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REVIEW ARTICLE

# Allogeneic Hematopoietic Stem Cell Transplantation for Myeloma: Time for an Obituary or Not Just Yet!

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**Abstract** The management of myeloma has evolved dramatically in the last two decades. High dose melphalan and autologous hematopoietic stem cell transplantation (HSCT) marked the beginning of this journey. This was followed by an explosion of novel agents which were approved for management of myeloma. Allogeneic HSCT which was deemed as the only curative option was largely abhorred due to high transplant-related mortality (TRM) until the advent of reduced intensity conditioning (RIC). An approach of tandem autologous and RIC-allogeneic transplantations has showed the best promise for cure for this condition, particularly for those with high-risk cytogenetics. Yet, allogeneic HSCT seems to have fallen out of favor due to the projected high TRM and late relapses, even though the alternatives do not offer a cure, but merely prolong survival. Offering an allogeneic HSCT as a final resort in unlikely to yield gratifying results. At the same time, allogeneic HSCT needs to evolve in a disease-specific manner to address the relevant concerns regarding TRM and relapse. With the introduction of effective GVHD prophylaxis in the form of post-transplantation cyclophosphamide, transplantation from a haploidentical family donor has become a reality. The challenge lies in segregating graft-vs-myeloma effect from a graft-versus-host effect. We discuss the pro-survival and anti-apoptotic pathways via CD28-CD86 interactions which confer survival advantages to myeloma cells and the possibility of disruption of this pathway in the context of haploidentical transplantation through the use of CTLA4Ig without incurring T cell alloreactivity.

**Keywords** Myeloma · Allogeneic transplantation · Haploidentical · CD28-CD86 · CTLA4Ig · NK cell

## Introduction

Repeated cycles of various alkylating agents along with corticosteroids was the only option for Myeloma until the 1990s, when the French group demonstrated for the first time that high dose melphalan followed by autologous hematopoietic stem cell rescue markedly improved both progression-free survival (PFS) as well as overall survival (OS) [1]. On the heels of these findings, the Arkansas group reported the rejuvenation of thalidomide as an effective anti-myeloma drug [2]. The next two decades saw an explosion of newer agents such as proteasome inhibitors (bortezomib, carfilizomib and ixazomib), immunomodulators (lenalidomide and pomalidomide), histone deacetylase inhibitors (vorinostat and pabinostat) and monoclonal antibodies targeting SLAMF7 (Elotuzumab) or CD38 (Daratumumab) which were effective in patients relapsing after an autologous HSCT [3, 4].

Allogeneic HSCT was developed on the premises of effective myeloablation and hematopoietic and immune reconstitution from the graft from a HLA-compatible donor, related or unrelated. Although acute leukemia and chronic myeloid leukemia remained the main indications for allograft in the first three decades, other hematological malignancies such as lymphomas and myeloma were also

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subsequently allografted with myeloablative conditioning. However, the European groups reported a high transplant-related mortality (TRM) of 40–50% in these patients [5, 6]. At the same time,30% patients were free of myeloma a decade later indicating its curative potential. Despite the potential for cure, allogeneic HSCT remained a dreaded option due to high TRM associated with it [7].

## Reduced Intensity Conditioning (RIC) and Rebirth of Allogeneic HSCT for Myeloma

The emergence of the concept that engraftment of donor HSC is possible without myeloablation in the late 90s saw a paradigm shift in the approach to allogeneic HSCT [8]. Patients beyond the age of 70 years were being offered an allogeneic BMT as there was a marked decrease in early attrition due to conditioning-related toxicity and early graft-versus-host disease (GVHD). However, this came at the cost of a higher relapse rate and often a late-onset GVHD. Several investigators from across the globe explored the possibility of an allogeneic option following high-dose melphalan and autologous rescue [9, 10]. The tandem approach was associated with a lower TRM (12%) and a better PFS at 5 years than autograft alone (35% vs 18%) as well as RIC-allograft alone (34% vs 22%). Despite these encouraging results, allogeneic HSCT did not gain much favor with myeloma experts and was largely doomed to obscurity by the end of 2000 [4, 11, 12].

## The Changing Landscape of Myeloma Therapy with Allogeneic HSCT Out of Consideration

From being a disease with limited treatment options in 1990, myeloma now supports multi-billion-dollar drug industry two decades later [13]. The current algorithmic approach to treatment of myeloma in patients younger than 65 years has retained an upfront autograft after a triplet induction followed by various forms of intensive consolidation employing newer agents and a prolonged lenalidomide maintenance [14]. Despite these approaches, cure for myeloma has been elusive and the focus has remained on prolonging the OS through multiple lines of therapy [15]. Notwithstanding the newer agents in the fray, upfront autologous HSCT has maintained its primacy in improving both PFS and OS. Despite prolongation of life through multiple lines of therapy, the quality of life in patients living through multiple relapses is severely compromised with continuous and/or repeated hospitalisations and interventions. Myeloma is a disease of the elderly with the median age at diagnosis being 65–70 years. Yet, 30% patients are diagnosed between the ages of 50–65 years and the question remains as to whether they should be offered a curative option? Intensification of conditioning by incrementing dose of melphalan, addition of bendamustine, busulfan or bortezomib (not really conditioning!) did not provide the elusive 'cure' for this conditioning and neither did any form of intensive consolidation [16–19].

## Why Allogeneic HSCT is Banished? Just Bad Press or More!

The major allegation leveled against an allograft in myeloma is the early TRM with the claim that even 10% TRM is too high for a condition where 5–10 years of life on autograft and multiple lines of therapy is feasible. In the current scenario, even those with a matched sibling donor would not be considered for an allograft unless they have relapsed after one autologous HSCT or may be two [20]. The TRM for an allogeneic HSCT undertaken after failure of an autograft and multiple lines of therapy is bound to be high and its efficacy is likely to be compromised in the face of drug-resistant disease. An analysis from EBMT on 413 such patients undergoing RIC-allograft showed a TRM of 21.5% at one year and a PFS of 23% at 5 years [21]. This might be interpreted as an allograft being an ineffective procedure or viewed as something that still can cure a handful of patients who are resistant to all lines of therapy. The paradox of the situation is that the same data would provide an accelerated approval for a new drug for myeloma or any other cancer for that matter [22–24]. In addition, an allograft performed for any form of leukemia after multiple relapses do not fetch much better results.

Secondly, late relapses have been witnessed following allograft after myeloma raising questions about its futility. The conversation regarding allograft would often converge on upfront mortality and late relapses, both being deemed as unacceptable.

A recent meta-analysis of 61 studies between 2007–2017 on 8698 patients showed a pooled estimate for OS, PFS and TRM of 46%, 27% and 27% respectively [25]. Disease relapse accounted for 51% of mortality. However, in 14 trials which accounted for cytogenetic risk category, adverse cytogenetics was not associated with a higher risk of relapse following an allogeneic HSCT.

## What Ails Allogeneic HSCT in General and Specifically in Myeloma

Allogeneic HSCT has long been viewed as a one-off procedure consisting of administration of conditioning regimen followed by infusion of the graft. This is followed by

continuation of GVHD prophylaxis if the graft is not T cell depleted (TCD) and monitoring for disease progression at fixed intervals. Some prefer to intervene at early indications of relapse of the malignancy and others do not. TRM from infections, RRT and GVHD range from 10–30% depending on duration of previous treatment and co-morbidity index.

Intervention following relapse of disease remains an inadequate approach and HSCT should be designed to prevent relapse [26, 27]. Myeloma has the propensity to be remain quiescent and evade immune-mediated assault to produce late relapses. Hence, allograft as it is carried out remains grossly insufficient to provide the optimum results in terms of prevention of disease relapse or progression. In addition, a TRM of more than 10% is unlikely to be acceptable to patients and myeloma physicians alike. Unless an allogeneic HSCT approach consistently produces a TRM of less than 10% with a relapse rate not exceeding 30%, there is little chance of salvaging allograft for myeloma from its exiled status, regionally or globally [28].

## Resurrection of Allogeneic HSCT in Myeloma

A combined approach of tandem auto-allo HSCT has yet produced the best long-term results in myeloma. Although a lot of interest lies in pharmacological maintenance therapy for myeloma and other malignancies, the potential for cure lies in early assault on the disease via immunologically driven processes from donor cells. The greatest concern in implementation of any such intervention is aggravation of T cell mediated alloreactivity in the form of GVHD. However, myeloma cells have been shown to be extremely sensitive not only to T cell mediated killing as evidenced by achievement of remission following donor lymphocyte infusions, but also drugs such as lenalidomide which potentiate the T cell cytotoxicity against myeloma. However, this is wrought with the risk of GVHD in the post-transplant setting and hence lies the understandable hesitation of transplant physicians in offering this as a prophylactic approach. On the other hand, myeloma cells are equally susceptible to NK cell mediated cytotoxicity as demonstrated in-vitro and also in the form of SLAMF7 directed drugs such as Elotuzumab which operate by enhancing NK cell mediated killing of myeloma cells.

Perhaps the best time for immunological eradication of residual cancer cells is immediately following the conditioning [29]. However, the immune system is immature, and no substantial anti-myeloma effect is plausible in the first 30 days after transplant apart from those lymphocytes transfused with the graft which could escape the immunosuppressive effects of GVHD prophylaxis employed. This possibility is further nullified following TCD grafts. Thus, without active intervention in the form of adoptive immunotherapy within this window, the best opportunity to achieve immunological eradication of residual myeloma cells would have been lost. On the other hand, cellular therapy in this period markedly increases the risk of significant GVHD. However, the use of prophylactic or preemptive DLI when applied have improved the outcome of myeloma [30]. Thus, the separation of the conjoint twins of allogeneic HSCT, GVT and GVHD continues to be its 'Holy grail' [31].

## Allogeneic HSCT as a Platform for Early Adoptive Immunotherapy

Adoptive immunotherapy has not been offered as a prophylactic approach within the first 30 days in any form of allogeneic HSCT [32, 33]. Recent introduction of post-transplantation cyclophosphamide (PTCy) has made it possible to consider haploidentical family donor HSCT at par with matched unrelated donor transplantation [34]. Several studies have compared HSCT from haploidentical family donor to matched unrelated or matched family donor with equivalent results in terms of GVHD, TRM and PFS [35, 36]. Although excellent results were obtained with PTCy based haploidentical HSCT in terms of GVHD and NRM, high rates of disease relapse are a major deterrent in offering this approach to patients with advanced malignancies [37].

In a cohort of refractory leukemia undergoing post-transplantation cyclophosphamide (PTCy) based haploidentical HSCT employing non-myeloablative conditioning in aplastic phase, we had employed DLI at day 35 post-transplant in 10 consecutive patients without witnessing any GVHD. However, 90% of those relapsed by 6 months [38]. This raised two questions for us. First and most important was the observation that DLI even in the setting of haploidentical HSCT can be administered as early as 35 days without invoking the wrath of GVHD. A plausible explanation for this was the Treg sparing effect of PTCy inducing early tolerance [39]. The second observation which was no less important, was that DLI is unlikely to be effective beyond 4 weeks of transplant in patients with active disease who have been minimally conditioned.

In the next cohort of patients, we achieved an improved PFS of 25% switching to a myeloablative conditioning [38]. Achieving a NRM of less than 20% in this very high-risk cohort prompted us to consider the next option which was employment of early G-CSF primed DLI at 21, 35 and 60 days post-transplant with myeloablative conditioning. The incidences of acute and chronic GVHD were 31% and 41% respectively with one-year NRM being 19%. Most remarkably, in this cohort of relapsed/refractory myeloid

malignancies the PFS was 66% at 2 years. This was the first study demonstrating the feasibility of early and prophylactic DLI following haploidentical HSCT in advanced leukemia which was undertaken with G-CSF mobilized CD3+ T cells within 4 weeks of transplant, in the context of myeloablative conditioning.

In another study, we had explored the feasibility of infusing CD56 enriched DLI at day +7 to exploit the endogenous surge of IL-15 which is expected following PTCy administration in those who were not eligible for MAC [40]. No acute GVHD was noted in this cohort and the PFS was 50%. Two important inferences were drawn from this study. First, in the context of PTCy based haploidentical HSCT, 1–10 million NK cells/kg can be administered with a log less CD3+T cells without significant GVHD as early as 7 days post-transplantation. Second, a single dose of NK cells might not suffice in this context to significantly impact the risk of DP.

## Can We Dissociate GVT from GVH- Touching the Forbidden Fruit!

We further evolved a novel strategy to optimize NK cell mediated cytotoxicity without being compromised by T cell mediated alloreactivity. In order to reduce T cell mediated alloreactivity in children undergoing haploidentical HSCT, we introduced the use of T cell costimulation blockade with CTLA4Ig at fixed times before and after infusion of the graft. Abatacept (CTLA4Ig) is a fully humanized protein construct, consisting of the extracellular domain of CTL4 and a genetically engineered fragment of the Fc region of human immunoglobulin G1 (IgG1) which binds to B7 ligands with high affinity impeding the CD28 mediated costimulation and T-cell activation [41]. This was associated with marked reduction in alloreactivity in children with aplastic anemia. In addition, we noted a relative but not absolute increase in mature $CD56^{dim}$ NK cells at 30 days in contrast to the preponderance of immature NK cells when CTLA4Ig was not employed [42].

In several animal models it had been shown that the use of CTLA4Ig in mismatched allograft models resulted in NK cell mediated graft rejection or in other words NK cells were resistant to costimulation blockade by CTLA4Ig [43]. Keane et al demonstrated that not only were the NK cells efficient in killing the target cells in presence of CTLA4Ig, this process was aided and abated by LFA1 [44]. In an elegant experiment, Peng et al demonstrated that CTLA4Ig aided tumor reduction in a melanoma mouse model and this effect was negated by depletion of NK cells [45]. Furthermore, the group showed an increase in NK cell cytotoxicity in presence of CTLA4Ig with upregulation of CD86, which they described as a putative activation receptor for NK cells.

Based on these premises, we developed a protocol for adoptive immunotherapy where DLI at fixed CD3+T cell doses of 1–10 million/kg were administered 12 h after CTLA4Ig infusion at 7, 21 and 35 days post-transplantation. In a pilot study on 30 patients with acute leukemia with high/very high DRI and 22/30 with greater than 5% marrow blasts, an EFS of 75% was achieved at 18 months with only 4% NRM and 6.7% acute GVHD [46]. Absence of disease progression (DP) in this cohort correlated with proliferation of mature NK cells at 30 days and this persisted for the first 100 days post-transplantation. NK cells do not acquire cytotoxic potential early after HSCT, as they express high levels of NKG2A at early stages of maturation and do not express the activation receptor CD16. In addition, acquisition of KIR receptor expression is key to enabling NK cells engage in target cell binding and killing. We had found that in patients without relapse, not only did $CD56^{dim}$ $CD16^{+}$ NK cells proliferate, they closely expressed the phenotype of mature donor NK cells with high KIR and low NKG2A expression. It generally takes several months or even a year for NK cells to achieve this phenotype. Thus, this simple yet novel approach enables generation of NK cell mediated GVT effect without being compromised by GVHD. It might not be unwise to state that may be for the first time we are able to dissociate a potent GVL effect from GVHD in a clinical setting with an approach which could be adapted globally bereft of technological challenges.

## Blocking the CD28-CD86 Pathway: a Perfectly Tailored Option for Myeloma!

Myeloma cells express CD28 receptor and high expression of this receptor indicates a poor prognosis for myeloma. This is because ligation of CD28 on myeloma cells with CD80/86 on dendritic cells lends survival advantage to these cells through an anti-apoptotic pathway [47]. Importantly, myeloma cells can express both CD28 and CD86 and an autocrine or a cis interaction between myeloma cells might be responsible for extramedullary survival of these cells [47]. CD28 pro-survival signaling is dependent upon downstream activation of phosphatidyl-inositol 3-kinase/Akt, inactivation of the transcription factor FoxO3a, and decreased expression of the pro-apoptotic molecule Bim. This pathway protects myeloma cells from chemotherapeutic as well as immunological killing resulting in resistance to both chemotherapeutic agents as well as immunological killing [48]. Blockade of this pathway makes myeloma cells susceptible to drugs as well as NK cell mediated killing.

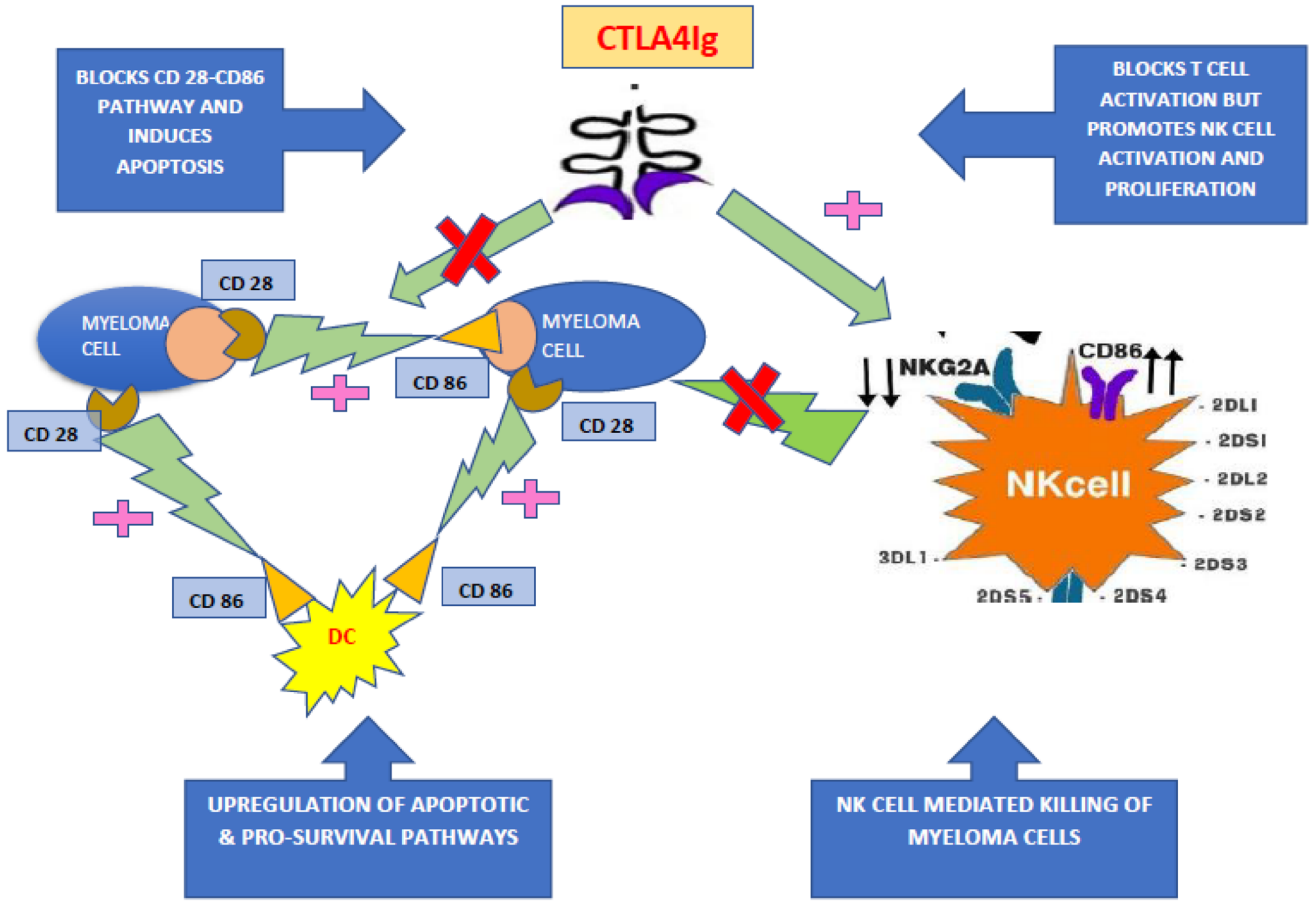


**Fig. 1** Pictorial illustration of the mechanism of myeloma cell survival through CD28-CD86 pathway and the effect of CTLA4Ig on inhibition of this pathway and simultaneous promotion of NK cell activation and killing of myeloma cells

CD28 blockade with CTLA4Ig is unlikely to be effective in combination with immunomodulators as lenalidomide for example is operational through cytotoxic T cell pathway and does not potentiate NK cell mediated killing [49]. In addition, repeated exposure to CTLA4Ig would be needed in order to sensitize myeloma cells to apoptotic pathway. Blockade of CD80-CD86 costimulatory pathway for T cells would result in immunological silence of T cells and might be counterproductive with repeated dosing in the context of proteasome inhibitors or immunomodulators as does long term use of dexamethasone in this context [50]. Hence, this approach is likely to reap benefits only if NK cell mediated anti-myeloma pathway is augmented.

Thus, administration of CTLA4Ig prior to conditioning might sensitize myeloma cells to lower doses of alkylating agents as shown in-vitro [47] and sequential DLI lays the platform for uninhibited assault on residual myeloma cells which otherwise are resistant to treatment as shown in Fig. 1. In this context, we have seen the expression of CD 28 and CD 86 to be upregulated in relapsed and refractory myeloma indicating survival of myeloma cells through this anti-apoptotic pathway. Two such patients had achieved a MRD negative remission and continue to be disease free two years post-transplant following CTLA4Ig primed DLI based haploidentical transplant protocol outlined above (unpublished data).

## Conclusions

Allogeneic HSCT has evolved over the last 5 decades and witnessed major paradigm shifts in conditioning, donor choice and prevention of GVHD. Yet, prevention of relapse has remained an elusive goal. We need to tailor allogeneic HSCT specific to the disease and its prognostic stage, rather than having a blanket approach of one for all. The key to this lies in a better understanding and dissection of individual arsenals in the immune armory as intensification of conditioning and post-transplant pharmacological interventions have their limitations. If the above approach proves successful in patients with myeloma, we might have resurrected the strongest weapon in our armory which was otherwise destined for oblivion.

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