Mini Review

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

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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; Immunoaparesis

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) ≥ 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]. Immunoaparesis 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 seroconverts after ASCT by Merz et al. [15]. A vaccine
“responder” was defined as a patient who converted seroconverts 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 seroconverts 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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