Renal Insufficiency

Subjects: Allergy

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Renal impairment is defined as serum creatinine (sCr) above the upper normal limit of 2 mg/dL or as an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m2.

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1. Introduction

Renal impairment is defined as serum creatinine (sCr) above the upper normal limit of 2 mg/dL or as an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m^2 [1]. Patients with r/r MM (relapsed and refractory multiple myeloma) present three different clinical pictures: (1) relapsed but not refractory, (2) relapsed and refractory and (3) primary refractory r/r MM [2].

Renal impairment may develop over time. It is estimated that 25 to 50% of multiple myeloma patients are affected in the course of their disease [3].

Relapsed multiple myeloma is defined as a progressive disease that occurs when a patient no longer responds to a previous therapy or requires a salvage therapy but does not yet meet the criteria ’primary refractory’ or ’relapsed and refractory’ based on the following laboratory and radiological findings: 25% increase on the lowest confirmed response in light of one or several of the following criteria: serum M protein (absolute increase must be 0.5 g/dL); serum M protein increases by 1 g/dL, when the lowest M component amounted to 5 g/dL; urine M protein (absolute increase must amount to 200 mg/24h). In patients without measurable serum and urine m protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL). Occurrence of a new lesion (en), 50% increase from nadir in SPD of >1 lesions or 50% increase in the longest diameter of a previous lesion >1 cm in the short axis; 50% increase in circulating plasma cells (at least 200 cells per litre) if this is the only measure for the disease. To qualify as a clinical relapse, one or several of the following criteria must be met:

- A marked increase in the size of existing plasmacytomas or bone lesions. A definitive increase is defined as a 50% increase (and 1 cm) serially measured by the SPD of the measurable lesion;
- Hypercalcemia (>11 mg/dL);
- A decrease of 2 g/dL in haemoglobin, with no link between the decrease and the therapy or any other states not induced by the myeloma;
- Increase in serum creatinine by 2 mg/dL or more at the start of the therapy and attributable to the myeloma;
- Hyperviscosity in connection with the serum paraprotein;
- Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not present a progression) [3];

Primary refractory multiple myeloma:

Patients are considered primary refractory when they have attained stable disease (SD) or progressive disease (PD) in first-line therapy [4].

2. The Pathophysiology of Renal Insufficiency in Multiple Myeloma

Renal failure in patients with MM results from the toxic effects of monoclonal light chains on renal structures, primarily the renal tubules. Light chain cast nephropathy occurs most often in MM patients with renal impairment. Therefore, light chain cast nephropathy is the most common diagnosis in patients with MM and significant renal insufficiency. A nephrotic syndrome occurs much more frequently in patients with amyloidosis or MIDD (monoclonal immunoglobulin deposition disease, 'Randall disease') (e.g., severe albuminuria, hypoalbuminemia in the serum and edemas) [5].

Hypercalcemia, dehydration, nephrotoxic drugs (aminoglycoside antibiotics and/or NSAR) and contrast agents contribute to the development or progression of preexisting RI by amplifying the toxic effect of light chains [6]. Cast nephropathy occurs when light chain production overcomes the capacity of tubular cells to endocytose and catabolize the filtered, free light chains. As a result, excess light chains form aggregates and casts with uromodulin in the distal nephron, leading to tubular obstruction and concomitant inflammation [7][8].

3. Novel Agents in the Therapy of Relapsed/Refractory Multiple Myeloma

The therapy options available for the treatment of multiple myeloma have improved considerably in the past 15 years once IMiDs and proteasome inhibitors had been approved. Despite the many different therapy combinations, most patients experience a relapse. In recent years, different active agents with varying mechanisms of action and distinct objectives have been studied, including cellular therapies, monoclonal antibodies and small molecules, in order to significantly prolong survival [9]. In recent years, many new drugs have been approved: pomalidomide, iberdomide, carfilzomib, ixazomib, marizomib, oprozomib, panobinostat and the three monoclonal antibodies daratumumab, isatuximab (which targets CD38) and elotuzumab. In addition, further substances have been developed which can be administered against lenalidomide-refractory as well as relapsed and refractory disease after two or more previous lines of therapy, such as monoclonal antibodies targeting BCMA, monoclonal antibodies targeting APRIL, monoclonal antibodies targeting immune checkpoints, DNA damaging agents (melflufen), inhibitors of BCL2 family proteins (venetoclax), MCL1 inhibitors, epigenetic inhibitors (histone deacetylase HDAC panobinostat) and inhibitors of nuclear cytoplasmic transport receptors, such as XPO1 inhibitor (selinexor). See **Table 1**.

Table 1. New drugs in the treatment of patients with RRMM and renal and hepatic insufficiency.

Drugs	Dose Adjustment Renal Insufficiency (RI)	Dose Adjustment Hepatic Insufficiency
Lenalidomide	**GFR 30–50 mL/min.: 10 mg/day GFR < 30 mL/min.: 7.5 mg/day Terminal RI: 5 mg/day On dialysis days, the dose should be administered post-dialysis**	**N.A.**
Pomalidomide	**No dose adjustment On dialysis days, the dose should be administered post-dialysis**	**No dose adjustment**
Iberdomide	**N.A.**	**N.A.**
Carfilzomib	**No dose adjustment On dialysis days, the dose should be administered post-dialysis**	**Mild/moderate hepatic insufficiency: no dose reduction Dose reduction recommended if liver transaminase levels are elevated**
Ixazomib	**GFR 60–30 mL/min.: no dose adjustment GFR < 30 mL/min. until dialysis: dose reduction to 3 mg Time of administration does not depend on time of dialysis**	**Mild hepatic insufficiency: no dose adjustment Moderate/severe hepatic insufficiency: dose reduction to 3 mg**
Marizomib and oprozomib	**N.A.**	**N.A.**
Daratumumab	**No dose adjustment**	**No dose adjustment**
Isatuximab	**Mild to severe RI: no dose adjustment**	**No dose adjustment**
Elotuzumab	**No dose adjustment**	**Mild hepatic insufficiency: no dose adjustment Moderate/severe hepatic insufficiency: N.A.**

Drugs	Dose Adjustment Renal Insufficiency (RI)	Dose Adjustment Hepatic Insufficiency
Blentamab mafoditin	EGFR 60–30 mL/min.: no dose adjustment EGFR < 30 mL/min.: N.A.	Bilirubin > ULN to < 1.5 x ULN or AST > ULN: no dose adjustment Moderate and severe hepatic insufficiency: N.A.
Idecabtagene vicleucel	N.A.	N.A.
Melflufen and selinexor	N.A.	N.A.
Venetoclax	GFR 90–30 mL/min.: no dose adjustment GFR < 30 mL/min. and dialysis: no therapy recommended	Moderate hepatic insufficiency: caution in the dose titration phase due to TLS (tumour lysis syndrome)

3.1. IMiDs

3.1.1. Thalidomide

Renal function has been shown not to influence the pharmacokinetics of thalidomide [10]. Thalidomide therapy in patients with renal failure or renal impairment does not increase the occurrence of adverse events. Therefore, the thalidomide dose does not need to be reduced for patients with renal impairment. No dose adjustment is needed, neither for renal nor for hepatic insufficiency. The dose does not need to be changed during haemodialysis. As thalidomide is known to have thrombogenic properties, the administration of prophylactic anticoagulation should be considered for patients with a dialysis shunt in order to prevent shunt thombrosis [11]. However, thalidomide is poorly tolerated in elderly patients.

3.1.2. Lenalidomide

Lenalidomide is a second-generation immunomodulatory drug (IMiD) used to treat patients with relapsed or refractory myeloma. Despite primary excretion by the kidney, a dose-adjusted treatment using lenalidomide is an effective therapy option for patients with MM and renal impairment [12]. PrE1003, a PrECOG study, has also demonstrated the potential to continuously dose patients suffering from severe renal insufficiency (CrCl < 30 but not on dialysis—group B) with at least 15 mg and possibly 25 mg of lenalidomide, although the number of patients treated was too small to deliver conclusive results. Overall, this simplifies the dosing to daily dosing in all patients irrespective of renal function, with the caveat that for patients with severe renal insufficiency the dose may have to be reduced to 15 mg [13]. Oehrlin collected the data of 26 patients undergoing therapy at four different German centres and, in a substantial proportion of the cases, showed improved renal function in patients with relapsed and/or refractory MM and renal impairment after treatment using lenalidomide/dexamethasone-based therapy schemata [14].

3.1.3. Pomalidomide

Pomalidomide is an IMiD developed after thalidomide and lenalidomide. Before being excreted, pomalidomide is largely metabolised by CYP450 in the liver, and unlike lenalidomide only 2% of the pomalidomide that has not been metabolised is excreted in urine [15]. The results of the MM-013 study show that patients with RRMM and moderate or severe RI, including those requiring haemodialysis, benefit from a therapy with pomalidomide in addition to low-dose dexamethasone, with ORRs of 39.4%. A daily pomalidomide dose of 4 mg plus low-dose dexamethasone is effective in patients with RRMM and moderate or severe RI, including patients at an advanced stage of the disease that require haemodialysis. The safety profile between the three groups was acceptable, and no new safety signals were observed [16]. As a third-line therapy, pomalidomide plus low-dose dexamethasone is safe and effective in patients with RRMM in whom lenalidomide-based therapy has failed; this is a clinically relevant patient population that is poorly represented in clinical studies [17].

3.1.4. Iberdomide

Iberdomide is a novel, orally administered and highly effective cereblon modulator [18]. The combination of IberDd (iberdomide plus daratumumab and dexamethasone) and IberVd (iberdomide plus bortezomib and dexamethasone) exhibits a favourable tolerability profile in patients with heavily pretreated RRMM with promising clinical activity; the same applies to patients who were refractory to their previous regimen and have previously been exposed to IMiD agents,

proteasome inhibitors and CD38 antibodies. Immune profiling data confirm that iberdomide and dexamethasone were pharmacodynamically active in a triplet combination and not augmented by the addition of daratumumab or bortezomib. This study is being continued for both cohorts with continued enrolment at a dose level of 1.6 mg. Updated findings, including for MTD/RP2D, will be presented. These results support further development of iberdomid-based therapies in patients with MM; phase three studies are planned to evaluate these combinations [19]. These studies evaluate the safety and tolerance of iberdomide in patients with renal impairment versus patients with normal renal function (study NCT04933747).

3.2. Proteasome Kinases Inhibitors

3.2.1. Bortezomib

Bortezomib is active and well-tolerated in patients with renal impairment, including those who require dialysis [20]. The pharmacokinetics of bortezomib are not affected by the degree of renal impairment as the primary metabolic pathway of bortezomib is oxidative deboronation by hepatic cytochrome P450 enzymes [21]. Bortezomib should be given after dialysis in the patients who are dialysed. Ludwig et al. reported the reversal of light-chain- induced acute renal failure with bortezomib-based therapy in five out of eight patients with MM. These patients received chemotherapy with a bortezomib-doxorubicin-dexamethasone regimen. Furthermore, other bortezomib-based regimens, such as bortezomib-cyclophosphamide-dexamethasone, can also be used [21]. In the HOVON65/GMMG-HD4 trial, bortezomib resulted in a superior outcome in patients with increased serum creatinine. In these patients, both median PFS (13 vs. 30 months; hazard ratio HR, 0.45; 95% CI, 0.26–0.78; and $p = 0.004$) and OS (21 vs. 54 months; HR, 0.33; 95% CI, 0.16–0.65; and $p = 0.001$) dramatically improved with bortezomib compared to thalidomide. Bortezomib maintenance after HDT and ASCT significantly improved the nCR plus CR rate from 31 to 49% [22]. Bortezomib at the standard dose of 1.3 mg m^2 should be considered an appropriate treatment option for the sizeable proportion of patients with relapsed MM who have any degree of renal impairment [23].

3.2.2. Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone PI that irreversibly binds to the β5-proteasome subunit and the LMP7 (iβ5) subunit of the immunoproteasome with greater affinity than bortezomib [24]. A phase two study comprising patients with MM and varying degrees of renal impairment showed no difference in carfilzomib clearance or exposure (15 or 20 mg/m^2) between patients with normal renal function and patients with varying degrees of renal impairment, including patients with terminal renal insufficiency (ESRD) [25]. In the ENDEAVOUR study, carfilzomib showed improved PFS and OS compared to bortezomib in patients with varying CrCL values, including in patients with severe renal impairment (CrCl < 15 to 50 mL/min). In all treatment groups, patients who reached complete renal remission exhibited better PFS and OS outcomes than non-responders. These results confirm that improved renal response comes with better survival outcomes in patients who have baseline renal impairment. Overall, the data suggest that Kd56 (carfilzomib 56 mg/2 plus dexamethasone) has a favourable benefit–risk profile and should be considered standard therapy in patients with RRMM, regardless of baseline renal function [26]. Based on the available pharmacokinetic data, no adjustment of the initial carfilzomib dose is recommended for patients with mild, moderate or severe baseline renal impairment, or for patients receiving chronic dialysis therapy. Pomalidomide/carfilzomib plus dexamethasone appeared to achieve a better response rate than pomalidomide/carfilzomib administered as a single agent. The combination of pomalidomide, carfilzomib and dexamethasone resulted in a much higher response rate than the therapy combining pomalidomide with dexamethasone [27].

3.2.3. Ixazomib

Ixazomib is an oral, highly selective and reversible proteasome inhibitor. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta-5-subunit of 20S proteasome, which leads to the disruption of cellular regulatory mechanisms, which in turn inhibits cell growth and survival pathways and results in the induction of apoptosis [28]. Based on the PK and safety results, a reduced ixazomib dose of 3 mg (on days 1, 8 and 15 of the 28-day cycles) in MM patients with severe renal insufficiency or ESRD requiring haemodialysis is recommended, compared to the recommended standard 4 mg dose for patients with normal renal function or mild or moderate RI. In patients requiring haemodialysis with ESRD, ixazomib can be administered regardless of the time of dialysis [29].

3.2.4. Marizomib

Marizomib is a β-lactone-γ-lactam proteasome inhibitor derived from the marine actinobacterium Salinispora tropica [30]. In addition to inducing apoptosis, marizomib regulates various signal pathways for cell growth and survival in MM cells. In reality, the initial justification for the therapeutic approach of proteasome inhibitors as anticancer drugs partly relied on their ability to inhibit growth and survival signals via NF-κB [31]. As with bortezomib, marizomib targets NF-κB; what is

important is that marizomib is a more potent inhibitor of NF-κB and related cytokine secretion than bortezomib [32]. Phase one studies showed relatively low toxicities and no indication of any neuropathy or thrombocytopenia. In a dose-escalation study comprising 15 patients with relapsed/refractory MM who were being treated with marizomib in monotherapy, three patients resistant to bortezomib responded at least partially [33]. Further studies are investigating the administration of marizomib in patients with RRMM.

3.2.5. Oprozomib

Oprozomib is an oral, irreversible PI derived from carfilzomib that demonstrates an effectiveness in cytotoxicity tests similar to that of carfilzomib. As with bortezomib and carfilzomib, it is highly selective for the CT-L (ß5) subunit of 20S proteasome [24].

The results indicate that therapy with oprozomib and dexamethasone improves gastrointestinal tolerability in patients with relapsed and/or refractory MM relative to single-agent oprozomib [34].

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