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Allogeneic haematopoietic cell transplantation for multiple myeloma: Reducing transplant-related mortality while harnessing the graft-versus-myeloma effect

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ABSTRACT

Allogeneic haematopoietic cell transplantation (allo-HCT) provides effective therapy for patients with various haematological malignancies. In multiple myeloma (MM) this approach can induce response rates in 35–75% of patients. However, the outcome is hampered by high rates of treatment-related mortality (TRM). Reduced intensity conditioning to lower TRM has been successfully applied. The fact that previous clinical reports have documented graft-versus-myeloma (GVM) activity without graft-versus-host disease (GVHD) suggests that at least two distinct immunocompetent cell populations mediating GVHD and/or GVM may exist. Further characterization of effectors after allo-HCT and their targets may help to clarify the immune response that mediates the GVM effect. This review considers the clinical results with myeloablative and reduced intensity conditioning prior to allo-HCT for MM, with emphasis on attempts to prevent GVHD while preserving the GVM effect. Strategies including donor lymphocyte infusions as part of the allogeneic protocol and antigenic targets for GVM effect are reviewed.

1. Introduction

Allogeneic haematopoietic cell transplantation (allo-HCT) in multiple myeloma (MM) is a potential curative treatment. Advantages in comparison to autologous haematopoietic cell transplantation (auto-HCT) are tumour-free grafts and the graft-versus-myeloma effect (GVM) mediated by the allogeneic donor immune system.[1,2] The existence of the GVM effect is supported by the observation that T-cell depletion of the graft reduces the progression-free survival (PFS) and patients with chronic graft-versus-host disease (GVHD) have a lower risk of relapse.[3,4] However, allo-HCT was associated with higher treatment related mortality (TRM) as compared to auto-HCT,[3] especially in the earlier phase of allo-transplants[5] and in the context of high-dose preparative conditioning.[5–12] Long-term, progression-free survival (PFS) rates of 20–55% have been observed after myeloablative dose conditioning.[5–12] Adverse risk factors for outcome after myeloablative dose conditioning include longer intervals from diagnosis to transplant, a high pretransplant beta-2 microglobulin level, chemotherapy resistance, extensive prior treatment, and advanced Durie Salmon Stage III.[4–12] More recently, reduced-intensity conditioning regimens have been used with reported overall-survival (OS) rates of 25–78% after 2 years.[13–18] Again, the occurrence of chronic GVHD was associated with a better OS and PFS as evidenced by a multicentre

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study of the EBMT,[18] suggesting the benefit from the GVM effect in this therapeutic strategy.

Direct comparison of allo-HCT and auto-HCT has evidenced that short-term survival is superior with the autologous approach, mainly due to a higher TRM in the first year with allo-HCT.[3] However, while patients treated with auto-HCT can experience late relapses, there is a plateau of the PFS and OS curves after 5 years for patients receiving allo-HCT, suggesting that long-term survival is superior with the allogeneic approach.

Further support of the existence of a GVM effect has been demonstrated by the efficacy of donor lymphocyte infusions (DLI) in patients relapsing after allo-HCT.[19–29]

In this review, we report on clinical experience collected with myeloablative dose conditioning for allografting in MM, reduced intensity conditioning regimens with or without preceding auto-HCT and allo-HCT with DLI as prophylaxis[19–22] for myeloma relapse or as relapse treatment.[23–29] Furthermore, potential molecular targets for the donor immune system on myeloma cells are discussed.

2. Clinical experience with myeloablative dose conditioning prior to allo-HCT

Initial experience with allo-HCT was collected with high-dose preparative conditioning including mostly alkylating agents such as Busulfan, Melphalan (Mel) and Cyclophosphamide (Cy) in combination with total body irradiation (TBI) as depicted in Table 1.[5–10] In a recent multicentre analysis by the British Society of Blood and Marrow Transplantation, comparing myeloablative dose conditioning with Mel/TBI versus Cy/TBI, a significant difference in OS between the groups could be detected.[9] The observation that the Mel/TBI group had a significantly better OS indicates a major impact of the employed antineoplastic substances on the outcome in the setting of myeloablative dose conditioning.[9]

Following myeloablative dose conditioning[5–12] prior to allo-HCT, long-term, disease-free survival rates of 20–55% have been reported (Table 1). Recently, Ballen reported a poor outcome after myeloablative dose unrelated allo-HCT for MM, with a 5-year OS of only 9%.[10] In total, 50% of patients achieved a complete or partial remission and the relapse rate was 34%, which is significantly lower than reported after auto-HCT.[30,31] The poor OS was caused by the high 100-day TRM of 42%, mostly due to infection.[10] Comparable TRM rates following myeloablative dose conditioning prior to unrelated donor transplant for MM have been reported by other groups.[5,8] The Seattle group reported a 100-day TRM of 44%[5] and PFS was 20% at 4.5 years in this study. The European Group for Blood and Marrow Transplantation reported a TRM of 41% after matched sibling transplants for MM.[6] More recent studies using related donors and myeloablative dose conditioning regimens have reported lower 100-day TRM rates of 16–34%.[2,7,8,32]

A majority of TRM after myeloablative dose allo-HCT is contributed to acute GVHD grade III–IV. The risk of acute GVHD reported after sibling transplants for MM ranged from 19% to 62%.[6–9] A recent study employing MHC matched unrelated donors (MUD) yielded an acute GVHD frequency of 47%, although 39% of the patients received a T-cell-depleted graft.[10]

Several investigators have reported the GVM effect, suggesting an important effect of the immune system that could be harnessed with unrelated transplant.[2,23–25,33] Since the risk of GVHD is often higher in unrelated than sibling allo-HCT, the GVM effect may be stronger for unrelated recipients. However, the presence of GVHD, which has been shown to correlate with a decreased risk of relapse in some studies, did not correlate with a lower relapse rate in a recent study including 71 patients, which received transplants from MUD.[10] A possible explanation may be the high TRM in this study that might have overruled the beneficial GVM effect.

The observation that allo-HCT has been associated with high TRM (20%–50%) in the first 180 days, even in adults younger than 55 years of age, has tempered enthusiasm with this approach and led to the early closure of the allogeneic bone marrow transplantation (BMT) arm in the United States intergroup trial.[5,34–36] Recent analysis of transplant registry data reported to the European Group for Blood and Marrow Transplant (EBMT) suggests that the TRM associated with conventional allografts has decreased in the more recent cohort of patients that received transplants between 1994–1998 with a TRM at 6 months of 21% compared with 38% in patients that received transplants between 1983 and 1993.[37] This decrease was mainly attributed to a lower risk of fatal infections and organ toxicity and was likely due to better patient selection as well as increasing experience with allografting.[37] The 3-year survival following allo-HCT was 55% in the later cohort compared with 35% in the earlier experience. The use of peripheral blood stem cells (PBSCs) rather than bone marrow (BM) was associated with earlier engraftment but no difference in survival or CR rates. However, it is important to note that the median age in the recent cohort was 44 years with a range of 18 to 57 years and patients received transplants a median of 10 months from diagnosis.[37]

With respect to recent studies, myeloablative dose preparative conditioning prior to allo-HCT has a limited role in MM. Because of its toxicity, it is mostly proposed to patients aged less than 60 years with an HLA-identical sibling. Selected trials on myeloablative dose conditioning prior to allo-HCT are depicted in Table 1.

3. Clinical experience with reduced intensity conditioning prior to allo-HCT

Recently, a new approach to allografting has been developed using reduced intensity conditioning and novel post-transplantation immunosuppression to assure engraftment and graft-versus-tumour effects.[38] Purine analog based reduced intensity chemotherapy can allow engraftment of allogeneic haematopoietic progenitor cells with acceptable toxicity in patients considered ineligible for myeloablative high-dose chemotherapy and allo-HCT either because of age or morbidity.[39–41] Therefore use of less intensive preparative regimens was also investigated for exploiting the GVM effect while simultaneously reducing toxicities seen with myeloablative therapies.[13–18] Conditioning regimens included mostly Fludarabine, Melphalan or Cyclophosphamide with or without 2Gy TBI in combination with *in vivo* T cell depletion by Anti-T-cell globuline (ATG),[13,15] or Alemtuzumab.[18] The outcome of a poor risk group of patients, consisting of 25 sibling and

Table 1 – Clinical results from studies employing standard dose conditioning for allografting in multiple myeloma

Reference	Pt[a] No	D[2] RD MUD	Age (median/ range)	Condi-tioning	GVHD prophylaxis	graft[b] BM PBC	GVHD[c] acute ⩾ II°/>III°	GVHD chronic (all/ex-tensive)	TRM[d] d+100/ 1 year	OS/PFS (after n years)	Median follow-up (months)	Conclusions (Statistical Analysis)
Bensinger *et al.* (1996) Seattle[5]	80	71 9	44 (28–56)	Bu/Cy (+TBI *n* = 23)	CyA (71) MTX (46) Pred (22)	100% 0	34% 19%	41% 29%	44% 66%	24% 20% (4.5 y)	54	Allograft can result in long-term PFS for a minority of patients. High TRM GVHD rates need to be reduced.
Bjorkstrand *et al.* (1996) Huddinge[6] EBMT multicenter	189	189 0	43 (23–59)	TBI Cy (*n* = 140)	CyA MTX (*n* = 82)	100% 0	53% 9%	n.s. n.s.	n.s. 41%	49% 40%	46	Allo- has a higher TRM than auto-HCT but also a lower relapse rate. Long-term follow-up is needed.
Kroger *et al.* (2003) Hamburg[7] DSMM multicenter	18	17 1	44 (29–53)	Bu/Cy/TBI	ATG CyA MTX	72% 28%	35% 6%	27% 7%	17% n.s.	77% 31% (6 y)	41	In vivo depletion with ATG results in a low rate of severe GVHD, low TRM and a substantial number of long-term survivors.
Lokhorst *et al.* (2003) Utrecht[8] HOVON 24 multicenter	53	53 0	48 (31–56)	Cy/TBI	CyA TCD	66% 34%	45% 11%	43% 30%	34% n.s.	56% n.s. (2 y)	38	Up-front myeloablative aHCT with TCD yields a low potential cure rate. DLI as prophylactic therapy should be tested.
Hunter *et al.* (2005) London[9]	139	139	52 (29–71)	Mel/TBI Cy/TBI	CyA MTX	54% 46%	62vs41% 6vs19%	n.s n.s.	n.s. 38%	44vs28% 36vs13% (4 y)	48	Mel/TBI was superior to Cy/TBI. The type of conditioning has a major impact on transplant outcome.
Ballen *et al.* (2005) Boston[10] (33 centers)	71	0 71	44 (22–60)	TBI based (64%)	TCD (het)	20% 80%	47% 34%	n.s. n.s.	42% n.s.	27% 21.3% (2 y)	n.s.	Strategies with less toxicity than myeloablative aHCT need to be evaluated.

D[2]: Donor: RD: Related donor, MUD: matched unrelated donor.
n.s. not specified, het: heterogeneous, Flu: Fludarabine, Mel: Melphalan, TCD: T-cell depletion, ATG: anti T-cell globulin, Cy: Cyclophosphamid, MTX: Methotrexat; MMF: Mycophenolate, FK506: Tacrolimus.
a Pt No: Patient number.
b Graft; BM: bone marrow, PBC: Peripheral blood stem cells, TCD T-cell depletion.
c GVHD: graft-versus-host disease (patients in %).
d TRM: Treatment related mortality.

6 MUD transplants, conditioned with Melphalan 100 mg/m^2 + Fludarabine and TBI had a median OS of only 15 months, despite a low day +100 TRM.[16] More recent studies have reported improved survival rates employing either Fludarabine and Melphalan alone or tandem autograft and allograft approaches[13,42–44] with PFS at 2 years of 33% and 56%, respectively. Comparable observations have been reported by the Seattle group[17] employing Fludarabine and low dose TBI (2Gy) with and PFS rate of 55% at 2 years. However, a recent analysis of prognostic factors from the Chronic Leukaemia Working Party of the EBMT on reduced intensity allo-HCT including 229 MM patients from 33 centre demonstrated a much lower PFS of 21% at 3 years.[18] Factors associated with an adverse outcome were chemoresistance, status beyond first remission, two or more prior auto-HCTs, male recipient and female donor, an unrelated donor and the use of Alemtuzumab in the conditioning.[18] The negative effect of Alemtuzumab in reduced intensity conditioning for MM was due to an increased relapse rate and a higher risk for infections due to profound depletion of T-cells and other cellular targets such as NK cells and host dendritic cells which also express CD52, the target of Alemtuzumab.

Of the post allo-HCT variables the development of any chronic GVHD was associated with increased OS and PFS supporting the importance of the GVM effect in the setting of reduced intensity conditioning.[18] The improved PFS and OS in patients with cGVHD has also been reported by other study groups.[15,45] Overall the outcome from reduced intensity conditioning for advanced disease and heavily pretreated patients reported by the EBMT is disappointing.[18] The reported series however begins to identify criteria for more appropriated patient selection that might help to improve outcomes after reduced intensity allo-HCT.[18] Beside the clinical criteria, cytogenetics or other biological markers may be helpful in identifying MM patients in whom the reduced intensity approach should be tested early in their disease course. Analysis of patients with deletion of the long arm of chromosome 13 (13q-) indicated a nearly 2 times higher risk of death after reduced intensity allo-HCT[46] as compared to patients without 13q-after reduced intensity conditioning which corresponds to the unfavorable disease course of this group after myeloablative chemotherapy. Selected trial employing reduced-intensity conditioning for MM are summarized in Table 2.

4. Auto-HCT preceding allo-HCT (Auto-allo-tandem HCT)

To reduce TRM of myeloablative allo-HCT, but retain the cytoreductive effect of high-dose chemotherapy, a combined approach including auto-HCT followed by reduced intensity conditioning with allografting was introduced by Carella et al. in 15 patients with malignant lymphoma.[47] With this approach the detrimental impact of pro-inflammatory cytokines due to tissue damage after high-dose chemotherapy should be separated from the beneficial GVT effect.

Experience with this combined approach in MM was gathered with a melphalan-based dose-reduced regimen (100 mg/m^2).[13,43] Interestingly, no primary or late graft failure was observed and all patients experienced a rapid sustained complete donor chimerism after reduced intensity conditioning.[43] This might be explained by the initial auto-HCT that might have induced significant host immunosuppression, which promoted rapid and sustained full donor engraftment after the following allo-HCT.[43] TRM due to GVHD after tandem auto-allo-HCT occurred in 10% of the patients and 12% developed extensive chronic GVHD.[43] The low incidence of severe acute and chronic GVHD, even after transplantation with grafts from unrelated donors,[43] might be explained by the incorporation of ATG into the preparative regimen. Due to the long half-time, ATG may not only facilitate engraftment but furthermore reduce the incidence of severe GVHD.[48,49] Despite the fact that 58% of the patients in the study by Kroger et al. received grafts from unrelated or mismatched-related donors, the incidence of acute and chronic GVHD was less than that observed in the study by the Seattle group (37% versus 45% and 40% versus 55%, respectively).[17,43]

The rate of complete remissions (CR) with negative immunofixation increased from 0% after induction or salvage therapy to 18% after autografting and to 73% after allografting.[43] This increase is superior to the CR rate increase achieved by a second auto-HCT.[50] This combined autografting-allografting approach was used mainly as part of the initial therapy in the reported studies.[13,42–44]

The higher rate of CR observed in this study[43] as compared to the data reported by the Seattle group[17] was most possibly due to the cytotoxic effect of melphalan and the fact that in the latter study[17] almost 50% of the patients had refractory or relapsed disease. Because of the delayed GVM effect a more cytotoxic conditioning regimen than low-dose TBI as employed by the Seattle group[17] may be advisable, especially in patients with risk of early relapse.

These studies suggest that the tandem auto-allo HCT protocol provides rapid and sustained engraftment with durable complete donor chimerism, tolerable toxicity, and low day +100 TRM. The high OS of 75% to 78% after 2 years[17,43] is encouraging but a longer follow-up is needed to determine late mortality and late relapse in comparison to conventional autografting or allografting in patients with MM.

5. Clinical experience with DLI following allo-HCT in multiple myeloma

Donor lymphocyte infusions (DLI) have been demonstrated to induce response rates in 40% to 67% of patients diagnosed with MM.[19–29] In different clinical settings, DLI were applied as prophylaxis[19–22] for myeloma relapse or as treatment[23–29] when relapse had occurred after allo-HSCT. Clinical evidence for the GVM effect has been documented in several case reports and small populations.[23–25] However, the results must be interpreted with respect to additional chemotherapy preceding DLI administration[28] or interferon (IFN)-α[25,28] for immunological modulation. Concerning the mode of action, IFN-α might enhance the GVM effect by increasing the expression of cell-surface molecules necessary for the interaction of effector cells with the neoplastic plama cell[51,52] or by a direct anti-myeloma effect. Although some patients seem to respond only to DLI when IFN-α is added, no randomized trial has been performed to evaluate the benefit from the cytokine in addition to DLIs.[53] Furthermore, corticosteroids, the most common employed treatment for GVHD occurring after DLI,

Table 2 – Clinical results from studies with reduced intensity conditioning for aHCT in multiple myeloma

Reference	Pt[a] No	D[2] RD MUD	Age (median/ range)	Condi- tioning	GVHD prophylaxis	graft[b] BM PBC	GVHD[c] acute ⩾ II°/>III°	GVHD chronic (all/ex-tensive)	TRM[d] d+100/ 1 year	2-year OS/PFS	Median follow-up (months)	Conclusions (Statistical Analysis)
Kroger *et al.* (2002) Hamburg[13]	21	0 21	50 (32–61)	Flu/Mel	ATG CyA MTX	24% 76%	38% 19%	37% 12%	10% 26%	74% 53%	13	RIC with pretransplant ATG followed by unrelated HCT reduces transplant rel. organ toxicity and induces high remis- sion rates.
Giralt *et al.* (2002) Houston[14]	22	13 9	51 (45–64)	Flu Mel	FK506 MTX	10% 90%	46% 27%	27% 27%	19% 40%	30% 19%	15	Flu/Mel combinations allow consistent engraftment in HCT from MUD and should be explored in pts with less advanced disease.
Einsele *et al.* (2003) Tubingen[15]	22	7 15	53 (36–66)	Flu/Cy/TBI	ATG CyA MMF	36% 64%	33% 5%	33% 5%	23% n.s.	25% 22%	7	Long-term disease control is achievable but restricted to pts responding to prior to salvage chemotherapy.
Badros *et al.* (2002) Little Rock[16]	31	25 6	56 (38–69)	Mel (+Flu/TBI $n = 6$)	CyA (+Pred $n = 6$)	10% 90%	58% n.s.	32% 13%	10% 19%	31% 31%	6	RIC induced excellent disease control in high-risk patients, but is associated with significant GVHD.
Maloney *et al.* (2003) Seattle[17]	52	52	52 (29–71)	TBI (2Gy) (+Flu $n = 9$)	CyA MMF	0 100%	38% 5.8%	64% 46%	2% 10%	78% 55%	18.4	Allo-HCT after cytoreductive auto-HCT reduced acute toxicities while achieving potent antitumor activities.
Crawley *et al.*(2005) Cambridge[18] (33 centers)	229	46 40	52 (32–66)	Flu based (96%)	ATG Camp (het)	20% 80% TCD	31% n.s.	50% 25%	10% 20%	40.6% 21.3% (3-years)	28	cGVHD associated with better OS/PFS Heavily pretreated pt do not profit from RIC

D[2]: Donor: RD: Related donor, MUD: matched unrelated donor.
n.s. not specified, het: heterogeneous, Flu: Fludarabine, Mel: Melphalan, ATG: anti T-cell globulin, Cy: Cyclophosphamid, MTX: Methotrexat; MMF: Mycophenolate, FK506: Tacrolimus.
a Pt No: Patient number.
b Graft; BM: bone marrow, PBC: Peripheral blood stem cells, TCD T-cell depletion.
c GVHD: graft-versus-host disease (patients in %).
d TRM: Treatment related mortality.

have anti-myeloma activity and thus may contribute to a response.

The response rates in the two larger studies [25 and 27 patients] on DLI for MM relapse after allo-HSCT demonstrated response rates of 40–52% as detailed in Table 3.[23–29] 22–28% of the responders achieved a CR and 14–30% a partial remission.[23–29] Of note, in the study of Salama et al., 3/10 responders (30%) had received additional chemotherapy prior to DLI administration.[28] The response to DLI treatment was highly correlated with the occurrence and severity of acute GVHD in one study,[28] in the other study[29] no correlation was detectable.

GVHD is the most significant complication after DLI for MM treatment.[23–29] In the two larger studies on DLI for myeloma, acute GVHD was documented in 52–56% and chronic GVHD in 26–44% of patients.[28,29]

Beside the relapse-treatment of MM after HSCT, DLI have been applied as part of the transplantation strategy after reduced intensity regimens[19–22] as summarized in Table 4. $CD8^+$ depleted DLIs as consolidation treatment, 6–9 months after T-cell depleted allogeneic HSCT resulted in response rate of 71%, with 43% CR.[19]

Reduced-intensity transplantation, including in vivo T-cell depletion with Alemtuzumab and adjuvant dose-escalating donor lymphocyte infusions in 14 patients demonstrated a 2 year estimated overall survival and progression free survival of 71% and 30%, respectively[21] and at a 2.2 year follow-up of this study,[22] including additional patients 58% are alive (Table 4). These data provide evidence, that DLI can be employed as a part of the treatment strategy for patients with persistent, relapsed, or progressive disease after reduced intensity conditioning and allo-HCT.

The clinicaly most relevant treatment related morbidity with DLI is the occurrence of GVHD.[19–29] Further clinical limitations may be the immune-escape of plasmocytoma in extramedullary tissues,[54–56] infectious complications and graft failure. However, OS and PFS survival after allo-HCT in patients relapsing from EM sites was not significantly different from BM relapse patients in a single centre investigation.[56] Despite a potential overlap between GVHD and graft-versus leukaemia effect (GVL), several animal models have demonstrated the feasibility of distinguishing these two effects of donor T cells.[57,58]

6. Molecular targets for the GVM effect after allo-HCT

Despite the widespread use of allo-HCT for MM the exact immunological mechanisms mediating GVM activity are not yet defined. The identification of target antigens present on MM cells and absent on non-malignant cells would be of major interest to induce MM specific donor T-cells *in vitro* for adoptive transfer and therefore improving the safety and efficiency of allografting. A potential tumour-specific target-antigen for donor derived T cells is the myeloma specific idiotypic determinant of immunglobulin variable regions[59–61] which has been employed to immunize the donor before allogeneic bone marrow transplantation. This resulted in a detectable anti-idiotype cellular immune response in both donor and allografted recipient.[62]

Other possible targets for donor derived T-lymphocyte that are present on MM cells are encoded by genes specifically overexpressed in certain tissues such as MUC1 and PRAME.[63] Myeloma cells were demonstrated to express underglycosylated MUC1 recognized by T cells in an HLA-unrestricted, but also restricted, fashion.[64,65] PRAME is frequently expressed in several tumour types including MM.[65–67] Another category of target antigens frequently present on MM cells are encoded by cancer germline specific genes (*MAGE*, *BAGE*, *GAGE*, *LAGE-1*, *NY-ESO-1*). These genes are frequently expressed in many tumour types but are silent in normal tissues except testis and placental trophoblast cells, both lacking HLA expression and therefore being unable to present antigenic peptides to CTL.[68]

Analysis of the MM gene expression database supplemented by immunohistochemistry for tumour protein expression in MM indicated that the Cancer-Testis antigen NY-ESO-1 is expressed in >60% of newly diagnosed and 100% of relapsed poor prognosis MM characterized by abnormal cytogenetics.[69] When examining the sera of MM patients, NY-ESO-1 specific antibodies were detected in 2/11 NY-ESO-1 positive and 1/21 NY-ESO-1 negative patients.[70] These and other data indicate the high immunogenicity of NY-ES0-1 and other Cancer-Testis antigens which present a potential target for donor derived T cells after allogeneic HCT.

7. Perspectives in treatment of multiple myeloma with allogeneic HCT

High-dose chemotherapy with allogeneic transplantation has the potential of adding a graft-versus-myeloma effect in addition to a stem cell product free of tumour cell contamination. However, despite high complete remission rates of 30–50%, disease-free survival at 5 years after allografting is only 25%, primarily because of the high TRM of 40 to 50%.[5–12] Purine analog containing reduced intensity chemotherapy in combination with PBSC grafts can allow engraftment of allogeneic haematopoietic progenitor cells with acceptable toxicity in patients considered ineligible for myeloablative dose therapy and allogeneic transplantation either because of age or medical condition. Therefore use of less intensive preparative regimens might provide an option for exploiting the GVM effect without the toxicities seen with myeloablative therapies. Furthermore, studies suggest that combining auto-HCT and allo-HCT provides tolerable toxicity, and low day +100 TRM and high OS of 75% to 78% after 2 years.[17,43] These results are encouraging but a longer follow-up is needed to determine late mortality and late relapse in comparison to conventional autografting or allografting in patients with MM.

Novel agents, such as thalidomide, lenalidomide, bortezomib, histone deacetylase (HDAC) inhibitors and others novel agents are currently under investigation for their potential to improve results after allogeneic HCT in patients with MM.

Further support of the existence of a GVM effect has been demonstrated by the efficacy of DLI in patients relapsing after allo-HCT.[19–29] Experience was collected with DLI as prophylaxis for myeloma relapse[19–22] or as relapse treatment[23–29] after allo-HSCT. The identification of target antigens present on MM cells and absent on non-malignant cells would be of major interest to induce MM specific donor T-cells *in vitro*

Table 3 – Donor lymphocyte infusions after allogeneic HSCT for relapse treatment

Reference	Treated patients	Type of HCT[e]	Cell dose ($CD3 \times 10^6$/kg) median	Add. IFN-α	Response[b] CR/PR overall	Time to resp.(weeks) median	GVHD ($\geqslant$II°) acute/ chronic	Outcome
Tricot (1996)[23] Little Rock, USA	1	MUD, TC-	1.2	no	1 CR	7	1/1	alive, cGVHD skin (14 months follow-up)
Verdonck (1996)[24] Utrecht, NE	2	MUD, TC-	110/330	no	2 CR	3/8	1/1	2 alive (2 years and 8 months follow-up)
Bertz (1997)[25] Freiburg, GE	1	sib, TC+	62	1	1 CR	6	0/1	dead cGVHD[d](5 years follow- up)
Orsini (1997)[26] Boston, USA	4	sib, TC-	1.2 (1–1.5)	no	2/1 3	6.5 (4–8)	3/3	1 alive,2 relapse 1 PD (3 years follow-up)
Lockhorst (1997)[27] [a]Utrecht, NE	13	sib, TC-	19.2 (1–330)	no	4/4 8	6 (4–10)	8/7	3 pts >1y (med response: 5 months)
Salama (2000)[28] Dallas, USA	25	24 sib TC+ 1 MUD TC+	100 (2–220)	4	7/3 10	4.4 (3–6)	13/11	4 pts >1 y 2 alive in CR (14 months follow-up)
Lokhorst (2000)[29] Utrecht, NE	27	sibl TC-	n.s.(1–330)	no	6/8 14	NS	15/7	OS 18 months (30 months follow-up)
Summary of the studies:	60	31 sibl TC- 25 sibl TC+ 3 MUD TC- 1 MUD TC+	79.5 (1–330)	5	20/15 35 (55%)	5.6 (3–10)	36/29 (56%/45%)	

a The treated patients are summarized within Lockhorst *et al.*[29]
b Best response to DLI treatment.
c n.s.: Not specified.
d Individual follow-up at the Freiburg University Medical Center, Germany.
e Type of stem cell transplantation: sibl: HLA matched siblings, MUD: HLA matched unrelated donor, TC-: T-lymphocyte depleted.

Table 4 – Strategies including DLI in the allogeneic HCT protocol

Reference	No. of DLI pts	Type of TX[a]	Cell dose ($CD4 \times 10^6$/kg) med (ra)[b]	DLI after HSCT (weeks)	Response[c] CR/PR overall	Time to resp. (weeks) med (ra)	GVHD ($\geqslant$II°) acute/ chronic	Outcome
Alyea (2001)[19] Boston, USA	14	sib, TC-	26 (10–30)	24–36	6/4 10	6.4 (1.2–2.3)	5/2	OS: 57% 5 CR 2.5 years follow-up
Badros (2001)[20] Little Rock, USA	14	sib, TC+	200 (120–220)	3–16	8/4 12	0.5 (0.3–1.5)	9/7	11 alive 6 CR 1 year follow-up
Peggs (2003)[21e] London, UK	14[e]	sib/MUD TC+ (Campath)	1–300	21–168	2/4 6	NS[d]	3/2	OS: 71% 2 years follow-up
Peggs (2004)[22] London, UK	19	12 sib, TC+ 7 MUD, TC+ (Campath)	45 (1–300)	21–168	1/8 9	NS (1–8)[f]	9/7	11 alive 2.2 years follow-up
Summary of the studies:								
	47	14 sibl TC- 26 sibl TC+ 7 MUD TC+	90 (1–300)	3–168	15/16 31 (67%)	3.5 (0.3–8)	23/16 (49%/34%)	

a Type of stem cell transplantation: sibl: HLA matched siblings, MUD: HLA matched unrelated donor, TC-: T-lymphocyte depleted.
b Median (range).
c Best response to DLI treatment.
d NS: Not specified.
e The treated patients are summarized within Peggs *et al.*[21]
f Time to response was evaluated by chimerism status.[22]

for adoptive transfer and therefore may improve the safety and efficiency of allografting.

Conflict of interest statement

None declared.

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