Received: 17 September 2023 | Accepted: 18 September 2023

DOI: 10.1111/bjh.19132

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

COMMENTARY

Finding the balance between immunoparesis recovery and multiple myeloma responses after autologous stem cell transplantation in the era of maintenance therapy and novel drugs

Alessandro Gozzetti | **Irene Bernareggi** | **Vincenzo Sammartano**

Hematology, University of Siena, Policlinico "Santa Maria alle Scotte", Siena, Italy

Correspondence
Alessandro Gozzetti, Hematology, University of Siena, Policlinico "Santa Maria alle Scotte", Viale Bracci 16, 53100 Siena, Italy.
Email: gozzetti@unisi.it

Commentary on: Kubicki et al. Polyclonal immunoglobulin recovery in patients with newly diagnosed myeloma receiving maintenance therapy after autologous haematopoietic stem cell transplantation with either carfilzomib, lenalidomide and dexamethasone or lenalidomide alone: subanalysis of the randomized phase 3 ATLAS trial. Br J Haematol 2023;203:792–802.

Keywords: autologous stem cell transplantation, immunoparesis recovery, multiple myeloma responses

In their paper the authors[1] reported recovery of polyclonal immunoglobulins in multiple myeloma (MM) patients after autologous stem cell transplantation (ASCT) and initial immunoparesis in the ATLAS phase III study that compared KRD (carfilzomib, lenalidomide and dexamethasone) and R (lenalidomide) as maintenance therapy. The authors found that patients in the R arm recovered a polyclonal status more than patients in the KRD arm. No difference was seen in terms of progression-free survival (PFS) and minimal residual disease (MRD) negativity status. This is the first study that did not show positive association of polyclonal recovery of immunoglobulin and PFS and overall survival in R-treated patients as maintenance therapy after ASCT. Limited by a relatively small number of patients, results from this trial make tremble previous trial associations of immunoparesis recovery and better survivals. In fact, the study highlights important aspects of MM treatment. Unlike the past, some anti-myeloma drugs can have an anti-tumour and an anti-normal B-cell compartment effect, resulting not only in reduced MM relapses but also in reduced immune recovery, respectively, with a potential higher risk of infections. Carfilzomib, a second-generation epoxyketone proteasome inhibitor that binds selectively and irreversibly to the proteasome, showed great efficacy in MM patients combined with an autotransplant strategy, also in high-risk cytogenetics patients.[2,3] Although the 'plasma cytotoxic' effects are well reported, the immunosuppressive effects of carfilzomib in a continuous maintenance therapy are not completely known.

Interestingly, lenalidomide is an immunomodulatory drug with direct anti-tumour activity and various effects on the tumour microenvironment. Polyclonal immunoglobulin recovery was documented in MM patients treated with lenalidomide and was associated with better PFS.[4,5] Ravi et al. evaluated changes in uninvolved immunoglobulins in newly diagnosed MM patients treated with different induction regimens. In particular, patients treated with lenalidomide and dexamethasone (RD), bortezomib and dexamethasone (VD) and bortezomib, lenalidomide and dexamethasone (VRD) had increased uninvolved immunoglobulins compared to those who received high-dose dexamethasone and bortezomib, cyclophosphamide and dexamethasone (VCD).[6] Indeed, preclinical data reported that lenalidomide interferes with the BCMA/BAFF/APRIL pathway, which is thought to determine immunoparesis in MM. In fact, soluble BCMA is overexpressed in MM patients and may bind with its ligands BAFF and APRIL, thus reducing B-cell activation and antibody production.[7] Lenalidomide is also known to enhance cellular immunity by Th1 cytokine production, T-cell activation and augmentation of NK cell function. Vo et al.[8] demonstrated that lenalidomide enhances the function of dendritic cells in patients with MM in vitro as it stimulates the capacity of allogenic T cells, inhibits the genesis of immunosuppressive cells, promotes Th1 polarisation of naïve T cells and induces cytotoxic MM-specific T-cell lymphocytes.[9] A study by Fostier et al. showed that lenalidomide maintenance therapy is associated in vivo with increased naïve CD8+ T cells, memory T cells and Treg cells with strong suppressive phenotype, augmented expression of both co-stimulatory molecules

and inhibitory checkpoint molecules on T cells, and reduced numbers of terminal effector CD8+ T cells and TIGIT+ CD8+ T cells. The balance between these complex effects ultimately stimulates the immune microenvironment against MM cells.

Among the latest therapeutic strategies for this disease, bispecific antibodies (BsAbs) have emerged as highly effective agents in the treatment of relapsed/refractory MM due to their ability to trigger an immune response against myeloma plasma cells. However, their efficacy is compromised by an exhausted immune environment. Since they rely on a robust T-cell-mediated response, a permissive microenvironment can enable tumour escape in this context. The precise mechanisms underlying this phenomenon are not yet fully understood but may involve processes such as T-cell anergy resulting from increased expression of checkpoint ligands and receptors like PD-L1. This leads to T-cell exhaustion, impaired cytokine production and reduced target cell lysis. Furthermore, an increase in Tregs induced by myeloid suppressive cells contributes to immune escape. Additionally, the progressive immunoparesis in MM, including the reduction or loss of BCMA expression, can also lead to treatment resistance.[10] A growing body of evidence increasingly emphasises the pivotal role of the immune microenvironment in determining the long-term effectiveness of immune therapies. Nonetheless, patients treated with BsAbs, who are typically heavily pretreated and immunocompromised, exhibit a high overall infection rate. The heightened incidence of infections in patients undergoing BsAb treatment can be attributed to several factors like extensive prior use of immunosuppressive drugs, hypogammaglobulinaemia due to plasma cell depletion, neutropenia and T-cell exhaustion during prolonged BsAb treatment. It is evident how hypogammaglobulinaemia and immunoparesis can have crucial implications in the treatment of MM.[11] However, result of this article is that it does not represent a hallmark of reduced PFS. In this scenario, the implications and subsequent therapeutic strategies to enhance the effectiveness of advanced treatment lines or to address infectious complications can be diverse, including prophylaxis and potential combination therapies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Alessandro Gozzetti https://orcid.org/0000-0003-0769-6891

REFERENCES

1. Kubicki T, Dytfeld D, Wróbel T, Jamroziak K, Robak P, Czyż J, et al. Polyclonal immunoglobulin recovery in patients with newly diagnosed myeloma receiving maintenance therapy after autologous haematopoietic stem cell transplantation with either carfilzomib, lenalidomide and dexamethasone or lenalidomide alone: subanalysis of the randomized phase 3 ATLAS trial. Br J Haematol. 2023;203:792–802.
2. Gozzetti A, Cerase A, Lotti F, Rossi D, Palumbo A, Petrucci MT, et al. Extramedullary intracranial localization of multiple myeloma and treatment with novel agents: a retrospective survey of 50 patients. Cancer. 2012;118:1574–84.
3. Mina R, Musto P, Rota-Scalabrini D, Paris L, Gamberi B, Palmas A, et al. Carfilzomib induction, consolidation, and maintenance with or without autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: pre-planned cytogenetic subgroup analysis of the randomised, phase 2 FORTE trial. Lancet Oncol. 2023;24:64–76.
4. Zamarin D, Devlin SM, Arcila ME, Landau H, Lesokhin A, Lendvai N, et al. Polyclonal immune activation and marrow plasmacytosis in multiple myeloma patients receiving long-term lenalidomide therapy: incidence and prognostic significance. Leukemia. 2013;27:2422–4.
5. Dimopoulos MA, Swern AS, Li JS, Hussein M, Weiss L, Nagarwala Y, et al. Efficacy and safety of long-term treatment with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. Blood Cancer J. 2014;4:e257.
6. Ravi P, Kumar S, Gonsalves W, Buadi F, Lacy MQ, Go RS, et al. Changes in uninvolved immunoglobulins during induction therapy for newly diagnosed multiple myeloma. Blood Cancer J. 2017;7:e569.
7. Sammartano V, Franceschini M, Fredducci S, Caroni F, Ciofini S, Pacelli P, et al. Anti-BCMA novel therapies for multiple myeloma. Cancer Drug Resist. 2023;6:169–81.
8. Vo MC, Anh-NguyenThi T, Lee HJ, Nguyen-Pham TN, Jaya Lakshmi T, Jung SH, et al. Lenalidomide enhances the function of dendritic cells generated from patients with multiple myeloma. Exp Hematol. 2017;46:48–55.
9. Fostier K, Caers J, Meuleman N, Broos K, Corthals J, Thielemans K, et al. Impact of lenalidomide maintenance on the immune environment of multiple myeloma patients with low tumor burden after autologous stem cell transplantation. Oncotarget. 2018 Apr 17;9(29):20476–89.
10. Swan D, Murphy P, Glavey S, Quinn J. Bispecific antibodies in multiple myeloma: opportunities to enhance efficacy and improve safety. Cancers (Basel). 2023;15:1819.
11. Gozzetti A, Cerase A. Novel Agents in CNS Myeloma Treatment. Central Nervous System Agents in Medicinal Chemistry. 2014;14(1):23–7. https://doi.org/10.2174/1871524914999140818111514

How to cite this article: Gozzetti A, Bernareggi I, Sammartano V. Finding the balance between immunoparesis recovery and multiple myeloma responses after autologous stem cell transplantation in the era of maintenance therapy and novel drugs. Br J Haematol. 2023;203(5):706–707. https://doi.org/10.1111/bjh.19132