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Controversies in Autologous Stem Cell Transplantation for the Treatment of Multiple Myeloma

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1. Introduction

The treatment paradigm for multiple myeloma has evolved considerably over the past three decades with the incorporation of autologous stem cell transplantation (ASCT) in upfront therapy for eligible patients, and the use of novel agents. As a result, although multiple myeloma remains an incurable disease, clinical outcomes have significantly improved. In this chapter we will review the seminal studies that established the role of ASCT in multiple myeloma and as well as the current controversies with regard to the role of ASCT in the management of myeloma in the era of novel agents. We will review conditioning regimens, post-transplant maintenance strategies with novel agents and immune modulation. We will summarize the current data on early versus late ASCT, single versus tandem transplant and the role of ASCT in patients with relapsed or progressive disease.

2. The role of autologous stem cell transplantation in multiple myeloma

The advent of autologous stem cell transplantation has changed the therapeutic landscape for the management of multiple myeloma and has been the standard frontline therapy for younger patients with normal renal function since the 1990's. The standard of care for multiple myeloma patients prior to the incorporation of ASCT was conventional chemotherapy using melphalan and prednisone with the primary goals of treatment being achievement of partial response or disease stabilization. Treatment complications and later resistance were associated with poor outcomes with median overall survival ranged between two and three years.

High-dose chemotherapy was initially explored as a therapeutic approach in the 1980's after a landmark study demonstrated its effectiveness in inducing 100-percent complete remission rates in nine high-risk multiple myeloma and plasma cell leukemia patients after pre-conditioning with high-dose melphalan. The observation that high-dose melphalan had significant anti-tumor activity and could overcome primary drug resistance was confirmed in a later study.

Since its initial description, there have been seven randomized clinical trials comparing high-dose ASCT to conventional chemotherapy (Table 1). The first of these trials was conducted by the Intergroupe Français du Myélome (IFM) in which 200 untreated multiple myeloma patients under 65 years of age were randomized to receive either conventional chemotherapy or high dose chemotherapy in combination with ASCT. Response rates were significantly higher in patients receiving high-dose chemotherapy and ASCT compared to those who received conventional chemotherapy alone (81% vs 57%, $p < 0.001$). Furthermore, patients who received high-dose therapy had a higher probability of 5-year event-free survival (28% vs 10%, $p = 0.01$) and estimated 5-year rate of overall survival (52% vs 12%, $p = 0.03$). Seven years later, the findings from the IFM study were corroborated by the British Medical Research Council Myeloma VII Trial (MRCM-VII) in a larger 407 patient multicenter study.

These findings prompted modifications to the disease response criteria as proposed by the International Myeloma Working Group as the achievement of complete responses (CRs), which were rare using conventional chemotherapy, became more achievable and, most importantly, were found to correlate with survival endpoints.

An additional five prospective randomized trials comparing ASCT to conventional chemotherapy followed. Most, but not all, demonstrated superiority of ASCT to conventional chemotherapy with respect to higher rates of CR and very good partial responses (VGPR) which ultimately translated into longer progression-free survival (PFS). An overall survival (OS) benefit was reported in three of the seven studies [5,6,12]. Differences in methodology and trial design between studies may account for some of the discordance in results. A systematic review and meta-analysis of these randomized trials reported improved overall median PFS with no significant improvement in OS following ASCT when compared to conventional chemotherapy.

In summary, high dose chemotherapy and ASCT has markedly improved the depth of response, overall response rates, and length of progression-free survival in multiple myeloma patients. Most importantly, ASCT has improved overall survival from a median of 36 months to 50-55 months, thereby establishing it as the standard of care for multiple myeloma patients under the age of 65 with normal renal function. However, there remains considerable heterogeneity between myeloma patients with regard to underlying disease characteristics and post-ASCT clinical responses. A number of prognostic markers have been identified that influence disease response to chemotherapy, ASCT and survival, specifically age, elevated β -2-microglobulin levels, LDH and serum free light chain ratio. Additionally, the recognition of recurrent chromosomal abnormalities, which have been reported in as many as 90% of patients has allowed myeloma patients to be categorized into low, in-

intermediate and high risk groups on the basis of these aberrations. Translocation (4;14), t(14;20), deletion 17p and gain of 1q have been well associated with poor disease responses and negatively impact overall survival. A recent update from the IFM group have demonstrated a 75% 8-year survival rate in patients who did not have these chromosomal abnormalities and β -2-microglobulin values less than 5.5mg/L.

Trial/group (Year of publication)	No. Patients	Age, years	Median Follow-up	Response Rates (%) (CCT vs ASCT)	EFS, mos (CCT vs ASCT)	OS, mos (CCT vs ASCT)
ORR: 57 vs 81						
IFM, (1996)	200	<65	7 years	CR: 5 vs 22	18 vs 28	44 vs 57
VGPR: 9 vs 16						
MAG91 (1998)	185	55-65	58 mos	ORR: 62 vs 86 CR: 5 vs 19	19 vs 24	50 vs 55
ORR: 67 vs 90						
BMRC VII, (2003)	407	<65	42 mos	CR: 8 vs 44 PR: 40 vs 42	19 vs 31	42 vs 54
ORR: 42 vs 73						
Italian MMSG M97G(2004)	194	50-70	39 mos	nCR: 6 vs 25	15.6 vs 28	42 vs 58+
ORR: 77 vs 70						
CR +MRD: 20 vs 36						
MAG95 (2005)	190	55-65	120 mos	PR: 38.5 vs 26 MR: 18 vs 7	19 vs 31	42 vs 54
PETHEMA, (2005)	164	<65	44 mos	CR: 11 vs 30	33 vs 42	66 vs 61
US Intergroup 9321 (2006)	516	\leq 70	76 mos	CR: 15 vs 17	14% vs 17%**	38% vs 38%**

Abbreviations: IFM: Intergruope Français du Myélome, MAG: Myélome Autogrefe, BMRC: British Medical Research Council, MMSG: Multiple Myeloma Study Group, PETHEMA: Programa para el Estudio de la Terapéutica en Hemaopatia Maligna, ORR: Overall response rate, CR: Complete remission, nCR: Near complete remission, VGPR: Very good partial response, PR: Partial response, MRD: Minimal residual disease, MR: Minimal response

** 7-year estimated EFS and OS rate

Table 1. Randomized trials comparing ASCT to conventional chemotherapy (CCT)

While clinical outcomes have improved significantly since the widespread implementation of ASCT, there are several unanswered questions relating to the use of ASCT in multiple myeloma, particularly in the era of novel therapies, which remain as areas of active investigation. However, before these controversies can be fully addressed, it is important to understand the role of novel agents and their impact on myeloma management before discussing their current use in the context of ASCT.

3. Immune modulation and the advent of novel agents

The concept of immune modulation was formulated and developed after a greater understanding of the complex interaction between myeloma cells and their microenvironment as well as the discovery that myeloma cells, through a variety of mechanisms, are inherently able to evade host natural immune defenses, thereby potentiating their own survival. The immune dysregulation that is known to accompany multiple myeloma is believed to be the result of multiple biological pathways and mechanisms including excess production of myeloma-derived cytokines, inadequate antigen presentation, resistance to NK-cell lysis and impaired activity of B, T and NK cells. Additionally, multiple myeloma is also associated with defective humoral and cellular immunity leading to abnormal B-cell differentiation and function. Reduced numbers of CD4⁺ T cells, abnormal Th1/Th2 CD4⁺ T-cell ratios, impaired cytotoxic T-cell responses, dysfunction of NK and NK T-cells and abnormal dendritic cell function further compound the immune dysfunction associated with multiple myeloma.

The immunomodulatory drugs (IMiDs), lenalidomide and pomalidomide are thalidomide analogs that were specifically developed in response to the resurgence of interest in thalidomide after it was incidentally discovered to be an effective treatment in patients with cutaneous leprosy presumably through inhibition of TNF α . Subsequent preclinical trials revealed that thalidomide, in fact, had several favorable properties that would optimize its use as an anti-cancer agent.

The IMiDs, were created with the intent to maximize the pleiotropic activity directed against myeloma cells that was demonstrated by thalidomide, and, in fact are 50,000 times more potent than thalidomide in their immunomodulatory properties, including CD4⁺ and CD8⁺ T-cell costimulation, Th1 cytokine production, NK and NK T-cell activation, and antibody-dependent cellular cytotoxicity. Furthermore, they also disrupt the interaction between myeloma cells and the tumor microenvironment through potent inhibition of angiogenesis and downregulation of inflammatory cytokines, specifically TNF α , from peripheral blood mononuclear cells. The IMiDs also directly exert anti-tumor proliferation effects. Additionally the IMiDs are more capable of stimulating T-cells without incurring the same degree of toxicity as thalidomide. The manipulation of the immune system by IMiDs has established their efficacy in the management of multiple myeloma. Lenalidomide and thalidomide, in addition to the proteasome inhibitor, bortezomib, are considered the main novel agents, and, in light of their significant disease activity, are now routinely integrated into multiple myeloma management in ASCT eligible and ineligible patients.

4. The impact of novel agents on induction and stem cell mobilization

Prior to the widespread use and incorporation of novel agents, the standard induction regimen was vincristine, doxorubicin and dexamethasone (VAD). Dexamethasone was the most active drug in this regimen and has long since remained the cornerstone of upfront treatment for multiple myeloma. The investigation and incorporation of novel agents into induction chemotherapy regimens was prompted by the discovery that the quality of disease response following induction therapy, preceding ASCT, corresponded to better clinical outcomes, including subsequent response to ASCT, PFS and OS. Novel agents were initially investigated to determine whether the rates of these responses could be improved. Table 3 summarizes the results of published studies using novel agents as part of induction therapy prior to ASCT.

Thalidomide-based induction regimens were initially compared to VAD and were found to produce higher VGPR, but not CR, rates prior to transplant. However, the increased incidence of thromboembolic complications and drug toxicity rendered the overall benefit of thalidomide containing regimens somewhat modest. A 10-year clinical follow-up study of 169 myeloma with advanced or refractory disease who were initially treated with thalidomide demonstrated remarkably improved event-free survival and OS in patients with normal cytogenetics and non-lambda light chain isotype.

Lenalidomide and high-dose dexamethasone (RD) was compared to lenalidomide and low-dose dexamethasone (Rd) as initial therapy in transplant eligible and ineligible patients and, while improved response rates (\geq VGPR) were significantly improved in patients receiving RD, increased toxicities and mortality were also more pronounced with this regimen, especially in patients older than 65 years of age. Furthermore, ASCT in combination with RD or Rd improved 3-year OS rates compared to patients who did not undergo ASCT [92% vs 79%]. Three drug-combinations using lenalidomide, bortezomib and dexamethasone (RVD) have also been investigated in a few phase I/II studies and have shown even greater improvements in response rates pre and post-transplant.

The proteasome inhibitor, bortezomib, in combination with dexamethasone was initially discovered to significantly improve near complete remission (nCR) and CR rates in the landmark IFM2005-1 trial when it was compared to VAD, VAD and dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) consolidation, and bortezomib and dexamethasone followed by DCEP consolidation followed by ASCT. Bortezomib-containing regimens resulted in higher CR/nCR rates irrespective of disease stage or cytogenetic risk. Post-transplant, these improved response rates were associated with improved CR, nCR and VGPR rates as well as improved PFS after a median follow-up of 32 months compared to patients treated with VAD alone (36 mos vs 30 mos). In the VISTA trial, the addition of bortezomib to melphalan and prednisone also produced longer OS, and was not found to incur more resistant relapses in a long term follow-up study. The IFM 2005-1 and VISTA trials were critical in establishing the role of bortezomib in induction therapy for myeloma. To further improve the depth of disease response several phase II and III clinical trials have evaluated the efficacy of adding a third novel agent, either lenalidomide or thalidomide, to

the bortezomib and dexamethasone backbone, and have demonstrated improved responses following the addition of a third agent.

Although novel agents have vastly improved the quality of disease response as well as overall response rates in the pre- and post-transplant settings, the use of these agents as part of induction therapy has resulted in greater difficulties with stem cell collection prior to autologous transplant, particularly with the use of lenalidomide and, to a lesser extent, bortezomib although the exact mechanisms by which stem cell collection is hindered has not yet been fully elucidated. To address this issue, the International Myeloma Working Group has recommended early stem cell mobilization, following 3-4 cycles of induction therapy. Mobilization using G-CSF alone or in combination with cyclophosphamide is typically considered adequate; and while a large multi-center randomized phase III trial demonstrated a significant improvement in the number of CD34+ cells/kg collected in patients receiving G-CSF and the CXCR4 inhibitor, plerixafor (AMD3100) compared to G-CSF and placebo, the routine use of plerixafor upfront for mobilization remains controversial.

5. The importance of pre-transplant disease response

Complete remissions in the pre-ASCT era were rare, but have now become a very attainable and desirable treatment goal in the pre and post-transplant settings, especially as they are considered to be strong surrogate markers for progression-free and survival overall survival in several studies. The prognostic impact of CR was not fully appreciated until ASCT was adopted as frontline therapy in the management of multiple myeloma, and this is reflected in the International Myeloma Working Group response criteria by the introduction of stringent CRs to further qualify the depth of response [Table 2]. Furthermore, the duration of CR is also described as a favorable prognostic variable ; however, in several patient subgroups, including those with a prior history of monoclonal gammopathy of undetermined significance and smoldering myeloma or with low-risk disease achievement of CR appears to be of less importance.

sCR: Meets criteria for CR plus normal FLC ratio and no clonal cells bone marrow IHC or immunofluorescence

CR: Absence of M protein in serum and urine by immunofixation, < 5% bone marrow plasma cells, no increase of lytic bone lesions, disappearance of soft tissue plasmacytomas

VGPR: Serum and urine M protein detectable by immunofixation but not on electrophoresis OR ≤ 90% reduction in serum M-protein plus urine M-protein <100mg/24hr

Abbreviations: IMWG: International Myeloma Working Group, sCR: stringent complete remission, CR: Complete Remission, VGPR: Very Good Partial Response, FLC: Free Light Chains, IHC: Immunohistochemistry

Table 2. IMWG Complete Response Criteria (Durie et al, Leukemia 2006)

Author, date of publication	No. of patients	Treatment regimen	Median follow-up	RR after induction (%)	RR after transplant (%)	PFS, median	OS
Rajkumar, 2006	207	TD vs Dex	207	CR: 4 vs 0 ≥ VGPR: --- ≥ PR: 63 vs 41	CR: --- ≥ VGPR: --- ≥ PR: ---	---	---
Lokhorst, 2010	536	VAD vs TAD	52 mos	CR: 2 vs 3 ≥ VGPR: 18 vs 37 ≥ PR: 57 vs 71	CR: 12 vs 14 ≥ VGPR: 44 vs 54 ≥ PR: 76 vs 84	22 vs 34 mos	60 vs 73 mos
Harousseau, 2010	482	VAD vs VD	31.2 mos	CR/nCR: 6.4 vs 14.8 ≥ VGPR: 15.1 vs 37.7 ≥ PR: 62.8 vs 72.5	CR/nCR: 18.4 vs 35 ≥ VGPR: 37.2 vs 54.3 ≥ PR: 77.1 vs 80.3	29.7 vs 36 mos	3 yr OS 77.4% vs 81.4%
Cavo, 2010	480	VTD vs TD	36 mos	CR/nCR: 31 vs 11 ≥ VGPR: 62 vs 28 ≥ PR: 93 vs 79	CR/nCR: 55 vs 41 ≥ VGPR: 82 vs 64 ≥ PR: 93 vs 84	68 % vs 56%*	86% vs 84%*
Rajkumar, 2010	445	RD vs Rd	35.8 mos	CR: 5 vs 4 ≥ VGPR: 71 vs 26 ≥ PR: 81 vs 70	---- ---- ----	19 vs 25 mos	2yr OS 87% vs 75%
Moreau, 2011	199	VD vs vtD	32 mos	CR: 22 vs 31 ≥ VGPR: 36 vs 49 ≥ PR: 81 vs 88	CR: 52 vs 61 ≥ VGPR: 58 vs 74 ≥ PR: 86 vs 89	30 vs 26 mos	---
Rosinol, 2012	386	VTD vs TD vs VBMCP/VBAD/B	35.2 mos	CR: 35 vs 14 vs 21 ≥ VGPR: 25 vs 15 vs 15 ≥ PR: 25 vs 33 vs 39	CR: 46 vs 24 vs 38 ≥ VGPR: --- ≥ PR: ---	56.2 vs 28.2 vs 35.3 mos	4yr OS 74% vs 65% vs 70%
Sonneveld, 2012	833	VAD vs PAD	41 mos	CR/nCR: 15 vs 11 ≥ VGPR: 14 vs 42 ≥ PR: 54 vs 78	CR/nCR: 15 vs 31 ≥ VGPR: 36 vs 62 ≥ PR: 75 vs 88	28 vs 35 mos	5 yr OS, 55% vs 65%

Abbreviations: TD: Thalidomide and Dexamethasone, Dex: Dexamethasone VAD: Vincristine, Adriamycin and Dexamethasone, TAD: Thalidomide, Adriamycin and Dexamethasone, VD: Bortezomib and Dexamethasone, VTD: Bortezomib, Thalidomide and Dexamethasone, RD: Lenalidomide and high-dose dexamethasone, Rd: Lenalidomide and low-dose dexamethasone, PAD: Bortezomib, Adriamycin and Dexamethasone, vtD: reduced dose bortezomib, thalidomide and Dexamethasone

Table 3. Published phase III studies using novel agents as part of induction therapy prior to ASCT

6. Early versus late transplant

Only one randomized trial has compared upfront ASCT to late ASCT at the time of relapse. Upfront ASCT improved event-free survival and quality of life compared to patients treated with conventional chemotherapy and who underwent ASCT as rescue treatment at the time of relapse; interestingly there was no appreciable difference in 5-year overall survival between the arms. However, in the era of novel agents and resultant improvements in complete remission rates, the question as to whether ASCT could potentially be delayed until disease relapse or progression has, again, resurfaced. The International Myeloma Working Group recommends that all eligible patients be offered ASCT at some point in their disease course and while there are no published randomized phase III trials incorporating the use of novel agents in induction therapy to support the use of ASCT upon disease relapse, many clinicians opt to collect stem cells early and preserve them for use following disease relapse. We believe that upfront ASCT should be the standard of care until ongoing trials establish that delayed ASCT after novel agents has a role.

7. Single ASCT versus tandem transplant

Tandem ASCT, as part of a more intensified treatment strategy (“total therapy”) was initially shown to improve CR rates, EFS and OS in comparison to standard therapy. The superiority of double ASCT was later appreciated in a landmark randomized clinical trial which demonstrated significantly improved OS, particularly in patients who had not achieved VGPR following transplant. Several other randomized trials have also attempted to compare single versus double ASCT and have reported conflicting results regarding the superiority of one approach over the other. A recent meta-analysis attempted to answer this question and concluded that tandem transplant offered no benefit in terms of disease outcomes and was, in fact, associated with greater morbidity; however, this analysis has received criticism due to the heterogeneity of the selected studies which were evaluated as well as variability in treatment methodology. A more recent analysis suggests that tandem ASCT does offer a survival benefit. Most clinicians speculate that tandem and single transplants are equivocal, however, there have been no definitive trials evaluating this issue and it remains an area of considerable debate.

8. Methods to improve conditioning regimens: The addition of total body irradiation or other agents to high-dose melphalan

The quality of disease response following pre-transplant conditioning is critical to the success of ASCT. High dose melphalan 200mg/m² is the standard conditioning chemotherapy regimen prior to autologous HSCT in multiple myeloma as this approach has demonstrated superior overall survival rates in comparison to chemotherapy alone. Various approaches to

improve responses to this conditioning regimen while minimizing toxicities have been evaluated in a number of studies.

Total body irradiation (TBI) in combination with melphalan demonstrated improved CR rates, relapse and progression rates and five year OS rates when compared to TBI and cyclophosphamide as a myeloablative conditioning regimen in myeloma patients undergoing allogeneic HSCT. A landmark study, however, in which melphalan and TBI was compared with high-dose melphalan 200mg/m² demonstrated more rapid hematologic recovery, reduced transfusion requirements, shorter hospitalization and improved survival in patients receiving high-dose melphalan alone. As such, the routine use of TBI in conjunction with melphalan is not widely used.

The alkylating agent, busulfan, has been used in several studies in combination melphalan with promising outcomes, particularly in patients with non-remission disease at the time of transplant. A recent analysis of multiple myeloma patients treated with oral busulfan and melphalan 140mg/m² compared to standard melphalan 200mg/m² did demonstrate improved median PFS (41 mos vs 31 mos, $p=0.009$), however, the increased incidence of veno-occlusive disease and transplant related mortality counteracted the benefits; additionally, patients who received busulfan had less access to salvage therapies using novel agents than patients who had relapsed following treatment with melphalan 200mg/m².

The Intergroupe Francophone du Myelome study group also evaluated the efficacy of adding bortezomib to high-dose melphalan in a recent phase II study and were able to demonstrate, that, in comparison to historical controls, patients treated with the bortezomib and melphalan achieved higher CR rates (35% vs 11%, $p=.001$) with no increase in hematologic toxicity.

9. Novel agents as post-transplant maintenance therapy

Maintenance with interferon, steroids, and chemotherapy has been tried in many centers for over 30 years with no clear benefit. Maintenance interferon frequently resulted in worsened quality of life; furthermore, future development of therapy-related myelodysplastic syndrome following chemotherapy led to these maintenance treatments to fall out of favor. The availability of novel agents and their tolerable toxicity profiles has renewed interest in post-transplant maintenance treatment. The results of this approach have, thus far, been encouraging, including upgrades in disease responses and improvements in PFS/EFS, and OS in many studies; however, none of these agents are currently approved in the post-transplant setting. The recently released consensus statement from the International Myeloma Working Group does not advocate for or against maintenance therapy and recommends that the decision to use maintenance therapy be made on an individualized basis. In the following paragraph we will review various agents with a brief summary of the randomized trials data.

9.1. Thalidomide

Thalidomide maintenance therapy following ASCT has been evaluated in six randomized clinical trials all of which have reported a significant improvement in progression free survival in patients receiving thalidomide maintenance versus the comparator arm, but only 3 had shown improvement in OS by 6-9 months. Two meta-analyses have confirmed improved OS with thalidomide maintenance. However, most patients (> 50%) eventually discontinued thalidomide, between 7 months and 2 years of treatment, due to side effects, particularly development of peripheral neuropathy. Interestingly, thalidomide maintenance does not benefit patients with poor-risk cytogenetics, and, in fact, this patient subset was shown to have a shorter survival duration. Similar results from the Total Therapy 2 study were reported although a longer follow up showed improvement in long-term survival in high risk disease, although the main impact was most appreciable in patients with favorable cytogenetics.

9.2. Lenalidomide

Lenalidomide has a favorable toxicity profile, and its efficacy extends beyond inhibition of the growth of myeloma cells as the drug also causes alterations within the bone marrow microenvironment leading to an enhancement of immune responses, thereby making it an ideal drug for post-transplant maintenance. Two very recently published trials from the Cancer and Leukemia Group B (CALGB) and IFM evaluated the efficacy of lenalidomide following transplant and demonstrated that lenalidomide maintenance therapy was associated with a significant improvement in PFS compared to placebo (48 vs 30.9 mos, and 41 vs 24 mos in the CALGB and IFM studies, respectively). The benefits of lenalidomide maintenance were appreciated across all patient subgroups, including those with high-risk cytogenetics, although the data is limited to a small number of patients in the IFM study, β 2-microglobulin and response following transplant. In the IFM-2005-02 trial, patients were given two courses of lenalidomide as consolidation treatment which led to an upgrade in the number of disease response with rates of CR increasing from 14% to 20% and responses higher than or equal to VGPR from 58% to 67%. The side effects were tolerable, mostly hematologic, and responded well to dose adjustments, supportive growth factor injections and transfusion support. A meta-analysis by the International Myeloma Working Group, which included a total of 1380 patients demonstrated a 65% reduction in risk of disease progression for patients treated with lenalidomide maintenance therapy. There is a notable increased risk of second cancers in association with this drug as noted by both IFM and CALGB. The IFM reported the incidence of second cancers as 3.1 per 100 patient years, compared to 1.2 per 100 patient years in the placebo group ($p = 0.002$). In the CALGB study, 8% of patients treated with lenalidomide developed second cancers, compared to 3% in the control arm.

9.3. Bortezomib

An interesting study to evaluate the effect of minimal residual disease, by qualitative and real-time quantitative polymerase chain reaction (RQ-PCR) after ASCT showed that a con-

solidation regimen comprised of bortezomib, thalidomide, and dexamethasone (VTD) increased CRs from 15% after ASCT to 49% after VTD. Most importantly, molecular remissions increased from 3% after ASCT to 18% after VTD. No patients had relapsed at the time of reporting (median follow-up, 42 months). These unprecedented levels of tumor cell reduction are very encouraging and have laid the foundation for a new area of investigation to better evaluate the depth of treatment response in myeloma.

A subsequent randomized phase 3 study specifically assessed the efficacy and safety of consolidation therapy using bortezomib, thalidomide and dexamethasone (VTD) versus thalidomide and dexamethasone (TD). Before starting consolidation, CR/nCR rates were not significantly different in the VTD and TD arms (63.1% vs 54.7%, respectively). However, after consolidation, CR (60.6% vs 46.6%) and CR/nCR (73.1% vs 60.9%) rates were significantly higher for VTD-treated versus TD-treated patients. With a median follow-up of 30.4 months from start of consolidation, 3-year PFS was significantly longer for the VTD group compared to TD (60% vs 48%). The VTD consolidation therapy was shown to significantly improve clinical outcomes after ASCT.

The evaluation of novel agents in the post-transplant setting has resulted in significant improvements in disease responses and survival endpoints. Moreover combination regimens in the form of consolidation and/or long term maintenance are well tolerated with further improvements and achievement of molecular remissions. Future studies to determine the optimal duration of maintenance therapy are urgently needed.

10. Combined ASCT/Allogeneic Hematopoietic Stem Cell Transplant approaches

Early trials evaluating myeloablative allogeneic stem cell transplantation in the treatment of multiple myeloma demonstrated improvements in relapse and progression rates attributed to graft versus myeloma effects; however, development of graft versus host disease and infectious complications resulted in high transplant-related mortality [TRM]. A critical advantage of allogeneic transplantation was the development of reduced intensity conditioning (RIC) regimens that were associated with decreased toxicities and profound graft versus tumor effects as demonstrated in early trials evaluating the efficacy of RIC in relapsed and refractory myeloma patients. However, higher rates of disease progression and relapse, were noted and attributed to the late use of this modality underscoring the importance of using effective regimens early before the disease becomes refractory especially since the goals of allogeneic transplant are curative in intent.

Combined sequential therapy utilizing ASCT for cytoreduction followed by RIC allogeneic transplant (i.e. the auto-allo approach) to exploit the graft versus myeloma effect has been compared to tandem ASCT in several studies; randomization in these trials was biological; i.e. patients with an HLA-matched sibling received RIC allogeneic transplant and all others underwent tandem ASCT. The first published study from the IFM compared tandem ASCT in 219 patients to auto-allo in 65 patients with high-risk multiple

myeloma and reported no significant difference in response rates or event-free survival between groups; however, there was an observed trend toward better overall survival in patients treated with tandem ASCT; these findings remained unchanged in a long-term follow-analysis from the same group. Subsequent comparisons have reported improved CR rates and PFS durations and only one has shown superior OS in auto-allo treated patients. However a recently published large multi-center phase 3 study reported that the auto-allo approach was not superior to auto-auto in terms of progression-free survival (43 % vs 46% at 3 years) or 3-year OS (77% vs 80%). Additionally, there was no significant difference in the development of grade 3-5 adverse events between groups by three years (46% vs 42%). Further modifications to allogeneic transplantation would be needed to offset the graft versus myeloma effect as well as the increase in transplant-related mortality. The Eastern Cooperative Oncology Group conducted a small trial in which 32 patients received non-myeloablative matched sibling donor transplant following ASCT and reported a 78% ORR (30% CR and 48% PR) with low TRM; however over half of patients developed chronic GVHD. A recent Swedish study compared auto-allo approach to single ASCT in 357 previously untreated multiple myeloma patients and was demonstrated that the auto-allo approach was superior in terms of PFS, OS and relapse rate with a 12% nonrelapse mortality rate. The data remain conflicting; however, a meta-analysis reviewing outcomes on 7 published and unpublished studies concluded that the auto-allo approach offers no benefit compared to autologous transplant approaches and is associated with higher TRM. The International Myeloma Working Group does not recommend the routine use of allogeneic transplantation, and, in fact, recommends consideration of RIC transplant only in the setting of a clinical trial.

11. Novel immunotherapy strategies

The post-transplant period is the ideal time point for immunotherapy as the disease burden is, theoretically, low. Immune function remains depressed following high-dose therapy for many months. Ex vivo expansion and subsequent transfer of autologous stimulated T cells may enhance host antitumor immunity and may also allow for enhancement of a post-transplant vaccination strategy against tumor-directed antigens. Early trials focused on the generation of antibodies against myeloma specific antigens. The idiotype [Id] protein has, in a number of pre-clinical studies, demonstrated powerful antibody responses that, in vitro, resulted in apoptosis of myeloma cells. However, durable clinical responses were not seen in subsequent clinical studies. Idiotype-pulsed dendritic cell vaccinations following ASCT have also demonstrated that cellular immune responses can be elicited in the context of minimal residual disease following transplantation; however, again, there is no definitive evidence that these vaccination strategies alter the course of disease. It has been suggested that the immune dysfunction in myeloma patients is the primary barrier to successful vaccination strategies. A low number of T-cells with activity against myeloma have been detected in multiple myeloma patients. Several attempts to expand T cells, collected from the peripheral blood of affected patients, and

infused after ASCT, have shown that rapid recovery of T-cell numbers can be achieved but, unfortunately, with no clear anti-myeloma benefits. The results of one interesting study in which myeloma patients received the conjugated pneumococcal vaccine before T-cell collection and after ASCT showed profound antibody responses, suggesting that T cells may improve immune responses to vaccination. A subsequent study in which adoptive transfer of vaccine primed autologous T-cells to the htert/survivin multi-peptide vaccine, a target in myeloma cells, corroborated these findings and demonstrated that vaccination was associated with robust antibody responses in most patients; however, again, there was no definitive activity directed against myeloma cells specifically. Clinical trials building on the expansion of T cells and targeting various myeloma antigen such as MAGE A3 and NYESO1 are ongoing. Of important note, several studies focusing on expansion of marrow infiltrating lymphocytes (MILs) had yielded interesting results with regards to antimyeloma activities, but, again, the clinical benefit was quite limited.

Several antibody trials in myeloma are ongoing. A recently published phase 1 study has provided encouraging evidence that elotuzumab in combination with lenalidomide yields impressive responses in relapsed and refractory myeloma; whether the responses seen in the relapsed setting can be confirmed and implemented in patients with minimal disease states would require further investigation. In light of these findings, it is suggested that enhancement of T-cell function could potentially lay the groundwork for subsequent trials aimed to improve immune function, and by extension, clinical outcomes following ASCT in myeloma patients.

12. Salvage ASCT for relapsed disease

At present, the optimal treatment approach for patients with relapsed disease following initial ASCT has not yet been defined. Potential options include treatment with novel agents, conventional chemotherapy or a second salvage ASCT. While the data evaluating the role of a second ASCT are limited, several small retrospective analyses have demonstrated that it is an effective and well tolerated treatment option with overall response rates reported between 55-90%. Overall survival and progression free survival is significantly improved for patients who have received fewer lines of therapy prior to transplant and for those who have experienced a late disease relapse. However, the length of time which constitutes a late relapse has varied between studies, ranging between 12 months and > 36 months. A recently published retrospective review suggested a time-dependent association between remission duration following initial ASCT and PFS following transplant. Patients who relapsed within 18 months of initial ASCT had significantly shorter PFS compared to those who relapsed between 18 and 36 months and those who relapsed 36 months or more (4.2 mos vs 13.8 mos vs 49.1 mos) [111]. Although larger studies would provide greater insight regarding the optimal timing of a second transplant, consideration of salvage ASCT is generally regarded as a feasible approach which offers the greatest benefit in select patients who have relapsed at least more than 12 months after their initial ASCT. Salvage allogeneic transplant following failure of initial autografting has also been compared to salvage ASCT in a limited number

of studies and has been reported to have comparable PFS due to lower rates of disease progression following allogeneic transplant, but superior OS in autografted patients; furthermore, the increased incidence of graft versus host disease in allografted patients has rendered this approach less preferable. Refinements in allogeneic transplant techniques may potentially generate renewed interest in this treatment approach.

13. Conclusion

The widespread implementation of autologous stem cell transplantation, in conjunction with novel agents, has revolutionized the management of multiple myeloma and has markedly altered the natural history of the disease by improving disease responses and response duration, which, by extension, have led to significant improvements in overall survival. While treatment options for multiple myeloma have expanded considerably over the past several decades, long-term survivorship remains low. Continued investigative efforts are targeted towards refining our current treatment modalities with the hope of ultimately developing a treatment approach which results in cure.

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