

# Supportive care in multiple myeloma

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## SUMMARY

Patients with multiple myeloma (MM) not only require treatments directed at their disease activity, but also need a wide range of supportive measures. In this review article supportive measures with respect to anaemia, infections, thromboembolic risk, bone disease, peripheral neuropathy and pain are discussed.

## INTRODUCTION

Patients with multiple myeloma (MM) not only require treatments directed at their disease activity but also a wide range of supportive measures to optimise their quality of life and prognosis at all stages of their disease. Many challenging aspects of myeloma management can be addressed and delivered by the treating haematologists, but collaboration with other relevant specialists may be required. Levels of unmet supportive care needs have been identified in a quarter of patients with myeloma.<sup>1</sup>

## ANAEMIA

About 75% of MM patients present with anaemia at diagnosis.<sup>2</sup> This is the result of several MM factors, including bone marrow infiltration, chronic inflammation, erythroblast apoptosis induced by myeloma cells and even iron deficiency.<sup>3</sup> In addition to this, toxic effects of the treatments (systemic anti-myeloma therapy or radiotherapy) can also contribute to this anomaly.<sup>3</sup>

For symptomatic patients requiring rapid improvement, red blood cell transfusions can help, but erythropoiesis-stimulating agents (ESAs) can also be used. ESAs reduce transfusion requirements and improve the quality of life,<sup>4</sup> but there is also evidence that ESAs may increase mortality during their administration and thus decrease the overall survival (OS) of patients.<sup>5</sup> Especially, the rate of thromboembolic events is increased. As such, treatment with ESAs may be initiated (at the dose of 40.000U per week) in patients with persistent symptomatic anaemia, but haemoglobin levels should not increase more than 12g/dl.<sup>6</sup>

## INFECTIONS

Patients with Monoclonal Gammopathy of Undetermined Significance (MGUS) have double the risk of infection com-

pared to the general population.<sup>7</sup> This infection risk is much higher in MM patients. Indeed, the risk of viral infection is increased tenfold, whereas the risk for bacterial infections is increased by a factor seven.<sup>8</sup> Not only the disease but also the patient (age, comorbidities) and the treatment factors contribute to significant deficits in all major arms of the immune system (hypogammaglobulinemia, numerical and functional deficits of B, T and NK cells), which increase the risk of infection even further.<sup>9</sup>

Based on a recent post-hoc analysis of the FIRST trial, which confirmed the increased risk of infection, showed that 65.4% of the newly diagnosed myeloma patients suffered from a treatment-emergent infection (TEI) during the first 18 months, reaching grade 3 or more severity in 21.1%.<sup>10</sup> Moreover, more than half of the patients who experienced a TEI, had their first episode during the first 4 months, resulting in an increased risk of death.<sup>10</sup> Indeed, infectious complications account for more than 1 in 5 deaths in the MM population.<sup>8</sup> A predictive model assessing the early  $\geq$ grade 3 infection risk is now available, based on 4 variables (B2 microglobulin, Haemoglobin, Eastern Cooperative Oncology Group status and the Lactate Dehydrogenase [LDH] levels). This model can help clinicians to guide the monitoring of the patients and adopt the best prevention strategy.<sup>10</sup>

## VIRAL INFECTIONS

The most « at-risk » periods for virus reactivation in myeloma patients is the period during and after an Autologous Stem Cell Transplantation (ASCT). This is related to the fact that recovery of CD4 and CD8 lymphocytes is critical in the control and prevention of viral infections and this is often delayed beyond neutrophil recover.<sup>11</sup> The maintenance and the disease progression period are also risky periods (*Table 1*). In addition, high-dose corticosteroid therapy (particularly

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**TABLE 1.** Risk factors for thromboembolic events in MM patients (Adapted from *Palumbo et al. Leukemia, 2008*).<sup>30</sup>

<b>Individual risk factors:</b>	0-1 risk factor: Aspirin ≥ 2 risk factors: LMWH
<ul style="list-style-type: none"> <li>• Obesity</li> <li>• Previous VTE</li> <li>• Central venous catheter or Pacemaker</li> <li>• Comorbidities (cardiac disease, diabetes, chronic renal disease, acute infection, immobilization)</li> <li>• Surgery (General surgery, any anesthesia, Trauma)</li> <li>• Medications (Erythropoietin)</li> <li>• Inherited Thrombophilia</li> </ul>	
<b>Myeloma-related risks</b>	Any risk factor: LMWH
<ul style="list-style-type: none"> <li>• Diagnosis</li> <li>• Hyperviscosity</li> </ul>	
<b>Therapy-related risks</b>	
<ul style="list-style-type: none"> <li>• High dose of dexamethasone (≥480 mg monthly)</li> <li>• Doxorubicin</li> <li>• Multiagent chemotherapy</li> </ul>	

above 3,200 mg of prednisolone over 2 months) confer an increased risk of viral infection as they induce lymphopenia.<sup>11</sup> Reactivation of Herpes Simplex Virus (HSV) was observed in up to 80% of patients with a haematological malignancy prior to use of antiviral prophylaxis.<sup>12</sup> The risk of Varicella Zoster Virus (VZV) reactivation is as high as 30%. It is particularly associated with bortezomib treatment and occurs mostly in the late period following ASCT.<sup>13</sup> Antiviral prophylaxis is associated with a risk reduction of HSV reactivation of 80-90% and should be prolonged for at least 6 to 12 months following ASCT to effectively protect against VZV reactivation.<sup>14,15</sup> Both Acyclovir (400 mg b.d., 800 mg daily) and Valacyclovir (500 mg daily) can be used.<sup>15</sup> Vaccination against VZV is recommended at least 2 years after ASCT as it is a live-attenuated vaccine.<sup>16</sup>

HBV reactivation is a well-recognized complication of immunosuppressive treatments for haematological malignancy, in particular in MM, with an average rate of 5% after ASCT.<sup>17</sup> HBV reactivation is also particularly associated with bortezomib.<sup>18</sup> The patients with a resolved infection and detectable antibodies (HbsAb) need to be closely monitored, as the HbsAb level could decline after ASCT.<sup>17</sup> Notwithstanding the fact that no cases of hepatitis B reactivation were reported with anti-CD38 therapies so far, the theoretical risk could be at least similar to what is seen with Rituximab.<sup>19</sup> Moreover, the suppressive effect on regulatory T-cells may result in an exaggerated T-cell-mediated immunological response and

hepatic attack upon recovery from immunosuppression.<sup>19</sup> In case of undetectable HbsAb levels or chronic infection, the patients must receive prophylaxis for at least 6 to 12 months after their ASCT.<sup>11</sup> An early vaccination could be proposed to reduce the prophylaxis duration.

Viral respiratory tract infections (RTIs) are common and are associated with significant morbidity, mortality and prolonged hospital stays in patients with MM.<sup>11</sup> Detected respiratory viruses include influenza, picornavirus or rhinoviruses, respiratory syncytial viruses (RSV), parainfluenza, adenovirus and human metapneumovirus, with winter and spring being the peak risk seasons.<sup>11</sup> Influenza is associated with the greatest morbidity and mortality (up to 33% during the H1N1 epidemic) in patients with MM and needs to be treated with a neuraminidase inhibitor (Oseltamivir) over a period of ten days.<sup>20</sup> In seasonal period, a MM patient with flu-like symptoms should be treated empirically with Oseltamivir until laboratory results are available. Even if myeloma patients have lower levels of antibodies after vaccination, seasonal influenza vaccination has been associated with a reduced upper RTIs incidence and a lower amount of hospitalizations.<sup>21</sup> A second vaccination against Influenza showed a doubling in the seroprotection rate (15 to 31%).<sup>22</sup> All MM patients, their family and caregivers should be vaccinated for influenza. There is a lack of data to recommend treatment for Parainfluenza or RSV infection for myeloma patients.<sup>23</sup>

**TABLE 1.** Recommendations for peripheral neuropathy management in MM patients treated with thalidomide, or bortezomib.<sup>38</sup>

	Grade 1	Grade 2	Grade 3	Grade 4
Dose modification for thalidomide*	Reduce thalidomide dose by 50%	Discontinue thalidomide. If the neuropathy resolves to grade 1 or better, treatment may be restarted at 50% dose reduction, if the benefit-to-risk ratio is favourable	Discontinue thalidomide	Discontinue thalidomide
Dose modification for bortezomib*	<ul style="list-style-type: none"> <li>If the patient is on a biweekly schedule<sup>†</sup>: reduce current bortezomib dose by one level<sup>‡</sup> or prolong dosing interval to once weekly</li> <li>If the patient is already on a weekly schedule: reduce current bortezomib dose by one level<sup>‡</sup></li> </ul>	<ul style="list-style-type: none"> <li>If the patient is on a biweekly schedule: reduce current bortezomib dose by one level<sup>‡</sup> or prolong dosing interval to once weekly</li> <li>If the patient is already on a weekly schedule: reduce current bortezomib dose by one level<sup>‡</sup> or consider temporary discontinuation of bortezomib. If the neuropathy resolves to grade 1 or better, once weekly treatment with reduced bortezomib dose may be restarted if the benefit-to-risk ratio is favourable</li> </ul>	Discontinue bortezomib	Discontinue bortezomib

Summary of Product Characteristics (SPC) guidelines were modified according to expert opinion and clinical practice in reference centres. \*If sensory peripheral neuropathy is associated with neuropathic pain, Common Toxicity Criteria (CTC) score is upgraded one severity level. †Patients ≥75 years may be immediately started on a once weekly regimen when initiating bortezomib treatment. ‡Bortezomib dose reduction: standard dose—1.3 mg/m<sup>2</sup>; dose reduced by one level—1.0 mg/m<sup>2</sup>; dose reduced by two levels—0.7 mg/m<sup>2</sup>.

**BACTERIAL INFECTIONS**

The risk for bacterial infections is particularly high in patients with active disease after the start of initial therapy, in patients with a history of frequent infections and in elderly, frail patients.<sup>23</sup>

Streptococcus Pneumoniae, Haemophilus Influenzae and Gram negative bacilli are the most frequent causes of bacterial infections in MM patients.<sup>24</sup> Prophylactic antibiotics may have a role in reducing infection rates but can potentially lead to increased Clostridium Difficile infection rates and antibiotic resistance. A British team recently showed that Levofloxacin prophylaxis during the first 12 weeks of therapy resulted in a reduced risk of infections and death without any resistant population emergence.<sup>25</sup> Trimetoprim-Sulfamethoxazole is an alternative as antibiotic prophylaxis or can be prescribed with Levofloxacin, further reducing the risk of infection.<sup>25</sup> The predictive model of the French team could be of interest to guide the clinician to adopt the best prevention strategy.<sup>10</sup> Vaccination against Pneumococcus and Haemophilus Influenzae has to be proposed as soon as possible, even if efficacy is not guaranteed.<sup>26</sup>

Recommendations for vaccination after ASCT have been published in different guidelines and can be consulted.<sup>16</sup> They were adapted from recommendations after ASCT since there are currently no trial data that confirm the interest of revaccination programs after ASCT. However, a recent American study showed the safety and efficacy of revaccination after ASCT during lenalidomide maintenance therapy.<sup>27</sup>

Immunoglobulin replacement should be envisaged for selected patients with significant hypogammaglobulinemia, recurrent infections, despite vaccinations and prophylaxis.<sup>3</sup> The therapy should be rechallenged every 6 months and subcutaneous administration could be more convenient for patients.

**THROMBOEMBOLIC RISK**

Plasma cell disorders and MM in particular, have a well-known association with thromboembolic complications.<sup>28,29</sup> However, compared to MM, these implications are more common in patients with lung or pancreatic cancer. Nevertheless, since the introduction of immunomodulatory agents (IMiDs), the thrombotic risk increased significantly, especially when they are combined with corticosteroid, carfilzomib, erythropoietin or adriamycin.<sup>30-32</sup> Low-molecular weight heparin (LMWH) and aspirin have been shown to be effective as thromboprophylaxis but have to be chosen on a case by case basis, taking into account risk factors for the individual patients (Table 1).<sup>6</sup> A fixed low-dose of warfarin is not recommended.<sup>6</sup> When warfarin is used in patients with a renal clearance under 30 ml/min for example, an INR level between 2 and 3 is recommended. Thrombotic prophylaxis in the absence of IMiD-based treatment must be continued for 4 to 6 months or as long as patients are considered to be high risk.<sup>6</sup> During IMiD treatment, the prophylaxis must be continued for as long as the treatment is prescribed.<sup>6</sup> In case of thromboembolic complication, the antimyeloma

treatment should be temporarily discontinued and restarted when the event has been stabilized, depending upon a benefit-risk assessment.<sup>32</sup> Notwithstanding the fact that new oral anticoagulants have been shown to be useful and safe in cancer patients<sup>33</sup>, these drugs have not been sufficiently studied in myeloma patients.

## BONE DISEASE

Up to 80% of MM patients present with bone lesions, which are mostly responsible for pain because of osteolysis, hypercalcemia, fracture and/or spinal compression.<sup>34</sup> The risk of fracture compression must be evaluated and surgical treatment or radiotherapy should be proposed if appropriate. Low-dose radiotherapy could also be used in case of painful lesions not responding to myeloma therapy.

Zoledronate is effective in reducing skeletal related events (SRE) and was shown to be associated with an increase in the OS.<sup>35</sup> The treatment should be started with or without evidence of bone lytic lesions for symptomatic myeloma patients and maintained until 2 years in patients with a complete or very good partial response and should be restarted at relapse.<sup>35</sup> As hypocalcaemia is a frequent adverse event with bisphosphonate treatment, all patients should receive calcium and vitamin D3 supplementation (600 mg calcium per day and 400 IU vitamin D3 per day).<sup>3</sup>

Denosumab is an antibody targeting RANKL which was compared to zoledronate in a phase III prospective trial, showing promising results with a lower rate of SRE and a prolonged progression free survival (PFS) (currently no evidence for an OS benefit).<sup>36</sup> While bisphosphonates have to be adapted to the renal clearance and should be avoided below 30 ml/minute, denosumab has a favourable kidney safety profile.<sup>36</sup>

Bisphosphonates and denosumab are associated with a similar rate of osteonecrosis of the jaw (ONJ) which is the most severe potential complication of bone disease treatment.<sup>36</sup> Because of that risk, a dental evaluation should be performed and any teeth with poor prognosis must be extracted before starting the treatment.<sup>26</sup> Moreover, if dental procedure is envisaged, the bisphosphonates should be stopped 90 days before and after invasive interventions.<sup>35</sup> Finally, if ONJ occurs, bisphosphonates must be suspended until recovery of the lesions.<sup>35</sup>

## PERIPHERAL NEUROPATHY

Peripheral neuropathy can occur when using neurotoxic antimyeloma drugs, with an incidence rising to 19% in newly diagnosed patients.<sup>37</sup> The occurrence of peripheral neuropathy may be explained by nerve or nerve root compression by bone lesions, fractures, plasmocytomas, amyloid

deposition or immune-mediated neurological damage by anti-myelin-associated glycoprotein (MAG) in case of IgM myeloma.<sup>38</sup> Rarely, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein and Skin abnormalities) syndrome can be observed. Of course, many patients present comorbidities such as diabetes mellitus, vitamin B12 deficiency or chronic renal failure which can also contribute to neuropathy and have to be assessed.

Several anti-MM drugs are known to induce neuropathy. Especially with thalidomide and bortezomib peripheral neuropathy forms a major aspect of MM management as up to 75% of the patients may experience that complication.<sup>37</sup> Peripheral neuropathy is usually symmetric and distal. Whereas thalidomide-induced neuropathy seems to be a cumulative permanent toxicity, bortezomib-induced neuropathy appears within the first five cycles and is rarely observed beyond.<sup>26</sup> Other antimyeloma drugs, including other proteasome inhibitors such as ixazomib and carfilzomib, are much less frequently responsible of neurotoxicity.<sup>39</sup>

The management of polyneuropathy in myeloma patients includes control of comorbidities and careful monitoring of patients with promptly dose and schedule modifications as complete reversibility is not the rule (*Table 2*).<sup>38</sup>

Neuropathic pain is often poorly responsive to standard analgesic regimes. All patients should be considered for multimodal analgesic treatment including an iopiod, ion channel blocker and serotonin–noradrenaline reuptake inhibitors SNRI26.

## ANTALGIC CONSIDERATIONS

Up to 67% of all MM patients report pain at diagnosis, although this may have been present for several months before and is mostly due to the disease process itself (predominantly from destructive bone disease, but occasionally from plasmacytomas directly affecting neural tissues).<sup>40</sup> Later, the pain should be assessed regularly at all stages of the disease, as the disease could progress or neuropathic pain could emerge from treatments.

Pain management in myeloma patients should be managed using a multimodal approach including evidence-based pharmacological therapies alongside non-drugs methods, such as radiotherapy, bisphosphonates and when appropriate interventional and psychological techniques.<sup>26</sup>

## CONCLUSIONS

Complications related to disease and/or anti-myeloma drugs contribute to increased morbidity and mortality of myeloma patients and consequently, the appropriate management of these complications is crucial for both patient quality of life and survival.

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