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Mini Review

Restoring Humoral Immunity after Autologous Stem Cell Transplantation in Multiple Myeloma and Response to Post-transplantation Vaccination

Amany R Keruakous*

University of Oklahoma Health Sciences Center, USA

***Corresponding author:** Amany R Keruakous, MD, University of Oklahoma Health Sciences Center, Stephenson Cancer Center, 800 NE 10th street, Oklahoma City, OK, 73104, USA.

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Objectives

I. Summarize the importance of humoral immunity in MM after ASCT

II. Generate a hypothesis to change the platform for the management of multiple myeloma into a personalized approach considering immune surveillance strategies

Keywords: Polyclonal immunoglobulins; Immune reconstitution after ASCT; Vaccination; Immunoparesis

Introduction

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains the standard of care for newly diagnosed multiple myeloma (MM). It improves progression-free survival (PFS) and overall survival (OS) [1]. However, MM is still an incurable disease [2].

There is an increased interest in immune reconstitution after ASCT, based on the premise that an early and sustained recovery of the immune system helps to eliminate residual disease and thereby improving the overall outcomes [3,4].

T-lymphocytes reconstitution, defined as absolute lymphocyte count (ALC) > or = 1000 at day +23 after ASCT, is a positive predictor of prolonged OS and PFS [4,5]. Additionally, B-lymphocytes activation is an important driver in cancer immune surveillance. In multiple myeloma, preserved levels of uninvolved immunoglobulins at diagnosis are independently associated with favorable outcomes [6].

Recovery of polyclonal immunoglobulins after ASCT in multiple myeloma is dependent on B-cell reconstitution to restore humoral immunity, which approximately concludes one year after ASCT [7]. Immunoparesis or suppression of polyclonal immunoglobulin is a very common condition in newly diagnosed myeloma patients, 80-90% at diagnosis and 75% at the time of ASCT [8].

Gao et al. [8] followed 108 patients who received ASCT with a median follow-up of 49 months. They showed that patients with recovered immunoglobulins 1 year after ASCT had a statistically significant longer OS of not reach versus 64 months in the group of patients who did not recover immunoglobulins.

Consistent results of 169 patients reported by Gonzalez-Calle et al. [9] showed that almost half of the patients did not recover their immunoglobulin levels after ASCT. Interestingly, the cohort with immunoglobulin recovery had a statistically significant longer progression-free survival than the group with persistent immunoparesis (median PFS 60.4 vs. 27.9 months, respectively), and improved overall survival (11.3 vs. 7.3 years, respectively).

Furthermore, additional studies supporting that recovery of immunoglobulins one year after ASCT is an independent

predictor of longer PFS and OS [10,11]. The authors postulated that immunoparesis might be connected to impaired immunosurveillance as well as increased infectious complications, hence the importance of post-transplantation vaccinations.

Because ASCT can deplete immunological memory, current guidelines recommend revaccination with inactivated vaccines 6-12 months after ASCT and live vaccines starting 24 months after ASCT [12,13]. Immunoglobulin recovery plays an important role to restore humoral immunity and subsequently successful vaccination.

For example, patients with high or normal CD19+ B-cell counts after AHCT had an improved response to vaccination against Haemophilus influenza type B (HiB); two doses of HiB were required in patients with low CD19+ B cell counts to achieve an adequate response to vaccination [14].

Data from 139 adults MM patients treated with a first ASCT, investigating the effect of high-dose melphalan and hematopoietic cell rescue on serotiters after ASCT by Merz et al. [15]. A vaccine "responder" was defined as a patient who converted serotiters from negative to positive, or retained positive immunity, to at least three pathogens after AHCT (approximately day 90) or after completion of vaccination. With a median follow up of 48.6 months, vaccine "responders" enjoyed better 4-year PFS than non-responders (79.8% versus 45.5%, respectively), as well as better OS.

Merz et al. [15] showed that restoration of immunity after ASCT in MM patients followed by vaccination resulted in improved PFS and OS. This is in line with a recent study demonstrating long-term survival in patients with a recovered polyclonal immunoglobulin production 1 year after ASCT. However, about 30% to 40% of patients show no response to vaccination after ASCT.

Therefore, assessment of serotiters after post-transplantation vaccination is recommended, especially for patients who did not recover polyclonal immunoglobulins after ASCT as they harbor a worse overall prognosis.

Although, revaccination after suboptimal response to first attempt vaccination is not the standard of care and the data is limited. For seasonal influenza and HiB, it has been demonstrated that a vaccination boost improves protection against the most common types [14,16].

In conclusion, lack of immunoparesis recovery one year after ASCT in MM patients is associated with significantly worse outcomes and should be considered when selecting maintenance regimen. Also, because 30% to 40% of patients show no response to vaccination, assessment of titers is recommended. Future studies investigating the biological basis of humoral response in MM and cancer immunosurveillance after ASCT are crucial.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

N/A

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