Treatment of Transplant-Eligible Patients with Multiple Myeloma in 2014

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KEYWORDS

• Stem cell transplantation • Melphalan • Corticosteroids • Toxicity • Dexamethasone

KEY POINTS

- Induction regimens containing a proteasome inhibitor and/or immunomodulatory agent with dexamethasone result in rapid disease control before autologous stem cell transplantation (ASCT).
- ASCT followed by consolidation and/or maintenance further improves depth of response following effective induction.
- Overall survival of transplant-eligible patients has been extended with modern therapeutic strategies.
- The optimal timing of ASCT and methods to prevent relapse following ASCT are under active investigation.
- Different patient populations may benefit differentially from currently available treatments.

INTRODUCTION

High-dose melphalan therapy (HDT) with autologous stem cell transplant (ASCT) has been an integral component of myeloma therapy for close to 3 decades after McElwain and Powles demonstrated the clinical relevance of melphalan dose and disease response in patients with relapsed and refractory disease.[1] These results led to the exploration of HDT-ASCT as consolidation of initial remission in newly diagnosed multiple myeloma (MM). Compared with conventional chemotherapy, HDT and ASCT were associated with improved outcomes including event-free, progression-free (PFS), and overall survival (OS).[2–8] Depth of response, particularly achievement of a complete response (CR), was associated with longer PFS and OS in MM and was likely responsible for the initial success of HDT and SCT.[9]

Novel induction regimens incorporating proteasome inhibitors (bortezomib and carfilzomib) and the immunomodulatory drugs (IMIDs) (thalidomide and lenalidomide)

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have demonstrated very high CR rates that compare to those produced with HDT and ASCT.[10] Proteasome inhibitors and IMIDs have changed the context in which patients are receiving HDT and ASCT. Ongoing studies are investigating in transplant-eligible patients whether HDT is required early in the course of the disease or can be used as salvage therapy.[11,12] In patients who received alkylator-based induction, early ASCT was associated with better quality-of-life (QOL) parameters such as time without symptoms and therapy-related toxicity.[2] As myeloma therapy evolves to include post-ASCT consolidation and maintenance, it will be important to incorporate QOL measurements into the current studies. Herein the authors describe the treatment of newly diagnosed transplant-eligible MM patients based on currently available data and highlight important studies that will instruct us as the field continues to move forward.

DEFINING AN OPTIMAL INDUCTION REGIMEN

Response before SCT has been shown to improve outcomes, but the optimal type and duration of induction has not been well defined.[13] In responding patients, treatment with a fixed number of induction cycles or treatment until best response is the common strategy. Randomized trials comparing conventional chemotherapy with a regimen that contains thalidomide, lenalidomide, and/or bortezomib along with corticosteroids have established that induction with an IMID, proteasome inhibitor, or both is the standard of care.[14–17] Deeper and quicker responses are typically achieved with 3-drug regimens such as thalidomide-bortezomib-dexamethasone, cyclophosphamide-bortezomib-dexamethasone, bortezomib-adriamycin-dexamethasone, or lenalidomide-bortezomib-dexamethasone versus 2-drug regimens, thalidomide-dexamethasone, lenalidomide-dexamethasone, or bortezomib-dexamethasone (VD), although the impact on OS has not been established (**Table 1**).[15–21] Attempts to increase to a 4-drug regimen are associated with increased toxicity and no clear advantage over 3-drug regimens.[22]

Notably few randomized studies comparing modern induction regimens have been performed to date; and lenalidomide-based combinations have not been compared with either bortezomib- or thalidomide-based combinations. A trial of VD versus reduced-dose bortezomib-thalidomide-dexamethasone (VTD) as induction pre-SCT conducted by the Intergroupe Francophone du Myelome (IFM) did not suggest a benefit of the 3-drug combination over the 2-drug combination in terms of the frequency of CR after 4 cycles (13% and 12%, $P = .74$), which was their primary end point.[23] However, higher very good partial response (VGPR) rates were noted with VTD compared with VD both before (49% vs 36%, $P = .05$) and after SCT (74% vs 58%, $P = .02$). In addition,

Table 1
Response and toxicity to selected induction regimens

Reference	Regimen	[a]ORR (%)	[a]CR (%)	Common Toxicities
[15]	VD	79	15	PN, GI toxicity, low PLTs
[16]	TD	79	11	Constipation, sedation, PN
[21]	[b]Ld	70	4	VTE, neutropenia
[16]	VTD	93	31	PN, GI toxicity, infection
[19]	RVD	74	6	PN, myelosuppression
[18]	VCD	96	46	Myelosuppression

Abbreviations: GI, gastrointestinal; PLT, platelet; PN, peripheral neuropathy; VTE, venous thromboembolism.

[a] Response rates following 4 cycles (unless otherwise indicated).

[b] Best response.