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Multiple Myeloma and Risk of Infection

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Abstract

The risk of developing any infection in myeloma patients is increased compared to matched controls. The increased susceptibility to infection in myeloma patients is complicated and multifactorial, probably resulting from the interplay between disease-related deficits in the innate or adaptive immune system, age- and disease-related complications and antineoplastic therapies. The majority of patients experience the first episode of severe infection before 4 months after myeloma diagnosis. The application of autologous and allogeneic stem cell transplantation and novel agents in myeloma has resulted in the emergence of infections not previously associated with myeloma. The understanding of the specific risk factors and periods during which patients are at risk of infection is the key for management of and the application of risk-adjusted prophylactic and treatment strategies.

Keywords: Myeloma infection; Novel agents; Prophylactic antibiotic; Vaccine; Risk score

Abbreviations: HSV: Herpes Simplex Virus; VZV: Varicella-Zoster Virus; BCMA: B-cell Maturation Antigen; IMiDs: Immunomodulatory Drugs; PIs: Proteasome Inhibitors; ISS: International Staging System; LDH: Lactate Dehydrogenase; BsAb: Bispecific Antibodies; CAR-T: Chimeric Antigen Receptor T-Lymphocytes; R/R: Relapsed/Refractory; CMV: Cytomegalovirus; CRS: Cytokine Release Syndrome

Introduction

The risk of developing any infection in myeloma patients is increased compared to matched controls [1]. The risk of infections was 4 to 5-fold higher than controls in the first year after diagnosis and remained elevated up to 5 years after myeloma diagnosis [1]. Infections are a notable cause of morbidity and mortality in the clinical course of myeloma patients [2]. The majority of patients experience the first episode of severe infection before 4 months [3]. In Danish registry study male gender, International Staging System (ISS) score II and III, and elevated lactate dehydrogenase (LDH) level were independently associated with higher risk of pneumonia within 6 months after myeloma diagnosis [3]. The infectious risk is particularly high during transplant phase in transplant-eligible patients, and during first month of induction in transplant-ineligible patients [4]. During maintenance phase, the incidence of grade ≥ 3 infection per month of treatment was 0.4 % with the highest incidence during ixazomib-based maintenance, followed by thalidomide, and lenalidomide-based regimens [4]. The mortality rate due to infections in myeloma ranged from 1.1% to 9.3% [2]. About 1.2% of patients died because of infections within the first 6 months (1% before 4 months) [3].

The most common infections in myeloma patients were bacterial, followed by viral [2]. Myeloma patients had an increased risk of the following bacterial infections: meningitis, septicemia, pneumonia, endocarditis, osteomyelitis, pyelonephritis, cellulitis, and the following viral infections: influenza and herpes zoster compared to controls [1]. The most common site of infection was the lung, followed by the genitourinary system [1]. The most common causative organisms for respiratory tract infections are *S. pneumonia, S. aureus and Hemophilus influenza* while for urinary tract infections are *E. coli* and gram-negative species such as *Pseudomonas*, *Proteus* and *Klebsiella* [2]. The application of stem cell transplantation has broadened the spectrum of infection in myeloma to include those caused by *Clostridium difficile*, cytomegalovirus, and opportunistic moulds. The incidence of fungal infections is low in non-transplanted myeloma patients. High-dose chemotherapy and autologous hematopoietic stem cell transplantation, is complicated by profound neutropenia and mucositis which are well-known predisposing factors for fungal infections [2].

Risk factors for Infectious Complications in Myeloma Patients

The increased susceptibility to infection in myeloma patients is complicated and multifactorial, probably resulting from the interplay between disease-related deficits in the innate or

adaptive immune system, age- and disease-related complications and antineoplastic therapies [5].

Age-related Complications

Myeloma affects old people who frequently experience age-related decline in physiologic reserve of various organs and other age-related conditions [6].

Myeloma-related Immunodeficiency

Myeloma-related deficits in the innate immunodeficiency include hypogammaglobulinemia, numerical and functional abnormalities of dendritic cells and inversion of CD4:CD8 ratio, abnormal Th1/Th2 CD4+ ratio, severe disruption of global T cell diversity, and natural killer cells dysfunction. Polyclonal hypogammaglobulinemia has been classically associated with encapsulated bacterial infection, such as *Streptococcus pneumonia and Hemophilus influenza* [7].

Myeloma and Treatment related Complications

Myeloma and treatment-associated organ dysfunctions and comorbidities include: renal failure; respiratory compromise, caused by collapse of thoracic vertebra and opiate therapy; severe alimentary mucosal damage (caused by chemotherapy, radiation therapy, or graft-versus-host disease); hyperglycemia induced by dexamethasone; transfusional iron overload; and multisystem involvement by myeloma associated deposition diseases (AL-amyloidosis and light chain deposition disease [4].

Treatment-related Risk factors

The type of anti-myeloma therapy used plays a role in the development of infection. The introduction of stem cell transplantation and the novel anti-myeloma agents such as proteasome inhibitors, immunomodulatory drugs (IMiDs), monoclonal antibodies, antibody-drug conjugates, and most recently bispecific antibodies (BsAb) and chimeric antigen receptor T-lymphocytes (CAR-T) have improved the outcome of multiple myeloma patients and have transformed myeloma into a chronic disease, with multiple relapses and salvage therapies. The levels CD4+ T cells, particularly naive and activated subsets, decrease significantly with increasing cycles of chemotherapy, resulting in cumulative immunosuppression and is strongly associated with opportunistic infections [6].

Immunomodulatory Drugs (IMiDs)

Myeloma patients treated with IMiD-based regimens have an increased risk of serious infection at all stages of treatment-induction, maintenance (10.5%), and relapsed/refractory (R/R) disease (16.6%). Transplant-eligible patients have a higher risk of serious infection with IMiD-based induction therapy, compared to transplant ineligible patients. Lenalidomide use during maintenance phase has twice the risk of serious infection compared to thalidomide use [7]. IMiDs disrupts granulocyte differentiation and induces neutropenia. The risk of infection varies depending on the specific type of IMiD. Lenalidomide and pomalidomide have a higher risk of therapy-induced neutropenia, which may contribute to this increased infection risk. Pomalidomide-based regimens have the highest risk of infection [7]. The use of thalidomide, and lenalidomide may predispose recipients to deep venous thrombosis and peripheral neuropathies. The presence of deep venous thrombosis at the site of a central venous catheter increases the risk of septic thrombophlebitis following bacteremia, and peripheral neuropathies increase the risk of trauma and soft-tissue infection, which may progress to osteomyelitis [6].

Proteasome Inhibitors (PIs)

PIs cause selective depletion of T-cells and a decline in viral antigen presentation leading to an increased risk of reactivation of viral infections [7]. The prevalence of herpes simplex virus (HSV), and varicella-zoster virus (VZV), significantly increased following treatment with bortezomib [6]. Bortezomib-based induction therapy had a two-fold risk of severe infection compared to thalidomide-based therapy [7].

Glucocorticoids

Glucocorticoid therapy increases the risk of all types of infections (bacterial, viral, and fungal). The risk of infection increased with age and was higher among diabetic patients, with higher glucocorticoid doses with the highest risk seen in prednisone doses over 20 mg daily. These patients had higher rates of cutaneous cellulitis, herpes zoster infections, blood stream infections, candidiasis, and lower respiratory tract infections [7].

Monoclonal Antibodies

Daratumumab selectively depletes NK-cells, which express CD38, and disrupts the innate immune response. It was noted that 22% of the patients treated with daratumumab developed reactivation of latent viral infections, including HSV, VZV, and cytomegalovirus (CMV) [5]. Triplet combination therapies containing daratumumab lead to higher rates of neutropenia and grade III–IV infections and pneumonias compared to doublet combination therapies [7].

Stem Cell Transplantation

ASCT has high rates of transplant-associated myelosuppression. The spectrum of infections depends on time elapsed from ASCT. Bacteremia is most common within the pre-engraftment phase (from day 0 till day +30 posttransplant) mostly due to treatment-induced neutropenia, mucositis, and indwelling catheter devices. Gram-positive pathogens are more commonly seen, likely due to increased use of fluoroquinolone prophylaxis. Late infections (more than 30 days after ASCT) are associated with, decreased lymphocyte counts, impaired cell mediated immunity and neutrophil recovery. Nearly 80% of myeloma patients experience a late infection within 100 days post-ASCT. Patients may be susceptible to VZV and CMV infections due to deficits in CD4 cells [7].

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CAR-T Cell Therapy

The increased risk of infection is due to poor immune function from the underlying malignancy and prior cytotoxic treatments. The lymphodepleting chemotherapy administered immediately prior to CAR-T infusion can cause profound cytopenias and may impair mucosal barriers [7]. Neutropenia develops in over 90 % of patients following lymphodepletion and CAR-T infusion with a median duration of 9 days, but can last more than 21 days. Bacterial infections are predominant during the first period of 30 days post-CAR-T infusion. The pattern of infections after CAR-T seems to be similar to that observed after auto-HCT [4]. Both steroids and/or tocilizumab used in the treatment of cytokine release syndrome (CRS) resulting from CAR-T can increase infection risk [7].

Bispecific Antibodies

Patients who were treated with B-cell maturation antigen (BCMA)-targeted bispecific antibodies had significantly higher rates of grade ≥3 infections than non-BCMA bi-specifics (25% vs 20%). Similarly, patients treated with bi-specifics in combination with other agents had significantly higher rate of all-grade infection than those receiving monotherapy (71% vs 52%). Several infections classically associated with T-cell depletion were identified. BCMA-targeted bispecifics and bispecific combination therapy requires vigilant infection screening and prophylaxis strategies [8].

Screening recommendations prior to commencement of myeloma therapy [9]

i. Universal screening for HBV with HBsAg, anti-HBcAb and anti-HBsAb serology (Strong recommendation, Level II evidence), HCV with Hepatitis C antibody, HIV with HIV 1 & 2 antibody-p24 combination assay (Moderate recommendation, Level III evidence), latent TB including country of birth, close contact with TB (Strong recommendation, Level II evidence), IgG VZV or HSV seropositivity prior to planned HCT to guide the need for post-HCT prophylaxis (Moderate recommendation, Level II evidence), and IgG CMV seropositivity prior to planned HCT and/or prior to commencement of treatment of relapsed/refractory disease for assessment of CMV reactivation (Moderate recommendation, Level II evidence).

ii. Screening for endemic tropical pathogens including country of birth, refugee status and area of residence (Marginal recommendation, Level III evidence).

Key Points to Concern

i. Fever in a myeloma patient almost always indicates infection and should be taken very seriously [2].

ii. Empiric treatment covering both encapsulated and gram-negative bacteria should be started while awaiting cultures results. The choice of antibiotics should always be determined according to the pattern of antibiotic resistance at each institution [2].

iii. The decision to administer antimicrobial prophylaxis and to vaccinate should be individualized based on patient age, disease associated organ dysfunction and the choice of anti-myeloma treatment. Prophylactic antibiotics during the first 2 months of anti-myeloma treatment may have a role in reducing the incidence of infection in myeloma patients. However, routine use of prophylactic antibiotics is not recommended due to the increased risks of developing *Clostridium difficile* infections and antibiotic resistance. The efficacy of preemptive vaccination, especially with killed, component and/or conjugated vaccines in myeloma patient is uncertain since three quarters of myeloma patients demonstrate suboptimal humoral immune responses and decreased polyclonal immunoglobulin synthesis. Even the antibody response is short-lived in patients who are able to mount a humoral immune response to vaccination, [2].

A Simple Score to Predict Early Severe Infections in Newly Diagnosed Multiple Myeloma Patients

Variables associated with increased risk of severe infection in the first 4 months included serum albumin ≤30 g/L, ECOG > 1, male sex, and non-IgA heavy chain. A simple risk score with these variables facilitated the identification of three risk groups with different probabilities of severe infection within the first 4 months: low-risk (score 0-2) 8.2%; intermediate-risk (score 3) 19.2%; and high-risk (score 4) 28.3%. Patients with intermediate/high risk could be candidates for prophylactic antibiotic therapies [3].

Conclusion

Fever in a myeloma patient almost always indicates infection and should be taken very seriously. Empiric treatment covering both encapsulated and gram-negative bacteria should be started while awaiting cultures results. The decision to vaccinate and administer antimicrobial prophylaxis should be individualized based on patient age, disease associated organ dysfunction and the choice of the anti-myeloma treatment.

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