LETTER TO THE EDITOR

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Immunoglobulin Replacement Therapy for Hypogammaglobulinemia in Multiple Myeloma Should Not Be Ignored

Multipl Myelomda Hipogamaglobulinemi için İmmünoglobulin Replasman Tedavisi İhmal Edilmemelidir

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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], as well as Yavaşoğlu's [2] comment on it, published in recent issues of your journal, were quite interesting. Here we would like to highlight another critical issue that may be overlooked, which is the role of immunoglobulin replacement therapy (IgRT) for hypogammaglobulinemia in multiple myeloma (MM) in the prevention of invasive fungal infection. Khadwal et al. [1] reported that a 65-year-old woman diagnosed with immunoglobulin G (IgG) kappa MM 4 years previously had died of her illness within 5 days of admission to the hospital and that invasive fungal infections were found in this patient. We noticed that this patient had severe hypogammaglobulinemia at the time of her final 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 there was a long period since the diagnosis or first chemotherapy of this MM patient.

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

IgRT and prophylactic antibiotics are two main strategies for the care of patients with SID, especially secondary to hematological diseases [3]. Recent data demonstrated that MM patients receiving IgRT had a lower reduction in the use of antibiotics, fewer days of hospitalization, and fewer infections compared to patients not receiving IgRT [4]. Moreover, in our country, hematological SID specialists are still lacking, and IgRT for SID patients is not covered by health insurance, which results in a high infection rate among MM patients.

Thus, in this letter, we want to highlight another critical issue that may overlooked, which is the role of IgRT for hypogammaglobulinemia in MM in the prevention of invasive fungal infection. Moreover, monitoring Ig levels at diagnosis or after chemotherapy for MM could further enhance the surveillance of fungal infection risk and reduce the mortality rate in MM patients.

Keywords: Immunoglobulin replacement therapy, Hypogammaglobulinemia, Multiple myeloma

Anahtar Sözcükler: İmmünoglobulin replasman tedavisi, Hipogamaglobulinemi, Multipl myelom

Ethics

Informed Consent: Not applicable.

Authorship Contributions

Concept: Q.Z., Y.W., W.P.; Design: Q.Z., Y.W., W.P.; Data Collection or Processing: Q.Z., Y.W., W.P.; Analysis or Interpretation: Q.Z., Y.W., W.P.; Literature Search: Q.Z., Y.W., W.P.; Writing: Q.Z., Y.W., W.P.

Conflict of Interest: No conflict of interest was declared by the authors.

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Reply from the Authors:

To the Editor,

We thank Zhang et al. [1] for their interest in our report titled "Invasive Aspergillosis and Candidiasis in a Patient with Plasma Cell Myeloma" [2]. We appreciate their comments and valid queries regarding that publication. Our patient was a non-smoker but had comorbidities including type 2 diabetes mellitus, hypertension, chronic renal disease, and hypogammaglobulinemia with serum immunoglobulin G (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). Since her diagnosis 4 years previously with IgG kappa multiple myeloma (MM) of stage III, the best response to therapy had been very good partial response until she developed the final relapse. She was scheduled to receive daratumumab in addition to VCD (bortezomib, cyclophosphamide, and dexamethasone) to manage that relapse, but it could not be administered due to active infection and poor general condition. It is evident that she had most risk factors predisposing to invasive fungal infections, including steroids, diabetic state, broad-spectrum antibiotics, hypogammaglobulinemia, two prior lines of chemotherapy and pre-terminal neutropenia prior to her death during her week-long hospitalization. She was not receiving antifungal prophylaxis. Bone marrow examination performed 3 weeks prior to her final admission had shown 50% plasma cells but no microbial agents were identified at that time. In the autopsy, the bone marrow 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 Zhang et al. [1] regarding the use of fungal prophylaxis for patients receiving high-dose chemotherapy, commonly given during acute leukemia therapy and hematopoietic stem cell transplantation. While there was previously no definite consensus for fungal prophylaxis, the International Myeloma Working Group recently published guidelines and recommendations on risk-adapted prophylaxis for infections in cases of MM [3]. They suggest bacterial, fungal, and antiviral prophylaxis for intermediate-risk and high-risk MM patients.

In view of the above guidelines, which became available 1 year after the death of the patient that we described, antifungal prophylaxis is indicated and should be given to all relapsed/refractory MM patients with underlying risk factors such as diabetes mellitus, renal failure, or hypogammaglobulinemia and those receiving high cumulative doses of steroids during induction as well as the maintenance phase, resulting in a net state of immunosuppression.

Sincerely,

Alka Khadwal, Kirti Gupta, Nabhajit Mallik, Madhurima Sharma, Pankaj Malhotra

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