REVIEW

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The use of novel agents in multiple myeloma patients with hepatic impairment

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ABSTRACT Novel drugs such as immunomodulators and proteasome inhibitors have improved the survival of patients with multiple myeloma. Like all therapeutic agents, appropriate dosing based on metabolism and clearance is important to maintain efficacy while avoiding toxicity. Hepatic impairment (HI) in multiple myeloma patients is rare but well described either due to disease or therapy-related factors. However, limited data are available on the appropriate use and dosing of the novel agent therapeutics in myeloma patients with HI. Furthermore, data on HI secondary to the novel agent toxicity are also sparse. This systematic review highlights the evidence on the use of novel agents like thalidomide, lenalidomide, pomalidomide, bortezomib and carfilzomib in patients with HI as well as their associated hepatic toxicities.

Multiple myeloma (MM) is a clonal plasma cell disorder, which predominantly affects the elderly resulting in more than 10,000 deaths annually in the United States [1]. The use of novel therapeutic agents such as immunomodulators (thalidomide, lenalidomide and pomalidomide) and proteasome inhibitors (bortezomib and carfilzomib) has led to significant improvements in the survival of MM [2–4]. Therapeutic dosing of these drugs with respect to the renal clearance of each individual patient is important in order to optimize efficacy and minimize toxicity [5]. In MM, one of the characteristic clinical features is renal impairment, signified by ‘R’ in the mnemonic ‘CRAB’ (hypercalcemia, renal insufficiency, anemia, bone disease) [6]. Approximately 20–40% of newly diagnosed MM patients have renal insufficiency, which may affect the dosing of the immunomodulatory drugs (IMiDs) [7].

Similarly, hepatic impairment (HI) either due to disease or therapy-related effects may require appropriate dosing of these drugs [8]. Disease-related HI may be due to plasmacytomas, sinusoidal infiltration, amyloid infiltration, light-chain deposition or thrombosis [8,9]. Therapy-related HI may be directly caused by various drugs or indirectly as in the cases of viral hepatitis, cytomegalovirus infection and graft-versus-host or veno-occlusive disease in patients who have undergone stem cell transplantation. Data to guide the dosing of novel agents in MM patients with baseline moderate to severe HI are sparse, since such patients are typically excluded from clinical trials. Furthermore, there is a rare potential for IMiDs and proteasome inhibitors to cause drug-induced acute hepatitis. Thus, here, we will review the dosing of these novel agents in patients with HI and summarize the evidence of therapy-related HI.

KEYWORDS

- hepatic impairment
- myeloma • novel agents

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Immunomodulators

Immunomodulators (IMiDs) exert their pleiotropic anti-MM effects through antiangiogenesis [10], impedance of cytokine production, immunomodulation *via* stimulation of cytotoxic T-cell [11,12] and NK-cell activity [13] and interaction with the bone marrow microenvironment [14]. They can also have direct cytotoxic effects on MM cells *via* inhibition of NF- κ B and apoptosis induction *via* the caspase 8/death receptor pathway [15]. The three IMiDs approved by the US FDA are thalidomide, lenalidomide and pomalidomide.

Thalidomide

Thalidomide (Thalomid®, Celgene, NJ, USA) is the prototype immunomodulator approved for the use in the induction treatment of newly diagnosed MM patients as well as consolidation and maintenance therapy after autologous stem cell transplantation. The dosage used for MM ranges from 50 to 200 mg orally once daily.

• Pharmacokinetics

Thalidomide is absorbed slowly leading to peak concentrations within 2–5 h after ingestion [16]. It is moderately protein-bound and undergoes nonenzymatic hydrolysis, with greater than 90% of the drug excreted renally as metabolites [16]. Less than 5% of the parent drug is eliminated by the kidneys as unchanged drug. In patients with MM, the half-life is approximately 5–7 h [16]. Thalidomide is not a substrate inhibitor or inducer of the CYP450 enzymes [16].

• Use in HI

There have been no HI studies conducted and no dosage adjustments are provided in the product labeling for patients with HI. However, in the clinical trials that led to the FDA approval of thalidomide, patients with a bilirubin greater than 1.5–2 mg/dl and liver aminotransferases (LFTs) greater than 2.5- to 3-times the upper limit of normal (ULN) were excluded [17,18].

• Thalidomide-related HI

In one of the clinical trials, grade 3–4 hyperbilirubinemia (greater than three- to ten-times the ULN) was reported in 2% of patients in both the thalidomide plus dexamethasone and dexamethasone arms [16,17]. Nine case reports in the literature describe hepatotoxicity from

thalidomide in patients with MM; five of the patients had fatal outcomes, one of which was due to disease progression and one due to infection (Table 1) [19–26]. The majority of patients were prescribed thalidomide 200 mg once daily and all except for one were female. One patient was a chronic hepatitis B carrier, one patient had hepatitis C and a third patient had non-alcoholic steatohepatitis. Onset of transaminitis ranged from 6 to 210 days, and LFTs ranged from 4- to approximately 50-times the ULN. The liver injury pattern appeared to be either hepatocellular or cholestatic alone or a combination of the two.

Lenalidomide

Lenalidomide (Revlimid®, Celgene) is a second-generation immunomodulator approved for the use in newly diagnosed and relapsed MM patients [27,28]. It has also been evaluated as consolidation and maintenance therapy in patients who have undergone autologous and allogeneic stem cell transplantation [29]. The dosage used for MM ranges from 5 to 25 mg orally once daily.

• Pharmacokinetics

Lenalidomide is absorbed rapidly, is not highly protein-bound and undergoes limited metabolism with greater than 80% of the parent compound excreted renally [30]. In patients with MM, the half-life is approximately 3–5 h [30]. Lenalidomide is not metabolized by CYP enzymes and is not an inducer or inhibitor of CYP enzymes and is a weak substrate of P-glycoprotein (P-gp) [30].

• Use in HI

There have been no dedicated HI studies conducted and no dose adjustments are provided in the product labeling for patients with HI, but warnings about hepatic failure, including fatalities, are noted [30]. In a pooled pharmacokinetic analysis of seven clinical trials evaluating patients with either myelodysplasia, MM or mantle cell lymphoma, mild HI (total bilirubin >1 to $\leq 1.5 \times$ ULN or AST > ULN) was seen in 16 patients and did not affect the renal clearance of lenalidomide [31]. Nevertheless, periodic monitoring of liver enzymes is advised and if transaminitis occurs, discontinuation of lenalidomide is recommended. Upon resolution of transaminitis, reinitiation at a lower starting dose may be warranted.

Table 1. Case reports of thalidomide-induced hepatotoxicity in patients with multiple myeloma.

Patient/treatment history	Dose (mg)	Onset (days)	Laboratory findings [†]	HI at baseline?	RI at baseline?	Outcome	Ref.
75-year-old female; treatment history N/A	N/A	~30	N/A	N/A	N/A	Death after hepatic failure/coma	[19]
79-year-old female IgA-λ; MGUS, no previous treatment	200	~49	AST 187; ALT 392; ALP 1172; Tbili 27.9; Dbili 17.5; INR 19.8 (on warfarin, after 4 weeks of thalidomide)	No	Acute on chronic	Death after 3 months from hepatic failure	[20]
57-year-old female IgG-κ; no previous treatment	200	~30	AST 214; ALT 398; ALP 175; bilirubin N/A	No	NA	Resolved after ~2 weeks of stopping drug	[20]
62-year-old female IgG-κ; MP, VAD, vinorelbine/ dexamethasone	200	~210	LFTs 50× ULN; bilirubin WNL; INR 4 (on warfarin)	No	Yes	Resolved after 1 week of stopping drug	[21]
64-year-old female; VAD, autoHCT	100	12	AST 510; ALT 598; ALP WNL; Tbili 16.7; Dbili 10.2; albumin 1.2 (3.7 pretreatment); INR 4.1 (1.1 pretreatment)	Chronic carrier state for HepB: HepBsAg + HepBeAg - HepBeAb + LFTs WNL	No	Death from coagulopathy, acidosis, renal failure	[22]
36-year-old female IgA-κ; no previous treatment	200	~40	AST 15× ULN; ALT 30× ULN; LDH WNL; bilirubin WNL	No	No	Resolution after 20 days of stopping drug	[23]
76-year-old female; no previous treatment	200	36	AST 2376; ALT 2205; bilirubin 5.59; INR >15 (on warfarin)	Nonalcoholic steatohepatitis diagnosed after liver biopsy	No	Resolution by 3 months of stopping drug	[24]
58-year-old female IgG; VAD	200	6	AST 305; ALT 829; ALP WNL; Tbili 9.4 mg/dl; Hep C RNA >107 copies/ml	Chronic asymptomatic hepatitis C	Yes	Resolution of transaminitis, but death 2 months later from disease progression	[25]
77-year-old male IgA-κ; no previous treatment	50	14	At 28 days: AST 271; ALT 333; ALP 4× ULN; GGT 4× ULN; Tbili 11.35; Dbili 6.36	No	Yes	Slow decrease in LFTs but not to normal; death 5 months from diagnosis due to pneumonia	[26]

[†]Albumin expressed in g/dl; AST, ALT, ALP in IU/l; bilirubin in mg/dl.
 ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; autoHCT: Autologous hematopoietic cell transplantation; Dbili: Direct bilirubin; GGT: Gamma glutamyl transferase; GVHD: Graft versus host disease; Hep: Hepatitis; INR: International normalized ratio; HI: Hepatic impairment; LDH: Lactate dehydrogenase; LFT: Liver aminotransferase; MGUS: Monoclonal gammopathy of undetermined significance; MP: Melphalan, prednisone; N/A: Not available; RI: Renal impairment; Tbili: Total bilirubin; ULN: Upper limit of normal; VAD: Vincristine, doxorubicin, dexamethasone; WNL: Within normal limits.

• Lenalidomide-related HI

Landmark trials that led to the approval of lenalidomide excluded patients with LFTs greater than three-times the ULN and a bilirubin greater than two-times the ULN [27,28]. No hepatic grade 3 or 4 adverse events (AEs) were reported in the MM-009 and MM-010 trials, which led to approval of lenalidomide in the relapsed/refractory MM population [27,28]. To our knowledge, five case reports of lenalidomide-induced hepatocellular and/or cholestatic injury have been reported in patients with MM (Table 2) [32–35]. All of the patients were male and three had renal insufficiency. One patient received lenalidomide as salvage therapy approximately 4 months after

allogeneic stem cell transplantation (alloHCT) after having received lenalidomide 2 years prior to alloHCT [32]. Liver biopsy demonstrated acute hepatitis and mild hepatic GVHD.

Based on the literature, the incidence of hepatotoxicity may be higher in patients with renal dysfunction, although patients with severe renal dysfunction have been excluded from clinical trials. Transaminitis occurred early after lenalidomide initiation, and resolved within approximately a month after drug discontinuation [31–34]. Elevation in liver enzymes measured two- to ten-times the ULN, with the highest measurements occurring in the patient with acute hepatitis B. Liver injury consisted of a hepatocellular

Table 2. Case reports of lenalidomide-induced hepatotoxicity in patients with multiple myeloma.

Patient/treatment history	Dose (mg)	Onset (days)	Laboratory findings [†]	HI at baseline?	RI at baseline?	Outcome	Ref.
50-year-old male; radiation, surgery, bortezomib/dexamethasone, autoHCT, cyclophosphamide/thalidomide/dexamethasone, alloHCT	10	9	AST 246; ALT 509; GGT 105; ALP 198; bilirubin WNL	Mild hepatic GVHD	N/A	Resolved after 1 month of stopping drug	[32]
67-year-old male IgG-λ; treatment history N/A	25	10 (cycle 2)	AST 145; ALT 139; ALP 190; Tbili 4.4; Dbili 3.3	No	Yes, acute on chronic	Resolved after 8 days of stopping drug	[33]
57-year-old male kappa-restricted; thalidomide, VAD, bortezomib, autoHCT	25	7	AST ~70; ALT ~100; ALP ~330; Tbili 7	No	Yes	Resolved after 16 days	[34]
38-year-old male IgA-λ; no previous treatment	10	10; 7 after reinitiation	AST 47; ALT 39; ALP 912; GGT WNL; Tbili 8.2; Dbili 6.1 Upon reinitiation: AST 37; ALT 59; ALP 998; GGT 18; Tbili 6.6; Dbili 4.2	No	Yes	Resolved after 12 days of stopping drug in both instances	[35]
62-year-old male IgA-κ; no previous treatment	10	~232	AST 55; ALT 47; ALP 890; GGT 22; Tbili 10.4; Dbili 6.4	No	No	Resolved after 9 days of stopping drug	[35]

[†]Albumin expressed in g/dl; AST, ALT, ALP in IU/l; bilirubin in mg/dl.

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; alloHCT: Allogeneic hematopoietic cell transplantation; autoHCT: Autologous hematopoietic cell transplantation; Dbili: Direct bilirubin; GGT: Gamma glutamyl transferase; HI: Hepatic impairment; LDH: Lactate dehydrogenase; LFT: Liver aminotransferase; MGUS: Monoclonal gammopathy of undetermined significance; N/A: Not available; RI: Renal impairment; Tbili: Total bilirubin; ULN: Upper limit of normal; VAD: Vincristine, doxorubicin, dexamethasone; WNL: Within normal limits.

plus cholestatic, cholestatic or hepatocellular only pattern of injury.

Pomalidomide

Pomalidomide (Pomalyst®, Celgene) is the newest immunomodulator FDA-approved for MM patients who have received at least two prior therapies including lenalidomide and bortezomib and have progression of disease up to 60 days after completion of the last therapy [36]. The dosage used for MM ranges from 1 to 4 mg orally once daily.

• Pharmacokinetics

Pomalidomide reaches a peak concentration within 2–3 h after administration, widely distributing into tissues at steady state and is not highly protein-bound [36]. It is a substrate for P-gp and primarily undergoes hepatic metabolism by CYP1A2 and CYP3A4, and to a lesser extent by CYP2C19 and CYP2D6 [36]. Two percent of pomalidomide is excreted renally as unchanged drug. In patients with MM, the half-life is approximately 7.5 h [36].

• Use in HI

There are no HI studies and no guidelines for dose adjustment in patients with HI are

provided. Clinical trials that led to the approval of pomalidomide excluded patients with LFTs greater than three-times the ULN or bilirubin greater than 2 mg/dl [37,38] and thus, should be avoided in these patients.

• Pomalidomide-related HI

In MM-002, the open-label Phase I/II clinical trial that led to the approval of pomalidomide and compared pomalidomide alone with pomalidomide plus low-dose dexamethasone, elevations in LFTs in greater than 5% of the study population were not reported [37]. To our knowledge, only one case report of hepatotoxicity related to pomalidomide has been reported in the literature (Table 3) [39]. A 47-year-old man with an extensive treatment history including three cycles of VDT-PACE, two autologous hematopoietic cell transplantations (autoHCTs), thalidomide maintenance, salvage bortezomib/dexamethasone, a nonmyeloablative-matched related donor alloHCT with fludarabine/total body irradiation conditioning and four cycles of carfilzomib developed extramedullary relapse 18 months after his alloHCT. Pomalidomide 2 mg orally daily for 21 days was prescribed in conjunction with dexamethasone 20 mg weekly. At the end of

the first cycle, the patient was admitted to the hospital with jaundice. Laboratory studies demonstrated hyperbilirubinemia, marked elevation of his LFTs and a prolonged international normalized ratio. Infectious etiologies were ruled out, and liver biopsy showed hepatic necrosis but no bile duct loss or inflammation of the endothelium. Although this patient had a history of severe chronic GVHD, the authors concluded that the biopsy findings were most consistent with drug-induced liver injury [39].

Proteasome inhibitors

Proteasomes serve an important cellular function in enabling the clearance of abnormal or mutant proteins in all cells; however, cancer cells are more heavily dependent on this clearance mechanism and are sensitive to proteasome inhibition leading to an antiproliferative and pro-apoptotic effects [40]. Proteasome inhibitors have been found to inhibit NF- κ B activity, alter the degradation of cell cycle-related proteins, disrupt the balance between pro- and anti-apoptotic proteins, induce endoplasmic reticulum stress and inhibit angiogenesis and DNA repair, all of which contribute to the cytotoxic effect on tumor cells [41].

Bortezomib

Bortezomib (Velcade®, Millennium Pharmaceuticals, MA, USA), a reversible peptide boronate inhibitor, was the first proteasome inhibitor approved for the induction treatment of MM and as salvage therapy in relapsed disease. It has also been evaluated as consolidation and maintenance therapy in patients who have undergone auto- and alloHCT. The usual dosage in MM ranges from 1 to 1.5 mg/m² given once or twice weekly either intravenously or subcutaneously; the latter mode of administration being more commonly used given the convenience and reduced incidence of peripheral neuropathy yet equivalent efficacy.

• Pharmacokinetics

Bortezomib has a large volume of distribution and is highly protein-bound [42]. The peak concentrations upon administration are approximately tenfold higher *via* the intravenous route compared with the subcutaneous route. Bortezomib undergoes deboronation into two primary metabolites, which are inactive against the proteasome and undergo hydroxylation to produce more inactive metabolites. CYP3A4 contributes to the majority of bortezomib's metabolism, followed by 2C19 and 1A2; 2D6 and 2C9 contribute to a minor extent [43]. The mean half-life ranges widely from 40 to approximately 200 h depending on the dose administered [42].

The elimination pathway of bortezomib is not well characterized, but is likely hepatic metabolism rather than renal clearance.

• HI studies

A Phase I multicenter study evaluated the maximal tolerated dose, the pharmacokinetics and pharmacodynamics of bortezomib in 61 patients of various tumor types with HI [44]. The various degrees of hepatic function included in the study were normal (bilirubin and AST $\leq$ ULN), mild (bilirubin $\leq$ ULN and AST $>$ ULN or bilirubin 1–1.5 $\times$ ULN and any AST), moderate (bilirubin $>$ 1.5–3 $\times$ ULN with any AST) and severe (bilirubin $>$ 3 $\times$ ULN with any AST) [44]. Bortezomib was administered on days 1, 4, 8 and 11 as an intravenous push. Patients with severe, moderate and mild HI started at 0.5, 0.7 and 1 mg/m², respectively, and doses were escalated in a 3+3 fashion up to the maximum of 1.3 mg/m², the normal dose [44].

Patients with mild HI underwent dose escalation to 1.3 mg/m², while doses were capped at 1 mg/m² for patients with moderate and severe HI based upon pharmacokinetic data that showed 60% higher dose-adjusted drug exposure in these patients [44]. No dose-limiting

Table 3. Case report of pomalidomide-induced hepatotoxicity in patients with multiple myeloma.

Patient/treatment history	Dose (mg)	Onset (days)	Laboratory findings [†]	HI at baseline?	RI at baseline?	Outcome	Ref.
47-year-old male plasma cell; VDT-PACE, autoHCT $\times$ 2, thalidomide, bortezomib/dexamethasone, alloHCT	2	21	AST 552; ALT 1241; ALP 337; Tbili 16.2; Dbili 12	N/A	N/A	Resolution of laboratory markers 2 weeks after drug discontinuation	[39]

[†]AST, ALT expressed in IU/l; bilirubin in mg/dl.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; alloHCT: Allogeneic hematopoietic cell transplantation; autoHCT: Autologous hematopoietic cell transplantation; Dbili: Direct bilirubin; HI: Hepatic impairment; N/A: Not available; RI: Renal impairment; Tbili: Total bilirubin; ULN: Upper limit of normal; VDT-PACE: Bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide.

Table 4. Case reports of bortezomib-induced hepatotoxicity in patients with multiple myeloma.

Patient/treatment history	Dose (mg)	Onset (days)	Laboratory findings†	HI at baseline?	RI at baseline?	Outcome	Ref.
68-year-old male IgA-κ; MP, VBAD, autoHCT, high-dose dexamethasone	1.3 mg/m ² days 1, 4, 8 and 11; reduced to 1 mg/m ² , then 0.7 mg/m ²	7 (after two doses of 1.3 mg/m ²) 6 (after one dose of 1 mg/m ²) 6 (after two doses of 0.7 mg/m ²)	At 1.3 mg/m ² : AST 1856; ALT 2865; LDH 6448; bilirubin up to 2.8 At 1 mg/m ² : AST 129; ALT 137 At 0.7 mg/m ² : AST 3285; ALT 2750; LDH 6129; bilirubin up to 2.8	Potential shock-related liver hypoxia secondary to pneumococcal pneumonia	ARF in setting of infection, septic shock	LFTs resolved	[47]
52-year-old male kappa; high-dose dexamethasone	1.3 mg/m ² days 1, 4, 8 and 11	8 (after two doses)	AST 1856; ALT 2856; ALP 510; GGT 139; bilirubin WNL	No	Yes	LFTs resolved after 2 weeks of stopping drug	[48]
70-year-old male kappa; no previous treatment	1.3 mg/m ² days 1, 4, 8 and 11	10 (after three doses)	AST 83; ALT 114; ALP 461; LDH 320; GGT 546; Tbili ~8 (peak at ~32); Dbili ~5	No	Yes, on hemodialysis	Death due to end-stage liver failure 2 months later	[49]

†Albumin expressed in g/dl; AST, ALT, ALP in IU/l; bilirubin in mg/dl.
ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; autoHCT: Autologous hematopoietic cell transplantation; Dbili: Direct bilirubin; GGT: Gamma glutamyl transferase; HI: Hepatic impairment; LDH: Lactate dehydrogenase; LFTs: Liver aminotransferases; N/A: Not available; RI: Renal impairment; Tbili: Total bilirubin; ULN: Upper limit of normal; VAD: Vincristine, doxorubicin, dexamethasone; VBAD: Vincristine, carmustine, doxorubicin, dexamethasone; WNL: Within normal limits.

toxicities (defined as grade 4 neutropenia/thrombocytopenia lasting ≥7 days, neutropenic fever with grade 3 or 4 neutropenia, ≥grade 3 nonhematologic toxicity, significant toxicity requiring dose reduction or specific liver toxicity) occurred [44]. Patients in the moderate and severe HI cohorts did not experience more grade 3 or greater AEs than patients in the normal hepatic function cohort, although this study had a small number of patients [44]. There was one death in the study attributed to hepatic failure. This study suggests that a dose of 0.7 mg/m² in patients with moderate and severe HI results in comparable drug exposure to 1.3 mg/m² in patients with normal hepatic function, and patients with mild HI do not require a dose adjustment [44].

Therefore, for patients with a bilirubin greater than 1.5-times the ULN, the starting dose of bortezomib should be reduced to 0.7 mg/m². Doses in subsequent cycles can be adjusted upward to 1 mg/m² or downward to 0.5 mg/m² based on tolerability. Acute liver failure, hepatitis, transaminitis and hyperbilirubinemia have occurred with bortezomib [42]; if this occurs, therapy should be interrupted and limited data are available to guide rechallenging these patients.

• Bortezomib-related HI

In both the VISTA and APEX trials, there were no hepatic inclusion criteria or any reported hepatic AEs [45,46]. To our knowledge, only three case reports of bortezomib-induced severe hepatitis have been reported in the literature (Table 4) [47–49]. In the first case, a 68-year-old man with relapsed MM experienced LFTs greater than 50-times the ULN and an increase in bilirubin approximately 3 days after the second dose of bortezomib at both the 1.3 and 0.7 mg/m² doses [47]. The patient was noted to have pneumonia and septic shock with acute renal failure during the initiation of bortezomib. In the second case, a 52-year-old man developed significant elevation in his LFTs with a normal bilirubin after the second dose of bortezomib during cycle 1 [48]. In the third case, a 70-year-old man on hemodialysis succumbed to end-stage liver failure after developing cholestatic and hepatocellular injury after three doses of bortezomib [49].

Carfilzomib

Carfilzomib (Kyprolis®, Onyx Pharmaceuticals, CA, USA) is an irreversible, tetrapeptide

epoxyketone, second-generation proteasome inhibitor. The irreversible binding and higher affinity for the proteasome translates into superior biological activity and cytotoxicity in bortezomib-resistant cell lines *in vitro* and *in vivo* [15,50]. It is currently indicated for patients with MM who have received at least two prior therapies including bortezomib and an IMiD and who have progressed on or within 60 days of completion of last therapy. It is administered as a 2–10 min intravenous infusion on 2 consecutive days for 3 weeks (on days 1 and 2, 8 and 9, and 15 and 16) with each cycle lasting 4 weeks [50]. For the first cycle, the dose is 20 mg/m² and then for the later cycles, the dose is increased to 27 mg/m² [50].

• Pharmacokinetics

Carfilzomib is highly protein-bound and undergoes rapid metabolism by peptidase cleavage and epoxide hydrolysis to inactive metabolites [50]. It is cleared extrahepatically with a half-life of approximately 30 min and is neither significantly metabolized by CYP450 enzymes nor affected by inhibitors or inducers of CYP450 [50].

• HI studies

No HI studies have been conducted with carfilzomib and there are no guidelines for dose adjustments in patients with varying degrees of HI at baseline. However, transaminitis, hyperbilirubinemia and hepatic failure, including fatalities, have been reported with carfilzomib. In the Phase II, multicenter open-label, single-arm study (PX-171-003-A1) that led to the FDA approval of carfilzomib, patients were excluded if they had LFTs greater than

or equal to three-times the ULN and/or total bilirubin concentrations greater than or equal to two-times the ULN [51]. The manufacturer recommends that if grade 3 (5–20× the ULN) or 4 (>20× the ULN) transaminitis occurs, then carfilzomib should be withheld until LFTs resolve or return to baseline. Reinitiation should occur at a reduced dose (27 mg/m² reduced to 20 mg/m² or 20 mg/m² reduced to 15 mg/m²) and can be escalated if tolerated [50].

• Carfilzomib-related HI

Integrated safety data of carfilzomib in 526 patients from four Phase II clinical studies revealed that any hepatic event was reported in 99 patients (19%), with 33 patients (6%) experiencing a grade 3 event and two patients each experiencing a grade 4 event and grade 5 event [52]. To our knowledge, no other case reports of carfilzomib-induced hepatotoxicity have been reported in the literature.

Conclusion

The IMiDs and proteasome inhibitors have changed the landscape of MM treatment significantly, and have afforded some patients prolonged progression-free and overall survival. The incidence of hepatotoxicity from the IMiDs and proteasome inhibitors is low based upon the current literature, although patients with varying degrees of HI have been excluded from clinical trials. Among the novel agents, only bortezomib has specific recommendations in the product labeling to guide dosing in patients with baseline HI. [Table 5](#) outlines general recommendations on the dose adjustments for each of the novel agents discussed above in the setting

Table 5. Summary of dose modifications as per the product labeling of the novel agents in multiple myeloma patients with hepatic impairment.

Novel agent	Dose modification for HI at baseline?	Dose modification for HI during treatment?
Thalidomide	N/A	N/A
Lenalidomide	N/A	Monitor LFTs periodically, stop lenalidomide upon elevation of LFTs after LFTs return to baseline, consider treatment w/lower dose
Pomalidomide	Avoid if bilirubin >2 gm/dl and LFTs >3× ULN	N/A
Bortezomib	Yes, If bilirubin >1.5 mg/dl start at 0.7 mg/m ² can escalate to 1 mg/m ² or reduce to 0.5 mg/m ² based on tolerability	Monitor LFTs during treatment If hepatotoxicity occurs, interrupt therapy to assess reversibility limited rechallenge information
Carfilzomib	N/A	Monitor LFTs and withhold treatment if grade 3/4 elevation of LFTs, bilirubin or other liver abnormalities occur after resolution, reinitiate at a reduced dose (from 27 to 20 mg/m ² , or from 20 to 15 mg/m ²) with frequent monitoring of liver function If tolerated, reduced dose may be escalated

HI: Hepatic impairment; LFTs: Liver aminotransferases; N/A: Not available; ULN: Upper limit of normal.

of HI. However, treating clinicians should use their judgment to decide if administration of a novel agent despite HI could improve a patient's hepatic function, especially if the impairment is secondary to the MM itself such as extramedullary hepatic involvement or infiltration.

Patients with a prior history of hepatitis B virus (HBV) infection are always at a risk of reactivation upon initiating cytotoxic or immunosuppressive therapy [53]. There is limited experience on the use of novel agents in MM patients who are at high risk for reactivation of either HBV. Nevertheless, for MM patients at high risk of HBV reactivation, antiviral therapies such as lamivudine, entecavir or tenofovir may be used concurrently with any of the novel agents and continued for at least 6 months after the myeloma-specific therapy is completed [53]. Although such prophylaxis is recommended, it is not preventative in all patients [54]. Similar antiviral prophylaxis is not recommended in patients with prior HCV infections who have a sustained virologic response [55].

Finally, clinicians should be cognizant of the potential for these novel agents to cause hepatocellular, cholestatic and/or mixed injury, and institute regular monitoring of hepatic function into their routine clinical practice. With time, as more experience is gained with respect to the use of these novel agents in HI, the clinical practice and care of MM patients will continue to improve.

Future perspective

The treatment of MM has improved significantly with a better understanding of the disease and the development of novel agents. Patients with severe HI are often excluded from clinical trials. Bortezomib is the only novel agent for which a dedicated pharmacokinetic study was conducted. As use of these drugs evolves in the induction, consolidation and maintenance settings, clinicians should be aware of the potential for hepatic injury, albeit rare, in MM patients with and without baseline HI. Hepatic injury may be more likely in those with viral hepatitis or after transplantation. Vigilance and reporting of hepatic adverse events by healthcare providers are encouraged to improve patient care.

Author contribution

LC Stansfield reviewed the literature and wrote the manuscript; WI Gonsalves and FK Buadi contributed to writing and editing the manuscript.

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EXECUTIVE SUMMARY

Immunomodulators

- Among the immunomodulators (IMiDs), pomalidomide undergoes extensive hepatic metabolism while thalidomide and lenalidomide undergo nonenzymatic hydrolysis and limited metabolism, respectively.
- Case reports suggest that all IMiDs can cause a hepatocellular, cholestatic or mixed pattern of injury.
- Periodic monitoring of liver aminotransferases and bilirubin is recommended in patients treated with lenalidomide as per the product labeling, but may be prudent to follow in patients treated with any of the IMiDs.

Proteasome inhibitors

- Bortezomib primarily undergoes hepatic metabolism while carfilzomib is metabolized and eliminated by nonhepatic pathways.
- Recommendations for dose adjustments to bortezomib in the setting of hyperbilirubinemia at baseline should be followed.
- Hepatic monitoring parameters once therapy has commenced are provided in the product labeling for bortezomib and carfilzomib.
- Hepatotoxicity is not a prominent adverse event related to the proteasome inhibitors, but regular monitoring is recommended.

References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- 1 Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J. Clin.* 64(1), 9–29 (2014).
- 2 Kumar SK, Raj SV, Dispenzieri A *et al.* Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 111(5), 2516–2520 (2008).
- **This paper demonstrates the importance of novel agents in the field of myeloma and how it has improved overall survival.**
- 3 Kumar SK, Dispenzieri A, Lacy MQ *et al.* Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 28(5), 1122–1128 (2014).
- 4 Gonsalves WL, Raj SV, Go RS *et al.* Trends in survival of patients with primary plasma cell leukemia: a population based analysis. *Blood* 124(6), 907–912 (2014).
- 5 Palumbo A, Bringhen S, Ludwig H *et al.* Personalized therapy in multiple myeloma according to patient age and vulnerability: a report of the European Myeloma Network (EMN). *Blood* 118(17), 4519–4529 (2011).
- **This is a state of the art paper describing the use of novel agents in a personalized fashion based on patient age and co-morbidities.**
- 6 Kyle RA, Raj SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. *Leukemia* 23(1), 3–9 (2009).
- 7 Palumbo A, Anderson K. Multiple myeloma. *N. Engl. J. Med.* 364(11), 1046–1060 (2011).
- 8 Bhandari MS, Mazumder A, Vesole DH. Liver involvement in multiple myeloma. *Clin. Lymphoma Myeloma* 7(8), 538–540 (2007).
- 9 Walz-Mattmuller R, Horny HP, Ruck P, Kaiserling E. Incidence and pattern of liver involvement in haematological malignancies. *Pathol. Res. Pract.* 194(11), 781–789 (1998).
- **This paper provides a pathologic description of various forms of liver involvement seen in myeloma.**
- 10 D'amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. *Proc. Natl Acad. Sci. USA* 91(9), 4082–4085 (1994).
- 11 Corral LG, Haslett PA, Muller GW *et al.* Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. *J. Immunol.* 163(1), 380–386 (1999).
- 12 Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. *J. Exp. Med.* 187(11), 1885–1892 (1998).
- 13 Davies FE, Raje N, Hideshima T *et al.* Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood* 98(1), 210–216 (2001).
- 14 Sedlarikova L, Kubiczka L, Sevcikova S, Hajek R. Mechanism of immunomodulatory drugs in multiple myeloma. *Leuk. Res.* 36(10), 1218–1224 (2012).
- 15 Mitsiades N, Mitsiades CS, Poulaki V *et al.* Biologic sequelae of nuclear factor-kappaB blockade in multiple myeloma: therapeutic applications. *Blood* 99(11), 4079–4086 (2002).
- 16 Celgene Corporation. Thalomid® (thalidomide) [Package insert] Summit, NJ, USA.
- 17 Raj SV, Blood E, Vesole D, Fonseca R, Greipp PR. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. *J. Clin. Oncol.* 24(3), 431–436 (2006).
- 18 Raj SV, Rosinol L, Hussein M *et al.* Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. *J. Clin. Oncol.* 26(13), 2171–2177 (2008).
- 19 Clark TE, Edom N, Larson J, Lindsey LJ. Thalomid (thalidomide) capsules: a review of the first 18 months of spontaneous postmarketing adverse event surveillance, including off-label prescribing. *Drug Saf.* 24(2), 87–117 (2001).
- 20 Dabak V, Kuriakose P. Thalidomide-induced severe hepatotoxicity. *Cancer Chemother. Pharmacol.* 63(4), 583–585 (2009).
- 21 Trojan A, Chasse E, Gay B, Pichert G, Taverna C. Severe hepatic toxicity due to thalidomide in relapsed multiple myeloma. *Ann. Oncol.* 14(3), 501–502 (2003).
- 22 Hamadani M, Benson DM Jr, Copelan EA. Thalidomide-induced fulminant hepatic failure. *Mayo Clin. Proc.* 82(5), 638 (2007).
- 23 Levesque E, Bradette M. Hepatotoxicity as a rare but serious side effect of thalidomide. *Ann. Hematol.* 88(2), 183–184 (2009).
- 24 Hanje AJ, Shamp JL, Thomas FB, Meis GM. Thalidomide-induced severe hepatotoxicity. *Pharmacotherapy* 26(7), 1018–1022 (2006).
- 25 Fowler R, Imrie K. Thalidomide-associated hepatitis: a case report. *Am. J. Hematol.* 66(4), 300–302 (2001).
- 26 Vilas-Boas F, Goncalves R, Sobrinho Simoes M, Lopes J, Macedo G. Thalidomide-induced acute cholestatic hepatitis: case report and review of the literature. *Gastroenterol. Hepatol.* 35(8), 560–566 (2012).
- 27 Dimopoulos M, Spencer A, Attal M *et al.* Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N. Engl. J. Med.* 357(21), 2123–2132 (2007).
- 28 Weber DM, Chen C, Niesvizky R *et al.* Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N. Engl. J. Med.* 357(21), 2133–2142 (2007).
- 29 Attal M, Lauwers-Cances V, Marit G *et al.* Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N. Engl. J. Med.* 366(19), 1782–1791 (2012).
- 30 Celgene Corporation. Revlimid® (lenalidomide) [Package insert] Summit, NJ, USA.
- 31 Chen N, Ette E, Zhou S, Weiss D, Palmisano M. Population pharmacokinetics and exposure-safety of lenalidomide in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma. *55th ASH Annual Meeting and Exposition*. New Orleans, LA, USA, 7–10 December 2013 (Abstract 3234).
- 32 Zanella MC, Rubbia-Brandt L, Giostra E, Chalandon Y, Hadengue A, Spahr L. A case of drug-induced hepatitis due to lenalidomide. *Case Rep. Gastroenterol.* 5(1), 217–222 (2011).
- 33 Nojkov B, Signori C, Konda A, Fontana RJ. Lenalidomide-associated hepatotoxicity – a case report and literature review. *Anticancer Res.* 32(9), 4117–4119 (2012).
- 34 Hussain S, Browne R, Chen J, Parekh S. Lenalidomide-induced severe hepatotoxicity. *Blood* 110(10), 3814 (2007).
- 35 Jena RK, Swain TR, Kansurkar SS, Swain M. Lenalidomide induced intrahepatic cholestasis in newly diagnosed patients of multiple myeloma. *Eur. J. Clin. Pharmacol.* 68(5), 881–884 (2012).
- 36 Celgene Corporation. Pomalyst® PIS (pomalidomide) Summit, NJ, USA (2014).
- 37 Richardson PG, Siegel DS, Vij R *et al.* Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized Phase 2 study. *Blood* 123(12), 1826–1832 (2014).

- 38 San Miguel J, Weisel K, Moreau P *et al.* Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, Phase 3 trial. *Lancet Oncol.* 14(11), 1055–1066 (2013).
- 39 Pauff JM, Gonzalez RS, Sajani KP, Kassim A, Jagasia M. Post-allograft pomalidomide and reversible hepatotoxicity. *Bone Marrow Transplant.* 49(10), 1341–1342 (2014).
- 40 Hideshima T, Richardson PG, Anderson KC. Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma. *Mol. Cancer Ther.* 10(11), 2034–2042 (2011).
- 41 Kubickova L, Pour L, Sedlarikova L, Hajek R, Sevcikova S. Proteasome inhibitors - molecular basis and current perspectives in multiple myeloma. *J. Cell Mol. Med.* 18(6), 947–961 (2014).
- 42 Velcade® PIB (bortezomib), Belgium: Janssen Pharmaceutica Nv, Cambridge, MA, USA: Millennium Pharmaceuticals, Inc. (2014).
- 43 Uttamsingh V, Lu C, Miwa G, Gan LS. Relative contributions of the five major human cytochromes P450, 1A2, 2C9, 2C19, 2D6, and 3A4, to the hepatic metabolism of the proteasome inhibitor bortezomib. *Drug Metab. Dispos.* 33(11), 1723–1728 (2005).
- 44 Lorusso PM, Venkatakrishnan K, Ramanathan RK *et al.* Pharmacokinetics and safety of bortezomib in patients with advanced malignancies and varying degrees of liver dysfunction: Phase I NCI Organ Dysfunction Working Group Study NCI-6432. *Clin. Cancer Res.* 18(10), 2954–2963 (2012).
- 45 San Miguel JF, Schlag R, Khuageva NK *et al.* Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N. Engl. J. Med.* 359(9), 906–917 (2008).
- 46 Richardson PG, Sonneveld P, Schuster MW *et al.* Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N. Engl. J. Med.* 352(24), 2487–2498 (2005).
- 47 Rosinol L, Montoto S, Cibeira MT, Blade J. Bortezomib-induced severe hepatitis in multiple myeloma: a case report. *Arch. Intern. Med.* 165(4), 464–465 (2005).
- 48 Kim Y, Kim KY, Lee SH *et al.* A case of drug-induced hepatitis due to bortezomib in multiple myeloma. *Immune Netw.* 12(3), 126–128 (2012).
- 49 Cornelis T, Beckers EA, Driessen AL, Van Der Sande FM, Koek GH. Bortezomib-associated fatal liver failure in a haemodialysis patient with multiple myeloma. *Clin. Toxicol. (Phila.)* 50(5), 444–445 (2012).
- 50 Kypriolis® PISF (carfilzomib), CA, USA: Onyx Pharmaceuticals (2012).
- 51 Siegel DS, Martin T, Wang M *et al.* A Phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. *Blood* 120(14), 2817–2825 (2012).
- 52 Siegel D, Martin T, Nooka A *et al.* Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 Phase II clinical studies. *Haematologica* 98(11), 1753–1761 (2013).
- 53 Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 50(3), 661–662 (2009).
- 54 Mya DH, Han ST, Linn YC, Hwang WY, Goh YT, Tan DC. Risk of hepatitis B reactivation and the role of novel agents and stem-cell transplantation in multiple myeloma patients with hepatitis B virus (HBV) infection. *Ann. Oncol.* 23(2), 421–426 (2012).
- 55 Recommendations for Testing, Managing, and Treating Hepatitis C. AASLD Practice guidelines for HCV (2014). www.med.upenn.edu