Autologous Stem Cell Transplantation in Multiple Myeloma

Subjects: Hematology

Contributor: Massimo Offidani

Multiple myeloma (MM) is a clonal plasma cells hematologic malignancy. The introduction of high-dose therapy in the 1990s as well as the development of drugs such as thalidomide, lenalidomide, and bortezomib in the 2000s led to an impressive improvement in outcome of patients with multiple myeloma (MM) eligible for autologous stem cell transplantation (ASCT). Clinical trials conducted in the first ten years of the twenty-first century established as standard therapy for these patients a therapeutic approach including induction, single or double ASCT, consolidation, and maintenance therapy. More recently, incorporating second-generation proteasome inhibitors carfilzomib and monoclonal antibody daratumumab into each phase of treatment significantly improved the efficacy of ASCT in terms of measurable residual disease (MRD) negativity, Progression Free Survival (PFS), and Overall Survival (OS).

multiple myeloma autologous stem cell transplantation induction consolidation maintenance

1. Introduction

Multiple myeloma (MM) is characterized by extreme inter-and intra-patient heterogenicities so much that there is the idea that MM should no longer considered a single disease but as different entities that are increasingly shared. MM is still an incurable disease, but this does not mean that there have been no changes in the MM outcome over the years since with the introduction of high-dose therapy in the 1990s and novel agents in the 2000s, a substantial improvement in overall survival (OS) has been observed, particularly in younger patients [1][2]. A recent analysis of 4329 newly diagnosed MM (NDMM) patients treated with autologous stem cell transplantation (ASCT) at the University of Arkansas from 1989 through 2018 demonstrated the possibility of curing a fraction of patients, ranging from 6.3% to 31.3%, depending on the year of treatment, with many patients who achieved normal life expectancies [3]. Another large series of patients treated in France in “real-life” studies confirmed these results, reporting a median OS longer than 10 years in patients who underwent ASCT between 2010 and 2014 [4]. The ability of extending long-term survival has to be attributed to a deeper degree of response obtained by incorporating novel agents into the transplantation strategy [3]. On the other hand, a prospective study (BMTSS) in which 1906 patients who underwent ASCT were followed for a median of nine years showed a decrease in late mortality related to myeloma, infection, and cardiac events over the past 25 years [5].

However, the increased efficacy of triplet or quadruplet induction regimens in achieving measurable residual disease (MRD) negativity raised the question regarding the role of early ASCT, and several clinical trials are assessing this issue. Although the current transplantation approach consists of various phases such as induction, ASCT, consolidation, and maintenance, it remains to be clarified the real importance of consolidation therapy as well as the best maintenance therapy and how long it should last. The concept of tailoring therapy based on MRD status instead of prolonging potentially toxic and unnecessary therapies is explored in many ongoing studies, and personalized therapy will be probably the future of MM therapy. The treatment of high-risk (HR) MM patients remains a challenge since the definition of HR disease is controversial and the optimal choice for it is not well defined.

2. Considerations with Stem Cell Mobilization and Harvesting

Mobilization is a crucial step in order to successfully harvest and collect the minimum target required to perform an autologous stem cell transplant (≥2 × 10^6 cells/kg CD34+ peripheral blood stem cells), usually achieved by using granulocyte colony-stimulating factor (G-CSF) [6]. Because around 20% of patients fail to mobilize the adequate number of CD34+ stem cells, a combination of intermediate dose (ID)–cyclophosphamide (4 g/m^2) and G-CSF (5 mg/kg/day started on day +2) has been established over the years as the standard mobilization regimen for those patients [6].

Plerixafor, a selective reversible inhibitor of the CXCR4 chemokine receptor, can be used as salvage therapy for patients who fail to mobilize.

The current standard practice for ASCT in MM is to cryopreserve mobilized peripheral blood stem cells (PBSC) to be subsequently infused after planned high-dose chemotherapy. A possible alternative that is being increasingly explored is to perform ASCT without cryopreservation. The major advantage of such an approach is the possibility to allow transplant procedures in developing countries with limited access to facilities for stem cell cryopreservation. Indeed, the cost of cryopreservation contributes to approximately 15% of transplant costs, and using fresh cells could be the only chance for hematology departments without cryopreservation laboratories. Further, some recent evidence suggests faster engraftment with the non-cryo approach. Overall, there is lack of comparative studies of fresh vs. cryopreserved stem cells for ASCT in MM, and only limited retrospective data are available.

3. A Look at ASCT in the Era of Novel Drugs, New Regimens, and CAR-T Cell Therapies

The availability of regimens inducing high MRD negativity rates after induction/consolidation therapies and, particularly, sustained MRD negativity in many patients led to questioning the role and timing of ASCT in MM patients. A phase III study conducted in Italy demonstrated the superiority of double ASCT compared with MPR (melphalan, prednisone, lenalidomide) for six cycles after an induction therapy with four cycles of lenalidomide plus

dexamethasone (Rd) in all patients. Progression free survival (PFS) was significantly longer in patients who received ASCT (median 43 months vs. 22.4 months, HR = 0.44, $p < 0.001$) as well as OS (4-year 81.6% vs. 65.3%, HR = 0.55, $p = 0.02$) [7]. In another similar phase III trial by EMN, patients received four cycles of Rd as induction, after which they were randomized to receive either six cycles of cyclophosphamide, lenalidomide, and dexamethasone (CRd) or ASCT.

The approval of CAR-T cell therapy for MM will probably change the role of ASCT in the near future. Idecabtagene vicleucel (Ide-Cel) was the first anti-BCMA CAR-T cell therapy approved by the Food and Drug Administration (FDA) for RRMM with ≥ three lines of previous therapies, and it is now experimented for NDMM. The phase I KarMMa-4 trial is enrolling high-risk NDMM patients who, after ≤ 3 cycles of an induction regimen, receive CAR-T cells as a consolidation strategy. Ciltacabtagene autoleucel (Cilta-Cl) is another anti-BCMA CAR-T product not yet approved. It was demonstrated to induce an ORR of about 98% in a very heavily pre-treated RRMM population included in the CARTITUDE-1 trial [8].

4. The Role of ASCT in High-Risk Patients

Despite recent advances in upfront therapy in MM, 15–20% of all patients have a predicted OS less than three years. This group of patients can be defined as high-risk MM patients (HR). The correct definition of “high-risk MM” is very difficult in the modern era, when not only stage ISS, cytogenetic abnormalities [t(4;14), t(14;16), t(14;20), copy number abnormalities such as gain(1q) and del(17p)], elevated LDH value, renal failure, the presence of extramedullary disease or plasma cell leukemia are considered markers of HR MM. Now it could be necessary to evaluate other novel aspects such as gene expression profiling, somatic mutations at diagnosis, chromothripsis, TP53 biallelic inactivation, and some dynamic characteristics such as deepness of response to therapy through MRD assessment (in bone marrow samples, imaging PET-CT or circulating plasma cells) in order to build a dynamic risk assessment [9][10]. Indeed, patients experiencing relapse within 18 months of diagnosis are considered to have functional HR MM. Unfortunately, randomized trials have not risk-stratified patients, but only had data moving from high-risk subgroups in either planned or post-hoc analyses [11].

5. The Role of ASCT in Relapsed MM Patients

The role of a second ASCT in patients with MM who relapse is debatable considering the plethora or regimens approved for treatment of these patients. According to the most recent guidelines published in 2015 by the American Society of Blood and Marrow Transplantation, European Society for Blood, and Marrow Transplantation, Blood and Marrow Transplantation Clinical Trials Network (BMT CTN) [12], a second ASCT can be planned in patients with a duration of remission longer than 18 months following up-front ASCT. However, considering the median PFS obtained with an approach including induction regimens with triplets or quadruplets, consolidation, and maintenance therapies, these guidelines seem to be outdated. Similarly, outdated are the two randomized clinical trials comparing a nontransplantation approach to salvage ASCT.

6. Conclusions

The introduction of 3-drug and, more recently, 4-drug combinations as induction and consolidation therapy after ASCT allowed us to achieve rates of MRD negativity, which was unthinkable until recently, leading to improved PFS and OS. MRD status and sustained MRD negativity have been found to be the best tools to predict the outcome of MM patients and, despite not routinely used in clinical practice, MRD assessment has to be implemented since it probably will be essential in the future management of MM. Several questions such as the optimal time point to assess MRD status remain unsolved, but ongoing trials evaluating MRD-driven therapies, particularly consolidation and maintenance, will clarify this issue.

Moving to the upfront setting, novel therapeutic approaches such as bispecific antibodies, antibody-drug conjugates, and CAR T cells could induce even better results, so in the next years, the role of ASCT is probably destined to change. Nowadays, data from clinical trials continue to demonstrate a significant benefit of ASCT, and it remains the cornerstone of treatment in eligible patients. Despite improvements, outcome of ultra-high-risk MM remains poor, so innovative therapies beyond quadruplets and ASCT have to be explored for these patients. Finally, the main challenges will be to better understand the biology of MM and to make every possible effort for improving the outcome of this heterogeneous disease by personalized precision therapies.

References

1. Kumar, S.K.; Rajkumar, V.; Dispenzieri, A.; Lacy, M.Q.; Hayman, S.R.; Buadi, F.K.; Zeldenrust, S.R.; Dingli, D.; Russell, S.J.; Lust, J.A.; et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008, 111, 2516–2520.
2. Brenner, H.; Gondos, A.; Pulte, D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 2008, 111, 2521–2526.
3. Nishimura, K.K.; Barlogie, B.; van Rhee, F.; Zangari, M.; Walker, B.A.; Rosenthal, A.; Schinke, C.; Thanendrarajan, S.; Davies, F.E.; Hoering, A.; et al. Long-term outcomes after autologous stem cell transplantation for multiple myeloma. Blood Adv. 2020, 4, 422–431.
4. Corre, J.; Perrot, A.; Hulin, C.; Caillot, D.; Stoppa, A.M.; Facon, T.; Leleu, X.; Dib, M.; Karlin, L.; Moreau, P.; et al. Improved survival in multiple myeloma during the 2005–2009 and 2010–2014 periods. Leukemia 2021, 35, 3600–3603.
5. Giri, S.; Chen, Y.; Wu, J.; Hageman, L.; Richman, J.; Francisco, L.; Landier, W.; Costa, L.; McDonald, A.; Murdaugh, D.; et al. Reduction in late mortality among patients with multiple myeloma treated with autologous peripheral blood stem cell transplantation—A Blood or Marrow Transplant Survivor Study report. Transpl. Cell Ther. 2021, 27, 840.e1–840.e7.

6. Giralt, S.; Costa, L.; Schriber, J.; Dipersio, J.; Maziarz, R.; McCarty, J.; Shaughnessy, P.; Snyder, E.; Bensinger, W.; Copelan, E.; et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: Consensus guidelines and recommendations. Biol. Blood Marrow Transpl. 2014, 20, 295–308.
7. Palumbo, A.; Cavallo, F.; Gay, F.; Di Raimondo, F.; Ben Yehuda, D.; Petrucci, M.T.; Pezzatti, S.; Caravita, T.; Cerrato, C.; Ribakovsky, E.; et al. Autologous transplantation and maintenance therapy in multiple myeloma. N. Engl. J. Med. 2014, 371, 895–905.
8. Martin, T.; Usmani, S.Z.; Berdeja, J.G.; Jakubowiak, A.; Agha, M.; Cohen, A.C.; Hari, P.; Avigan, A.; Deol, A.; Htut, M.; et al. Updated results from CARTITUDE-1: Phase 1b/2 study of ciltacabtagene autoleucel, a B-Cell Maturation Antigen-directed Chimeric Antigen Receptor T cell therapy, in patients with relapsed/refractory multiple myeloma. Blood 2021, 138 (Suppl. S1), 549.
9. Costa, L.J.; Usmani, S.Z. Defining and managing high-risk multiple myeloma: Current concepts. J. Natl. Compr. Cancer Netw. 2020, 18, 1730–1737.
10. Derman, B.A.; Kosuri, S.; Jakubowiak, A. Knowing the unknowns in high risk multiple myeloma. Blood Rev. 2022, 51, 100887.
11. Pawlyn, C. High-risk myeloma: A challenge to define and to determine the optimal treatment. Lancet Haematol. 2021, 8, e4–e6.
12. Giralt, S.; Garderet, L.; Durie, B.; Cook, G.; Gahrton, G.; Bruno, B.; Hari, P.; Lokhorst, H.; McCarthy, P.; Krishnan, A.; et al. American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma. Biol. Blood Marrow Transplant. 2015, 21, 2039–2051.

Retrieved from https://encyclopedia.pub/entry/history/show/48043