially dangerous amounts of acetaminophen through regulations has proven effective in reducing overdoses [82]. Better labeling and patient education are still required in countries with unlimited access, nonetheless, to prevent both purposeful and inadvertent overdoses. The significance of the gut microbiota in preventing DILI will probably continue to be understood, allowing for the development of new therapeutic strategies. Its ability to guard against acetaminophen-induced and other types of acute DILI is currently being investigated [83]. Thus, in patients diagnosed with MPNs who are to be started on potentially hepatotoxicity-inducing targeted agents, we recommend checking liver function tests before therapy initiation, as well as regularly during treatment. Moreover, the management of each case should be tailored to the comorbidities and concurrent medication of the patient, especially in subjects who suffer from MPNs and exhibit a high burden of cardiometabolic disorders [84]. Thus, DILI can be avoided in some instances. Moreover, further research should focus on identifying new hepatoprotective agents that could enable clinicians to overcome DILI and avoid drug cessation or dose

reductions/interruptions which aid in the resolution of liver toxicity but might impact the treatment of the hematological malignancy.

CONCLUSION

Data on liver toxicity induced by targeted anticancer therapy in MPNs is scarce, however, the use of TKIs has been linked to hepatotoxicity and/or DILI in CML, PV, ET and MF in clinical trials and real-world data. Minor liver injury can be overcome with drug discontinuation and/or dose reductions/interruptions and administration of hepatoprotective agents, whereas careful consideration must be given to cases in which severe hepatotoxicity occurs.

Figure Legends

Figure 1. Management of TKI-induced hepatotoxicity according to European LeukemiaNet recommendations.

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