MULTIPLE MYELOMA AND RENAL FAILURE

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Disclosure: No potential conflict of interest.
Received: 04.11.14 **Accepted:** 30.12.14
Citation: EMJ Oncol. 2015;3[1]:65-69.

ABSTRACT

Renal failure (RF) occurs in approximately 20-30% of multiple myeloma (MM) patients at diagnosis and in more than 50% of patients with advanced disease. The pathogenesis of RF is related to the production of monoclonal light chains that can damage either the tubule (myeloma kidney) or the glomeruli (light chain deposition disease or amyloid light-chain amyloidosis). In the past, the prognosis of patients with MM and RF was considered poor due to the limited number of effective and non-nephrotoxic drugs that were available. At present, novel drugs acting both on MM clone and on bone marrow microenvironment have been introduced into clinical practice; among them, bortezomib-containing regimens have proved to be the most effective. High-dose myeloablative therapy followed by autologous stem cell rescue can also be proposed in younger patients with no other relevant comorbidities.

Keywords: Myeloma, renal failure, light chains.

EPIDEMIOLOGY AND PATHOGENESIS OF RENAL FAILURE (RF) IN MULTIPLE MYELOMA (MM)

MM is a clonal B cell neoplasm characterised by proliferation and accumulation of B lymphocytes and plasma cells in the bone marrow and, more rarely, at extramedullary sites. Its annual incidence is 6/100,000 in Western countries, thus representing the second most common haematological malignancy after non-Hodgkin's lymphomas.[1] RF occurs in approximately 20-30% of MM patients at diagnosis and in more than 50% of patients with advanced disease.[2] The incidence of this complication in the different reports varies depending on its definition, either serum creatinine above 2 mg/dl or reduced glomerular filtration rate (GFR). Recently, the International Myeloma Working Group has provided recommendations on the definition of renal impairment, using the estimated GFR (eGFR) using the modification of diet in renal disease as the guiding parameter.[3] Stages of renal impairment can thus be classified upon the degree of eGFR, which can be mildly (60-89 ml/min), moderately (30-59 ml/min), or severely (15-29 ml/min) reduced, with end-stage renal disease defined as eGFR <15 ml/min. RF occurs by various mechanisms, the most frequent of which is tubular damage caused by cast formation.[4] Light chains are filtered through the glomeruli and then endocytosed and catabolised by the cells of the proximal tubule. When a large number of light chains are produced, the catabolic capacity of the proximal tubule is overwhelmed and an excess of light chains reaches the distal nephron, where they complex with Tamm-Horsfall protein, forming tubular casts that finally cause tubular obstruction. Light chains can also damage proximal tubular cells, leading to Fanconi syndrome, and induce interstitial fibrosis due to the production of pro-inflammatory cytokines (interleukin-6, tumour necrosis factor alpha).[5]

At the glomerular level, light chain deposition can result in amyloidosis (mostly lambda chains) or light chain deposition disease (LCDD) (kappa chains); glomerular damage, either caused by vascular deposition of amyloid fibrils, or granular deposits in the mesangium, finally results in nephrotic syndrome.[6] All the conditions described above can be worsened by comorbidities such as

diabetic nephropathy or nephroangiosclerosis, or by extrarenal factors such as dehydration, hypercalcaemia, hyperuricaemia, and concomitant use of contrast media or nephrotoxic drugs such as non-steroidal anti-inflammatory drugs. Bence Jones MM is more frequently associated with RF than other MM isotypes except immunoglobulin D MM, in this rare condition renal insufficiency is observed in 100% of cases.[2] In the case of RF in a patient with monoclonal gammopathy of unknown significance (MGUS), differential diagnosis between all the conditions mentioned above must be carried out. In the presence of albuminuria or non-selective proteinuria, subcutaneous abdominal fat aspiration should be performed in order to confirm the presence of amyloidosis; if this is excluded the patient should undergo renal biopsy in order to diagnose the presence of LCDD or non-MGUS related nephropathies. In the case of MM secreting only light chains (Bence Jones), or in oligosecretory MM, serum free light chains should be evaluated, as a greater correspondence to tumour load as compared to Bence Jones proteinuria has been demonstrated.[7]

ANTIMYELOMA THERAPY (AMT)

AMT is of crucial relevance for MM patients with RF, since a prompt reduction of tumour burden combined with adequate supportive care can lead to improvement of renal function in a significant percentage of cases,[8,9] although reversal of RF can potentially be observed even after the completion of an agitated saline contrast test (ASCT).[10] To achieve this important goal, rapidly effective non-nephrotoxic induction regimens should be selected. In the majority of the studies performed in the past, induction therapy consisted either of vincristine-doxorubicin-dexamethasone, eventually modified by replacing doxorubicin with another anthracycline, or of high-dose dexamethasone.[8,9,11,12] In recent years, both immunomodulatory drugs and bortezomib have been routinely used in various combinations in induction therapy prior to ASCT and have subsequently been employed as induction regimens in patients with MM and RF. Thalidomide-dexamethasone is active in relapsed/refractory MM patients with RF[13] with an acceptable toxicity profile. Pharmacokinetic studies have demonstrated that the kidney is apparently not involved in thalidomide metabolism, as the drug undergoes spontaneous hydrolysis in plasma, and only a small amount of thalidomide is excreted unchanged in the urine.[14] Furthermore, no correlation between thalidomide clearance and renal function has been observed.[15] Although two small studies have shown an unexplained incidence of hyperkalaemia in MM patients with RF treated with thalidomide,[16,17] the data were not confirmed in a larger case series[13] or in patients with newly diagnosed MM.[18]

Major concerns arose regarding the use of lenalidomide in patients with RF. Although direct damage to the kidney has not been demonstrated in MM, worsening of renal function has been described in patients with amyloid light-chain amyloidosis.[19] Lenalidomide is excreted by the kidney, so that its clearance decreases in patients with RF, with a consequent 6-12 hour increase in plasma half-life and area under the curve.[20] Retrospective evaluation of relapsed refractory MM patients with some degree of renal impairment treated with full dose lenalidomide in the context of clinical trials including mainly patients with normal renal function[21,22] confirmed the efficacy of the drug but also the occurrence of haematological toxicity, mainly thrombocytopaenia, which can potentially lead to more frequent treatment discontinuations. Later reports[23,24] that were mainly focused on patients with RF showed that a proper dose reduction can limit haematological toxicity. These data were confirmed also by the FIRST clinical trial[25] aimed at evaluating the efficacy of long-term lenalidomide-dexamethasone in MM patients ineligible for transplant.

Treatment of patients with MM and RF with bortezomib-containing regimens has shown interesting results in terms of both efficacy and improvement of renal function.[26,27] Sub-analyses of the data of a large randomised trial conducted in newly diagnosed MM patients[28,29] have shown that response rate and toxicity in the bortezomib-melphalan-prednisone arm (VMP) was not affected by RF; moreover, as compared to the melphalan-prednisone arm, treatment with VMP resulted in a higher percentage of patients achieving a normal renal function in a shorter period of time. Several studies[29-31] pointed out that reversal of RF after bortezomib-containing regimens is related to the response to therapy. Furthermore, these regimens warrant rapid responses, and this could be crucial in increasing the chances of reverting RF. Bortezomib seems to act specifically on the pathogenesis of myeloma-related RF, as inhibition of nuclear factor kappa-B could potentially prevent cytokine-mediated inflammatory damage to the interstitium that is observed in myeloma kidney[5,32] or mesangial alterations that can be detected in

light-chain deposition disease.[6,33] A recent report aimed at retrospectively comparing the role of novel agents in reverting RF in newly diagnosed MM confirmed a greater efficacy of bortezomib-containing regimens.[34]

Other novel drugs have shown efficacy in MM patients with RF in the relapsed/refractory setting, and will probably be proposed as induction therapy at disease onset in the near future. Among them, carfilzomib, a novel proteasome inhibitor, was initially demonstrated to be effective even in dialysis-dependent patients without necessity of dose reductions;[35] recent results of a multicentre European trial,[36] however, seem to suggest that the drug should be administered with caution in patients with renal insufficiency. Bendamustine, a unique bifunctional alkylating agent, has been used both in combination with steroids and with bortezomib in newly diagnosed or relapsed-refractory MM; interesting results were also reported in patients with RF so that its use could be proposed in the context of induction therapy for MM patients with RF.[37]

Renal insufficiency has long been considered an exclusion criterion for major trials aimed at evaluating the efficacy of ASCT in MM.[38,39] Antineoplastic drugs have a narrow therapeutic index so that major toxic events can occur in patients with reduced excretory organ function due to an increase in dose intensity that is frequently difficult to predict. An early animal study[40] has reported, in the case of RF, an increased toxicity of melphalan related to a longer terminal half-life of the drug. Conversely, more recent reports have pointed out that MM patients with RF can be treated with high-dose melphalan showing a spectrum of toxicity similar to that reported in patients with normal renal function.[41,42] Other reports have demonstrated the feasibility of autologous haematopoietic stem cell (SC) transplant in a small series of patients with MM and chronic RF using different conditioning regimens,[11,12,43-45] but data concerning toxicity were more controversial. These initial studies were important as they allowed for depiction of the problem of SC priming and transplant conditioning. In fact, both SC priming and conditioning regimens should include drugs that do not undergo renal excretion, for this purpose cyclophosphamide, busulfan, and melphalan have been used in the different studies. Cyclophosphamide, both as a parent compound and as an alkylating moiety, is excreted through the kidney in percentages ranging from 1-30%,[46] and this seems to be independent from renal function; however, when used for SC priming, a dose reduction could be reasonable in patients with RF.

SC mobilisation performed using granulocyte-colony stimulating factor (G-CSF) alone has been proposed by several groups in order to avoid cyclophosphamide-related toxicity;[11-13] an alternative strategy could also be represented by plerixafor, which has been successfully used as an adjunct to G-CSF for SC priming in a small series of patients with MM and RF.[47] Busulfan has been employed in preparative regimens for SC transplant in MM patients;[38,39] only negligible amounts of the compound are eliminated through the kidney, as the liver is the major site of drug metabolism. In the case of melphalan, initial data were more controversial, as several studies suggested that the pharmacokinetic parameters are related to creatinine clearance,[48,49] while other authors demonstrated that the main route of melphalan elimination is spontaneous degradation;[50] most reports, however, agree on the wide interindividual differences in drug metabolism.[41,50] Despite these contrasting findings it is well known that, at present, high-dose melphalan is the most effective preparative regimen for ASCT in MM,[51] and it is thus correct to include it in high-dose programmes for patients in RF; most authors agree on the fact that a dose reduction (80-140 mg/m^2) should be made in order to avoid excessive mucosal toxicity. Several recent reports have addressed the issue of the combination of bortezomib and busulfan as a preparative regimen for ASCT in MM;[52,53] these data, however, should be confirmed in large clinical trials.

SUPPORTIVE THERAPY

Nephrologic consultation is mandatory when taking care of MM patients with RF. Dehydration and hypercalcaemia must be carefully avoided and infections must be promptly treated. Nephrotoxic drugs should not be administered; in particular, non-steroidal anti-inflammatory drugs should be replaced with morphine derivatives for pain control. All the pharmacokinetic properties of each drug must be evaluated prior to administration in order to perform dose reduction with respect to creatinine clearance. For dialysis-dependent patients, the timing of administration of each drug must be evaluated prior to the dialytic procedure in order to avoid under or over-exposition of the patient to the drug. Bisphosphonates can be used in patients with RF, provided it is accompanied by an

appropriate dose reduction schedule as per the manufacturer's recommendations.[54] As the management of the myeloma kidney relies on the rapid removal of nephrotoxic light chains from the serum, plasma exchange was proposed several years ago as a possible method to achieve this goal. Initial studies showed a beneficial effect of plasma exchange in improving renal function;[55] this was not confirmed by later trials.[56] Recently, mechanical removal of serum light chains by high cut-off haemodialysis has been evaluated, and encouraging results were obtained when this method was used in combination with dexamethasone ± bortezomib-based regimens.[57]

FINAL REMARKS

Although different mechanisms can be responsible for or contribute to the occurrence of RF in MM patients, prompt reduction of tumour load can lead to an improvement in renal function in a significant percentage of patients, and in general, an appropriate antimyeloma therapy can result in prolonged patient survival.

Acknowledgements

This work is supported in part by the Italian Association against Leukemia – Rimini Section (RiminiAIL).

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