REVIEW ARTICLE

Decreasing or Increasing Role of Autologous Stem Cell Transplantation in Multiple Myeloma?

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ABSTRACT

During the past four decades, autologous stem cell transplantation (ASCT) has been the first choice and the standard option for the treatment of newly diagnosed patients with multiple myeloma. The introduction of new agents such as thalidomide, lenalidomide, and bortezomib has led to a clear improvement in basic approach and those agents became the standard of care in the induction phase; however, they were not able to play the role of ASCT in term of progression-free survival and overall survival. Debate continues about the best induction, consolidation, and maintenance taking into account the toxicities of these new agents. The new monoclonal antibody (anti CD38) starts to take its place in the induction setting and it seems to be a promising agent in the high-risk group. Until recently, ASCT is the standard treatment for newly diagnosed patients.

Key words: Autologous, multiple, myeloma, stem cell, transplantation

INTRODUCTION

Multiple myeloma (MM) forms about 10% of hematologic malignancies and the first indication for autologous stem cell transplantation (ASCT) among these malignancies.[1,2] The introduction of high-dose chemotherapy (HDC) followed by ASCT has become the standard of care in newly diagnosed patients[3,4] after huge efforts and trials conducted in both Europe and the United States.[5,6] Koreth *et al*. demonstrated that ASCT has failed to add the maximum to the overall survival (OS); however, the event-free survival was improved.[7] Debate is still ongoing about the precise timing of ASCT, is it upfront, after complete response (CR) or upon progression or relapse?[6] During the last three decades, we have witnessed a dramatic shift in MM patients' approach after the introduction of the new agents such as thalidomide, lenalidomide, and bortezomib before or after HD/ASCT. This new combination has improved CR on the molecular level.[8] New trials are evaluating the new monoclonal antibodies (anti-CD38) in both induction and maintenance setting. To which extent, the introduction of these new agents may influence the utilization of ASCT? In this review, we are going to answer this question and other questions regarding the feasibility of ASCT taking into account several variables such as age, performance status, renal function, best induction, best maintenance, and other related issues.

UPFRONT ASCT IN NEWLY DIAGNOSED ELIGIBLE PATIENTS

ASCT proceeded by conditioning with high-dose Melphalan is considered the standard of care in newly diagnosed patients with MM.[9,10] First reports defined eligible patients as those younger than 65 years old as a cutoff; however, several bone marrow transplantation communities extended the cutoff age to exceed 65 years.[11] Trials are conducted to evaluate high-dose Melphalan in patients older than 65 years and found that treatment-related mortality (TRM) was zero at day +100 when comparing 140 mg/m^2 and 200 mg/m^2.[12] Other trials compared 200 mg/m^2 in younger patients versus 100mg/m^2 in a tandem mode in patients between 65 and 75 years old with no difference in progression-free survival (PFS), OS, or TRM.[13] However, other factors should be taken into consideration in older age groups such as renal functions,

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performance status, and other comorbidities. In some centers, ASCTs are performed on elderly patients according to every patient's characteristics and outside clinical trials.

Renal function impairment is one of the most important presenting signs in patients with MM attributed to high light chain burden. This impairment is much more profound in patients over 65 years; however, there is no contraindication for ASCT in this subgroup of patients. In these cases, toxicities attributed to HD chemotherapy are more frequent than those with normal renal functions.[14,15] Report from the Polish society of MM demonstrated that dialysis-dependent cases are more likely to develop toxicities such as infections and mucositis; however, PFS and OS rates were comparable to other patients presenting with normal functions.[16]

HISTORY AND PRESENT OF INDUCTION CHEMOTHERAPY

Before and after the era of ASCT, induction chemotherapy was the major treatment that aims to reduce the burden of plasma cell in bone marrow, improving the local environment and facilitate engraftment as well. The first induction backbone was the alkylating agents, then the triplet of vincristine, doxorubicin, and dexamethasone (VAD).[1] This induction was replaced by either thalidomide or bortezomib or both which proven to better than VAD in term of complete response (CR).[17,18] Later trials showed that the triplet of bortezomib, thalidomide, and dexamethasone (VTD) was superior to VD and TD.[19,20] Thus, VTD became the standard induction of choice in MM patients prepared for ASCT with 3–4 cycles given. Some centers give six cycles to attain a more profound response; however, peripheral neuropathy may limit this trend in some patients.[20] Soon after, VTD was replaced by many MM societies by VRD after replacing thalidomide with the newer version lenalidomide. VRD demonstrated better PFS and OS when compared to VTD.[21] The new monoclonal antibody against CD38 daratumumab (DARA) was evaluated in the induction phase in combination with VRD and VTD, showing some encouraging results when compared with VRD alone.[22,23] DARA was also combined in a Phase II trial with bortezomib, cyclophosphamide, and dexamethasone and also used in a Phase Ib trial with carfilzomib and lenalidomide demonstrating a response rate exceeding 95% in both trials.[24,25]

CHEMOPRIMING

Mobilization of hematopoietic stem cells (CD34) with a minimum of 2×10^6 CD34 per kg of body weight is essential for good engraftment; however, the optimal amount is 5×10^6 CD34/kg which can be done by a steady-state mobilization after giving granulocytes colony-stimulating factor (G-CSF) over several days or chemopriming through preparation with chemotherapeutic agents.[26] The two approved cytokines for mobilization are filgrastim (10 μg/kg/day for 4–6 days and apheresis on days 5 or 6) according to the optimal number of CD34 in peripheral blood. The other cytokines are lenograstim (10 μg/kg/day for 4–6 days and apheresis between days 5 and 7); however, mobilization using G-CSF alone is still suboptimal.[27] The most commonly used agent for chemopriming is high-dose cyclophosphamide (2–4 g/m^2), followed by filgrastim or lenograstim (5 μg/kg/day 1–5 days after completion of chemotherapy. This procedure can offer a good CD34 amount; however, the time to transplantation is prolonged and toxicities are reported as well.[28] In some patients who fail to mobilize the optimal amount of CD34, the chemokine receptor-4 (CXCR-4) antagonist (plerixafor) can increase the mobilization effect of G-CSF.[27] Trials compared to the addition of cytarabine to G-CSF versus G-CSF alone in Phase III randomized trials reported better results in the cytarabine arm; however, toxicity profile was high.[29] We should stress that using lenalidomide in the induction may impair mobilization process through upgrading CXCR-4 receptors; however, this process can be antagonist by plerixafor which found to be effective in this case.[30]

CONDITIONING

Intravenous Melphalan at a dose of 200 mg/m^2 is the best high-dose conditioning regimen so far. Attempts to replace it with oral Melphalan or intravenous busulfan have failed.[31] The combination of intravenous busulfan 130 mg/m^2 over 4 days and Melphalan 70 mg/m^2 for over 2 days demonstrated better PFS with no significant improvement in response rate.[32] In a randomized trial conducted by Bensinger *et al*., a comparison between Melphalan 200 mg/m^2 and 280 mg/m^2 demonstrated better ORR with no impact on PFS and OS.[33]

THE ROLE OF CONSOLIDATION AND MAINTENANCE AFTER ASCT

The Italian myeloma study group reported better CR and PFS rates using VTD compared with the TD arm in both induction and consolidation after ASCT[34] and this result was better in patients demonstrating good response after ASCT which reflected in complete pathologic and molecular response.[8] Sonneveld *et al*. reported better PFS with two cycles of VRD proceeding lenalidomide compared with lenalidomide as consolidation;[35] however, VRD failed to prolong PFS in patients with a high-risk profile of cytogenetic abnormalities [*t*(4:14) and/or del17p and/or *t*(14:16)].[35] These results indicate that VRD as consolidation before maintenance with lenalidomide is of benefit in those young patients with low-risk cytogenetic profile. Results do not support the regular indication of consolidation after ASCT and more randomized trials are needed to support the former idea.

Consolidation and maintenance are thought to deepen the first response obtained after ASCT and to prevent relapse and prolong survival; however, ASCT is not a curative procedure that is why concentration was made on maintenance therapy with the new agents such as thalidomide and lenalidomide.[36] Thalidomide was the first agent to use in the maintenance setting after being tested in several randomized trials. This agent showed a good response; however, the OS rate was not encouraging. Since thalidomide can lead to a profound peripheral neuropathy, the duration of use was limited to 6–12 months, as reported Spencer *et al*.[37] Lenalidomide was also tested in maintenance and demonstrated better response than placebo and led to prolongation of PFS in all subgroups of patients, especially in those attained more deep response after ASCT. OS improved in the lenalidomide arm except in women older than 60 years, presenting with a bad cytogenetic profile.[38] The treatment-limiting duration of lenalidomide is determined by the progression of secondary tumor which was reported and toxicities. Thus, thalidomide is given at a dose of 100 mg/day and lenalidomide at a low dose for a period of time in the light of side effects.[38] A designed plan is illustrated in Figure 1 showing the current practice and the future direction in treatment of newly diagnosed cases of MM.

NON-TRANSPLANT STRATEGY

Before the era of the new agents, two large trials compared HDC followed by ASCT with HDC alone demonstrated prolonged of both PFS and OS.[5,6] Most trials were conducted before 2010 and did not include the new agents until recently where four phase III trials compared HDC followed by ASCT with a combination of the new agents, as illustrated in Table 1.

Speed look on the former four trials demonstrates that induction followed by ASCT was better in term of PFS and OS than non-transplant strategy. The most important trial thereafter was the IFM 2009 where 700 newly diagnosed patients to receive three RVD cycles then divided into two arms: The first arm received one course of high-dose Melphalan followed by ASCT then another two RVD cycles, where patients in the second arm received another five cycles of RVD. Higher complete remission rates were observed in the ASCT arm (59% vs. 48%; $P = 0.03$) and minimal residual disease negativity (79% vs. 65%; $P < 0.001$); however, no difference in term of OS was observed at 4 years.[6] All conducted trials comparing ASCT versus non-ASCT arm demonstrated better response and PFS rates; however, OS was not significant unless in two trials, therefore, ASCT continues to be the standard of care in newly diagnosed patients. Early ASCT was evaluated in three trials with the improvement of interval to relapse; however, no difference was reported in term of OS.[39] In real practice, to answer the question whether early or delayed ASCT, randomized trials are needed with stratification of patients according to their clinical, biologic, and cytogenetic profile, then we can know which patient will get a better benefit from early or delayed one.

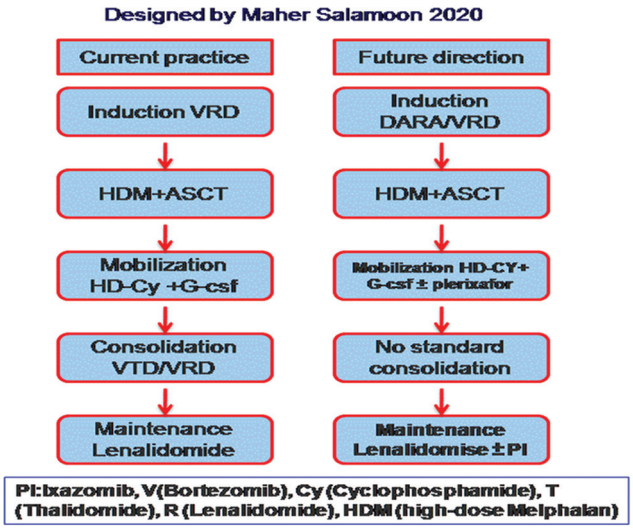

Figure 1: The present practice and future direction in approaching newly diagnosed patients with multiple myeloma

Table 1: The main four Phase III randomized trials comparing HD-chemotherapy followed by ASCT with treatment with new agents

Author	Study design	PFS	OS
Attal *et al.*	RVD × 5 cycles versus HD-M + ASCT (×1) + RVD × 2 cycles	50 versus 36 mon. *P*<0.001	4 y: 81% versus 80% *P*:NS
Cavo *et al.*	VMP × 4 cycles versus HD-M + ASCT (×1 versus ×2)	3 y: 66% versus 58% *P*<0.037	NA
Gay *et al.*	CRD × 6 cycles versus HD-M + ASCT (×2)	43 versus 29 mon.	4 y: 86% versus 73% *P*<0.004
Palumbo *et al.*	MPR × 6 cycles versus HD-M + ASCT (×2)	43 versus 22 mon. *P*<0.001	4 y: 82% versus 65% *P*=0.02

HD-M: High-dose Melphalan, RVD: Lenalidomide, bortezomib, and dexamethasone, CRD: Cyclophosphamide, lenalidomide, and dexamethasone, MPR: Melphalan, prednisolone and lenalidomide, VMP: Bortezomib, Melphalan, and prednisolone, PFS: Progression-free survival, OS: Overall survival, ASCT: Autologous stem cell transplantation

Another issue to be raised is the difference between single versus tandem ASCT. The IFM trial demonstrated that tandem transplant showed longer PFS (36 vs. 25 months $P = 0.03$) and better OS (58 vs. 48 $P = 0.01$). In a subgroup analysis, patients with better results were those who have not had a near-complete response after the first ASCT.[40]

The former results were supported by an Italian study conducted by Cavo *et al*. demonstrated better response and PFS rates; however, OS was similar in both arms (median, 71 vs. 65 months; $P = 0.9$).[41] Cavo *et al.* also published data from pooled three trials reporting better PFS and OS in the tandem arm compared with the single ASCT.[42]

DISCUSSION AND CONCLUSION

The introduction of new agents did not replace the role of ASCT, which remains so far the standard of care in newly diagnosed patients with MM. during the past 4 decades, ASCT has been compared with the HDC; however, the new agents replaced the high-dose in comparison and it is early to talk about complete replacement of ASCT by the new agents. The first step was comparing RD with VRD which showed superior results in term of PFS and OS. VRD seems to be comparable to ASCT in term of PFS and OS as well.[21] The emerging role of the new agents was clarified in four Phase III trials illustrated in Table 1. Trials should be conducted in a randomized fashion to evaluate the real role of the new agents with and without ASCT. The new monoclonal antibody daratumumab should be included in the induction phase in combination with VRD because of its encouraging results. Most societies concentrate on adding a new agent to the known triplet VRD then compare it with ASCT; however, studies should be oriented toward improving the induction to serve those ASCT ineligible patients. The development of induction is also an important trend toward improving results in a high-risk group. As we know, ASCT is a process that takes time (induction, chemopriming, and stem cell mobilization and conditioning) and this time takes about 3 months in the median which is not calculated when PFS and OS are studied which is a great bias. If we omit the time to perform the procedure, then VRD could exceed ASCT in term of OS since results are comparable. Finally, it is early to talk about a decreasing role of ASCT in MM; however, the new agents along with the monoclonal antibodies may delay the procedure in some patients the thing that must be determined after conducting a big randomized trial for this purpose.

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