Clinical Decision Making in Multiple Myeloma for the Transplant-Eligible Patient—Upfront Transplant Versus Maintenance Therapy

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Introduction

High dose chemotherapy with autologous stem cell transplant (ASCT) following induction therapy has been the mainstay of treatment of multiple myeloma since the mid-90s given the improvement in progression-free survival (PFS) and potentially overall survival (OS). However, with the development of novel therapies, the role and optimal timing of ASCT have come into question. The role of consolidation therapy posttransplant as well as maintenance therapy have also been investigated. Given the long-established correlation between depth of response and prolonged survival, there has been an increasing interest in striving for minimal residual disease (MRD) as a surrogate end point for risk-adapted treatment, particularly in the consolidation and maintenance setting. Here, we review the current progress in the treatment of transplant-eligible multiple myeloma (MM) as it pertains to the role of ASCT, consolidation, and maintenance therapy.

The Role of High Dose Chemotherapy With Autologous Stem Cell Rescue in Multiple Myeloma in the Era of Conventional Cytotoxic Chemotherapy

Before the introduction of proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs), high dose melphalan with ASCT following induction therapy was considered the standard approach for transplant-eligible patients with newly diagnosed MM. The first randomized controlled trial from the Intergroupe Francais du Myelome (IFM90), published in 1996, randomized newly diagnosed MM patients to an older chemotherapy regimen (vincristine/carmustine, cyclophosphamide, prednisone alternating with carmustine, vincristine, adriamycin, prednisone; VMCP/BVAP) for 12 cycles versus 4 to 6 cycles of VMCP/BVAP followed by high dose therapy with autologous bone marrow transplant.[1] Those patients randomized to the transplant arm compared with the high dose chemotherapy arm had a superior 5-year event-free survival (EFS) (28% versus 10%, respectively, $P = .01$) and OS (52% versus 12%, respectively $P = .03$). Seven years later, the United Kingdom's Medical Research Council (MRC VII) published their trial randomizing newly diagnosed MM patients to adriamycin, carmustine, cyclophosphamide, and melphalan for 4 to 12 cycles or to adriamycin, vincristine, cyclophosphamide, and methylprednisolone for a minimum of 3 cycles followed by high-dose melphalan with autologous ASCT.[2] The patients randomized to ASCT versus non-ASCT demonstrated an improvement in PFS (32 vs 20 months, respectively, ($P <.001$), and a trend toward improved OS (55 vs 42 months, respectively, $P = .04$). Both of these trials restricted eligibility to patients under the age of 65 years and utilized interferon maintenance posttransplant.

Subsequent randomized trials comparing single ASCT versus conventional chemotherapy demonstrated a benefit in PFS in the ASCT versus delayed or non-ASCT arm, although no benefit in OS was demonstrated.[3-5] These studies, however, with the exception of the 2005 Fermand trial, did not truly compare transplant versus no transplant. Patients who progressed were eligible for salvage transplant. Thus, they compared early versus delayed transplant. A systematic review and meta-analysis of 9 randomized controlled trials published between 1990-2000 evaluating upfront single ASCT versus standard-dose therapy (with conventional cytotoxic chemotherapy) concluded that upfront ASCT provided a PFS but not an OS benefit,[6] although this analysis may be compromised due to the mixture of studies comparing early versus late transplant and transplant versus no transplant. The preponderence of evidence suggests a survival benefit of ASCT. A preplanned or unplanned introduction of delayed ASCT does not call into question the role of ASCT.

Novel Therapies Have Changed Survival Outcomes in Multiple Myeloma and the Role of ASCT

Therapy for MM has markedly changed in the past decade with the introduction of PIs (bortezomib was approved in 2003) and IMiDs (lenalidomide and thalidomide were FDA approved in 2006). As such, survival has improved significantly for patients with MM over the past decade, with 5-year OS improving from 31% to 56% in patients diagnosed between 2001-2005 and 2006-2010, respectively.[7]

Thus, with the achievement of high response rates with PIs and IMiDs, including an overall response rate of 100% with the combination of bortezomib, lenalidomide, and dexamethasone

in newly diagnosed MM,[8] the role of ASCT as part of frontline therapy has become a matter of debate.

Only 1 trial has evaluated the role of ASCT versus no transplant with the use of IMiDs as part of therapy. Palumbo et al randomized 273 patients under 65 years of age or younger after induction with lenalidomide and dexamethasone for 4 cycles to either consolidation of melphalan, prednisone, and lenalidomide (MPR) for 6 cycles or to 2 cycles of high dose melphalan with ASCT.[9] Patients were subsequently randomized to lenalidomide maintenance or no maintenance. The study design was to perform ASCT in the non-transplant arm at the time of disease progression. With a median follow-up of 51.2 months, both PFS (43 months vs 22.4 months, (P <.001) and 4-year OS (81.6% vs 65.3%; P = .02) were significantly longer with high-dose melphalan with ASCT compared with MPR. Of note, of those randomized to MPR, only 63% received the planned ASCT at first relapse, which may have led to the significant difference in OS. However, this may be reflective of community practice. Regarding maintenance therapy among those randomized to both the transplant and non-transplant arm, the median PFS was significantly longer with lenalidomide maintenance than with no maintenance (41.9 months vs. 21.6 months; P <.001) but 3-year OS was not significantly prolonged (88% versus 79.2%; P = .14).

Thus, newly diagnosed patients under the age of 65 years receiving upfront ASCT, utilizing either older conventional regimens or modern IMiD-based therapies, have shown significant prolongation of PFS compared to those receiving non-ASCT chemotherapy consolidation. Transplant serves as another treatment modality with efficacy in MM, and as long as the disease remains incurable, there is no reason to remove this therapeutic option from the treatment armamentarium. Although most therapies may be administered at any time, ASCT may be tolerated earlier in the disease course when the patient has less exposure to therapeutic intervention. Although the accepted standard of care does include high-dose therapy with ASCT, there are outstanding research investigations into the timing of transplant, the incorporation of consolidation therapy, and the use of maintenance therapy.

Timing of Autologous Transplant: Early Versus Late

Two older multicenter, international, randomized studies compared outcomes with early versus delayed transplant, both completed prior to the incorporation of IMiD- or PI-based agents into treatment algorithms. Fermand et al showed an improvement in EFS and improvement in quality of life in terms of time without symptoms, treatment, or treatment toxicity (TWiSTT) in patients transplanted early, although there was no benefit in OS.[3] Similarly, Barlogie et al compared high dose therapy with melphalan 140 mg/m^2 and total body irradiation 12 centigray to maintenance with vincristine, carmustine, melphalan, cyclophosphamide and prednisone (VBMCP). Upon disease progression, the patients in the VBMCP arm were to receive autologous transplantation. There was no differences in response rate, PFS or OS between arms, possibly due to an inferior transplant preparative regimen.[10]

Although prospective, randomized clinical trials evaluating the outcomes of early versus delayed ASCT in the era of IMiD- and PI-based therapies are ongoing (IFM/DFCI 2009 study NCT01208662 and the European Intergroup Trial), no results are currently available. The IFM/DFCI 2009/CTN 1304 parallel phase III study is randomizing newly diagnosed MM patients treated with induction bortezomib, lenalidomide, and dexamethasone (RVD) for 3 cycles and cyclophosphamide for stem cell mobilization to either melphalan 200 mg/m^2 with ASCT followed by 2 cycles of RVD consolidation or 5 cycles of RVD consolidation. Both arms receive lenalidomide maintenance for 1 year in the IFM cohort and until progression in the US cohort. Enrollment has been completed in Europe, but is ongoing in the United States. The ongoing European Intergroup Trial randomizes newly diagnosed patients treated with 3 cycles of bortezomib, cyclophosphamide, dexamethasone (VCD) and stem cell collection to either high-dose melphalan or bortezomib, melphalan, prednisone (VMP) followed by another randomization to 2 cycles of VRD followed by lenalidomide maintenance or lenalidomide maintenance alone until progression.

A retrospective analysis of 290 patients with newly diagnosed MM who received IMiD-based initial therapy (thalidomide-dex or lenalidomide-dex) before ASCT revealed no significant difference in time to progression (20 months vs 16 months, P value non-significant) after ASCT and 4-year OS (68% vs 64%) between patients who received early versus delayed ASCT, respectively.[11] Another retrospective study evaluating the outcome of 167 newly diagnosed patients receiving IMiD- or PI-based induction showed a difference in PFS (28 months vs 23 months; P = .055) but not in OS in patients receiving early versus delayed ASCT, respectively.[12]

Until the results of the 2 large prospective studies become available, upfront ASCT remains the standard of care for transplant eligible, newly diagnosed MM patients. In fact, the International Myeloma Working Group (IMWG) continues to support high-dose therapy with autologous transplant as consolidation following induction therapy,[13] as does the UK Myeloma Forum ("HDT with ASCT should be part of primary treatment in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function [Grade A recommendation; level IB evidence] and HDT with ASCT should be considered in patients aged older than 65 years with good performance status [Grade B recommendation; level IIA evidence[14] and the European Myeloma Network ["Novel-agent-based induction and up-front autologous stem cell transplantation in medically fit patients remains the standard of care (1A)."].[15] Finally, the American Society for Blood and Marrow Transplant (ASBMT) also

recommend autologous stem cell transplant as consolidation for induction therapy.[16]

It is also important to note that relapses after ASCT generally respond to salvage therapy with IMiD- and PI-based therapy, while there is no definitive proof that the disease responds as well to melphalan-based high-dose chemotherapy after prolonged exposure to combination therapy.

Consolidation Therapy

Posttransplant consolidation strategies defined as the administration of 2to 4 cycles of therapy after ASCT, were developed with the goal of extending post-transplant remission and ultimately OS.

One of the initial trials incorporating post-ASCT consolidation was reported by Attal et al (IFM 2005-02) in which patients received 2 months of lenalidomide 25 mg daily prior to randomization to maintenance with lenalidomide 10 mg daily or placebo. They observed an improvement in the rate of a complete or very good partial response: 58% before consolidation versus 69% after consolidation (P <.001).[17] However, it is unclear if the deeper response was a result of the lenalidomide consolidation or as a result of continued response from the transplant.

A number of other trials using a combination of bortezomib or IMiD-based therapy for posttransplant consolidation: the Nordic Myeloma Study Group conducted a randomized study comparing bortezomib as consolidation therapy given after ASCT with no consolidation in bortezomib-naïve newly diagnosed MM patients. Although deeper responses were observed post-consolidation, (ie, ≥ very good partial response 71% vs 57%; P <.01in the consolidation vs non-consolidation therapy groups, respectively), this did not translate into a significant improvement in median PFS (27 vs 20 months; P = .05).[18] In a phase III study, the Italian investigators (GIMEMA MM0305) randomized 474 newly diagnosed patients to bortezomib-thalidomide-dexamethasone (VTD) or thalidomide-dexamethasone (TD) therapy before and after tandem ASCT.[19] VTD consolidation significantly increased complete response (CR) and CR/nCR rates posttransplant but TD did not, and translated into a significantly longer 3-year PFS (68% vs 56% in the VTD vs TD groups; P = .057, respectively). Those with high-risk cytogenetics, especially t(4;14), had the greatest benefit from induction and consolidation with VTD. A small IFM phase II study of 31 newly diagnosed MM patients evaluated VRD as induction and posttransplant consolidation (two 21-day cycles) and showed an improvement in ≥VGPR from 70% at the completion of ASCT to 87% at the completion of consolidation.[20]

Taken together, most of trials examining the role of post-ASCT consolidation show improvement in the depth of response, but conclusive improvement in PFS and OS has yet to be determined, with the exception 1 trial of t[4,14] patients receiving bortezomib-based consolidation. Many of the currently ongoing transplant trials, such as the BMT CTN (Blood and Marrow Transplant Clinical Trials Network) 0702 (NCT02322320) and the IFM/DFCI 2009 are incorporating consolidation strategies, with most using PI/IMiD/corticosteroid combinations for 2 to 4 cycles followed by varying durations of lenalidomide maintenance therapy.

Maintenance Therapy

Maintenance therapy, particularly in the post ASCT setting, consists of the administration of reduced-intensity treatments on a continuous, long-term basis with the dual purpose of deepening and potentially prolonging the previously achieved responses. It is clear from 3 randomized trials that lenalidomide maintenance (10 mg daily) provides a 14- to 26-month improvement in PFS compared with observation.[17,21,22] However, only the CALGB (Cancer and Leukemia Group B) 100104 trial, in a retrospective subgroup analysis, demonstrated an improvement in OS.[21] The median OS was not achieved in the lenalidomide arm, whereas it was 73 months in the placebo arm (P = .008), although the study design was not powered to detect early survival differences with a median follow-up of 48 months. Three subsequent analyses of the IFM trial with a median follow-up of 64 months failed to demonstrate a difference in OS with maintenance lenalidomide compared to placebo.[17,23,24]

The improvement with lenalidomide maintenance in PFS comes with a number of absolute or potential disadvantages: (1) at least a 2- to 3-fold increase in the risk of second primary malignancies; (2) an approximate 15% discontinuation rate due to toxicities, in particular myelosuppression; (3) the propagation of lenalidomide-resistant clones by continuous, metronomic, subtherapeutic lenalidomide administration, potentially negating the future use of lenalidomide for anti-MM therapy; (4) shorter duration of PFS2 (defined as PFS with the next line of therapy after progression on maintenance lenalidomide) in patients with prior lenalidomide exposure; and (5) the high cost—financial and otherwise—to the patient and health care system (especially in the absence of clear improvement in OS).

Data investigating the use of bortezomib in the maintenance setting is available from 2 large randomized trials. The HOVON/GMMG4 group conducted a randomized trial that found that bortezomib-based induction followed by ASCT with bortezomib maintenance provided a superior PFS and OS compared with non-bortezomib induction followed by ASCT with thalidomide maintenance (hazard ratio [HR] = 0.78, P = .002 and HR = 0.78, P = .027, respectively).[25] Another study, conducted by the Spanish Myeloma Group, completed a 3-arm posttransplant maintenance trial in standard-risk patients that compared interferon vs thalidomide vs thalidomide/bortezomib.[26] There was an improvement in PFS but not OS in the thalidomide/bortezomib cohort. Although both studies showed bortezomib maintenance therapy to be effective, the optimal use of bortezomib remains

unclear in terms of the scheme as well as the duration of therapy. Furthermore, bortezomib-associated peripheral neuropathy, shown to affect 38% of those treated with subcutaneous bortezomib,[27] must be weighed against the benefits.

Minimal Residual Disease

Techniques for assessing MM disease burden have transitioned from serum and urine protein electrophoresis and immunofixation to highly sensitive, novel assays developed to measure cellular minimal residual disease (MRD) in the bone marrow and peripheral blood of MM patients. As such, MRD assessment has gained importance in the depth of response. Multiparameter flow cytometry can detect phenotypically aberrant clonal plasma cells in >95% of MM patients with a sensitivity of up to 10^{-4}.[28,29] The analysis of MRD by molecular techniques relies on the study of immunoglobulin gene rearrangements, and can identify a molecular marker in >90% of patients.[30] The 3 main techniques available to analyze immunoglobulin gene rearrangements are fluorescent polymerase chain reaction (PCR) using family primers of immunoglobulin genes with a sensitivity of 10^{-3},[31] allele-specific oligonucleotide (PCR),[30,32] and high-throughput sequencing, applicable to 80% to 90% of patients and reaching a sensitivity of up to 10^{-6}.[33]

Several studies have shown that patients achieving MRD negativity have improved PFS and OS post-ASCT,[30,32-34] maintenance,[29] and non-ASCT transplant-eligible settings.[35] It is important to note that MRD-negativity can provide a degree of uncertainty in prognosis in that it is unclear whether there is a true absence of clonality versus a sampling inaccuracy. MRD-positivity, however, is almost always an adverse prognostic feature. It is important to note that although we have data that MRD negativity is a favorable prognostic factor, there are no data that it should be a goal of therapy or guide therapeutic decisions. Some examples of unanswered questions regarding MRD include the following: (1) Do patients achieving MRD-negativity before transplant benefit from an early transplant or should these patients be considered for consolidation/maintenance therapy followed by high-dose chemotherapy with ASCT at first relapse. (2) Do patients with MRD-positivity after transplant require consolidation and maintenance? (3) Can maintenance therapy be discontinued once MRD-negativity has been achieved? (4) Is MRD negativity a surrogate marker for prognosis in high risk myeloma? Clinical trials are being designed with these very important questions in mind. The ultimate goal is to use MRD assessments as a risk stratification tool to dictate therapy and for earlier identification of response in the setting of clinical studies.

Conclusion

The initial incorporation of high-dose melphalan followed by ASCT and subsequent introduction of PI and IMiD-based therapy pre- and post-ASCT has dramatically changed the treatment landscape for MM. Although ASCT is standard of care for treatment of transplant-eligible MM patients, the ideal timing for its use has been challenged by the marked efficacy of novel drugs. Until prospective studies prove otherwise, ASCT as consolidation after first remission is still recommended. Extended treatment with consolidation and maintenance therapy improves the quality and duration of clinical responses; however the optimal timing, doses, and duration of therapy have not yet been defined. Further, the exact population of patients for whom these therapies will provide the most benefit has yet to be elucidated. Further research, including the use of MRD assessment, cytogenetic risk stratification, and prospective clinical trials, will ultimately allow us to individualize treatment.

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