Challenge of Comparing Upfront Versus Deferred HDM-ASCT

Subjects: Oncology

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The standards of care for the initial treatment of patients with newly diagnosed multiple myeloma (NDMM) who are eligible for high-dose melphalan and autologous stem cell transplantation (HDM-ASCT) include highly active triplet and quadruplet regimens based on proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. These regimens are resulting in improved outcomes and increasingly high rates of minimal residual disease (MRD)-negative responses without HDM-ASCT as part of the upfront therapy.

autologous stem cell transplantation | genotoxicity | high-dose melphalan | minimal residual disease | multiple myeloma | transplant-eligible | treatment personalization

1. Introduction

Multiple myeloma (MM) is the second most common individual hematologic malignancy [1][2], with an estimated global incidence of almost 180,000 new cases and 120,000 deaths in 2020, comprising approximately 1% of the global cancer burden [1]. The disease more commonly affects males (~56% of cases) and is generally a disease of the elderly, with the median age at diagnosis in the United States being 69 years [3]. MM exhibits substantial heterogeneity at diagnosis and throughout the disease course associated with multiple disease-related and patient-related characteristics including disease stage [4][5], cytogenetic abnormalities [6], age, and frailty [7][8], providing the context for the drive to develop personalized treatment approaches [9][10][11]. Overall survival (OS) has increased markedly over the past four decades, with the 5-year survival rate in the United States more than doubling to 59.8% [3] and the median OS in younger, fitter patients reaching approximately 10 years [12]. This is associated with the introduction and widespread adoption of high-dose melphalan plus autologous stem cell transplantation (HDM-ASCT) as a frontline therapy in eligible patients and, more importantly, the more recent development and use of numerous highly active novel agents and regimens throughout the disease course in multiple lines of therapy [13][14]. Such progress is rapid and ongoing, as evidenced by the recent approvals by the United States Food and Drug Administration (FDA) in 2021–2023 of the chimeric antigen receptor (CAR) T cell therapies idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) [15][16], and of the bispecific antibodies teclistamab, elranatamab, and talquetamab [17][18][19].

Current Treatment of Newly Diagnosed MM (NDMM) and the Role of HDM-ASCT

The current standards of care for the treatment of NDMM are based on three classes of agents: the proteasome inhibitors (PIs; bortezomib, carfilzomib, ixazomib), the immunomodulatory drugs (lenalidomide, pomalidomide, thalidomide), and the monoclonal antibodies (mAbs; anti-CD38 mAbs daratumumab, isatuximab; anti-SLAMF7 mAb elotuzumab) [13][20]. These agents are administered in combination—typically with dexamethasone—as triplet and, increasingly, quadruplet induction therapies, and as single-agent or doublet maintenance regimens as part of frontline therapy [13][20]. Post-induction consolidation therapy depends on a patient's eligibility for HDM-ASCT, which remains the standard approach for patients aged ≤65–70 years without contraindicating comorbidities [13][20].

The use of HDM-ASCT as a standard in transplant-eligible patients was initially established based on randomized trials versus chemotherapy in the era prior to novel agents, in which transplant resulted in improved progression-free survival (PFS) and OS [21][22]. More recently, large phase 2 and phase 3 studies incorporating triplet novel-agent induction, with or without consolidation, and maintenance therapy have further demonstrated that the addition of HDM-ASCT confers a highly significant PFS benefit [23][24][25][26][27][28]. For example, the DETERMINATION phase 3 trial showed that the addition of HDM-ASCT to lenalidomide-bortezomib-dexamethasone (RVd) induction, plus lenalidomide maintenance to progression, resulted in a nearly 2-year median PFS benefit (67.5 vs. 46.2 months) and a 35% reduction in the risk of progression (RVd-alone vs. RVd + ASCT hazard ratio [HR] 1.53) [24]. The Intergroupe Francophone du Myélome (IFM) 2009 phase 3 trial, which had a similar design but administered lenalidomide maintenance for 1 year only, also showed a substantial PFS benefit with the addition of a transplant (median PFS 47.3 vs. 35.0 months, HR 1.43), although this was markedly less than the duration of disease control seen in both arms of DETERMINATION [23].

However, the importance and feasibility of the personalization of therapy is growing [9][10][11]. In the context of increasingly active quadruplet induction regimens [29][30][31][32] and our growing understanding of the mutagenic effects of melphalan [24][33][34][35][36], as well as no OS benefit having been demonstrated with HDM-ASCT in recent studies [23][24][25][26][37], the role of HDM-ASCT as a standard approach for all-comers in transplant-eligible NDMM is being challenged. Indeed, several treatment guidelines and recommendations are including deferred HDM-ASCT as a possible option for select patients in the frontline setting (**Table 1**).

Table 1. Recent treatment guidelines and recommendations for NDMM including early or deferred HDM-ASCT.

Publication	Year Published	Early HDM-ASCT	Deferred HDM-ASCT
EHA-ESMO Clinical Practice Guidelines [20]	2021	"For patients <70 years without comorbidities, induction therapy followed by HDM and ASCT is the recommended treatment"	Not included
BSH/Myeloma UK guidelines [38]	2021	"Recommended for younger, fitter patients"	"Lack of OS benefit … likely to be largely due to the use of delayed ASCT … supports the use of deferred ASCT as a clinical option… [the fact that] patients in the non-ASCT arm of the IFM 2009 study

Publication	Year Published	Early HDM-ASCT	Deferred HDM-ASCT
			were unable to receive ASCT at relapse due to disease refractoriness reinforces the benefit of upfront ASCT where feasible”
ASTCT Clinical Practice Recommendations [39]	2022	“The panel recommends early autologous transplantation as a consolidation therapy in eligible, newly diagnosed myeloma patients after 4–6 cycles of induction”	“The panel recommends mobilization and storage of peripheral blood stem cells in newly diagnosed myeloma patients not undergoing autologous transplantation after first line of therapy for future use as a treatment at first relapse”
Rajkumar, update on diagnosis, risk-stratification and management [40]	2022	“ASCT should be considered in all eligible patients”	“In standard-risk patients responding well to therapy, ASCT can be delayed until first relapse provided stem cells are harvested early in the disease course”
mSMART guidelines [41]	2023	Preferred for standard-risk patients [t (11;14), t (6;14), trisomies], recommended for high-risk patients	An option for standard-risk patients

ASCT, autologous stem cell transplantation; ASTCT, American Society for Transplantation and Cellular Therapy; BSH, British Society of Haematology; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; HDM, high-dose melphalan; mSMART, Stratification for Myeloma and Risk-adapted Therapy; NDMM, newly diagnosed multiple myeloma.

2. The Challenge of Comparing Upfront Versus Deferred HDM-ASCT

It is important to acknowledge that directly comparing outcomes with upfront or deferred HDM-ASCT is challenging due to multiple potential confounders. For example, there is an inherent immortal time bias towards patients who receive deferred HDM-ASCT as a second-line therapy, because these patients must have already received frontline therapy and must still be young and fit enough to undergo HDM-ASCT as part of their second-line treatment [42]. Early analyses suggested that there were no differences in OS between the two approaches, and this may have been due, in part, to such potential bias [42][43][44]. However, there is the potential for bias in the opposite direction too if the group receiving deferred ASCT largely includes patients with an earlier need for second-line therapy following failure of their front-line regimen, i.e., those with more aggressive relapses. Moreover, in the context of the rapidly expanding range of highly active treatment options for relapsed/refractory MM (RRMM), a PFS benefit with upfront HDM-ASCT versus a non-transplant approach could result in a delayed need for second-line therapy, during which time additional novel, active treatment options might be approved in this setting.

Furthermore, for such comparisons, trials with a lengthy follow-up are required in order to evaluate outcomes through both first- and second-line therapy, which may be substantial for transplant-eligible patients in the modern era [12]. The IFM 2009 and DETERMINATION trials provide valuable data in this regard, as both trials recommended HDM-ASCT as second-line therapy following RVd alone [24][25]. In IFM 2009, with a median follow-up of 7.5 years, 262/350 (74.9%) and 217/350 (62.0%) patients on the RVd-alone and RVd + ASCT arms, respectively, required second-line therapy, with 201/262 (76.7%) versus 49/217 (22.6%) of them having received

ASCT as part of that treatment. As in earlier studies of early versus later transplant, no difference in OS (8-year rate: 60.2% vs. 62.2%) was seen between arms [23], suggesting that deferred ASCT as part of the second-line therapy represents a reasonable clinical option. This is supported by several studies demonstrating substantial efficacy with HDM-ASCT in the RRMM setting [14][45][46]. Interestingly, however, in DETERMINATION no difference in OS (5-year rate: 79.2% vs. 80.7%) was seen between RVd alone and RVd + ASCT after a median follow-up of almost 6.5 years [24], despite only 78/279 (28.0%) RVd-alone patients who had discontinued protocol therapy having received subsequent HDM-ASCT. These findings, in the context of the large PFS benefit with RVd + ASCT, suggest the possibility of competing risk impacting OS.

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