Renal Toxicities of Novel Agents Used for Treatment of Multiple Myeloma

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Abstract

Survival for patients with multiple myeloma has significantly improved in the last decade in large part due to the development of proteasome inhibitors and immunomodulatory drugs. These next generation agents with novel mechanisms of action as well as targeted therapies are being used both in the preclinical and clinical settings for patients with myeloma. These agents include monoclonal antibodies, deacetylase inhibitors, kinase inhibitors, agents affecting various signaling pathways, immune check point inhibitors, and other targeted therapies. In some cases, off target effects of these therapies can lead to unanticipated effects on the kidney that can range from electrolyte disorders to AKI. In this review, we discuss the nephrotoxicities of novel agents currently in practice as well as in development for the treatment of myeloma.

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Introduction

Treatment of multiple myeloma (MM) has significantly improved in recent decades. Whereas alkylating agents in combination with steroids were the standard of care for several years, novel immunomodulatory agents (IMiD) and targeted therapies have changed the treatment paradigms and outcomes for this disease (Figure 1). Table 1 lists the novel agents and their mechanisms of action.

Three percent of all kidney biopsies performed have paraprotein-mediated kidney disease. In addition, some novel MM therapies have also been reported to cause kidney injury. These adverse effects are likely to have negative effects on prognosis and may limit the ability of the patient to receive effective treatment. Given myeloma itself can lead to kidney disease, distinguishing between myeloma-related kidney disease and drug toxicity is difficult without a kidney biopsy. Thrombocytopenia at the time of presentation often precludes a kidney biopsy. In this review, we discuss novel agents being used in the treatment of MM and their related nephrotoxicities. Table 2 (Food and Drug Administration [FDA] approved agents) and Table 3 (agents in clinical trials for MM) provide a summary of the detailed kidney toxicities of all agents used in MM classified by their mechanism of action.

Alkylating Agents, Anthracyclines, and Platinum-Based Therapies

Combination cytotoxic therapies were common regimens for treatment of MM before the arrival of newer agents, especially in patients with high tumor burden and frequent relapses (1–5). Aggressive cytoreduction with a combination chemotherapeutic regimen such as steroids, cyclophosphamide, etoposide, and cisplatin (DCEP) (6) with or without bortezomib (V-DCEP) (5) or a combination such as bortezomib, thalidomide, steroids, cisplatin, doxorubicin, cyclophosphamide, and etoposide (VTD-PACE) (7) is a reasonable salvage regimen. Cisplatin is the most nephrotoxic of the traditional chemotherapies used for MM (1) known to cause dose dependent acute tubular necrosis. Besides acute tubular necrosis, it is known to cause hypomagnesemia, fanconi syndrome, thrombotic microangiopathy (TMA), and salt wasting syndrome (Table 2). Given the scope of this article, nephrotoxicities of traditional chemotherapy agents used in MM (alkylating agents, anthracyclines, and platinum-based therapies) will not be discussed (1–4,8).

Proteasome Inhibitors

Proteasomes are enzyme complexes responsible for degradation of intracellular proteins and clearing the misfolded/unfolded and cytotoxic proteins, and are critical for the maintenance of protein homeostasis within a cell. It has been hypothesized that cancer cells are more dependent on proteasomes for clearance of abnormal or mutant proteins. In fact, several preclinical studies have shown that malignant cells are more sensitive to proteasome inhibition than normal cells (9).

Bortezomib

Bortezomib is a proteasome inhibitor (PI) used for treatment of MM (10,11). In terms of nephrotoxicity, five cases of TMA have been reported with this agent thus far (12–15). However, these TMA cases are complex and the causality between bortezomib and these

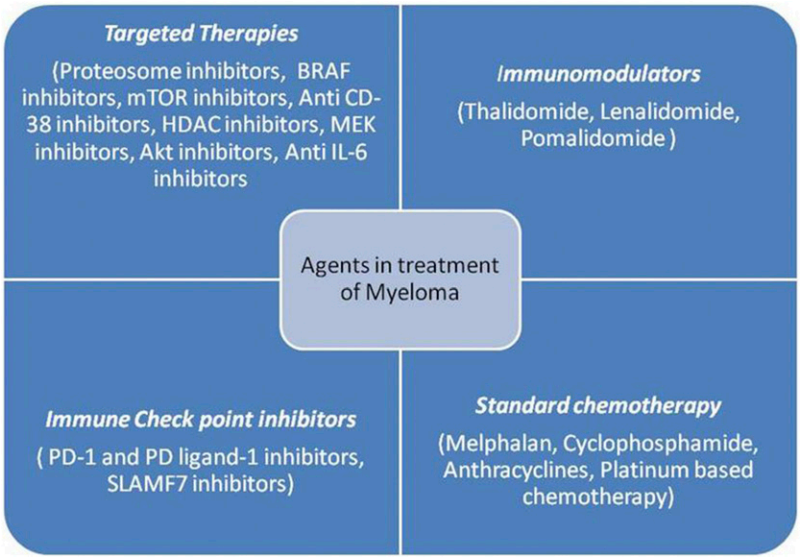

Figure 1. | **Four classes of agents that can be used to treat multiple myeloma**. Akt, serine-threonine protein kinase B; BRAF, v-Raf murine sarcoma viral oncogene homolog B; HDAC, histone deactylase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PD, programmed cell death protein; SLAMF7, signaling lymphocytic activation molecule F7.

Table 1. Novel antimyeloma agents in the market or in development and their mechanism of action

Class	Name of Drug	Mechanism of Action
Proteasome inhibitors	Bortezomib, Carfilzomib, Ixazomib	Inhibiting the ubiquitin-proteasome system regulating the growth of normal and tumor cells
Immunomodulatory drugs	Thalidomide, Lenalidomide, Pomalidomide	Enhance antimyeloma immune response
HDAC inhibitors	Vorinostat, Panobinostat	Epigenetic modulators
mTOR inhibitors	Temsirolimus, Everolimus	Inhibiting the intracellular signaling kinases
Immune check point inhibitors	Nivolumab, Pembrolizumab	Enhance the immune response to cancer cells and specifically PD1 and PD1 ligand responses
BRAF inhibitors	Vemurafenib, Dabrafenib	Target a specific gene mutation in some cases of myeloma
MEK inhibitors	Tramatenib, Selumetinib	Inhibition of overactive MAPK/ERK pathway
SLAMF7 inhibitors	Elotuzumab	Myeloma cell membrane bound SLAM receptor inhibitors
Anti–IL-6 agents	Siltuximab	Myeloma cell membrane bound IL-6 receptor inhibitors
Anti-KIR agents	Lirilumab	Improves immune response to cancer cells
CD38 antibody	Daratumumab	Myeloma cell membrane bound cd38 receptor inhibitors
Akt inhibitors	Perifosine	Intracellular signaling kinase inhibitors

HDAC, histone deactylase; mTOR, mammalian target of rapamycin; PD, programmed cell death protein; BRAF, v-Raf murine sarcoma viral oncogene homolog B; MEK, mitogen-activated protein kinase; MAPK, mitogen-activated protein kinases; ERK, extracellular signal-regulated kinases; SLAMF7, signaling lymphocytic activation molecule F7; KIR, killer Ig receptor; Akt, serine-threonine protein kinase B.

events is not definitive. For example, Morita *et al.* reported the onset of TMA 8 days after commencing treatment with bortezomib and steroids in a patient with MM who had undergone a sequential autologous and allogenic stem cell transplant (12). In another case, Moore *et al.* reported a case of TMA in a newly diagnosed myeloma patient that occurred 2 days after treatment with bortezomib and which resolved spontaneously in a few days (13). In this

Table 2. Summary of known renal toxicities of Food and Drug Administration approved antimyeloma agents

Class/Drug Name	Published Toxicities in the Literature	CKD Dosing	ESRD Dosing
Traditional chemotherapy			
Cisplatin	ATN, TMA, hypomagnesemia, fanconi syndrome, renal salt wasting	Reduce dose by 25% (46–60 ml/min CrCl) Reduce dose by 50% (10–45 ml/min CrCl)	HD: Reduce dose by 50% and administer after HD; CAPD: reduce dose by 50%; CRRT: reduce dose by 25%
Melphalan	AKI, hyponatremia	Reduce dose by 15% (46–60 ml/min CrCl) Reduce dose by 25% (10–45 ml/min CrCl)	Limited data
Cyclophosphamide	Hemorrhagic cystitis, hyponatremia	No dosing adjustment needed	HD: reduce dose by 50% and administer after HD; CAPD: reduce dose by 25%; CRRT: no adjustment needed
Anthracyclines	Collapsing glomerulopathy, FSGS, minimal change disease, TMA	No dosing adjustment needed	No dosing adjustment needed
Immunomodulators			
Lenalidomide	AKI, AIN, fanconi syndrome, minimal change disease	10 mg daily (30–60 ml/min CrCl) 15 mg every 48 h (10–29 ml/min CrCl)	HD: 5 mg daily after HD
Pomalidomide	AKI, crystal nephropathy	CrCl<45ml/min avoid use	Insufficient data
Proteasome inhibitors			
Bortezomib	TMA	Reduce dose if GFR<20 cc/min	Dose after dialysis and consider dose reduction (but insufficient data)
Carfilzomib	TMA, prerenal, tumor lysis like syndrome, ATN	No dose adjustment	Dose after dialysis
Ixazomib	None reported	Insufficient data	Insufficient data
HDAC inhibitors			
Panobinostat	None reported	No dose adjustment	Insufficient data
SLAMF7 inhibitors			
Elotuzumab	AKI	No dose adjustment	No dose adjustment
Anti-CD38 agents			
Daratumumab	None reported	No dose adjustment	No dose adjustment

ATN, acute tubular necrosis; TMA, thrombotic microangiopathy; CrCl, creatinine clearance; HD, hemodialysis; CAPD, continuous automated peritoneal dialysis; CRRT, continuous RRT; AIN, acute interstitial nephritis; HDAC, histone deactylase; SLAMF7, signaling lymphocytic activation molecule F7.

particular case, ADAMTS13 activity was low initially after treatment and remained low with bortezomib rechallenge, even though TMA did not reoccur (13). Three other cases reported in the literature (14,15) report TMA after multiple doses of the agent. Unfortunately, none of these cases had biopsy-proven kidney disease and most of the diagnoses were made clinically. A mechanistic link between PI and TMA may be mediated by the inhibition of the ubiquitination of IκB which prevents NF-κB from entering the nucleus and ultimately leads to decreased vascular endothelial growth factor production which has been linked to the development of TMA (16–19). In addition, a case of acute interstitial nephritis (AIN) with granuloma formation has been reported with bortezomib (20).

Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone PI approved for the treatment of relapsed refractory MM (21). In a phase 2 study of this drug in 266 patients, AKI was reported in 25% of the patients. Although the majority of the kidney adverse effects were mild, progressive kidney disease was reported in 3.8% of patients, leading to discontinuation of the drug in two patients (22). There are now additional cases of AKI from carfilzomib reported in the literature

Table 3. Summary of known renal toxicities of antimyeloma agents (not Food and Drug Administration approved to treat myeloma) currently in clinical trials

Class/Drug Name	Published Toxicities in the Literature	Trial Stage	CKD Dosing	ESRD dosing
mTOR inhibitors				
Temsirolimus	Proteinuria, FSGS, ATN	Phase 2 trials	No dose adjustment	Insufficient data
Everolimus	Proteinuria	Phase 1 trials	Individualized dosing on the basis of therapeutic drug monitoring	Insufficient data
Sirolimus	FSGS, TMA, ATN	Phase 1 trials	Individualized dosing on the basis of therapeutic drug monitoring	Insufficient data
BRAF inhibitors				
Vemurafenib	AIN, ATN, subnephrotic proteinuria, hypokalemia, hyponatremia, fanconi syndrome	Phase 2 trials	No dose adjustment but also not well studied	Insufficient data
Dabrafenib	AKI, AIN, hypophosphatemia	Phase 2 trials	No dose adjustment	Insufficient data
HDAC inhibitors				
Vorinostat	None reported	Phase 3 trials	No dose adjustment	Insufficient data
MEK inhibitors				
Trametinib	Hypertension, hyponatremia, AKI	Phase 2 trials	No dose adjustment, for <30 cc/min – not studied	Insufficient data
Immune check point inhibitors				
Nivolumab	AIN, hyponatremia	Phase 3 trials	No dose adjustment	Insufficient data
Pembrolizumab	AIN, hyponatremia	Phase 3 trials	No dose adjustment	Insufficient data
Anti–IL-6 agents				
Siltuximab	Hyperkalemia, Hyperurecemia	Phase 2 trials	No dose adjustment if GFR>15 cc/min	Insufficient data
Anti-KIR agents				
Lirilumab	AKI, hypophosphatemia	Phase 1 trials	No data available	No data available
Akt inhibitors				
Perifosine	Hypophosphatemia	Phase 3 trials	No data available	No data available

mTOR, mammalian target of rapamycin; ATN, acute tubular necrosis; TMA, thrombotic microangiopathy; BRAF, v-Raf murine sarcoma viral oncogene homolog B; AIN, acute interstitial nephritis; HDAC, histone deactylase inhibitors; MEK, mitogen-activated protein kinase; KIR, killer Ig receptor; Akt, serine-threonine protein kinase B.

(23–27). The possible mechanisms listed are diverse and summarized in Table 2. They range from prerenal insults, tumor lysis–like phenomenon, to biopsy-proven TMA (23–26). In the initial two cases (23,24), AKI was transient and was clinically consistent with a 'prerenal' insult. In addition, in one of the cases, *N*-acetylcysteine was helpful in ameliorating the severity of the carfilzomib-mediated kidney injury when the patient was rechallenged with the chemotherapy agent (24). Similar to bortezomib, carfilzomib has been associated with TMA with four reported cases in the literature (27–29). In the case published by Sullivan *et al.* (28), the patient developed TMA within a few months after receiving carfilzomib. The patient did not undergo a kidney biopsy and received three sessions of plasmapheresis for presumed thrombotic thrombocytopenic purpura, which was stopped once the ADAMTS13 levels returned to the normal range. Given the clinical improvement with stopping the drug and initiation of plasmapheresis, the authors speculate that plasmapheresis expedited the removal of protein-bound carfilzomib or another offending agent. Two more cases of biopsy-proven TMA with carfilzomib have been reported by Qaquish *et al.* (29). Both patients received plasmapheresis for several days with no improvement in the renal or hematologic parameters. ADAMTS13 levels were measured in both patients and were reported in the normal range. Interestingly, the authors measured von Willebrand factor multimers in the peripheral blood plasma samples and showed that none of the patients treated with carfilzomib accumulated ultra large von Willebrand factor multimers after treatment with carfilzomib. The authors speculate that carfilzomib, similar to bortezomib, causes TMA through a dose-dependent toxic mechanism in which plasmapheresis is unlikely to show any clinical benefit.

Recently, Yui *et al.* published the largest case series of PI induced TMA (30). The series by Yui *et al.* describes 11 patients from six centers around the world that developed TMA after either carfilzomib (eight cases) and or bortezomib (three cases) treatment. Six patients were diagnosed within 21 days of the initiation of the drug and the rest 6–17 months later. Diagnosis was made on the basis of lab values of lactate dehydrogenase, haptoglobin, schistocytes on blood smear, and presence of thrombocytopenia and anemia. Median creatinine was 3.12 mg/dl and five patients required dialysis. Two patients underwent a kidney biopsy which confirmed TMA. Four patients were treated with plasmapheresis and three with eculizumab. Eight of the 11 patients had complete resolution of TMA after discontinuation of the PI. Autoantibodies to the ADAMTS13 was an unlikely cause of the TMA in this series of patients given the normal ADAMTS13 levels. Yui *et al.* have suggested an immune-mediated mechanism accounting for the early onset TMA (<21 days) and dose-dependent toxicity for those cases that happen later during the course of treatment (30).

A recent phase 3 trial that studied carfilzomib versus low dose steroids with optional cyclophosphamide in relapsed MM (FOCUS) found grade 3 AKI in 8% in the carfilzomib arm compared with 3% in the control (31). Renal adverse events occurred more frequently in patients within the carfilzomib group compared with placebo (24% versus 9%). Overall, these events occurred more frequently in patients with lower creatinine clearance <30 ml/min and the majority of them had known renal manifestations of MM. In addition, hypertension (HTN) occurred in 15% of carfilzomib patients compared with 6% of the control (31).

Bortezomib, a boronate peptide, is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome, whereas carfilzomib, a tetrapeptide epoxyketone PI, binds irreversibly and inhibits the chymotrypsin-like activity of the 20S proteasome. This structural difference could perhaps explain the different kidney-related side effects of these agents. Recent animal studies and clinical case reports with carfilzomib revealed that the drug increased the resting vasoconstricting tone and amplified the spasmogenic effect of different agents and also led to impairment of vasodilation by inducing endothelial dysfunction (32–35). Given the information from the FOCUS trial, and several more cases of HTN and TMA reported with carfilzomib as compared with bortezomib, it appears that carfilzomib is more nephrotoxic than bortezomib (31–35).

Ixazomib

Ixazomib is a novel oral PI that is active in both the relapsed refractory setting and in newly diagnosed MM. On the basis of a recent randomized controlled trial in relapsed MM, ixazomib was recently approved in the United States for the treatment of relapsed myeloma. No known renal toxicities have been reported with this agent (36).

Immunomodulators (Thalidomide, Lenalidomide, and Pomalidomide)

IMiDs, which include thalidomide, lenalidomide, and pomalidomide, are used for treatment of relapsed or recurrent myeloma. Their exact mechanism of action is unknown; however, they likely act *via* a variety of mechanisms including immune-modulation, antiangiogenic, anti-inflammatory, and antiproliferative effects (37). Thalidomide, the first generation IMiD, is metabolized *via* nonenzymatic hydrolysis and only <1% of unchanged drug is excreted in the urine (38). In the initial report showing thalidomide activity against MM, eight out of 84 patients had a >50% in serum creatinine. In these cases, the kidney injury was believed to be due to progression of underlying disease and not related to the drug (39). In clinical practice, the use of thalidomide has not been associated with nephrotoxicity.

The second generation IMiD lenalidomide has shown effectiveness against MM in two pivotal trials (40,41). There were no reports of kidney toxicity in either study although Weber *et al.* reported that 6.2% of patients in the lenalidomide group developed hypokalemia versus 1.1% in the placebo group (40). After lenalidomide was approved for treatment of MM, a number of reports have linked it to kidney dysfunction (42–47). In most patients, kidney disease developed without evidence of malignancy progression. Furthermore, one patient developed fanconi syndrome (42) and one patient had a drug reaction with eosinophilia, rash, and systemic symptoms (DRESS syndrome) (45). A case of minimal change disease was reported in a patient with Waldenström macroglobulinemia being treated with lenalidomide (47). The largest series of AKI associated with this drug was noted by Specter *et al.* (46), when they studied patients with amyloidosis. Twenty-seven of 41 patients (66%) studied at a single center with light chain amyloidosis

developed kidney dysfunction during lenalidomide treatment. The kidney dysfunction was severe in 13 of these patients (32%); four of whom required initiation of dialysis (10%). The median time to kidney dysfunction after starting lenalidomide was 44 days (interquartile range, 15–108 days). Four of eight patients without underlying renal amyloidosis developed kidney dysfunction. Patients with severe kidney dysfunction were older and had a higher frequency of underlying renal amyloidosis, greater urinary protein excretion, and lower serum albumin (46).

Pomalidomide is another second generation IMiD. Of the three trials addressing its efficacy in MM, only one study reported high incidence of grade 3–4 kidney toxicity (11%) (48–50). One case of AKI and crystal nephropathy was attributed to pomalidomide. However, confounding factors included concurrent use of levofloxacin which may have contributed to both AKI and crystal formation (51).

In summary, both lenalidomide and pomalidomide have been associated with kidney dysfunction; however, clinicians must be careful when assessing patients with worsening kidney disease on IMiD as a number of other causes including progression of MM could be responsible for decline in kidney function.

BRAF Inhibitors (Vemurafenib and Dabrafenib)

The discovery of mutations in the BRAF oncogene led to an era of targeted therapy in patients with malignant melanoma, colorectal cancer, and lung cancer (52–55). BRAF mutations lead to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, resulting in enhanced gene transcription, cellular proliferation, and oncogenic activity. The most common mutation encountered in patients with melanoma is V600E. Discovery of this mutation led to the approval of vemurafenib and dabrafenib for treatment of BRAF V600E mutation–positive melanomas. Use of these drugs in MM is limited to small studies (56,57). This is partly due to the low prevalence (<10%) of the BRAF V600E mutation in patients with myeloma (56–58).

Extrapolating the data from the use of BRAF inhibitors in melanoma patients, one can predict that this class of drugs may lead to adverse kidney outcomes in patients with MM. Specific toxicities have included tubular and interstitial damage (acute as well as chronic). The onset of injury varies, with some cases being reported within a few weeks of drug initiation and others occurring after a 1–2 month period. The kidney injury within weeks of drug initiation is likely allergic interstitial nephritis, whereas that occurring at a later period may be tubular toxicity (59–63). Overall, vemurafenib has a much higher rate of associated kidney injury as compared with dabrafenib (63). A recent review on this topic summarizes the kidney toxicities associated with BRAF inhibitors when used in melanoma patients (64).

MAPK Enzymes Mitogen-Activated Protein Kinase Kinase Enzymes Inhibitors

MAP2K kinases (MEK1 and MEK2) are attractive therapeutic targets in several cancers because they are essential in the mitogen-activated protein kinase kinase enzymes (MEK)/MAPK pathway which when dysregulated leads to increased cell survival and metastasis (65,66). Trametinib (MEK inhibitor), by itself, has not been associated with nephrotoxicity. Monotherapy with this agent can lead to HTN, but cases of AKI and hyponatremia were noted more frequently in patients treated with combined trametinib and dabrafenib in patients with melanoma (67). Kidney toxicity may result from a combination effect with the BRAF inhibitors rather than a solo effect of an MEK inhibitor (68).

In MM, the MEK inhibitor AZD6244 (Selumetinib, ARRY-142886) has demonstrated *in vitro* and *in vivo* activity against myeloma cells (69–71). The most common toxicities associated were anemia, neutropenia, thrombocytopenia, diarrhea, fatigue, increased creatine phosphokinase, limb edema, and acneiform rash. There were three deaths (two from sepsis and one from AKI). Although the data are limited, kidney toxicities appear to be uncommon with this agent.

Signaling Lymphocytic Activation Molecule F7

Elotuzumab is a fully humanized IgG1 monoclonal antibody targeted against signaling lymphocytic activation molecule F7 (SLAMF7, also called CS1 [cell-surface glycoprotein CD2 subset 1]) (72,73). CS1 belongs to a family of lymphocytic activation molecule surface glycoproteins. It has been shown that CS1 expression is present in malignant plasma cells at the gene and protein levels. In addition, high levels of CS1 were noted in patients with monoclonal gammopathies of undetermined significance, smoldering myeloma, plasmacytomas, and MM (72,73), making CS1 a compelling target for immunotherapy for MM. Interestingly, the expression of SLAMF7 was present in >95% of myeloma cells regardless of the cytogenetics of the myeloma cells (73).

Elotuzumab promotes death of myeloma cells by CS1-CS1 interaction between natural killer (NK) cells and myeloma cells (72). Elotuzumab was studied in 35 patients with relapsed/refractory MM (74). Although 44.1% of the study patients had serious adverse events, AKI was noted in only two patients (5.9%). One of the patients had severe AKI that required hemodialysis (74). It was also studied in combination with lenalidomide (75) with favorable results and AKI was not reported in that particular study. Further phase 3 studies have been initiated (76,77) with no known nephrotoxicities reported thus far.

Akt/Mammalian Target of Rapamycin Pathway Inhibitors

The phosphatidylinositol-3-kinase family is made up of a group of serine/threonine and lipid kinases that serve as the intracellular initiation point for several signaling cascades such as the G-coupled protein receptor. Through the production of phospho-inositol triphosphate3, the phosphorylated form of membrane-bound phosphoinositides, these pathways activate Akt, a serine-threonine kinase that has been implicated in oncogenesis (78,79). In one of these pathways, Akt indirectly activates the mammalian target of rapamycin (mTOR) pathway through the activity of the tuberous sclerosis complex 1/2. mTOR includes two distinct protein complexes, mTOR complex 1 and 2 (mTORC1 and mTORC2). Thus, Akt leads to activation of mTORC1 which subsequently leads to increased cellular proliferation.

mTORC2 has been shown to be important in the regulation of cytoskeletal integrity (including that of the glomerular podocyte) (80–83). In one study higher levels of activated, phosphorylated Akt correlated with more advanced MM (84).

Perifosine is an alkylphospholipid that inhibits the Akt pathway (decreases Akt phosphorylation) leading to apoptosis of MM cells and also enhances the cytotoxic effects of other agents such as bortezomib (85,86). Potent Akt inhibitors are showing promise and are in development for the potential treatment of MM as well as several other cancers (87–90). Interestingly, and for unclear reasons, perifosine use was associated with a high rate of hypophosphatemia in the phase 1 trial (87).

mTOR inhibitors such as rapamycin, everolimus, and others have shown preclinical promise in the therapy of MM especially when combined with other therapies, with partial response rates as high as 33% (91–93). The extensive experience with mTOR inhibitors in solid organ transplantation as well as recent advances in the understanding of the role of the Akt/mTOR pathway in maintenance of podocyte viability leads to concerns about short- and long-term kidney toxicities with these agents (80,81). Recently, Canaud and colleagues identified the Akt pathway as critical to the maintenance of podocyte structure and integrity when under stress (such as with reduced nephron numbers) (80). Mechanistically, this pathway may account for the clinical observation of proteinuria with mTOR inhibitors (*i.e.*, mTORC2 inhibition may decrease the amount of active, phosphorylated Akt and thus alter cytoskeletal integrity and promote podocyte apoptosis). Theoretically, the risk of proteinuria and podocyte injury could also be associated with Akt inhibitors as well as mTOR inhibitors, especially if these are not isoform specific. Ischemic preconditioning which experimentally protects the kidney tubules against subsequent ischemia-reperfusion may also rely on the Akt pathway (94). So far, the clinical experience with Akt inhibitors is limited to small trials with perifosine (95) with no reported nephrotoxicities.

Proteinuria and, more rarely, kidney dysfunction have been reported in patients taking mTOR inhibitors (96). The phenomena appear to be dose-dependent and reversible with cessation of the medication. The actual incidence of mTOR-induced proteinuria is likely low on the basis of analyses of clinical trial data. For instance, in 94 patients enrolled in four sirolimus trials there was one case of nephrotic-range proteinuria which remitted with drug withdrawal (97). In trials of everolimus for treatment of tuberous sclerosis–associated subependymal giant-cell astrocytomas and angiomyolipomas, the rate of proteinuria was 4% with drug and 8% with placebo treated patients (98). In terms of longer-term use and changes in GFR, extensive use in patients with calcineurin-inhibitor–induced renal allograft dysfunction has shown that mTOR inhibitors do not appear to be associated with any increased risk of kidney dysfunction (99–101). However, there are occasional case reports of mTOR inhibitor–associated glomerulopathy and acute tubular necrosis with newer agents such as temsirolimus, as well as an increased incidence in mTOR-associated rises in serum creatinine in a trial of temsirolimus versus IF-α or both in patients with advanced renal cell cancer (102,103).

More recently, dual mTORC1/2 kinase inhibitors are being studied in clinical trials. The advantage of these newer agents is that the mTORC2 activation of Akt is also inhibited by these agents and thus they may lead to more effective inhibition of cancer cell proliferation (104). Thus far, no kidney toxicity has been described with these agents but given the mechanisms of action, vigilance for these toxicities should be high.

Anti–IL-6 Monoclonal Antibodies in MM

IL-6 plays a critical role in the pathogenesis of MM. It is both an autocrine and paracrine growth factor contributing to the proliferation of myeloma cells as well as being involved in the inhibition of tumor cell apoptosis (105). Thus, blockade of IL-6 would seem a logical antimyeloma drug strategy and this has been achieved with chimeric anti–IL-6 monoclonal antibodies. Phase 2 studies with siltuximab, an anti–IL-6 monoclonal antibody, in patients with refractory or relapsed MM have been reported (106,107). Of note, siltuximab has received FDA approval for the treatment of Castleman disease where the drug has shown efficacy (108).

Specific kidney toxicity of siltuximab has not been reported. However, several electrolyte disorders appear to be more common in patients taking this medication as compared with placebo or other agents, at least in one trial. For instance, hyperuricemia (13%) and hyperkalemia (4%) were seen in the trial with siltuximab in Castleman disease (109). However, these adverse events were not reported in other trials (106,107). Given the limited experience with this drug, more studies will be needed to confidently exclude kidney-specific adverse effects.

Programmed Cell Death–1 and Ligand Target in MM

This pathway includes two proteins called programmed death–1 (PD-1), which is expressed on the surface of immune cells, and programmed death ligand–1 (PD-L1), which is expressed on cancer cells. When PD-1 and PD-L1 join together, they form a biochemical "shield" protecting tumor cells from being destroyed by the immune system. Anti–PD-1 agents are humanized monoclonal antibodies that bind the PD-1 molecule, which are present on tumor infiltrating lymphocytes and regulatory T cells. They prevent the engagement of PD-1 to its ligand on tumor cells (PD-L1 and PD-L2) thereby asserting antineoplastic activity. The object of blocking programmed cell death is to restore the activation of the immune system directed to tumor cells. These immune check point inhibitors are being considered for treatment of MM (110).

Nivolumab was the first anti–PD-1 antibody, tested initially in melanoma. In December 2014, the FDA granted an accelerated approval to nivolumab for the treatment of patients with unresectable or metastatic melanoma and renal cell cancer (111,112). In one trial (111), there was an increased incidence of elevated creatinine noted in the nivolumab-treated group as compared with the chemotherapy-treated group (13% versus 9%). Steroids helped resolve the renal dysfunction in 50% of the cases. The FDA label has recommendations (113) to start steroids as the creatinine rises with the presumption that AKI is

immune-mediated. Only recently, there were several biopsy-proven cases of AIN related to nivolumab described in two case series (114,115). All patients were also on other drugs (proton pump inhibitors, nonsteroidal anti-inflammatory drugs) linked to AIN, but in most cases, the use of these drugs preceded anti–PD-1 antibody therapy. The authors believe that PD-1 inhibitor therapy may release suppression of T cell immunity that normally permits renal tolerance of drugs known to be associated with AIN.

Pembrolizumab (MK-3475) is another monoclonal antibody therapy designed to directly block the interaction between PD-1 and its ligands. This drug has been used in melanoma and hematologic malignancies since 2014 (116). In the initial trials, AIN was confirmed by kidney biopsy in two out of three patients with AKI. All three patients fully recovered kidney function after treatment with high-dose corticosteroids (≥40 mg prednisone or equivalent per day) followed by a corticosteroid taper (116–119). Shirali *et al.* (114) and Cortazar *et al.* (115) reported several biopsy-proven cases of AIN with this agent. Given the immune-mediated mechanism of action of this drug, AIN will likely be seen when these agents are used to treat MM as well.

Anti–Killer Ig-Like Receptor Agents in Myeloma

NK cells, members of the innate immune system, are important players of host immunity in controlling various cancers. NK cell function, including cytotoxicity and cytokine release, is governed by a balance between signals received from surface inhibitory and activating receptors (120). Class 1 HLA molecules, present in all tissue types, bind to the inhibitory killer Ig-like receptors (KIRs) on NK cells to prevent inadvertent activation against normal tissues (121). Upon malignant transformation of cells, HLA class 1 expression is reduced or lost, resulting in escape from antitumor T cells. However, a mature NK cell can still be activated due to lack of binding of inhibitory KIRs by MHC class 1, resulting in unsuppressed activating signals (122). NK cells directly kill tumor cells *via* different pathways including release of cytoplasmic granules containing perforin and granzyme which cause cell lysis, or *via* release of TNF leading to cell apoptosis (123). Lirilumab, or IPH2101 (formerly 1–7F9), is a human, IgG4 monoclonal antibody against common inhibitory KIRs (KIR2DL-1, -2, and -3), that blocks KIR-ligand interaction and augments NK cell killing of tumor cells. So far, this new agent has been tried in treatment of refractory or relapsed myeloma as a single agent (124) and in combination with other immune-modulating agents (125).

One patient with a 10-year history of MM and seven prior lines of therapy developed kidney failure requiring dialysis after receiving the first dose of 0.075 mg/kg of the IPH2101. It was thought to be related to the study drug or disease progression. The same patient also developed hyperkalemia and hyperuricemia. None of the patients developed autoimmunity. IPH2101 has been used with lenalidomide in 15 patients with myeloma at varying doses (113). No cases of AKI were reported, but one patient developed hypophosphatemia. Studies using this agent in treatment of other hematopoietic and metastatic solid organ cancers are underway. In summary, there is limited clinical data regarding use of anti-KIR antibodies. Kidney toxicity appears to be rare but until additional data are obtained it would be prudent to pay attention to kidney function and electrolytes including serum uric acid and phosphorus when using these agents.

Other Agents against MM

Lin *et al.* described relatively high expression of CD38 on myeloma cells (126); this in combination with its role in cell signaling identified CD38 as a potential therapeutic antibody target for the treatment of MM. A humanized anti-CD38 monoclonal antibody, SAR650984, is currently in clinical development (127,128), whereas daratumumab, a human IgG1κ monoclonal antibody against CD38, was recently approved by the FDA for treatment of previously treated MM (129). So far, clinical trials have not reported any clinically significant kidney adverse events associated with the use of CD38 monoclonal antibodies.

A typical characteristic of human cancers, including MM, is the deregulation of DNA methylation and post-translational modifications, especially histone acetylation, leading to deregulation of gene transcription (130). The histone acetyltransferases and histone deacetylases (HDACs) act in opposition to each other to regulate acetylation levels of histones and nonhistone proteins (130). HDAC inhibitors (HDACi) inhibit the removal of acetyl groups by HDAC enzymes, leading to maintenance of histone and nonhistone protein acetylation, accumulation of histones and other proteins, and reactivation of epigenetically silenced tumor suppressor genes, causing cell-cycle arrest and apoptosis (131). Two HDACi have been approved for various cancers in the United States: vorinostat (132) for cutaneous T cell lymphoma and panobinostat for MM (133). Completed clinical trials so far have not reported any clinically significant kidney adverse effects associated with HDACi use; there is, however, significant preclinical evidence supporting the beneficial effects of HDACi in various models of kidney disease. *In vitro*, HDACs are implicated in renal fibrogenesis, possibly through inflammatory and profibrotic gene regulations and cell signaling pathways; there is also evidence for a regulatory role of HDACs in the pathogenesis of polycystic kidney disease (134). Wang *et al.* (135) demonstrated an upregulation of HDACs in podocytes treated with advanced glycation end products, high glucose, and TGF-β (common detrimental factors in diabetic nephropathy), suggesting a contribution of HDACs to podocyte injury. Liu *et al.* demonstrated that HDAC inhibition attenuated development of renal fibrosis and suppressed activation and proliferation of renal interstitial fibroblasts (136). These studies suggest a future potential for HDAC inhibition in treatment of renal diseases.

FDA Adverse Event Reporting System Database Review of Antimyeloma Agents

As part of this review, we evaluated all kidney toxicities reported with the novel antimyeloma agents discussed above to the FDA Adverse Event Reporting System (FAERS), from the third quarter of 2011 to the second quarter of 2015. Table 4 summarizes our findings. Lenolidomide, everolimus, and bortezomib were the top three offenders with AKI as the

Table 4. Common reported renal adverse reactions to the Food and Drug Administration Adverse Event Reporting System database from the third quarter of 2011 to the first quarter of 2015 for antimyeloma agents discussed in this review

Drug Name	Renal Impairment[a]	Hypokalemia	Hyponatremia	Hypomagnesemia	Hyperkalemia	Hypophosphatemia	Hypernatremia	Grand Total
Lenalidomide	881[b]	136	61	33	25	28	8	1172
Everolimus	586[b]	52	35	23	24	19	4	743
Bortezomib	325[b]	65	51	10	25	24	9	509
Sirolimus	249[b]	8	13	2	9	7	0	288
Vemurafenib	176[b]	11	18	2	4	0	0	228
Pomalidomide	113[b]	4	10	2	3	0	1	133
Carfilzomib	85[b]	12	8	2	8	9	0	130
Vorinostat	44[b]	26	26	0	10	16	2	124
Dabrafenib	32[b]	2	13	2	0	1	0	50
Trametinib	28[b]	1	11	3	0	1	0	44
Nivolumab	20[b]	5	14	2	4	1	0	44
Pembrolizumab	16	3	19[b]	0	1	0	0	39
Panobinostat	11[b]	2	3	1	2	2	0	22

There are important limitations with the Food and Drug Administration Adverse Event Reporting System database. The events are reported by providers and/or patients and there could be a reporting bias. In addition, not all demographic and comorbidity information is available to help identify if other nephrotoxic risk factors are present, such as: use of nonsteroidal anti-inflammatory agents, history of hypertension or diabetes mellitus, known kidney disease, recent use of contrast agent, or recent use of standard chemotherapy that could be nephrotoxic. Most importantly, it is not possible to determine if an event is truly caused by the drug as opposed to the underlying disease or concomitant medications.

[a]Renal impairment comprises proteinuria, ARF, AKI, elevated creatinine, hypercreatinemia, and nephritis. Selumetinib and Siltuximab had <2 events reported total to the Food and Drug Administration hence are not listed.

[b]Most common reported reaction.

most common finding reported, possibly due to much greater use of these drugs. Importantly, the toxicities reported here are not just for when these agents are used in MM, but for other cancer treatments as well. Despite the limitations of FAERS (Table 4), it still provides valuable information regarding the renal adverse effects of these therapies.

Conclusions

The use of novel targeted therapies has led to significant improvements in survival and overall prognosis with many malignancies. However, there is evolving knowledge of renal adverse events with these agents. Timely recognition of these toxicities can aid in the proper management of patients with myeloma. In this review, we recognized that there are multiple ways novel antimyeloma therapies can affect renal function. In addition, newer targeted agents are entering clinical trials. With the advent of novel targeted therapies and their use in myeloma, nephrologists and hematologists need to be more vigilant of the renal toxicity potential of these agents.

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