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Review

Donor Lymphocyte Infusion to Enhance the Graft-versus-Myeloma Effect

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Abstract: Donor lymphocyte infusion (DLI) has the potential to significantly deepen the response after allogeneic stem cell transplantation (ASCT) in multiple myeloma (MM). Subsequently, DLI offers the opportunity for long-term progression-free and, most importantly, overall survival for patients with MM. DLI application is a complex procedure, whereby many factors need to be considered (e.g., patient-oriented factors prior to application, disease-specific factors, as well as possible combinations with further therapies during and after DLI). There are two settings in which DLI can be given, they are as follows: as a salvage option in progressive disease or in the prophylactic setting for MM patients with resolved disease to further deepen the response. While the first studies used DLI in the salvage setting, results for prophylactic DLI appear to be associated with better and prolonged outcomes. Furthermore, DLI (both prophylactic and salvage) given earlier after ASCT (3–6 months) appear to be associated with better outcomes. The incorporation of novel agents showed similar responses and survival after DLI. However, updated and larger evaluations are urgently needed to determine the specific role of multiple variables in such a complex treatment environment of ASCT in an ever-evolving field of MM. This review underlines the rationale for DLI after ASCT, results in the salvage and prophylactic settings, patterns of disease progression after DLI, as well as avenues to further enhance the graft-versus-myeloma effect exerted by DLI.

Keywords: graft-versus-myeloma; donor lymphocyte infusion; myeloma; allogeneic stem cell transplantation; prophylaxis; salvage; relapse

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1. Introduction

Multiple myeloma (MM) is a yet incurable hematologic malignancy that has benefited from the advent of novel agents over the last decade. Despite major advances in treating MM throughout the disease course, allogeneic stem cell transplantation (alloSCT) remains a potentially curative treatment option [1,2]. However, the application of alloSCT is increasingly challenged by new therapies and its inherent association with treatment-associated morbidity and mortality [3,4]. Therefore, the proper incorporation of alloSCT within a whole (immune-) therapeutic environment, which improves outcome of specific subgroups of patients, needs yet to be identified, especially in the advent of ever-improving outcomes using novel agents [5–7].

Alloreactive immune effector cells originating from an MM-free graft may exert graft-versus-myeloma (GVM) effects, which can lead to the long-term control of disease [8]. One immunotherapeutic approach post-alloSCT is donor lymphocyte infusion (DLI), which is believed to augment these GVM effects supporting MM control, by deepening responses [9,10]. On the other hand, DLI may cause graft-versus-host disease (GVHD), which could become life threatening if it is acute, whereas even chronic GVHD may be important for the exertion of GVM effects [11]. Here, we present a comprehensive review of the role and the potential benefits and risks of DLI in post-alloSCT therapy for MM.

2. Prophylactic Setting

Although DLI was mostly given in the context of refractory or progressive disease posttransplant (see above), this modality of immunotherapy has also been adopted for and incorporated into the prophylactic post-alloSCT setting for patients with resolved disease. These prophylactic applications of DLI using a prespecified schedule or planned escalated incremental doses during T-cell reconstitution may enhance donor-derived T-cell reconstitution and further support the GVM effect.

One early single-center analysis of 24 patients undergoing CD6 T-cell-depleted alloSCT from HLA-identical sibling donors between 1996 and 1999 evaluated prophylactic CD4+ DLI 6 to 9 months after alloSCT [12]. All patients, including patients with complete remission after alloSCT, were eligible to receive DLI if there was no evidence of GVHD and if they were not receiving medication for GVHD. The first 11 patients received a single infusion of 3×10^7 cells/kg, and 3 patients received a single infusion of 1×10^7 cells/kg. After DLI, no other immune-modulating therapy nor prophylaxis for GVHD was given. Fourteen patients received DLI, 3 in complete response and 11 with persistent disease after BMT. Significant GVM responses were noted, resulting in 6 complete responses and 4 partial responses in patients with previous persistent disease. After DLI, 50% of the patients developed higher-grade acute GVHD (grades > 2). Survival at 2 years for all patients was 55%, and progression-free survival was 42%. The 14 patients receiving DLI showed a better 2-year progression-free survival of 65% when compared with a historical cohort of MM patients. This study also highlights the importance of patient selection and management, since only 58% of the included patients could actually receive DLI.

A long-term follow-up and single-center study of prophylactic DLI [13] recently underlined these findings, but also highlighted the complexity of the alloSCT treatment platform [14]. This study had a long-term follow-up of >5 years. A total of 61 patients with MM, who did not relapse nor develop disease progression after alloSCT, were treated with prophylactic escalating DLI, including a total of 132 DLI procedures. The overall response rate was high (77%). Thirty-three patients (54%) upgraded their remission status, with a quarter of patients even achieving molecular remission. The cumulative incidence of acute GVHD was moderate (33%), and no treatment-related mortality was observed. After a median follow-up of 69 months from the first DLI, 8-year progression-free and overall survival were 43% and 67%, respectively, with rates of 62% and 83% for patients in molecular remission. In multivariable analysis, molecular remission was the only independent prognostic factor for progression-free survival, while for overall survival, only cytogenetics were significantly associated with survival (i.e., worse outcome for high-risk cytogenetics). In that study, no impact of novel agents was observed. However, the use of novel agents was associated with more DLI procedures [13,15,16]. Furthermore, patients who received unstimulated DLI had a higher risk of acute GVHD, which was not associated with higher response rates in comparison with those who received G-CSF-stimulated T cells that were obtained from the original alloSCT product. These findings are in line with a recent comparison of stimulated and unstimulated DLI, showing no significant differences regarding response, survival, and safety [17]. The main results of the studies in both the prophylactic and salvage setting are listed in Tables 1 and 2.

Table 1. Results of prophylactic donor lymphocyte infusion (DLI).

Study (Year)	N	Graft Type	Dose (Range), $\times 10^6$ Cells/kg	Response, %	Acute GVHD, n	Survival
Alyea [12] (2001)	14	MRD	10–30	86	7	PFS: 65% 2y
Badros [18] (2001)	14	MRD	120–220	86	10	OS: 69% 1y
Peggs [19] (2003)	20	MRD/MUD	1–100	50	3	PFS: 30% 2y OS: 71% 2y
Kröger [10] (2009)	32	MRD/MUD	0.5–200	78	13	PFS: 54% 5y
Gröger [13] (2018)	61	MRD/MUD	0.3–100	77	7	PFS: 43% 8y OS: 67% 8y

Abbreviations: MRD, matched related donor; MUD, matched unrelated donor; GVHD, graft-versus-host disease; y, years; m, months; N, number; DLI, donor lymphocyte infusion; PFS, progression-free survival; OS, overall survival.

Table 2. Results of salvage DLI.

Study (Year)	N	Graft Type	Dose (Range), $\times 10^6$ Cells/kg	Response, %	Acute GVHD, n	Survival
Lokhorst [9] (1997)	13	MRD	1–330	62	9	54% 1y
Salama [20] (2000)	25	MRD/MUD	2–224	36	13	48% 1y
Lokhorst [21] (2004)	54	MRD	1–500	52	31	PFS: 19m OS: 23m
El-Cheikh [22] (2012)	9	MRD/MUD	10–100	75	1	PFS: 50% 2y OS: 69% 2y
Montefusco [23] (2013)	19	MRD/MUD	0.5–100	68	2	PFS: 31% 3y OS: 73% 3y

Abbreviations: MRD, matched related donor; MUD, matched unrelated donor; GVHD, graft-versus-host disease; y, years; m, months; N, number; DLI, donor lymphocyte infusion; PFS, progression-free survival; OS, overall survival.

3. Salvage Setting

Donor lymphocyte infusions have long been an important strategy for patients with hematologic malignancies who have experienced relapse after alloSCT [24]. Early on, the most impressive results have been obtained in patients with post-alloSCT relapsed chronic myelogenous leukemia, especially when initiated in patients with cytogenetic relapse or in those who have relapsed into the chronic phase [25,26]. In the late 1990s, the first reports suggested antitumor effects in MM patients. In 1996, Tricot et al. [8] reported the achievement of complete remission with a single dose of CD3+ cells in an MM patient who had progressed after alloSCT, providing the first proof-of-concept for utilizing DLI to induce a GVM effect.

Soon after that, one retrospective study evaluated the impact of DLI in 13 patients with relapsed MM after alloSCT [9]. The patients received a total of 29 DLIs with T-cell doses ranging from 1×10^6/kg to 33×10^7/kg. Doses, sometimes with escalated levels, were repeated if no response or another relapse was observed after DLI. Eight patients responded, with 4 even achieving complete remission, while the others achieved partial remission. Median time from dli to response was 6 weeks. Major toxicities were secondary to GVHD, which was observed in >50% of patients and in >80% of the responders. Fatal aplasia was seen in 2 patients who responded. The only prognostic factors for response were single T-cell doses $>1 \times 10^8$/kg and the occurrence of acute GVHD. This first experience identified the importance of individual dosing schemes and acute GVHD, suggesting escalating doses until the maximum response has been achieved.

A follow-up and extension included 27 patients who received 52 DLI courses for a median of 30 months after alloSCT [21]. Fourteen patients (52%) responded to DLI, with

6 patients achieving complete remission (22%). Five patients remained in remission for more than 30 months after DLI. Acute GVHD was present in 55% of the patients. Two patients died due to aplasia. The median overall survival was 18 months. Comparing responders and DLI-resistant patients, the median survival was not reached compared with 11 months. In two patients, sustained molecular remission was observed. Again, one key factor that was associated with response was a cell dose >1 $\times$ 10^8/kg.

Subsequently, a study from 4 Dutch transplant centers was reported [27], analyzing 54 patients (with a median age of 52 years), of whom 50 showed relapse following myeloablative partially T-cell-depleted alloSCT, and 4 following non-T-cell-depleted myeloablative alloSCT. Most patients received high-dose cyclophosphamide and total body irradiation (12 Gy) conditioning. A total of 95 DLI procedures (range, 1–7) for a median of 20 months were given. The T-cell doses of DLI varied between 1 $\times$ 10^6 and 5 $\times$ 10^8 cells/kg. Most patients received a starting dose of 1 $\times$ 10^7 cells/kg. Dose escalation was done in the absence of response and acute GVHD until 3 months after the first DLI. Forty patients received reinduction therapy before DLI with vincristine/adriamycin/dexamethasone, dexamethasone alone, or melphalan alone. Response rates were comparable with previous findings, and progression-free and overall survival were 19 and 23 months, respectively. Acute GVHD after DLI was the strongest predictor of response. In patients with deletion of chromosome 13, as determined by double-color fluorescence in situ hybridization (FISH), no difference in outcome was seen.

Another study on dose-escalating salvage DLI was undergone in patients receiving reduced-intensity conditioning [28]. Grade 3–4 acute GVHD was found in 14% of patients and 1 patient died because of grade 4 acute GVHD. Despite the lower median cell dose for unrelated DLI (1 $\times$ 10^6 compared with 4.7 $\times$ 10^6 CD3+ cells/kg for related DLI), only the unrelated DLI recipients showed acute GVHD. With respect to responses, 19% showed complete response and partial remission, respectively. Stable disease was seen in 29%, while 33% of patients showed progressive disease. Median time from dli and response was 2 months. One-third of patients showed response after the first DLI. The median follow-up from DLI was 7 months, and 71% of the patients were alive, with three patients still in complete remission at the last follow-up at 8–14 months.

To assess the impact of combination approaches, a prospective phase 2 study evaluated the efficacy and safety of the combination of bortezomib/dexamethasone followed by DLI [23]. Patients received 3 cycles of bortezomib/dexamethasone followed by escalated doses of DLIs in the cases of response or at least stable disease. Fourteen days after the third course, and in the absence of acute GVHD, DLI was administered every 6 weeks at escalating cell doses, for up to 4 infusions. For the transplants from HLA-identical siblings, the infusions were done at the following cell doses: 5 $\times$ 10^6 CD3+/kg, 1 $\times$ 10^7 CD3+/kg, 5 $\times$ 10^7 CD3+/kg, and 1 $\times$ 10^8 CD3+/kg. For transplants from HLA-mismatched siblings or matched unrelated donors, the infusion scheme consisted of 5 $\times$ 10^5 CD3+/kg, 1 $\times$ 10^6 CD3+/kg, 5 $\times$ 10^6 CD3+/kg, and 1 $\times$ 10^7 CD3+/kg. In the case of complete remission before the first DLI, the patients received only the first 2 DLI doses. The study included 19 patients with a median age of 57 years. Fourteen patients received HLA-identical sibling alloSCT and 5 received matched unrelated donor alloSCT. Before DLI, the response rate was 62%, including 1 complete remission. After DLI, the response rate was 68%, observing a significant deepening of responses, showing 3 stringent complete responses and 2 complete responses. At a median follow-up of 40 months, 3-year progression-free survival and overall survival rates were 31% and 73%, respectively. Notably, no severe GVHD was seen.

4. Prognostic Factors in Salvage Setting

Importantly, it needs to be stressed that most analyses included only a small number of patients and may not depict accurate relations because of the lack of control settings. In a retrospective study of 48 relapsed MM patients and 15 patients with persistent disease after non-myeloablative alloSCT, prognostic factors for efficacy of DLI were analyzed [29]. The conditioning consisted of TBI (Total body irradiation) only, TBI and fludarabine,

melphalan only, or thiotepa and cyclophosphamide. The overall survival after DLI was 24 months (1–51 months). The median overall survival was not reached for responders while non-responders showed a median survival of 24 months. Progression-free survival was remarkably higher in patients with complete response (28 months), compared with those achieving only partial remission (7 months). The only significant prognostic factor for response to DLI was the occurrence of acute GVHD, and patients who received their DLI earlier after alloSCT appeared to benefit more than patients who received their DLI one year after alloSCT.

5. DLI and Patterns of Disease Progression

To date, the clinical kinetics of alloreactive T cells in controlling MM progression or even inducing regression are not fully understood. An efficient GVM response requires accurate targeting of malignant cells by antigen-specific T cells in all sites of MM infiltration. While homing of T cells to the bone marrow was found to happen constitutively, other tissues may need ligand specificity of T cells, or inflammatory environments [30,31]. As a result, the strength of the immune response may differ and result in differential progression patterns of MM after cellular therapy such as alloSCT and DLI [32].

One study hypothesized that alloSCT and DLI modulate patterns of MM progression. To test this, marrow and focal progression were assessed as separate events in a cohort of 43 patients who underwent alloSCT with planned DLI in comparison with outcomes of a cohort of 12 patients who did not receive alloSCT [33]. After DLI, complete disappearance of MM cells in the bone marrow occurred in 86% of evaluable patients. The probabilities of so-called bone marrow progression-free survival at 2 years after DLI was 62%. In contrast, the probability of focal progression-free survival was 28%. In sum, donor-derived T-cell responses effectively reduce bone marrow infiltration, while focal progression did not seem to be successfully influenced.

In contrast, one study from Minnema et al. [32] showed that the treatment of extramedullary relapse after alloSCT, using DLI in combination with bortezomib or thalidomide, showed complete responses and did not differ in comparison with those who did not have extramedullary relapse. Notably, patients with only skin involvement showed complete response after DLI, while patients with multiple involvements of the kidney, skin, and lymph nodes showed no response. Whether antitumor effects are not only site-specific when comparing marrow and extramedullary sites, but also organ-specific, needs to be addressed in future studies.

6. Improving DLI Effects

6.1. Enhance the Immune Response

Despite the impressive results of recent long-term outcome data of prophylactic DLI [13], and due to the consistent refinement of novel agent treatment schedules combining steroids, immunomodulation, and monoclonal antibodies, alloSCT is nowadays no longer considered part of the standard upfront or sometimes even second-line therapy for MM. Therefore, strategies to alter the balance between GVM and GVHD, and diminish toxicity, need to be explored.

Based on findings from animal models, the presence of host-dendritic cells (host-DC) in mixed chimeric recipients is considered crucial for the development of an adequate antitumor effect. Host-DCs are more able to prime donor T cells against the host antigens expressed on malignant cells [34–36]. However, after alloSCT, MM patients rapidly convert to complete donor chimerism in the DC compartment, often before the establishment of an effective anti-MM response [37]. Therefore, combining DLI with the infusion of host-DC was hypothesized to maximize GVM. However, the host-DCs may be infused as such to induce a GVM effect, as they already express the mismatched minor histocompatibility antigens. On the other hand and in addition, host-DCs may be loaded with the host hematopoietic minor histocompatibility antigens to guide the immune response towards MM cells [38]. One clinical phase 1/2 study tested this hypothesis [39]. Myeloma patients

with persistent measurable disease after alloSCT and a first DLI were included. From 15 patients, 11 received a second equivalent dose of DLI combined with the repeated administration of a host-DC vaccine. The first 7 patients were treated with unloaded host-DCs, whereas the last four patients received a minor histocompatibility antigen-loaded host-DC vaccine. A portion of the vaccine included a control antigen. No new GVHD occurred and toxicity was mild. All evaluable patients developed objective T-cell responses against the control, 60% demonstrated anti-host T-cell responses, and 25% of patients with minor histocompatibility antigen-loaded host-DC vaccine induced an objective T-cell response against the relevant minor histocompatibility antigen peptide. However, only one patient showed stringent complete response. Despite its safety, this approach may need refinement, by developing more immunogenic products or by combining this vaccine with other immune boosting strategies [39,40].

6.2. Tumor-Specific T Cells

Another option could be the tumor-specific T cells. Previously, emerging tumor-specific T cells targeting the Wilms' tumor 1 (WT1) protein were associated with increased relapse-free survival in patients with hematologic malignancies after alloSCT [41,42]. In MM, one study examined responses after WT1-specific cytotoxic T lymphocytes (CTL) in relapsed MM and high-risk cytogenetics who were undergoing T-cell-depleted alloSCT followed by DLI [43]. Of 24 patients, all showed WT1-CTL responses before alloSCT, which were associated with pre-alloSCT tumor burden. All patients subsequently developed increased WT1-CTL frequencies, in the absence of graft-versus-host disease. Immunohistochemical analyses of WT1 and CD138 in bone marrow specimens demonstrated consistent coexpression within MM cells. Furthermore, WT1 expression in the bone marrow correlated with disease outcome. These first evaluations suggested an association of emerging WT1-CTL and GVM, supporting the idea of combined adoptive immunotherapies. However, translations into the clinical reality for MM patients are lacking.

Since GVM responses involve T-cell recognition of tumor-specific peptides presented by major histocompatibility complex molecules, it may be possible to identify and select donor T cells that provide beneficial antitumor responses but minimal GVHD risk. In this regard, immune transcriptome analyses of T-cell receptor (TCR) Vβ CDR3-size and -sequence is being used to characterize alloreactive versus tumor-specific T-cell responses. Previous studies showed that the Vβ families were involved in the GVM and GVH response in an MM alloSCT model, and found that the Vβ 2, 3 and 8.3 families of T cells were specifically involved in the GVM response [44]. The implication of these results would be that MM-specific T-cell subfamilies might be positively selected from the donor and could therefore be infused into MM patients after alloSCT [45]. As a result, no prior definition of target antigens would be needed. To test this rationale, one recent study used an allogeneic B10.D2→Balb/c alloSCT model with MOPC315.BM MM cells, first demonstrating that MM-bearing Balb/c mice initially respond to irradiation and auto-alloSCT but eventually relapse, similar to MM patients in the real world. After infusing mice with B10.D2 T cells from only the TCR Vβ 2, 3 and 8.3 repertoire, which was pre-activated in vitro, consistent GVM without GVHD or disease relapse was observed. These data highlight the possibility that tumor-specific allogeneic T-cell therapy may lead to long-term disease-free survival without GVHD in patients with MM.

6.3. Cancer/Testis Antigens

The specific expression of cancer/testis antigen patterns has been associated with disease stage and poor clinical prognostic indictors in MM [46]. Due to the immunosuppressive characteristics of MM, cancer/testis antigens have been studied in several treatment strategies. Responses specifically to New York esophageal squamous cell carcinoma 1 (NY-ESO-1) and melanoma-associated antigen (MAGE) have been the most reported, by simultaneously detecting serum antibodies as well as antigen-specific CD8+ T cells [47,48]. Importantly, strong antibody responses against cancer/testis antigens were preferentially

found in patients undergoing alloSCT, which could therefore be targets for future post-alloSCT immunotherapy [49]. Moreover, primary autoantibodies against intracellular MM-specific tumor antigens such as NY-ESO-1 were rare but functional. Theoretically, they may have the ability to affect cellular anti-tumor immunity by developing monovalent and polyvalent immune complexes [50]. To further increase anti-MM responses, vaccines against these antigen targets may also provide treatment opportunities, using NY-ESO-1 pre-exposed dendritic cells or recombinant MAGE peptide plasmids [51]. However, no robust clinical trial data are currently existing, and more research is needed to find avenues identifying and realizing the full potential of cancer/testis antigens in MM and alloSCT.

6.4. Novel Agents

One study aimed to combine reduced-intensity alloSCT and escalating DLI with novel agents (thalidomide, bortezomib, and lenalidomide) to target complete remission [10]. Thirty-two patients achieving only partial remission after alloSCT were included. Complete remission was achieved >50%. After a median follow-up of 56 months, progression-free survival for patients who achieved complete remission was 58% in comparison with 35% for those who did not, while overall survival was 90% compared with 62%, respectively. Patients with molecular complete remission had significantly better progression-free and overall survival than patients without, showing 84% compared with 38% and 100% compared with 71%, respectively. Incidence of acute GVHD grades >2 was 33% and severe grade 3 GVHD was 7%. None of the patients developed grade 4 GVHD. These findings highlighted the utility of combination therapy post-alloSCT to deepen responses and, subsequently, improve outcomes with signals for cure in some patients.

7. Conclusions

Donor lymphocyte infusion, especially in the prophylactic setting, has the potential to significantly deepen the response after alloSCT, thereby offering the opportunity for long-term progression-free and, most importantly, overall survival for patients with MM. However, the dissection of the subgroup of patients who may benefit from alloSCT from those who may benefit from less toxic novel agent approaches remains crucial [52]. Limited evidence points to subgroups with high-risk MM patients, young and motivated patients [53–55]. Moreover, DLI application is a complex procedure, whereby many factors need to be considered (e.g., patient-oriented factors prior to application, disease-specific factors, as well as possible combinations with further therapies during and after DLI). The incorporation of novel agents showed similar responses and survival after DLI. To date, no specific information is available on the efficacy and safety of DLI after different transplant settings or maintenance approaches. Moreover, other cellular therapy approaches such as chimeric antigen receptor T-cell therapy, which was most recently approved for relapsed/refractory MM [56], and other immunotherapeutic approaches such as bispecific antibodies, will surely challenge alloSCT and DLI even further [57]. With promising responses across immunotherapeutic approaches, the myeloma community may be confident that immunotherapy will manifest itself for personalized myeloma therapy, although a cure does not seem achievable yet using these new treatment options.

Considering alloSCT, updated and larger evaluations are urgently needed to determine the specific role of multiple variables in such a complex treatment environment of alloSCT in an ever-evolving field of MM.

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