Do Not Ignore the Immunoglobulin Replacement Therapy for Hypogammaglobulinemia in Multiple Myeloma Patient

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To the Editor,
The letter entitled “Invasive Aspergillosis and Candidiasis in a Patient with Plasma Cell Myeloma,” written by Khadwal et al.[1], and Irfan’s comment[2] published in a recent issue of your journal, was quite interesting. Here we would like to highlight another critical issue that may overlooked, which is the role of immunoglobulin replacement therapy (IgRT) for hypogammaglobulinemia in multiple myeloma (MM) patients in the prevention of invasive fungal infection. Khadwal et al.[1] reported that a 65-year-old woman diagnosed with IgG kappa MM 4 years ago, died of her illness within 5 days of admission to the hospital at this admission and invasive fungal infections were also found in this patient. We notice that this patient had severe hypogammaglobulinemia at this admission, including IgG of 364 mg/dL (normal:658-1837 mg/dL), IgM of <21.0 mg/dL (normal:40-263 mg/dL), and IgA of 41.0 mg/dL (normal: 71-263 mg/dL). However, from our perspective, severe hypogammaglobulinemia was not temporarily induced, and it was a long period since the diagnosis or first chemotherapy on this MM patient.

As we know, the overall survival of MM patients has significantly improved since the bortezomib and lenalidomide. However, chemotherapy is significantly associated with myelosuppression or DNA synthesis inhibition, further impairing humoral or cellular immunity. Then these chemotherapies significantly reduced Ig production and resulted in secondary immunodeficiency (SID) in MM patients. Given these results, MM patients who received chemotherapies are at a high infection risk and the infections are still the main cause of morbidity and mortality in MM patients.

Thus, IgRT and prophylactic antibiotics are two main strategies for the care of SID patients, especially secondary to hematological diseases[3]. Recent data demonstrated MM patients receiving IgRT had a lower reduction in the use of antibiotics, fewer days of hospitalization, and the number of infections when compared with patients not receiving IgRT[4]. Moreover, in our country, hematologic
SID specialists are still lacking, and IgRT for SID patients is not covered by health insurance which results in a high infection rate in MM patients. Thus, in this letter, we want to highlight another critical issue that may be overlooked, which is the role of IgRT for hypogammaglobulinemia in MM patients in the prevention of invasive fungal infection. Moreover, monitoring the Ig levels on the diagnosis or after chemotherapy of MM, could further enhance the surveillance of fungal infection risk and reduce the mortality rate in MM patients.

References

Reply:

To the Editor,
We thank the authors for their interest in our report titled “Invasive Aspergillosis and candidiasis in a patient with plasma cell myeloma” (1). We appreciate the comments and the valid queries raised regarding the same. Our patient was a non-smoker but had comorbidities viz., Type 2 diabetes mellitus, hypertension, chronic renal disease and hypogammaglobulinemia – serum IgG 364 mg/dl (normal=658-1837 mg/dl), IgM <21.0 mg/dl (normal=40-263 mg/dl) and IgA 41.0 mg/dl (normal=71-263 mg/dl). Since her diagnosis 4 years ago as IgG kappa Multiple myeloma stage III, the best response to therapy had been very good partial response (VGPR) only until she developed the current relapse. She was planned to receive daratumumab in addition to VCD (Bortezomib, cyclophosphamide and Dexamethasone) to manage the relapse but could not be given due to active infections and poor general condition. It is evident that she had most risk factors predisposing to invasive fungal infections i.e., steroids, diabetic state, broad spectrum antibiotics, hypogammaglobulinemia, prior two lines of chemotherapy and pre-terminal neutropenia prior to her demise during her week-long hospitalization). She was not on antifungal prophylaxis. Bone marrow examination performed three weeks prior to current admission, had shown 50% plasma cells but no microbial agents were identified at that time. Bone marrow at autopsy revealed small clusters of plasma cells (<5%) with relative depletion of normal hemopoietic elements. No fungal hyphae were identified in the sections.

We agree with the authors regarding use of fungal prophylaxis in patients receiving high dose chemotherapy, commonly given during acute leukemia therapy and hematopoietic stem cell transplant. While earlier there was no definite consensus for fungal prophylaxis, recently International Myeloma Working Group 2022 had published guideline and...
recommendations on risk adapted prophylaxis for infections in multiple myeloma (MM) (2). These suggest bacterial, fungal and antiviral prophylaxis for intermediate and high-risk MM patients. In view of above guidelines (available a year following the demise of the index patient), antifungal prophylaxis is indicated and should be given to all relapsed, refractory MM patients with underlying risk factors such as diabetes mellitus, renal failure, hypogammaglobulinemia and those receiving high cumulative dose of steroids during induction as well as maintenance phase resulting in a net state of immunosuppression.

Thanking you,

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Kirti Gupta,
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Madhurima Sharma,
Pankaj Malhotra

References