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The Current Role of Stem Cell Transplantation in Multiple Myeloma

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1. Introduction

Multiple myeloma accounts for 10% of hematological cancers and 1% of all cancers. It is currently the most common indication for ASCT in North America and Europe. ASCT remains the standard of care in eligible patients aged below 65-70 years (though age is not a criterion in the United States) performed either upfront or at relapse. It is mostly performed upfront after induction therapy. The attainment of complete response (CR) is held to be a surrogate for improved survival and is the aim of the ASCT. CR is characterized by undetectable serum and urine monoclonal proteins (by immnofixation), absence of plasmacytosis (<5% plasma cells in marrow), disappearance of plasmacytomas and stable or improving bone disease. Stringent CR (sCR) is a new criterion which refers to normalization of the free light chain ratios (FLC) as well as the absence of monoclonal plasma cells in the marrow. Very good partial response (VGPR) refers to the absence of monoclonal proteins by electrophoresis but not by immunofixation or more than 90% reduction in level of serum M component proteins as well as urinary M proteins less than 100 mg/24 hours.[1]

With conventional chemotherapy comprising melphalan and prednisolone, CR was attained in less than 5% patients. However the median OS in patients achieving CR was 5.1 years as compared to 3.3 years for other responders.[2] ASCT has helped improve CR and VGPR rates over and above CC and is usually performed after induction therapy as consolidation.

Introduction of agents like bortezomib, lenalidomide, thalidomide, liposomal doxorubicin has resulted in Higher rates of CR and very good partial response (VGPR).

Ongoing debates regarding redefining the inclusion criteria/timing and expected benefits of ASCT as compared to maintenance with these drugs however await further trials.

2. ASCT in myeloma

Prospective randomized trials have been conducted to evaluate the efficacy of ASCT in terms of attainment of CR, response rate (RR), improvements in progression free survival (PFS) and overall survival (OS) as well as transplant-related mortality (TRM). [3],[4],[5],[6],[7],[8]

CR rates, median PFS, median OS and TRM have ranged from 17 to 44.5%, 25 to 42 months, 47.8 to 67 months and 3 to 7%, respectively. [3],[4],[5],[6],[7],[8]

However, only two of the trials, the French Intergroup Study (IFM) [3] and the British (MRC VII trial,) [4] demonstrated a survival advantage with ASCT. The French trial demonstrated median OS of 57 months vs. 37 months and the British trial demonstrated a median OS of 54.1 months vs. 42.3 months of ASCT over conventional chemotherapy (CC).

However other trials had some deficiencies. The Spanish study (PETHEMA) demonstrated improved CR rates (30% vs. 11%) with ASCT as compared to CC but no improvement in OS (61 vs. 66 months). This has been ascribed to the fact that only responding patients were taken up for transplant. Refractory patients who were not taken up for the study could also have derived benefit from ASCT. [5]

Two of the trials were designed specifically to look at the effect of upfront vs. delayed transplant (in the case of relapse or refractory disease) upon the survival rates. There was no difference in OS though the French trial reported higher CR rates and better PFS in favor of early transplant. [6],[7]

In another large US intergroup trial comparing CC with ASCT no difference could be demonstrated partly because of the cross over allowed for transplant at relapse in patients on the CC arm as also the fact that the combination of total body irradiation and melphalan dose of 140 mg/m 2 rather than the standard 200 mg/m 2 resulted in a disappointing CR rate of 17%. [8]

The trials incorporating melphalan and TBI had lower CR rates (17-22%) [3],[8] as compared to those in which melphalan 200 mg/m2 was used resulting in CR rates of 30-44%. [4],[5],[6],[7] Thus melphalan 200 mg/m 2 is now the conditioning regimen of choice. These days, most centers claim a TRM of 1% or less, thus rendering ASCT an acceptably safe treatment modality.

CR has been demonstrated to be the most important factor influencing long term survival. In the French IFM study, patients achieving a CR/VGPR had significantly higher 5 year OS rates of 72% as compared to 39% among patients who had a PR. [3] In a retrospective analysis of 721 newly diagnosed patients who underwent ASCT it was found that patients achieving CR had a median survival of 9-14 years compared to 5.9 years for patients who achieved PR. [9]

3. Improving efficacy of ASCT

3.1 Induction therapy and ASCT

The most common treatment strategy involves use of induction chemotherapy followed by HDT- ASCT (in eligible patients).

Initial regimens (vincristine, adriamycin, dexamethasone /dexamethasone /thalidomide, dexamethasone)

Initially the most popular regimens used were single agent pulsed dexamethasone or vincristine, adriamycin and dexamethasone (VAD). Response rates (RR) of 40-43% (CR rates ranging from 0 to 3%) have been reported with dexamethasone. [10],[11],[12] With VAD RR ranging from 52 to 67% and CR rates ranging from 3 to 9% have been described. [13],[14]

Following VAD the next common induction regimen was the oral regimen of thalidomide and dexamethasone (TD). RR ranging from 76 to 80% and CR rates ranging from 7 to 25% have been observed. [12],[13],[14],[15]

After ASCT, CR rates ranging from 30 to 48.2% (post VAD induction) have been described. [13],[14],[16] However studies using thalidomide/dexamethasone and single agent dexamethasone have demonstrated essentially similar results. [10],[11],[12],[13],[14],[15],[16]

In a study it was found that at 6 months post-transplant, the benefit of ThalDex over VAD was not seen and the VGPR or better rates were comparable (44.4% in the ThalDex arm and 41.7% in the VAD arm). [14] Thus ASCT seems to cover for the seeming inefficiencies of these induction regimens.

4. Newer combinations

Bortezomib and dexamethasone

The doublet of bortezomib and dexamethasone (VD) has been associated with RR ranging from 67 to 88% (VGPR or better rates ranging from 23 to 47%) and CR/nCR rates ranging from 13 to 21%. Post-ASCT, RR in the range of 90%, CR/nCR rates of up to 35% and VGPR or better rates up to 62% have been described. [17],[18],[19],[20]

Lenalidomide and dexamethasone

Lenalidomide and dexamethasone (LD) use was associated with RR of 91% and 18% CR rates. In patients who underwent ASCT the 2 year OS and PFS was 92% and 83% respectively as compared to 90% and 59% for those who did not undergo ASCT. However the yield of stem cells diminished upon prolonged use of this combination and hence it has been suggested that an early stem cell harvest might be necessary in the case of patients planned for delayed ASCT. [21]

Bortezomib-based combinations with other drugs

Bortezomib, doxorubicin and dexamethasone (PAD) was evaluated as induction using bortezomib 1.3 mg/m 2 (PAD1, N=21) or 1.0 mg/m 2 (PAD2, N=20). Complete/very good partial response rates with PAD1/PAD2 were 62%/42% post-induction and 81%/53% post-transplant. PFS (29 vs. 24 months), OS (2 years: 95% vs. 73%) were statistically similar but favored PAD1 versus PAD2. [22] Thus standard dose bortezomib was associated with better response rates as compared to the lower dose in which however the toxicity was lesser. This result was also suggested in earlier reports. With low dose bortezomib, CR rates of 11% were seen which improved to 37% post-ASCT. [23] RR of 95% and CR rates of 24% was seen with standard dose bortezomib and post-ASCT CR rates improved to 57% (81% had VGPR or better responses). [24]

Liposomal doxorubicin-based regimens

Bortezomib, liposomal doxorubicin and dexamethasone have been used with RR 93% (63% VGPR or better) and CR rates of 43%. Following ASCT CR rates improved to 65% (75% of the responses were VGPR or better). [25]

In regimens excluding dexamethasone (Bortezomib, Liposomal Doxorubicin alone) RR of 79% and CR rates of 28% have been observed. [26]

The three drug regimen of dexamethasone, vincristine, liposomal doxorubicin (DVd) yielded response rates of 66%. [27] 4 drug regimens comprising of dexamethasone, vincristine, liposomal doxorubicin and thalidomide (DVd+T) have been used with RR 74-83% and CR rates varying from 10-36%. [28],[29]

Bortezomib and thalidomide/ lenalidomide combinations

The three drug combination (VTD) of bortezomib, thalidomide and dexamethasone has resulted in 87% RR and up to 36% CR/nCR rates. After ASCT, CR/nCR rates improved to 57%. VGPR or better rates were seen in 77% cases. In this GIMEMA trial the high CR rates achieved after induction with VTD were not influenced by the presence of deletion 13 or t(4;14) thus suggesting their role in overcoming high risk cytogenetics. [30]

Use of VDT PACE (cisplatin, doxorubicin, dexamethasone, etoposide) resulted in OR 89% and CR rates of 22%. After ASCT CR/nCR rates improved to 75%. [31]

The combination of lenalidomide, bortezomib, dexame-thasone yielded CR rates of 20% and RR of 87%. [32] Thus ASCT improves upon the response rates of the induction regimens including those incorporating newer agents.

4.1 Tandem transplants

Tandem transplants have been used to improve the results of ASCT. 69% CR rates were reported with tandem ASCT in a very select group of patients. [33] Barlogie reported a 41% CR rate with such a strategy (total therapy). [34] Attal et al compared single vs. tandem ASCT in 399 patients and found that though the CR rates were equivalent (42 vs. 50%), the 7 year EFS and OS were significantly improved (10% vs. 20% EFS, 21% vs. 42% OS), [35] while the Bologna [36] trial has not shown a significant benefit for tandem transplantation.

Tandem transplants are useful in patients having PR or stable disease in response to the first transplant and are not usually recommended in those who have had a CR or VGPR.

Additionally it has been suggested that the negative impact of having both cytogenetic abnormalities: deletion 13 and t(4;14), which were associated with very low VGPR rates with TD, were offset by tandem transplantation. The VGPR rates were 12% in this subgroup of patients as compared to VGPR rates of 41-50% in patients with either of these abnormalities when given an induction regimen comprising of TD. The 3 year PFS and OS were nearly identical after tandem ASCT (70% vs. 77% and 92% vs. 88%, respectively). [37]

4.2 Other agents in tandem ASCT

The total therapy II trial included thalidomide into the induction, consolidation, tandem ASCT and maintenance strategy. After transplantation the CR rate in the thalidomide arm was 62% vs. no thalidomide 43% and though the EFS improved (48% vs. 38%) there was no difference in OS because of the more aggressive nature of the disease at relapse in those who were on thalidomide. [38],[39]

The total therapy III trial has incorporated VDT-PACE into induction, consolidation, tandem ASCT and maintenance strategy and have reported 83% CR/nCR rates for patients 24 months into the program. [40]

With better CR/VGPR rates after a single ASCT seen upon incorporation of the newer induction regimens, the requirement of a tandem transplant is expected to reduce.

Use of drug combinations: Bortezomib and melphalan in the conditioning regimen

In a preliminary study, a combination of bortezomib and melphalan was used in the conditioning regimen in 35 poor risk patients (including those who did not achieve VGPR after a first transplant). Three months after ASCT, 63% VGPR including 31% CR was observed suggesting that the combination had the potential to better the responses seen with melphalan alone but this would require confirmation from other studies: especially from those in which bortezomib was used as the induction regimen. [41]

5. Renal failure and transplantation

The Arkansas group studied autologous SCT in 81 patients with renal failure (including 38 patients on dialysis). Melphalan 140 mg/m 2 appeared as effective as melphalan 200 mg/m 2 as a conditioning regimen and was less toxic. 13 (24%) of the 54 patients evaluable for renal function improvement became dialysis free at a median of 4 months after transplant. 5 year EFS and OS of 59 patients on dialysis at the time of ASCT were 24% and 36%. [42],[43]

The PETHEMA (Spanish) group reported studied 14 patients and reported a TRM of 29% and a 3 year OS of 49%. [44]

In another study involving 46 patients with myeloma and renal impairment (21% dialysis dependent), 15(32%) showed improvement of CrCl of at least 25% above baseline. TRM of 4% and 3 year PFS and OS of 36% and 64% were reported. [45]

6. Allogenic stem cell transplantation

Allogenic SCT has the potential to induce molecular remissions and is at least theoretically the only possible curative treatment modality. [46],[47] The high incidence of infections and GVHD has limited its utility.

Initial studies suggested a CR rate of 44%. The overall actuarial survival rate was 32% at 4 years and 28% at 7 years. The overall relapse-free survival rate of patients in CR after BMT was 34% at 6 years. [48]

Most studies have reported TRM's ranging from 37-55% while only the EBMT study (1994-1998) reported a TRM of 30%. [49] Data suggest that only 10-20% patients are long term survivors: many of them in molecular remission. [49],[50],[51],[52]

Neither use of peripheral blood stem cells or T cell depletion has resulted in a decrease in TRM. [53],[54]

In the Dutch-Belgian Hemato-Oncology Cooperative Group, T cell-depleted allogeneic transplantation in 53 patients resulted in a medial survival of only 25 months. [55]

A similar treatment strategy employed at Dana Farber in 66 patients resulted in a nonrelapse TRM of 35%, with a PFS at 4 years of 23%. [47]

The toxicities of the procedure limit it's use to the minority of patients who are less than 55 years of age and have a HLA matched donor. Even then, the high TRM results in short term

survival benefits in favor of the auologous transplant as compared to the allogenic transplant thus making this treatment strategy unviable at most centers. [56]

7. Reduced intensity allogenic transplantation

This treatment strategy was implemented in order to reduce the TRM while retaining the graft versus myeloma effect. [57],[58],[59],[60],[61],[62],[63]

The conditioning regimens consisted of 1) Fludarabine /melphalan with / without in vivo T cell depletion with antithymocyte globulin (ATG) or alemtuzumab or 2) low dose TBI with/without fludarabine. [57],[58],[59],[60],[61],[62],[63]

This strategy has also been associated with substantial toxicity with a TRM of approximately 20%, acute GVHD rates of 30% and chronic GVHD rates of 50%. Low tumor burden at time of transplantation was associated with better survival. [57],[58],[59],[60],[61],[62],[63]

8. Tandem autologous and reduced intensity allogenic transplantation

The strategy of reducing tumor load with autologous transplant and following up with reduced intensity allogenic transplantation has also been studied. In one major study, TRM at 100 days was 11%, the incidence of acute and chronic GVHD were 38% and 40% respectively: the CR rate being 73%. [64]

Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin has been studied and found to be effective with relatively low transplantation-related mortality: I year TRM of 26% and CR rate of 40%. [65]

RIST using TBI of 2 Gy as the conditioning regimen were associated with CR rates of 53-57%, chronic GVHD rates of 74% and an EFS of 36-37% with a PFS of 25-30% 6 years post transplant. [66],[67]

3 studies have compared tandem ASCT with tandem ASCT/ RIST. Tandem ASCT/RIST arms were associated with TRM ranging from 11-18%, 50% to 74% incidence of extensive chronic GVHD, one-third of the patients were on immunosuppressive drugs at 5 years, donor lymphocyte infusions were ineffective at relapse, and PFS and OS was similar to tandem ASCT except in the Italian study which found an increased CR rate and survival advantage with allogenic ASCT. [68],[69],[70] In view of these differing studies, the results of a major ongoing Bone Marrow Transplant Clinical Trial Network study are eagerly awaited.

In our opinion RIST should not be offered outside of a clinical trial in view of significant TRM and GVHD risks as compared to autologous SCT.

9. Conclusion

ASCT represents one of the most important therapeutic options in the treatment of eligible patients suffering from multiple myeloma.

Newer drugs like thalidomide, bortezomib and lenalidomide have resulted in a marked improvement in relapse rates.

Regimens like MPT (melphalan, prednisone and thalidomide), [71],[72],[73] MPV (melphalan, bortezomib and prednisone) [74] and MPR (melphalan, prednisone and lenalidomide) [75] have yielded impressive results with RR varying from 76% to 89% and CR rates varying from 15.6 to 30% in patients ineligible for transplantation.

The MPT regimen was in fact superior to the intermediate dose (melphalan 100 mg/m 2) ASCT. [73] However the survival benefit has to be assessed against high dose chemotherapy in order to claim equivalence or superiority to HDT-ASCT.

ASCT remains the standard of care in eligible patients. Better induction strategies will hopefully improve the results . There is a debate whether patients in CR/nCR or even VGPR after induction therapy should be subjected to upfront ASCT or placed on maintenance therapy. In such a situation ASCT could then serve as a treatment option at relapse. The role of allogenic transplantation also keeps evolving but is tempered by the spectre of increased procedure-related morbidity and mortality. Non myeloablative transplants done after initial ASCT offer some promise but at the expense of great morbidity and at present cannot be offered outside the purview of a clinical trial. .[76,77]

10. References

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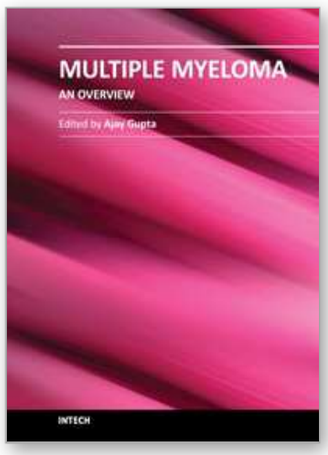

Multiple Myeloma - An Overview

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Multiple myeloma is a malignant disorder characterized by the proliferation of plasma cells. Much insight has been gained into the molecular pathways that lead to myeloma and indeed much more remains to be done. The understanding of these pathways is closely linked to their therapeutic implications and is stressed upon in the initial chapters. Recently, the introduction of newer agents such as bortezomib, lenalidomide, thalidomide, liposomal doxorubicin, etc. has led to a flurry of trials aimed at testing various combinations in order to improve survival. Higher response rates observed with these agents have led to their integration into induction therapies. The role of various new therapies vis a vis transplantation has also been examined. Recent advances in the management of plasmacytomas , renal dysfunction, dentistry as well as mobilization of stem cells in the context of myeloma have also found exclusive mention. Since brevity is the soul of wit our attempt has been to present before the reader a comprehensive yet brief text on this important subject.

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