Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Review

J Exp Clin Med
2023; 40(3): 659-663
**doi:** 10.52142/omujecm.40.3.38

# Autologous hematopoietic stemcell transplantation in multiple myeloma

**Ayşe Nur GÜL, Engin KELKİTLİ***

Department of Hematology, Faculty of Medicine, Ondokuz Mayıs University, Samsun, Türkiye

**Received:** 11.02.2023 • **Accepted/Published Online:** 21.03.2023 • **Final Version:** 30.09.2023

**Abstract**

Treating multiple myeloma with high-level dose chemotherapy supported by transplanted autologous stem cells is still the primary and appropriate therapeutic strategy in affected patients. Today, although the responses have improved considerably, especially during the treatment with the induction of the combination of immunomodulatory medication and proteasome blockers, no treatment approach has taken autologous stem cell transplantation into the background. In this review, we will share the recent place of autologous stem cell transplantation in myeloma will be discussed from pretransplant treatment to posttransplant.

**Keywords:** autologous stem cell transplantation, indication, multiple myeloma

## 1. Introduction

Plasma cell myeloma represents one per cent of all cancers and approximately 10% of all hematological malignancies. Multiple myeloma is slightly less familiar in women than in men. At diagnosis, the average age is around 65 years (1). MM is rough to heal because of the disease and patient-associated heterogeneities. Unfortunately, multiple myeloma persists as an incurable condition. Also, most patients experience one or more recurrences (2). For over two decades, an excessive-concentration dose of chemotherapy followed by autologous stem cell transplantation has been the standard care for newly investigated multiple myeloma in individuals over 65 years. Still, today it is not correct to talk about a specific chronological age limit (3). We know that HCT after high-dose chemotherapy is not a proper therapeutic procedure. Still, overall survival and event-free survival are extended and opposed to treatment with standard myeloma treatments. Age is not enough of a criterion for evaluating autologous stem cell transplantation suitability. Age, cardiac, urinary, pulmonary functions and performance status all must be assessed. Today, especially the developments in supportive treatments allow high-dose chemotherapy supported by autologous stem cell transplantation to be successfully applied up to the age of 80. In this review, initial therapy, stem cell mobilization and storage, the timing of autologous stem cell transplantation, conditioning regimen, care during transplantation, single or tandem transplantation and posttransplant follow-up will be discussed in patients eligible for autologous transplantation.

## 2. Treatment before autologous stem cell transplant

Even before autologous stem cell transplantation therapy, patients are classified as either standard or high risk based on risk rating. The risk classification in multiple myeloma is shown in Table 1 (4). For patients with standard risk MM, three-drug administrations are preferable to two-drug regimens, as randomized studies suggest that they improve OS (5). The use of four drug regimens is evolving. The triple-drug regimen can be selected according to the patient's comorbid conditions. Nowadays, the VRD regimen is preferred, but if the patient has acute renal failure or thromboembolism, VCD may be selected. If possible high-risk patients should be referred to clinical trials. In the absence of clinical studies, the VRD regimen or another regimen with daratumumab may be preferred. Drugs such as melphalan that damage the hematopoietic stem cell compartment should not be used in the initial treatment; also, more than four cycles should not be used in regimens containing lenalidomide.

**Table 1.** Risk stratification of multiple myeloma

| High Risk | Standard Risk |
|---|---|
| t(4;14) | Trisomies |
| t(14;16) | t(11;14) |
| t(14;20) | t(6;14) |
| Del 17p | |
| p53 mutation | |
| Gain 1q | |
| R-ISS Stage 3 | |
| High Plasma Cell S-phase | |
| GEP: High-risk signature | |

t: Translocation; R-ISS: Revised International Staging System; GEP: Gene Expression Profiling

*Correspondence: ekelkitli@gmail.com

### 3. Stem cell mobilization and storage

Hematopoietic stem cell (HSC) collection, also called mobilization, is a prerequisite for ASCT. Several variables affect the CD34+ cells collection target value, including the planned number of transplants and mobilization strategies (6). Most studies have shown that transplantation with Peripheral blood stem cells (PBSC) leads to a great harvest of stem cells (7). The optimal CD34+ cell harvest is above 5.106 CD34+/kg; a minimum threshold of 2.106 CD34+/kg is required to achieve engraftment. So, how is stem cell harvesting done? It should be noted that hematopoietic progenitor stem cells must be harvested before the patient is subjected to alkylating medications (8). Hematopoietic stem cells can be collected by apheresis from the peripheral bloodstream after excitation with granulocyte colony-stimulating factor (G-CSF) or with additional chemotherapy. They may be gathered directly from the bone marrow. Peripheral blood progenitor cells (PBPCs) are the appropriate type of bone marrow cells for the transplantation process in MM. Usually, G-CSF is the principal critical agent used in hematopoietic stem cell transplantation (9). The maximum standard dose of G-CSF used was 10 μg/kg/day. Daily administration for one time by G-CSF resulted in mobilization; these results similar to double daily administration. In contrast, the total amount of stem cells that come to the periphery is highest on days 5 and 7. Generally, G-CSF is administrated for four days continuously, whereas apheresis onsets on the 5$^{th}$ day. (10). G-CSF biosimilar drugs have similarities to the original agent, such as safety, quality, pharmacokinetic properties of bioequivalent and effectiveness (11).

Another option for mobilization is chemotherapy-based mobilization. Chemotherapy used for mobilization can be applied separately from the standard treatment or included in the induction or rescue therapy regimen, depending on the centre's experience. Several studies have reported increased efficacy by combining hematopoietic growth factors and chemotherapy (6). The most commonly used chemo mobilization agents are high-dose cyclophosphamide and etoposide (12).

Plerixafor is a reversible and selective inhibitor of CXCR4, approved by the FDA for use in combination with G-CSF to facilitate the mobilization of HPC in MM patients. As a result of the disruption of the interactivity among CXCR4 and its ligand with plerixafor, HPCs emerge from the bone marrow microenvironment into the circulation, resulting in an increased number of HPCs (13). In addition, the plerixafor inhibitor utilized with G-CSF to promote stem cell mobilization in patients severely from significant risk of mobilization malfunction seems reasonable based on the available evidence. Inadequately mobilized patients were frequently known as patients with a peripheral blood CD34+ stem cell count below 20 x $10^6$/L at maximum stimulation or with a collection yield was less than 2 x $10^6$ CD34+ cells/kg with a maximum of four apheresis methods (14). Mobilization failure develops in around fifteen per cent of mobilized patients. The main predictive risk factors regarding mobilize loss are listed in table 2 (6). Among patients affected with mobilization failure, remobilization or bone marrow stem cell collection can also be carried out through a more intensive system or novel regiment. In addition, cytokines can also be used in association with plerixafor and/or chemotherapy, but not alone. In all patients receiving G-CSF only as a mobilizing therapy, a 2 to 4 weeks rest period followed by remobilization can be performed using plerixafor, and G-CSF is combined with chemotherapy (15). It is essential to know patients at risk for failed mobilization. Lenalidomide is a medication which is more effective and widely used for induction medicine of MM patients and is known to harm HPC mobilization. Early collection and mobilization of stem cells during 4-6 cycles after the first therapy is recommended for patients with MM who are eligible for ASCT (16).

**Table 2.** Factors related to risk of mobilization failure

| |
|---|
| **Treatment-related** |
| High numbers of previous chemotherapy (≥ two lines of chemotherapy) |
| Exposure to alkylating agents, purine analogues, or lenalidomide |
| Extended field radiotherapy to bone marrow-containing sites |
| **Patient-related** |
| Older age (>65 y) |
| Female sex |
| Diagnosis of non-Hodgkin lymphoma |
| Diabetes and smoking |
| **At mobilization** |
| The longer interval from the last chemotherapy to mobilization initiation |
| Bone marrow infiltration by primary disease (cellularity < 30%) at mobilization |
| Pre-apheresis peripheral blood $CD34^+$ cell number (<20 × $10^6$/μL) |
| Low day-one apheresis yield |
| Collection procedure |
| Timing of apheresis, |
| Type of cell separator used |
| Rate and volume of whole blood processed |

**4. Timing of ASCT**

It remains unclear how the improvement in survival after MM diagnosis is related to the timing of ASCT. Although it predates the era of new agents, the first phase of the third RCT to address the timing of ASCT demonstrated that, even though ASCT was previously associated with superior PFS, no difference was observed in OS, delaying ASCT until the time of relapse. In a recent IFM 2009 study, early and delayed autologous stem cell transplantation was compared in patients who underwent VRD induction. It was shown that the rate of minimal residual disease and progression-free survival was higher in patients who underwent early transplantation. Although there is no variation in overall survival with the help of effective salvage therapies and delayed autologous stem cell transplantation, autologous stem cell transplantation is considered a standard treatment after 4-6 cycles of induction therapy in suitable patients (3).

**5. Conditioning Regimen**

Currently, the standard conditioning regimen for patients with MM scheduled for ASCT is melphalan 200 mg/m$^2$. In a phase III RCT, patients receiving melphalan 200 mg/m$^2$ had superior OS at 45 months (65.8% vs 45.5%; P = .05) and less toxicity observed compared to patients receiving 140 mg/m$^2$ of melphalan with 8 Gy total body irradiation. In comparison, Patients with impaired renal function before ASCT are at higher risk of ASCT-related morbidity and mortality. Therefore, 140 mg/m$^2$ melphalan is recommended for individuals with creatinine clearance below 60 mL/min and undergoing ASCT (17, 18).

**6. Care During Transplantation**

After 24 hours of the conditioning regimen, peripheral blood progenitor cells (PBPCs) are reinfused. In addition, the pancytopenia period begins. So during this period, attention should be paid to avoiding infections and gastrointestinal toxicity, and hematological support should be provided. Depending on their level of cytopenia and immunodeficiency, patients are at risk of bacterial, viral and fungal infections in the post-transplant period. Febrile neutropenia is observed in approximately 40 per cent of patients with MM undergoing autologous HCT (19). Prophylactic treatments to avoid infection contain antifungal and antiviral drugs, which are recommended during increased risk.

Consequently, the most significant adverse event of high-dose chemotherapy is gastrointestinal toxicity. Nausea, mucositis, and diarrhea are common. Mucositis may occur in more than half of patients and may limit oral intake. Hematopoietic colony-stimulating factors like G-CSF can be accelerated to engulf the neutrophil. Usually, neutrophil engraftment occurs between days 12 to 14, and platelet engraftment is generally expected on days 14 to 16. According to the patient and transfusion policy of the centres, red blood cells and platelet transfusions are applied when necessary.

**7. Single or Tandem transplantation**

A Tandem (double) stem cell transplant is the second one scheduled within six months of the first. This approach idea was first explored in newly diagnosed patients by Barlogie et al. in 1999, and it is performance encouraging results with an average of EFS and OS of 43 and 68 months, respectively (20). Subsequently, two randomized trials confirmed the benefit of tandem transplantation with EFS but not OS (21, 22). In one meta-analysis, tandem ASCT was associated with improving response rates, but OS did not show an advantage (23). In some studies, the survival benefit of tandem ASCT was observed only in patients who did not achieve CR or perfect partial response (VGPR) after initial transplantation. In other words, patients who already received VGPR after their first transplant did not benefit significantly from the second ASCT (21, 22). NCCN guidelines (2023, version 3) recommended that sufficient stem cells be harvested to do two transplants in all transplant-eligible patients and that a second ASCT may be considered for patients who achieve a little under VGPR following the first HDT. In the STaMINA study, 758 patients undergoing a first autologous HCT were randomized 1:1:1 to receive a second autologous HCT followed by lenalidomide maintenance; four courses of bortezomib, lenalidomide and dexamethasone (VRd) followed by lenalidomide maintenance or lenalidomide maintenance alone. All three arms showed similar progression-free survival (PFS) and OS at 38 months (24). Currently, most patients with MM routinely undergo tandem autologous HCT. Since high-risk patients have worse outcomes than standard-risk MM, tandem HCT may be considered in selected patients with high-risk MM.

**8. Posttransplant Follow**

All autologous stem cell transplant patients should receive antifungal, antiviral and anti-pneumocystis jiroveci pneumonia prophylaxis and should be included in the vaccination program after six months (25). Patients should be evaluated for response to treatment after autologous stem cell transplantation. Patients are assessed on day 100 following HCT and should be reassessed every three to four months. High-risk patients may be evaluated earlier for treatment decisions such as tandem transplantation, consolidation, or dual drug maintenance. A second HCT at relapse is recommended for patients who tolerate the first transplant and experience sustained remission after the first HCT. This includes patients with progression-free survival (PFS) of at least three years after maintenance HCT or at least two years of PFS after HCT without maintenance (26). Two randomized studies showed an improved PFS with second autologous HCT versus therapy with chemotherapy only in patients with late relapse after the first stem cell transplant (27, 28).

**9. Conclusion**

ASCT remains integral to managing previously untreated patients of multiple myeloma and has value in the direction of patients with relapsed MM. Studies have shown that adding new agents before and after ASCT can lead to an improvement

in CR rate as well as delayed progression and prolonged OS. The complete response is that following ASCT is associated with beneficial long-term outcomes. Alternative treatment strategies are required to enhance results in patients who do not achieve post-transplant CR, especially those who are influenced by high-risk diseases.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Funding**

There is no funding source for this research project.

**Acknowledgments**

None to declare.

**Authors' contributions**

Concept: A.N.G., E.K., Design: A.N.G., E.K., Data Collection or Processing: A.N.G., E.K., Analysis or Interpretation: A.N.G., E.K., Literature Search: A.N.G., E.K., Writing: A.N.G., E.K.

**References**

1. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022;97(8):1086-107.
2. Offidani M, Corvatta L, More S, Manieri MV, Olivieri A. An update on novel multiple myeloma targets. Expert Rev Hematol. 2022;15(6):519-37.
3. Attal M, Lauwers-Cances V, Hulin C, Leleu X, Caillot D, Escoffre M, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017;376(14):1311-20.
4. Kumar SK, Mikhael JR, Buadi FK, Dingli D, Dispenzieri A, Fonseca R, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc. 2009;84(12):1095-110.
5. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Blade J, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. Blood. 2011;117(23):6063-73.
6. Arora S, Majhail NS, Liu H. Hematopoietic Progenitor Cell Mobilization for Autologous Stem Cell Transplantation in Multiple Myeloma in Contemporary Era. Clin Lymphoma Myeloma Leuk. 2019;19(4):200-5.
7. Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA, Ferrant A, et al. Randomized trial of filgrastim-mobilized peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet. 1996;347(8998):353-7.
8. Lemoli RM, Martinelli G, Zamagni E, Motta MR, Rizzi S, Terragna C, et al. Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34+ cells to support single or tandem high-dose chemotherapy. Blood. 2000;95(7):2234-9.
9. Vesole DH, Tricot G, Jagannath S, Desikan KR, Siegel D, Bracy D, et al. Autotransplants in multiple myeloma: what have we learned? Blood. 1996;88(3):838-47.
10. Anderlini P, Donato M, Lauppe MJ, Huh YO, Martin TG, Chan KW, et al. A comparative study of once-daily versus twice-daily filgrastim administration for the mobilization and collection of CD34+ peripheral blood progenitor cells in normal donors. Br J Haematol. 2000;109(4):770-2.
11. Schmitt M, Hoffmann JM, Lorenz K, Publicover A, Schmitt A, Nagler A. Mobilization of autologous and allogeneic peripheral blood stem cells for transplantation in haematological malignancies using biosimilar G-CSF. Vox Sang. 2016;111(2):178-86.
12. Wood WA, Whitley J, Moore D, Sharf A, Irons R, Rao K, et al. Chemomobilization with Etoposide is Highly Effective in Patients with Multiple Myeloma and Overcomes the Effects of Age and Prior Therapy. Biol Blood Marrow Transplant. 2011;17(1):141-6.
13. Fricker SP. Physiology and pharmacology of plerixafor. Transfus Med Hemother. 2013;40(4):237-45.
14. Wuchter P, Ran D, Bruckner T, Schmitt T, Witzens-Harig M, Neben K, et al. Poor mobilization of hematopoietic stem cells-definitions, incidence, risk factors, and impact on outcome of autologous transplantation. Biol Blood Marrow Transplant. 2010;16(4):490-9.
15. Giralt S, Costa L, Schriber J, Dipersio J, Maziarz R, McCarty J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant. 2014;20(3):295-308.
16. Paripati H, Stewart AK, Cabou S, Dueck A, Zepeda VJ, Pirooz N, et al. Compromised stem cell mobilization following induction therapy with lenalidomide in myeloma. Leukemia. 2008;22(6):1282-4.
17. Moreau P, Facon T, Attal M, Hulin C, Michallet M, Maloisel F, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Blood. 2002;99(3):731-5.
18. Dimopoulos MA, Sonneveld P, Leung N, Merlini G, Ludwig H, Kastritis E, et al. International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment. J Clin Oncol. 2016;34(13):1544-57.
19. Jones JA, Qazilbash MH, Shih YC, Cantor SB, Cooksley CD, Elting LS. In-hospital complications of autologous hematopoietic stem cell transplantation for lymphoid malignancies: clinical and economic outcomes from the Nationwide Inpatient Sample. Cancer. 2008;112(5):1096-105.
20. Barlogie B, Jagannath S, Desikan KR, Mattox S, Vesole D, Siegel D, et al. Total therapy with tandem transplants for newly diagnosed multiple myeloma. Blood. 1999;93(1):55-65.
21. Cavo M, Tosi P, Zamagni E, Cellini C, Tacchetti P, Patriarca F, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol. 2007;25(17):2434-41.
22. Sonneveld P, van der Holt B, Segeren CM, Vellenga E, Croockewit AJ, Verhoe GE, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. Haematologica. 2007;92(7):928-35.
23. Kumar A, Kharfan-Dabaja MA, Glasmacher A, Djulbegovic B. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and metaanalysis. J Natl Cancer Inst. 2009;101(2):100-6.

**24.** Stadtmauer EA, Pasquini MC, Blackwell B, Hari P, Bashey A, Devine S, et al. Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial. J Clin Oncol. 2019;37(7):589-97.

**25.** Dykewicz CA, Centers for Disease C, Prevention, Infectious Diseases Society of A, American Society of B, Marrow T. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis. 2001;33(2):139-44.

**26.** Shah N, Ahmed F, Bashir Q, Qureshi S, Dinh Y, Rondon G, et al. Durable remission with salvage second autotransplants in patients with multiple myeloma. Cancer. 2012;118(14):3549-55.

**27.** Cook G, Williams C, Brown JM, Cairns DA, Cavenagh J, Snowden JA, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomized, open-label, phase 3 trial. Lancet Oncol. 2014;15(8):874-85.

**28.** Goldschmidt H, Baertsch MA, Schlenzka J, Becker N, Habermehl C, Hielscher T, et al. Salvage autologous transplant and lenalidomide maintenance vs. lenalidomide/dexamethasone for relapsed multiple myeloma: the randomized GMMG phase III trial ReLApsE. Leukemia. 2021;35(4):1134-44.