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Hematopoietic Stem Cell Transplantation in Myeloma in the Era of Novel Agents

Hamed NAM

Hematology Department, Alexandria University, Egypt

Corresponding author: Hamed NAM

drhamedn@hotmail.com

Professor of Hematology, Hematology Department, Alexandria University, Egypt.

Tel: 20 3 5921675

Abstract

This article describes consensus recommendation as well as recent trials dealing with auto-HCT as upfront therapy, as salvage therapy for relapsed myeloma patient and as second transplant for refractory patients. It also describes management of high risk myeloma.

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Introduction

Autologous stem cell transplantation (auto-HCT) remains a standard of care in myeloma (MM) despite the era of novel therapy. Almost all MM patients demonstrate cytogenetic abnormalities at presentation, with a significant minority having "high risk" (HR) mutations [1]. The median overall survival (OS) for patients with standard risk fluorescence in situ hybridization undergoing early auto-HCT approaches 10 years [2]. The risk of complications during transplant correlates with the patient's baseline organ function, underlying comorbidities and the type of chemotherapy used as a conditioning regimen [3]. Individuals with HR features face early relapse and death. Allogeneic SCT offers a graft *vs.* myeloma (GVM) effect [1] that may be associated with reasonable outcome in HR myeloma patients, but this will require further research [2].

The paradigm for transplant-eligible patients consists of induction, stem-cell mobilization, and auto-HCT, followed by consolidation and/or maintenance. Auto-HCT is also indicated in MM, at first progression and as second transplant for relapsed disease [4].

Auto-HCT after Initiation of Therapy

Preparative regimen

No combination of agents to date has proven safer or more effective than melphalan 200 mg/m^2 as a preparative regimen [5]. However, it carries a high risk of gastrointestinal toxicity including oral mucositis, nausea, vomiting, and diarrhea. Oral mucositis ranges from erythema of the superficial mucosa layer to severe ulcerations due to damage of submucosal layers [3].

Recommendations for follow-up after auto-HCT

In patients with measurable disease, monitoring should start 2 to 3 months after auto-HCT with serum and/or urine M protein, serial involved free light chain (FLC) assay, and serum FLC ratio and continue every 3 months [5].

BM biopsy may be required in oligosecretory plasma cell disorder and in patients with no measurable disease. Retrospective data suggests that patients with less BM disease burden have improved outcomes, even with negative serum and urine markers [5].

BM examination and FLC ratio are required to document CR, near CR, and stringent CR status or to assess cause of persistent cytopenias [5].

The definitions of immunophenotypic CR and molecular CR have been incorporated into the IMWG criteria [5].

In patients with known lesions at diagnosis, serial radiography/positron emission tomography/computed tomography (PET/CT) after transplantation may be used to follow response to therapy or evaluate new symptoms. PET/CT is not routinely required in asymptomatic patients not suspected to have relapse or progression of disease after HCT [5].

MRD testing after auto-HCT in MM can reveal patients at risk for poorer outcomes and should be considered for disease evaluation (grade B) [5]. Multiparametric flow cytometry following the European Myeloma Network consensus guidelines should be the method of choice [5]. Time to progression among patients who achieved CR, was significantly superior for MRD-negative patients (clone frequency $<1 \times 10^{-5}$) compared with MRD-positive patients [6].

Recommendations for therapy after Auto-HCT

Despite the marked improvement in outcome with this approach, most patients will eventually experience disease progression. Inclusion of post auto-HCT consolidation/maintenance strategies is used to improve long-term disease control [7].

Consolidation therapy is a planned course of therapy aimed at increasing the depth of response. It consists of a limited number of cycles of a single agent or combination therapy or a second transplant step. The enhanced rate and quality of responses offered by consolidation therapy contribute to improved clinical outcome including extending progression-free survival (PFS) [8]. Consolidation after auto-HCT is not routinely recommended but can be considered in the setting of a clinical trial [5]. According to the largest U.S. randomized controlled trial of post-transplant therapy for MM, the addition of triple therapy with bortezomib, lenalidomide and dexamethasone for consolidation or a second auto-HCT in the upfront treatment of MM is not superior to a single transplant followed by lenalidomide maintenance [9]. However, another randomized study, showed observed benefit of two consolidation cycles of velcade, lenalidomide and dexamethasone in low-risk cytogenetics patients but not in high-risk cytogenetics patients [10].

Maintenance therapy is then applied for a prolonged period ≥ 12 months and typically for at least 2 to 3 years and even until progression. Its overall aim is to maintain the depth of response achieved in previous treatments by applying lower dose of novel treatments than that used during either induction or consolidation [8]. Maintenance with an immunomodulatory drug (thalidomide or lenalidomide) is recommended unless a contraindication exists (grade A). Post auto-HCT lenalidomide maintenance continued until progression is preferred [5]. Thalidomide should be administered at the minimal effective dose and possibly for no longer than 1 year. Thalidomide maintenance after auto-HCT can be helpful to prolong EFS or PFS in fit patients with MM [8]. Post auto-HCT bortezomib consolidation and maintenance may be considered in patients with high-risk disease with renal failure or adverse chromosome changes (grade D) [5].

Newer treatment strategies such as checkpoint inhibition may also prove beneficial in the post auto-HCT setting. Next generation of clinical trials on post auto-HCT treatment strategies will incorporate monoclonal antibodies, proteasome inhibitors, and other novel pathway modulatory agents with the goal of achieving even deeper responses and longer durations of disease control [7].

Long-term management of MM patients after auto-HCT

Resumption of bisphosphonate therapy and prophylactic anticoagulation or antiplatelet therapy for patients receiving thalidomide or lenalidomide therapy.

Patients on lenalidomide maintenance therapy should be followed closely and monitored for hematological and non-hematological cancers [7]

Transplantation as a Salvage Therapy for Relapsed MM

The expert committee defined salvage HCT as either an autologous or allogeneic HCT performed on MM patients who had failed a prior line of therapy. This definition would encompass multiple scenarios ranging from transplantation-naïve patients failing frontline treatment to patients who had failed multiple therapies without ever having anS HCT [11].

All eligible patients for auto-HCT should be considered for peripheral blood apheresis sufficient for 2 autografts in the event a second autograft is necessary in the salvage setting [5]. The International Myeloma Working Group guidelines for mobilization, suggest using of plerixafor as a mobilization strategy in patients who did not have enough cells collected for salvage HCT [11].

Recommendations for salvage autologous HCT

Transplant-eligible patients who do not undergo upfront auto-HCT should be offered auto-HCT at time of first relapse [7].

High-dose therapy and autologous HCT should be considered appropriate therapy for relapsing patients after primary therapy that includes an autologous HCT with initial remission duration of more than 18 months [7]. Chemosensitivity and remission duration after the first autograft were the most important prognostic factors for subsequent long-term disease control. However, it is still uncertain whether all patients would benefit from salvage autograft regardless of remission duration. The number of lines of prior therapy had a significant impact on outcomes. So salvage autologous HCT should be considered an integral component of initial salvage strategies and not for those who have failed all prior therapies “last-ditch effort” [11].

High-dose therapy and autologous HCT can be used as a bridging strategy to allogeneic HCT [11].

Future Trials

Autologous HCT consolidation should be explored as a strategy to develop novel conditioning regimens or post-HCT strategies in patients with short (less than 18 months remissions) after primary therapy [11]. The role of post salvage HCT maintenance needs to be explored in the context of well-designed prospective trials including new agents, such as monoclonal antibodies, immune-modulating agents, and oral proteasome inhibitors [11]. Prospective randomized trials to define the role of salvage autologous HCT in relapsing MM patients after primary therapy and comparing it to “best non-HCT” therapy are in need to be performed [11].

Auto-HCT for Patients with Refractory Disease

Primary refractory MM was defined by the Spanish myeloma group as never having achieved a minimal response or better. These patients underwent either tandem autologous or auto-HCT followed by RIC allogeneic transplantation. There was no impact

of pretransplantation salvage on TRM, PFS, or OS, suggesting that those with suboptimal response to induction could still derive a benefit from high-dose chemotherapy [11].

Recommendations for Allo-HCT

Upfront myeloablative allo-HCT is not routinely recommended (grade A) [5]. Planned RIC-allo-HCT after auto-HCT has not been found to be superior over tandem auto-HCT in the majority of clinical trials and, therefore, is not recommended (grade A) [5]. Allo-HCT salvage therapy for relapsed MM has not been shown to be superior to salvage auto-HCT and is not routinely recommended outside a clinical trial (grade D) [5]. RIC allogeneic HCT should be considered appropriate therapy for younger patients with good performance status and, with early relapse (less than 24 months) after primary therapy that included an autologous HCT. It may also considered in patients with high-risk features (such as del 17p, t[4;14], t[14;16], high-risk gene expression profile, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HCT [11]. Disease control prior to allo-HCT is necessary for long-term disease control. Patients with high volume disease do not respond well to allo-HCT. Allo-HCT can be considered, ideally in the context of a clinical trial [7].

Current Protocols

Allo-HCT using the myeloablative conditioning regimen FluBu4 (fludarabine and busulfan) for high-risk MM appeared to be safe with low TRM compared to that reported with the commonly used reduced-intensity fludarabine/melphalan regimen. The most common regimen-related toxicities were oral mucositis and transient abnormal liver function tests. Serious and life-threatening toxicities occurred only in those with pre-existing organ-specific comorbidities. The engraftments were early with no cases of graft failure. Acute and chronic GVHD rates were similar to that reported for fludarabine/melphalan regimens. This novel low-TRM regimen may be used for testing addition of a MM-targeted agent with anti-GVHD property (e.g., carfilzomib or newer agents) and/or maintenance therapy with these agents to decrease relapse/progression in high-risk MM patients [12].

The role of post allogeneic HCT maintenance therapy needs to be further explored in the context of well-designed prospective trials [5]. Randomized phase 2 study of maintenance ixazomib, after allo-HCT for high-risk MM and in first relapse after an auto-HCT is under study. The conditioning regimen was melphalan-bortezomib [11].

How to Manage High Risk Myeloma?

Genetically defined HR myeloma patients appear to need prolonged intensive therapy. The hypothesis is that these patients are at risk for clonal evolution and lack durable response to successive therapies. Aside from clinical trials, young and healthy enough patients have to use the most highly active regimens, followed by tandem auto-HCT as consolidation, followed by consolidation/maintenance with a PI. Some may consider allo-SCT in younger patients with HR cytogenetics. HR patients have done so poorly that the risk of treatment-related morbidity and mortality introduced by allo-HCT may be outweighed by the risk of death using standard approaches. There are no solid data to support this recommendation [2].

What is New in Tandem HCT?

Tandem auto/auto-HCT

Uniform response criteria for MRD testing needs to be accurately defined to be utilized as an endpoint for drug approval in MM. Monitoring of the light chains on PC sub-populations by multicolor flow-MRD in adjunction to surface markers is a significant predictor of clinical outcome. Flow MRD-negative patients in conventional CR after the second transplant showed a significantly better clinical outcome in terms of PFS when compared with flow MRD-positive. The impact of post-transplant flow MRD assessment was recently reported to be independent of induction regimen prior transplant. It may have a role in improving clinical management of MM patients treated with up-front tandem auto-HCT in the next future [12].

Tandem auto/allo-HCTs

The use of upfront tandem reduced-intensity related donor allo-HCT after auto-HCT may be associated with improved PFS over single or tandem auto-HCTs in early-stage high-risk MM, but not consistently in standard-risk disease [13]. However, subsequent meta-analyses of randomized controlled trials showed no definite benefits. The reason for the higher TRM and relapse in allo-HCT for MM remains unknown, but it may be attributed to patient age, regimen-related toxicity of myeloablative conditioning, a less potent GVM effect, and possibly other poorly understood myeloma-specific factors [13].

Conclusion

Further trials are in progress exploring newly developed agents in upfront auto-HCT at induction, consolidation and maintenance phase as well as relapsed disease after primary therapy.

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