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Infections in Patients with Multiple Myeloma in the Era of Novel Agents and Stem Cell Therapies

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Abstract

Multiple myeloma is a common hematologic malignancy that is associated with reduced cellular as well as humoral immunity ultimately causing various infectious complications. The recent advances in the management of myeloma have led not only to prolonged survival but also to shifts in the incidence as well as the spectrum of infections encountered. This book chapter will be an updated review on the infectious complications in patients with multiple myeloma in the era of novel agents, stem cell therapies, and monoclonal antibodies. It will cover causes of immunosuppression, timing, and types as well as management of the various infections reported with various therapeutic modalities that are currently utilized in the management of myeloma patients.

Keywords: multiple myeloma, hematopoietic stem cell transplantation, novel therapies, monoclonal antibodies, infectious complications

1. Introduction to multiple myeloma

Multiple myeloma (MM), the second most common hematologic malignancy (HM), is a plasma cell neoplasm characterized by production of a monoclonal immunoglobulin that ultimately leads to several complications including anemia, renal dysfunction, bone disease, immunodeficiency, and various infections [1–5].

Over the past two decades, the outcomes of patients with MM have improved substantially due to the following: (1) the widespread utilization of high-dose (HD) chemotherapy followed by autologous stem cell transplantation (HSCT), (2) the introduction of several novel therapies and monoclonal antibodies, (3) the evolution of advanced technology that facilitated

understanding of the biology of the disease and helped in the diagnosis, risk stratification and follow-up of patients, (4) the evolution of new therapeutic strategies such as consolidation and maintenance treatments as well as total and continuous therapy, and (5) improvements in supportive care and antimicrobial therapies [1, 3–12]. Currently, the following novel therapies are available for patients with MM: (1) immunomodulatory agents such as thalidomide, lenalidomide, and pomalidomide; (2) proteasome inhibitors such as bortezomib, carfilzomib, and ixazomib; (3) monoclonal antibodies such as daratumumab and elotuzumab; and (4) histone deacetylase inhibitors such as panobinostat and vorinostat [1, 3, 4, 6, 9, 11]. Unfortunately, despite the remarkable progress achieved in the diagnostics and therapeutics and the plethora of therapeutic modalities, MM remains incurable [1, 4, 5, 7, 11]. The numerous treatment modalities that are available for patients with MM have shown their effectiveness, but they have their own adverse effects including bone marrow (BM) suppression and infectious complications that may be life-threatening [13–15].

The standard induction therapy in patients with newly diagnosed MM is the triplet regimen of bortezomib, lenalidomide, and dexamethasone [4, 16]. Autologous HSCT is the standard of care for transplant-eligible patients either upfront or at relapse [4, 10, 16]. Studies have shown that post-HSCT consolidation and maintenance treatments can further improve the outcome of patients with MM [10, 16, 17]. Monitoring disease response at various stages of treatment is essential and studies have shown that monitoring of minimal residual disease is associated with longer progression-free survival (PFS) and overall survival (OS) [18, 19].

2. Early mortality in MM

In patients with MM, several studies have shown that risk factors for early mortality include male gender, age >75 years, poor performance status, presence of comorbid medical conditions such as renal failure and hypertension, low platelet count, low serum albumin level, elevated serum levels of calcium and lactic dehydrogenase, low body mass index, presentation with primary plasma cell leukemia, advanced stage of disease at presentation, and infectious complications [20–25]. Two major studies that included 451 and 299 patients with MM showed that 65 and 45% of early deaths were attributable to infections [20, 21].

Despite the use of prophylactic antimicrobials, infections remain a leading cause of mortality and morbidity in patients with MM [26]. In patients with MM, approximately 45% of deaths occurring within 60 days of diagnosis are caused by various infections, predominantly pneumonia and sepsis [20, 26].

3. Reduced immunity in patients with MM

In patients with MM, causes of immunosuppression include: (1) the immunosuppressive effects of the disease or the direct immunosuppression caused by tumor cells, particularly in advanced stage or refractory disease, (2) therapeutic interventions to control MM, such

as corticosteroids, cytotoxic chemotherapy, and the novel therapies such as thalidomide, lenalidomide and bortezomib reduce the immunity further by different mechanisms including neutropenia and mucositis, (3) old age and its immunosuppressive effects, (4) impairment of the capacity of the immune system to mount effective responses or challenges to infection or vaccination, (5) further suppression of the immune system by the administration of HD chemotherapy (melphalan) followed by autologous HSCT, and (6) presence of comorbid medical conditions [14, 27–31].

In patients with MM, the risks of infectious complications and disease progression are enhanced by following forms of dysfunction of the immune system: reduced antigen presentation, high cytokine levels and increased suppressive cells such as CD8 Tregs [32, 33]. Both cellular and humoral components of the immune system are suppressed in patients with MM [28, 34, 35]. Hypogammaglobulinemia or immunoparesis is associated with unfavorable prognosis in newly diagnosed patients with MM [34]. In a Danish study that included 2558 patients with MM, immunoparesis at diagnosis was not confirmed to be an independent prognostic factor for OS, but quantitative immunoparesis was found to be associated with a shorter PFS [34].

Patients with MM have increased susceptibility to infections due to the profound B-cell dysfunction or the depression in humoral immunity [36]. These patients are 10 times more prone to infections than patients with Waldenström's macroglobulinemia and 5 times more prone to infections than individuals with monoclonal gammopathy of undetermined significance [36]. MM patients have increased susceptibility to severe pneumococcal infections, and they respond poorly to pneumococcal vaccination [35, 36].

The highest risk of infection occurs within the first month after the diagnosis of MM, particularly in patients with renal failure [14, 36]. The infections that are encountered in patients with MM include urinary tract infection, pneumonia, septicemia, fungal infections, and viral infections such as *influenza virus* and *varicella zoster virus* (VZV) infections [14, 36]. However, bacterial infections predominate particularly those caused by: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* [14, 36]. The advent of autologous HSCT and the introduction of novel therapies in patients with MM have led to a shift in the spectrum of infections with increased incidence of viral and fungal infections [13, 36]. In a recent study, mitogen stimulation of cytokine release profiling for interleukin (IL)-5, IL-13, Th1, and Th2 was used to predict the risk of infections in patients with MM during maintenance therapy, but only IL-5 response was found to be predictive of infection on multivariate analysis [37].

4. Infectious complications in MM

The risk factors for infectious complications in patients with MM can be divided into patient-related factors, disease-related factors, and treatment-related factors as shown in **Table 1** [13, 14, 38–45]. However, the infections encountered in patients with MM include: (1) bacterial infections, predominantly involving respiratory and urinary tract, caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Escherichia coli*,

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- 1 Patient-related factors:
 - Female gender
 - Old age
 - Poor performance status and poor general condition
 - Presence of comorbid medical conditions
 - Hyperglycemia and uncontrolled diabetes mellitus
 - Renal dysfunction/failure
 - Increased serum ferritin level
 - 2 Disease-related factors:
 - Active disease
 - Advanced disease; stage III according to international staging system
 - Relapsed and refractory disease
 - Immune dysfunction:
 - Suppression of cellular and humoral immunity including hypogammaglobulinemia
 - Low CD4+ cell count
 - Dysfunction of natural killer cells
 - 3 Treatment-related factors:
 - High-dose chemotherapy: melphalan, cyclophosphamide
 - Novel therapies:
 - Immunomodulatory agents: thalidomide, lenalidomide, pomalidomide
 - Proteasome inhibitors: bortezomib, carfilzomib
 - Monoclonal antibodies: daratumumab, elotuzumab
 - Neutropenia and lymphopenia
 - Mucositis
 - Presence of central venous catheters
 - Corticosteroids: high dose or prolonged duration of therapy
 - Autologous hematopoietic stem cell transplantation
 - Allogeneic hematopoietic stem cell transplantation
-

Table 1. Risk factors for infectious complications in multiple myeloma.

Pseudomonas aeruginosa, and *Enterobacteriaceae*; (2) viral infections caused by *herpes simplex virus* (HSV), VZV, and *cytomegalovirus* (CMV); (3) fungal infections caused by *Candida* species and *Aspergillus* species; and (4) *Pneumocystis jiroveci pneumonia* (PJP) [14, 43, 44, 46–48].

The sites of infections in patients with MM include: (1) upper and lower respiratory tract with otitis, sinusitis, and pneumonia; (2) urinary tract; (3) brain with meningitis; (4) skin with VZV infection; (5) heart with endocarditis; (6) bone and joint infections; and (7) bacteremia [14, 43, 47–51]. Bacterial infections are the most frequent etiological agents. However, invasive fungal infections (IFIs) caused by molds such as *Aspergillus* species and *Fusarium* species have been

increasingly reported [50]. The incidence of infections in MM patients has bimodal peaks: bacterial infections dominate 4–6 and 70–72 months after the diagnosis, while viral infections dominate 7–9 and 52–54 months after the diagnosis of MM [13].

In patients with MM having active disease, the following types of infections are common: bacteremia, pneumonia, sinusitis, otitis, meningitis, and IFIs [14, 50]. In active disease, Gram-negative bacterial (GNB) particularly encapsulated bacteria and fungi are common causes of infectious complications [14].

Patients with MM are at high risk of developing infections as infections in these patients have been reported to be 10 times more than that in healthy individuals. Also, the new novel therapies make patients with MM at higher risk of infectious complications than myeloma patients treated with cytotoxic chemotherapy [52, 53]. Even, prior to the diagnosis of MM, there is an underlying immune disturbance, which may predispose to various infections such as VZV, sinusitis, cystitis, and bronchitis that may be encountered during the disease evolution [54].

4.1. Neutropenia and febrile neutropenia

Neutropenia is a hematologic adverse event of medications characterized by an absolute neutrophil count (ANC) lower than 1500 cells/mL [55]. Neutropenia is a well-recognized complication of cytotoxic chemotherapy. Also, it develops in patients with MM receiving novel therapies or undergoing HSCT [55–57]. Prolonged and severe neutropenia increases the risk of febrile neutropenia (FN) and serious infections that may be life-threatening [57]. Persistent neutropenia causes not only delay in administration of chemotherapy or novel therapies, but also dose reductions in the next cycle of chemotherapy. Nevertheless, once the ANC reaches ≥ 1000 cells/mL, scheduled treatment may be resumed [55].

FN is a serious effect of chemotherapy, and it has the following adverse consequences: delay in administration of scheduled therapies, costs of hospitalization, and increased risk of morbidity and mortality in immunocompromised individuals [58]. Several studies have shown that the following risk factors for neutropenia and FN in patients with MM: (1) heavily pretreated disease and relapsed and refractory (R/R)-MM, (2) elderly patients with comorbid medical conditions, and (3) use of the following drugs particularly in combination with other agents such as lenalidomide, bendamustine, and the combination of bendamustine, bortezomib and dexamethasone [55, 58–60].

Management of patients with prolonged neutropenia and FN includes: (1) thorough physical evaluation for the site or source of infection, (2) taking enough cultures and septic screens, (3) administration of prophylactic and empirical antimicrobials, and (4) pre-emptive or prophylactic administration of granulocyte-colony stimulating factor (G-CSF) in patients who are expected to have prolonged or severe neutropenia [58, 59]. However, the choice of empirical antibiotic therapy in patients with HMs having FN depends on the risk stratification of the individual patient [61, 62]. In low-risk (LR) patients with FN, duration of neutropenia is <1 week and there are no comorbid medical conditions; while in high-risk (HR) patients with FN, the duration of neutropenia is >1 week and there are comorbid medical conditions [61, 62]. In case the patient is stratified as LR, oral antibiotics such as ciprofloxacin or levofloxacin are sufficient,

while if the patient belongs to the HR group, intravenous (IV) antibiotics may need to be administered. IV ceftazidime, piperacillin-tazobactam, or a carbapenem can be given as single agents or in combination with either vancomycin or an aminoglycoside [62–65]. However, the fact that there is a recent increase in the incidence of Gram-positive bacteria (GPB) cultured from neutropenic patients with MM has to be taken into consideration [56]. Empirical antifungal therapy can be used in patients with persistent fever despite the use of broad-spectrum antibiotics [61, 62, 66]. In addition, recombinant G-CSF is commonly used to reduce the incidence, duration, and severity of FN [57]. Studies have shown that the use of G-CSF as primary prophylaxis improves quality of life, is cost-effective as it reduces the: days of hospitalization, infectious complications, and incidence of chemotherapy interruptions [58, 59].

4.2. Bacterial and bloodstream infections in MM

Bloodstream infections (BSIs) are important causes of morbidity and mortality in patients with HMs, and they contribute to delayed administration of planned chemotherapy, increased length of hospitalization, and increased health care costs [29]. The risk factors for bacteremia or bacterial BSIs in patients with HMs include the primary disease, neutropenia induced by intensive chemotherapy, and mucositis due to the cytotoxic effects of chemotherapy on the cells of gastrointestinal tract [67, 68]. In recent years, there has been a shift in prevalence of the causative organisms for bacterial BSIs in patients with HMs from GPB to GNB. Also, there has been increasing frequency of antimicrobial resistance in GNB [69]. Therefore, in patients with HMs having FN, BSIs caused by GNB should initially be treated with non-carbapenem-based anti-pseudomonal therapy taking into consideration the antimicrobial stewardship [67].

In patients with MM undergoing autologous HSCT, mucositis and chemotherapy-induced neutropenia are risk factors for the development of bacteremia [67, 68]. In two retrospective studies on BSIs that included 421 patients with MM, the following results were obtained: (1) the independent risk factors for BSIs were: advanced stage of disease, poor performance status, and receipt of autologous HSCT; (2) GPB, mainly *Streptococcus pneumoniae*, were responsible for the majority of BSIs during the induction phase of treatment while GNB, mainly *Escherichia coli*, were responsible for the majority of BSIs in progressive disease; (3) the highest incidence of BSIs was encountered during the first 3 months from the diagnosis and during disease progression; (4) admissions to the intensive care unit were required in 23% of patients with BSIs; and (5) mortality rates due to BSIs were 11.5% in patients with progressive disease and 50% in patients with newly diagnosed MM [29, 70].

Bacteremia may antedate the diagnosis of MM and may be related to the use of venous catheters used during stem cell collection or autologous HSCT [71, 72]. Polymicrobial or multiple microbiologically confirmed infections are frequent and may cause serious consequences in recipients of HSCT [73]. Several studies have shown that the use of ciprofloxacin or levofloxacin prophylaxis in patients with MM undergoing autologous HSCT is associated with significant reduction in the incidence of FN, bacteremia, and pneumonia [68, 74, 75]. On the contrary, a randomized phase III study that included 212 MM patients undergoing induction therapy showed that the prophylactic use of antibiotics did not decrease the incidence of serious bacterial infections, thus obviating the need for the routine use of antibacterial prophylaxis in

patients with MM receiving induction therapy [76]. However, other studies have shown that the addition of doxycycline to ciprofloxacin and the sequential use of levofloxacin followed by ertapenem in patients with MM subjected to autologous HSCT reduce the frequency of FN episodes, bacteremia, and documented bacterial infections without increasing the rate of serious complications [77, 78].

4.3. Viral infections in MM

Reactivation of CMV after autologous HSCT performed for patients with MM is relatively common and is mainly encountered in patients receiving tandem rather than single HSCT; HD-melphalan conditioning therapy; and induction with combination therapy particularly bortezomib, thalidomide, and dexamethasone [79]. Also, reactivation of *human herpes virus-6* is relatively common following autologous HSCT and is usually associated with postengraftment fever [80]. Several studies performed in patients with MM have shown that the risk factors for reactivation of VZV, HSV, and *hepatitis-B virus* (HBV) include (1) progressive disease, (2) treatment with proteasome inhibitors such as bortezomib, (3) treatment with immunomodulatory agents particularly lenalidomide, and (4) HSCT [81–87].

Viremia caused by CMV is common and is often associated with fever, while CMV disease with biopsy proven tissue infiltration is rare in patients with MM receiving autologous HSCT [79]. CMV surveillance should be considered in patients with MM subjected to autologous HSCT, particularly those receiving tandem transplants, HD-melphalan and combination therapies for induction [79]. Acyclovir or valacyclovir prophylaxis should be offered to HR patients including recipients of HSCT, patients with progressive disease, and patients treated with bortezomib or lenalidomide [81–87].

4.4. Fungal infections in MM

Candidemia and IFIs are major complications in patients with HMs who develop prolonged and severe neutropenia. Additionally, IFIs are difficult to diagnose in these severely immunocompromised patients [88–91]. In patients with MM prior to the introduction of novel therapies, IFIs were encountered in patients treated with traditional intensive cytotoxic chemotherapeutic regimens and mortality rates due to IFIs were reaching 60% [91]. In the era of novel therapies, IFIs are associated with mortality rate of approximately 44% and are mainly encountered in MM patients having: (1) progressive disease, (2) ≥ 3 lines of therapy administered, (3) received HSCT, particularly in the early post-transplant period, and (4) history of IFI treated [91–93].

Over the past two decades, the spectrum of *Candida* species infections has shifted to *non-albicans* species, which frequently exhibit decreased susceptibility to fluconazole [89]. Empirical antifungal agents are recommended in patients with HMs having neutropenia and persistent or recurrent fever despite appropriate antibiotic therapy [88]. In patients with candidemia or invasive infection caused by *Candida* species, echinocandins such as caspofungin, liposomal amphotericin-B, and voriconazole are the treatments of choice, while voriconazole is the treatment of choice for IFIs caused by *Aspergillus* species [67, 89, 90, 92]. However, fluconazole is still the most common antifungal agent used for prophylaxis in HR patients and in recipients of HSCT [91, 92].

4.5. Tuberculosis in patients with MM

Tuberculosis (TB) is the most common cause of death from a single infectious agent worldwide [94]. In patients with HMs and in recipients of HSCT living in geographic locations that are endemic for TB, these infections are uncommon, but they cause significant morbidity and mortality [95, 96]. Early diagnosis, prompt administration of anti-TB chemotherapy, and adherence to treatment schedules are associated with successful outcome, while delayed management, drug resistance, and presence of disseminated infection are associated with poor prognosis and high mortality rates [95, 96].

The incidence of TB infection is higher in patients with MM than in the general population. Also, patients with MM have higher risk of mortality compared to MM patients without TB [97]. The risk factors for TB infection in patients with MM include: (1) the disease itself with its associated immunological abnormalities that include hypogammaglobulinemia as well as abnormal T cell-mediated and humoral immunities, (2) treatment of MM that includes corticosteroids, cytotoxic chemotherapy, and novel therapies such as bortezomib, (3) old age, (4) alcohol use disorder, (5) poor socioeconomic conditions, (6) HSCT, and (7) presence of comorbid medical conditions such as diabetes mellitus and malnutrition [94–104].

TB infections in patients with MM can be primary infections or reactivation of old or latent TB infections [94, 100, 101]. Reactivation of TB may be induced by (1) HD corticosteroids, (2) cytotoxic chemotherapy, (3) administration of novel therapies, and (4) autologous as well as allogeneic HSCT [95, 104]. In patients with MM receiving bortezomib-containing regimens, TB infections are uncommon [94]. In a retrospective analysis of 115 patients with MM treated with bortezomib-based therapy: TB infection was diagnosed in 7% of cases, bortezomib therapy was interrupted in 50% of the patients treated for TB and this affected outcome of patients significantly, but none of the patients died because of uncontrolled TB infection. In these patients, early diagnosis and prompt anti-TB treatment were essential to avoid further worsening of the outcome [94].

TB infections may be diagnosed at the time of diagnosis of MM or may evolve during or after treatment of MM [98–100, 105]. In patients with MM, TB infections have been reported to involve: (1) lungs with pulmonary infiltration, lung nodules, and bronchiectasis; (2) spine causing paraspinal masses and spinal cord compression; and (3) meninges with TB meningitis [98–100, 105]. However, spinal TB is the most serious form of TB infections [100]. TB infections in MM patients may coexist with infections caused by other microorganisms such as *Staphylococcus aureus* [99].

TB infections are 10–40 times more common in recipients of HSCT than in the general population. Also, approximately 80% of *Mycobacterium tuberculosis* infections encountered in recipients of HSCT have been reported in allograft recipients [96, 103, 104]. Patients with MM having latent TB or history of treated TB infection planned for novel therapies or subjected to cytotoxic chemotherapy or HSCT should receive isoniazid prophylaxis to prevent reactivation of their TB infections [95, 96, 101].

4.6. Bone and joint infections in MM

Bone and joint infections are uncommon in patients with MM. These infections manifest as: osteomyelitis, septic arthritis, and prosthetic joint infections [51, 106]. The pathogens encountered are similar to those cultured in patients without myeloma, although GPB predominate and polymicrobial infections occur less frequently [51]. In patients with MM treated with radiotherapy or IV bisphosphonates, there is a risk of developing osteonecrosis of the jaw [106, 107]. Patients with osteonecrosis of the jaw are at risk for developing infections and often require long-term antimicrobial therapy [108]. Having history of jaw osteonecrosis is not a contraindication for HSCT as the outcome of these patients is not worsened by HSCT itself [108].

5. Infections associated with use of novel agents

Infections represent a significant cause of morbidity and a leading cause of death in patients with MM [13, 53]. The novel therapies that have been introduced over the past decade have improved the survival of patients with MM [53, 109]. Consequently, management of disease complications such as infections has become an important issue as patients with MM survive longer [53]. The pattern of infection and the risk factors for infection in MM patients have shifted due to the evolution of new therapies and the widespread use of HSCT [13, 43].

Several studies have shown that the use of immunomodulatory agents such as thalidomide and lenalidomide and proteasome inhibitors such as bortezomib, particularly if they are used in drug combinations that include corticosteroids in the treatment of MM at any stage, induction, relapse, or maintenance, are associated with increased risk of infectious complications, thus making the use of antimicrobial prophylaxis with fluoroquinolones, acyclovir, cotrimoxazole, and fluconazole essential [13, 52, 110, 111]. Also, in a meta-analysis that included 13 clinical trials, with 2402 patients participating, the use of daratumumab and elotuzumab in the treatment of R/R-MM was associated with myelosuppression in the form of neutropenia and lymphopenia and subsequent risk of infectious complications such as pneumonia [109].

5.1. Infections associated with use of thalidomide

Thalidomide is not significantly myelotoxic, so the risk of infection in patients with MM receiving thalidomide alone is very low [14]. However, severe infections have been encountered once thalidomide is used in combination with other drugs in the treatment of MM. Therefore, antibiotic prophylaxis is needed once thalidomide is used in combination with other drugs such as dexamethasone [112].

5.2. Infections associated with use of lenalidomide

Lenalidomide has more potent costimulatory effects on CD4+ and CD8+ cells than thalidomide, and it causes neutropenia as part of myelosuppression, which is highest during the initial cycles of therapy and then it decreases thereafter [14, 31, 113].

Serious infections and even deaths have been encountered with the use of lenalidomide [31]. Several studies have shown the following results once lenalidomide is combined with dexamethasone: (1) various infections are prone to occur, and (2) these infectious complications may be severe to the extent that the patients need hospitalization to receive G-CSF and IV antimicrobial therapy, (3) respiratory tract infections are common, and (4) viral infections such as VZV may be encountered requiring treatment as well as prophylaxis with acyclovir [14, 82, 113–116].

5.3. Infections associated with use of pomalidomide

Pomalidomide causes neutropenia [44, 116, 117]. When combined with dexamethasone in the treatment of patients with MM, severe infections may develop and pneumonia is a commonly encountered infection [44, 116, 117].

Infection is the second most common cause of death, after disease progression, in MM patients treated with pomalidomide [44]. Patient receiving pomalidomide therapy may have interruption of their scheduled treatment in case of severe infection and may need: G-CSF administration, antimicrobial prophylaxis with quinolones and cotrimoxazole, and even revaccination [44, 116, 117].

5.4. Infections associated with use of bortezomib

Bortezomib causes decreased lymphocytic count and imbalance in T-lymphocyte subsets due to its potent immunosuppressive effect on T cells [14, 118–120]. Several studies have shown that the use of bortezomib in the treatment of patients with MM is associated with development of the following infectious complications: (1) viral infections such as HSV and VZV infections mainly in patients with IgG type of myeloma, (2) fungal infections, (3) bacterial infections, mainly in IgG type of MM, and (4) TB reactivation, which is more pronounced in patients receiving other drugs, such as thalidomide and cyclophosphamide, in combination with bortezomib [14, 118, 119, 121]. However, one study found that *Epstein–Barr virus* (EBV)-positive B-cells were more susceptible to killing by bortezomib. Hence, the drug could represent a novel strategy for the treatment of certain EBV-associated lymphomas [122].

5.5. Infections associated with use of carfilzomib

Carfilzomib causes BM suppression that includes lymphopenia [123, 124]. The use of carfilzomib in the treatment of MM has been associated with the following infections: bacterial pneumonia, viral respiratory tract infections, and bacterial sepsis [123, 124].

5.6. Infections associated with use of daratumumab

Daratumumab has the following effects: neutropenia, lymphopenia, hyperglycemia, and decrease in natural killer cells, which play a major role in the immune clearance of virally infected cells [125, 126]. The use of daratumumab in the treatment of MM patients is associated with the following infections: nasopharyngitis, pneumonia, and viral infections such as VZV [125–128].

5.7. Infections associated with use of elotuzumab

Elotuzumab can cause neutropenia, lymphopenia, and hyperglycemia [129–132]. Several studies have shown that its use in the treatment of patients with MM is associated with the following infections: pneumonia, sepsis, and even leishmaniasis [129–131, 133].

5.8. Infections related to corticosteroids and bisphosphonates

Corticosteroids predispose to infectious complications by causing immune suppression and hyperglycemia [13, 14, 39]. The following infections have been reported in patients with MM receiving corticosteroid therapy: (1) *Candida albicans* and non-*albicans Candida*; (2) *Mycobacteriaceae*; (3) viruses such as HSV, VZV, CMV, and respiratory viruses; (4) encapsulated bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Enterobacter aerogenes*; and (5) PJP [13, 14, 39]. The use of bisphosphonates in patients with MM is associated with osteomyelitis and osteonecrosis of the jaw [14].

6. Infections related to HSCT in MM

Prior to the era of novel therapies for MM, studies in patients with HMs receiving autologous HSCT showed that there was no significant difference in incidence, type of infection, and clinical course of infection between patients with MM and patients with other HMs [134, 135]. However, a recent study showed that in-hospital mortality in patients with MM receiving autologous HSCT was approximately 1.5% and that there was no significant difference in mortality between elderly individuals and young patients [136]. Nevertheless, elderly patients were more likely to develop complications such as pneumonia, septic shock, acute respiratory failure needing endotracheal intubation, acute renal failure, and cardiac arrhythmias [136].

In patients with MM having dialysis-dependent renal failure are at higher risk of FN and infectious complications such as septic shock compared to patients without renal failure [137]. Patients with MM subjected to autologous HSCT are at higher risk of developing bacterial meningitis, which is associated with high rates of mortality and morbidity [138]. MM patients having MBL2 (mannan-binding lectin, which is part of the innate immune system that protects against severe infections during autologous HSCT) polymorphism are at risk of severe infections particularly after receiving HD-melphalan and autologous HSCT [139]. In addition to the administration of prophylactic antimicrobials in patients with HR-MM and in recipients of HSCT, strategies to reduce the incidence of infectious complications include administration of IV immunoglobulins and vaccination despite the likelihood of vaccination failure [140, 141].

During stem cell mobilization, infections related to central venous catheters are likely to occur with predominance of GPB [142]. Conditioning therapy with HD-melphalan causes mucositis and myelosuppression with neutropenia [14]. The use of melphalan is associated with colitis, pneumonia, and bacteremia, and these infections are usually caused by the following encapsulated bacteria, *Candida* species and *Aspergillus* species [14].

During the post-transplant period, organisms such as *Clostridium difficile*, CMV, HSV, VZV, PJP, and other opportunistic organisms dominate [13, 14, 141]. The sites of infection during this period are gastrointestinal, respiratory, and urinary tracts [13, 14]. In the pre-engraftment period of time: bacteremia, pneumonia, cellulitis, and gastrointestinal infections with *Clostridium difficile* occur, while VZV, CMV, *Clostridium difficile*, and PJP with gastrointestinal tract, lung and skin infections dominate in the post-engraftment period of time [14]. Bacteremia in recipients of autologous HSCT is associated with previous bortezomib therapy and elevated beta-2 microglobulin level [141]. Recently, a significant increase in the incidence of infections caused by multidrug resistant organisms (MDROs) has been encountered [143]. Also, colonization with MDROs in recipients of autologous HSCT has negative impact on OS due to the profound immunosuppression caused by the HMs and their treatments [143].

Reactivation of HBV is a well-recognized complication in patients with chronic HBV infection undergoing cytotoxic chemotherapy or immunosuppressive treatment [144]. In patients undergoing autologous HSCT, reverse seroconversion of HBV is not a rare complication and this poses concerns about possible complications in such severely immunocompromised individuals [144]. There is an extremely low incidence of PJP in recipients of autologous HSCT; thus, routine PJP prophylaxis should not be offered routinely to this population group. However, patients who require systemic corticosteroid therapy in the post-transplant period are candidates for PJP prophylaxis [145].

7. Conclusions and future directions

The introduction of the novel agents in the treatment of patients with MM has led to unprecedented improvements in survival rates. However, these novel therapies have their own toxicities that include BM suppression and various infectious complications. These infections include bacterial, viral, fungal, mycobacterial, and parasitic infections. Also, they can be local or disseminated and can affect the bloodstream and may invade internal organs, thus causing life-threatening illnesses.

As these infectious complications vary according to the stage of the disease and the specific agents used, prospective and multicentric studies are needed to explore the real extent of these infections in order to establish guidelines for the use of antimicrobial agents in the prophylaxis as well as the treatment of the various infections that can be encountered.

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