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REPOSITIONING AUTOLOGOUS STEM CELL TRANSPLANTATION IN THE MANAGEMENT OF NEWLY DIAGNOSED MULTIPLE MYELOMA

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High-dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) has been a cornerstone of treatment for patients with newly diagnosed multiple myeloma (NDMM) for the last three decades. The essence of this treatment is the powerful anti-myeloma effect of melphalan when administered at standardized high doses that require rescue with autologous hematopoietic stem cell transplantation for optimal safety. This procedure is considered mainstream therapy for patients up to the age of 70 (and older patients in some contexts), is available worldwide and has demonstrated progression-free survival advantage over a strategy of deferred transplantation in multiple historical and recent randomized trial, including in the context of modern, triplet therapy (Table 1).

Autologous transplantation, however, carries substantial inconvenience and toxicity. It causes universal alopecia, pancytopenia exposing patients to the risk of infections, potentially serious gastrointestinal toxicity and transient yet pronounced impairment in quality of life[1]. ASCT also likely contributes to the long-term risk of second malignant neoplasms in patients with multiple myeloma[2]. It is therefore a genuine pursuit to identify circumstances when autologous stem cell transplant may not be necessary. Here we provide a critical review of the most recent available data appraising the role of autologous transplantation in newly diagnosed myeloma, discuss existing challenges with current evidence an ongoing research effort that might lead to a more refined use of this therapy in the future.

PROGRESSION-FREE SURVIVAL, BUT NO OVERALL SURVIVAL ADVANTAGE

There has not been a randomized clinical trial in the last two decades that compares ASCT vs. no-ASCT in NDMM[1,3-6]. Every single one compares a strategy of upfront vs. deferred ASCT, with transplant being offered at time of first progression. Every one of these trials were designed and powered to test impact of upfront ASCT in progression-free survival (PFS), and showed that deferring ASCT jeopardizes PFS. Strictly speaking, all those trials were "positive" and demonstrated an improvement in PFS, the primary endpoint, for upfront ASCT even in the setting of triplet therapy with a proteasome inhibitor (PI) and immunomodulatory agent (IMiD) and dexamethasone.

While these trials often reported overall survival (OS) as a secondary endpoint, none reported difference in OS favoring either arm generating the hypothesis, and often the narrative, that ASCT might be dispensed from the initial therapy without affecting OS. There are, however, several limitations to this extrapolation.

First, all these trials included ASCT at the time of initial progression. Therefore, by trial design, patients eventually paid the "penalty" of the ASCT toxicity since progression in the deferred transplant arm seems unavoidable. So if the objective is to avoid to harm from ASCT while preserving OS, this strategy is flaw. Rate of ASCT at the time of progression varies substantially across trial, and was reportedly < 30% in the recent DETERMINATION trial, however that

trial was affected by substantial early censoring and post progression therapy not fully described.

Secondly, randomized clinical trials are planed rigorously around a central hypothesis that guides the statistical design. None of these trials were planned around an OS hypothesis, therefore did not have the proper number of participants and duration of follow up to test an OS benefit of upfront ASCT. That is particularly important as the median OS of patients treated with triplet therapy and ASCT seem to exceed 10 years. Therefore, OS comparisons in these trials are plagued by a very high risk of type 2 error.

Thirdly, and most importantly, OS may just be an unfeasible and unreasonable endpoint to appraise therapies in transplant-eligible, NDMM. In current era, patients often experience deeper and prolonged responses during second line therapy and beyond. In a condition with OS now exceeding 10 years, the therapies available at time of recurrence are often different and superior to the therapies available at the time of trial design. Since these trials do not control post-progression therapy, the heterogeneity introduced makes post progression data extremely challenging to interpret. This is true not only for ASCT. In fact, drugs that are pivotal in the management of younger patients with NDMM, such as lenalidomide and bortezomib, have not been shown to improve OS in transplant-eligible NDMM (exception for lenalidomide in the maintenance setting). In fact, all evidence for OS impact of PI, IMiD and, most recently, anti-CD38 monoclonal antibodies in NDMM comes from trials of non-transplant-eligible patients with NDMM, a population with much higher rate of events and more limited post-progression survivorship. If we were to reject upfront ASCT on the basis of lack of OS advantage despite PFS benefit, we would have to reject bortezomib, lenalidomide and daratumumab as part of upfront therapy in order to stay consistent.

ASCT AND RISK STRATA

NDMM is a notoriously heterogenous condition in terms of clinical presentation and, most importantly, clinical outcome. Such heterogeneity is recognized by multiple prognostic system based on clinical characteristics and presence of certain chromosome abnormalities. More recently, the presence of gene expression signatures and single-gene mutations were demonstrated to affect long term prognosis. However, with very few exceptions, randomized clinical trials in NDMM define population by age and organ function, not by disease characteristics. While the overall result of the trial captures the typical effect of the intervention, it may miss nuances in particular disease subsets.

Cytogenetic risk, for instance, appears to modulate the impact of upfront ASCT in NDMM. In the EMN-02 trial, a pronounced impact of upfront ASCT on PFS (HR 0.63, 95% CI 0.46-0.88) and OS (HR 0.66, 95% C.I. 0.45-0.99) was seen in patients with high-risk chromosome abnormalities, either del17p, t(4;14) or t(14;16). In fact, patients with high risk cytogenetics appear to benefit from tandem vs. single ASCT in terms of PFS (HR 0.59, 95% C.I. 0.34-1.03)[5]. In the more recent DETERMINATION trial, high-risk patients treated with triplet induction and consolidation therapy and ASCT had median PFS of 55.5 months vs. 17.1 months in those who deferred transplantationl[1].

To further characterize the interaction of cytogenetic risk and ASCT, Bal and colleagues quantified the MM clone using next generation sequencing before and after ASCT, in a cohort of patients homogenously treated with quadruplet induction. Patients with one or more high-risk chromosome abnormalities had greater reduction in disease burden and a higher conversion to minimal residual disease (MRD) negativity[7].

In aggregate, the literature indicates that although ASCT prolongs PFS for patients across the risk spectrum, higher impact is afforded to those with high-risk disease, a fact that can influence the risk-benefit discussion for individual patients.

ASCT IN THE SETTING OF QUADRUPLET THERAPY

Anti-CD 38 monoclonal antibodies daratumumab and isatuximab increase the frequency and depth of response when added to other MM drugs in various settings, including transplant-eligible patients with NDMM. In the CASSIOPEIA trial, patients who received daratumumab in addition to bortezomib, thalidomide and dexamethasone (Dara-VTd) for induction and post ASCT consolidation had longer PFS than patients who received VTd alone[8]. In the randomized phase 2 GRIFFIN study, the addition of daratumumab to bortezomib, lenalidomide and dexamethasone (VRd) induction, VRd consolidation and lenalidomide maintenance also increased the frequency of patients reaching stringent complete response, MRD negativity and improved PFS[9]. More recently, in the GMMG-HD7 trial, Isatuximab added to VRd also improved the proportion of patients achieving MRD negativity prior to ASCT[10]. However, no trial has directly compared upfront ASCT vs. deferred or no ASCT in the setting of quadruplet induction therapy.

In principle, the improvement in conventional therapy, demonstrated by higher proportion of patients achieving MRD negativity even before ASCT, strengthens the case for deferral of transplantation. A lesson learned from prior trials however is that benefit of transplant is not homogenous in the population with NDMM. A transplant vs. non-transplant trial in the setting of quadruplets is unlikely to happen. Instead, we should challenge transplant in risk and response-defined favorable subsets.

ASCT IN PATIENTS WITH DEEP RESPONSE TO INDUCTION THERAPY

Among patients with NDMM exposed to the same therapy, the achievement of deep response, characterized by minimal residual disease < 10^{-5} or even <10^{-6} by next generation flow cytometry or next-generation sequencing is a strong predictor of long term PFS and OS and at least partially mitigate the impact of staging and cytogenetic abnormalities on long term prognosis. Both IFM-2009[11] and DETERMINATION[1] trials indicate that patients achieving MRD negativity with and without ASCT have similar long-term prognosis, leading to an interest in deferring ASCT in patients who achieve MRD negativity post induction. This approach, while logical, has a few caveats. None of these trials systematically evaluated MRD post induction and pre ASCT. The comparisons presented related to MRD pre-maintenance, therefore after multiple cycles of induction/consolidation, and past the decision for ASCT. If one looks at the control arm of GRIFFIN, only 5.8 % of patients achieve MRD negativity after 4 cycles of RVd[12]. With improvement in induction strategies, particularly with assimilation of anti-CD38 antibodies, a higher proportion of patients reach MRD negativity post induction. In GRIFFIN, 21.2% achieved MRD negativity after 4 cycles of Dara-RVd and in MASTER[13] 38% achieved MRD negativity after 4 cycles of daratumumab, carfilzomib, lenalidomide and dexamethasone. The question of transplant deferral in patients achieving MRD negativity in the setting of quadruplet induction is currently being answered in prospective randomized trials (NCT04934475, NCT05231629).

TREATMENT ACCESS AND ASCT

Despite being available worldwide, access to ASCT is still not universal, limited by number of centers offering the therapy and center capacity. This reality is certain to have a negative impact on clinical outcomes. In a recent publication, it was identified that the waiting period for allogeneic transplantation has an independent negative impact on patient survival[14]. This is a reflection of the limited transplant capacity in developing countries.

Despite the development of new drugs and technologies for the treatment of patients with multiple myeloma, the availability of such technologies is still limited for a large proportion of these patients. Therefore, access to early ASCT gains even more importance, and remains one of the main therapeutic choices, particularly in low- and middle-income countries.

FUTURE DIRECTIONS

Multiple myeloma therapy continues to rapidly evolve. Broader use of anti-CD38 monoclonal antibodies in the newly diagnosed setting, provides the perspective of a large proportion of patients achieving MRD negative responses even without ASCT. Innovations recently introduced in the relapsed and refractory setting, particularly chimeric antigen receptor T (CAR-T)[15,16] cells and bispecific T-cell engagers[17-19], are expected to quickly arrive at the newly diagnosed setting in the context of well-designed clinical trials. It will be crucial to answer whether improvements in induction regimens will be able to provide similar outcomes with deferral of ASCT, particularly among patients achieving MRD negativity. It is also expected that CAR-T cell therapies and even bispecific T-cell engagers will challenge ASCT as best consolidative strategy after modern induction regimens. While we would welcome the opportunity to provide similar or improved outcomes to our patients without the toxicity of ASCT, we should expect the future comparators match or exceed its efficacy, but without compromising safety, access, and affordability. Until them, ASCT remains a dependable, safe, and available strategy to reach deep and prolong responses in a large proportion of our patients.

TABLE 1 – Modern trials comparing upfront vs. deferred ASCT for patients with newly diagnosed multiple myeloma

	N	Induction Regimen	Median PFS (months) (ASCT vs control)	Median OS (months) (ASCT vs control)
RV-MM-PI-2093	273	RD	41.9 vs. 21.6 (HR 0.47, 0.33-0.65)	N.R. vs. N.R. (HR 0.64, 0.36-1.15)
IFM-20094	700	RVD x 3 cycles	50 vs 36 (HR 0.65, 0.53-0.80)	N.R. vs. N.R. (HR 1.16, 0.80-1.68)
EMN-025	1197	VCD x 3-4 cycles	56.7 vs. 41.9 (HR 0.73, 0.62-0.85)	N.R. vs. N.R. (HR 0.90, 0.71–1.13)
FORTE6	315	KRD*	N.R. vs. N.R. (HR 0.61, 0.43-0.88)	N.R. vs. N.R. (HR 0.94, 0.54–1.63)
Determination1	722	RVD x 3 cycles	67.5 vs. 46.2 (HR 0.65, 0.52-0.81)	N.R. vs. N.R. (HR 0.90, 0.61–1.37)

RD= lenalidomide, dexamethasone; VCD= bortezomib, cyclophosphamide and dexamethasone; RVD= lenalidomide, bortezomib and dexamethasone; KRD= carfilzomib, lenalidomide, dexamethasone, *Carfilzomib, cyclophosphamide, dexamethasone arm not represented

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