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# FIFTY YEARS OF MELPHALAN USE IN HEMATOPOIETIC STEM CELL TRANSPLANTATION

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## Abstract

Melphalan remains the most widely used agent in preparative regimens for hematopoietic stem-cell transplantation. From its initial discovery more than 50 years ago, it has been gradually incorporated in the conditioning regimens for both autologous and allogeneic transplantation due to its myeloablative properties and broad antitumor effects as a DNA alkylating agent. Melphalan remains the mainstay conditioning for multiple myeloma and lymphomas; and has been used successfully in preparative regimens of a variety of other hematological and non-hematological malignancies. The addition of newer agents to conditioning like bortezomib or lenalidomide for myeloma, or clofarabine for myeloid malignancies, may improve antitumor effects for transplantation, while in combination with alemtuzumab may represent a backbone for future cellular therapy due to reliable engraftment and low toxicity profile. This review summarizes the development and the current use of this remarkable drug in hematopoietic stem-cell transplantation.

### Keywords

melphalan; stem cell transplantation; conditioning regimens

## INTRODUCTION

Melphalan was first synthesized in 1953 by substituting L-phenylalanine for the methyl group on nitrogen mustard(1). Since then, it has been used in the treatment of various malignancies including ovarian cancer, breast cancer, neuroblastoma, lymphomas, acute leukemias, and multiple myeloma (MM). Due to its broad antitumor activity, ability to ablate the bone marrow, minimal extramedullary toxicity(2), and potent immunosuppressive effects, melphalan found a distinctive role in autologous (ASCT) and allogeneic stem cell



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transplantation (allo-SCT). As a single agent, melphalan was found to be adequately immunosuppressive and myeloablative allowing engraftment with HLA-identical sibling allografts(3). Here we reviewed the role of melphalan in stem cell transplantation for hematological malignancies.

A detailed review of melphalan's clinical pharmacology can be found elsewhere(4). Briefly, melphalan is a dialkylating agent with two alkyl groups. It is not cell-cycle specific and is transported into cells by amino acid transport systems(5). In plasma, up to 90% of melphalan is bound to plasma proteins(6), while penetration into CSF is low(7, 8). Melphalan is eliminated by spontaneous chemical hydrolysis and renal excretion which may involve active renal tubular secretion in addition to glomerular filtration(6, 9). Although variable, melphalan's biological half-life is approximately 60 minutes, allowing infusion of stem cells within 8 hours of melphalan administration(10–12). Its clearance is influenced by the creatinine clearance, fat free mass, and hematocrit(13). However, to what extent renal dysfunction influences efficacy and toxicity of melphalan remains unclear. At least in one study, renal insufficiency was found to increase melphalan-induced myelosuppression(14).

Bone marrow suppression is the dose limiting toxicity of melphalan. Although it is considered to be myeloablative at doses of 140 mg/$m^2$ and above(4, 15), neutrophil recovery is accomplished within 30 days of 140 mg/m2 melphalan in most patients even without stem cell support(16). With stem cell support, its dose limiting toxicity is mucositis(17). Administration of ice chips before, during, and after melphalan administration may decrease the severity of mucositis by vasoconstriction and decreased blood flow to mucosae(18). Furthermore, amifostine, a cytoprotective agent, may decrease the severity of mucositis and allow higher doses of melphalan to be given before transplantation(19). Other adverse effects of melphalan include nausea, vomiting, diarrhea(20), alopecia(21), transaminitis(22), and interstitial pneumonitis(23). Cardiac arrhythmias have also been observed with greater incidence after administration of higher doses of melphalan, although its causality remains unclear (24) (19).

As an alkylating agent, melphalan is recognized as being carcinogenic. Long-term risk of secondary leukemia/myelodysplastic syndrome after ASCT with melphalan containing regimens may be as high as 7%(25). However, due to scant number of long-term studies evaluating the risk of secondary malignancies post-transplantation and frequent utilization of melphalan with other agents in conditioning, it is difficult to estimate the relative increase, if any, in cancer incidence post-transplantation attributed to melphalan. Moreover, leukomogenesis due to pre-transplant chemotherapy may be more substantial than that due to the conditioning regimen, further diluting the accuracy of the risk estimates(26).

## MULTIPLE MYELOMA

Myeloma has been the most common indication for melphalan conditioning in transplantation. Despite the advent of novel myeloma agents, MM remains an incurable disease and ASCT is generally recommended for all eligible patients(27). Blokhin and colleagues reported the earliest clinical use of melphalan for patients with MM in 1958(28). Six patients were treated and considerable reduction in the tumor size was observed in 3 of

these patients. The earliest report of high-dose melphalan therapy followed by autologous stem-cell rescue for myeloma patients came from McElwain and Powels in 1983, who treated a 34-year old man with plasma cell leukemia with melphalan 140 mg/m$^{2,}$ (29) leading to complete remission (CR). Subsequently, Selby et al. reported their experience of high-dose melphalan (140 mg/m$^2$) therapy for 58 myeloma patients(21). The median time to leukocyte and platelet recovery in previously untreated patients was 28 and 24 days, respectively. A CR rate of 27% was achieved in previously untreated patients. However, 17% of patients died within the first two months due to sepsis or bleeding, and almost all patients relapsed after a median duration of remission of 19 months. In 1986, Barlogie and colleagues from MD Anderson Cancer Center (MDACC) reported their experience with high-dose melphalan for treatment of 23 refractory myeloma patients(30). Sixteen patients received a dose of 80–100 mg/m$^2$ and 7 were given 140 mg/m$^2$ followed by autologous marrow infusion. While the tumor mass was reduced by more than 75% in 14 patients, 6 melphalan-related deaths occurred in patients who did not receive autologous stem cell support. Despite higher doses of melphalan, minimal leukocyte recovery to at least 200/μL occurred significantly faster and more uniformly in patients who received autologous stem cell support. Furthermore, only one melphalan-related death was encountered in this group.

## Single autologous stem cell transplantation

High-dose therapy with melphalan and ASCT for MM was associated with improved CR rates and prolongation of overall survival (OS)(31, 32). This was first demonstrated by Attal and colleagues, who randomized 200 previously untreated myeloma patients under the age of 65 years to receive either conventional chemotherapy or high-dose melphalan therapy and ASCT(31). Patients randomized to high-dose therapy had significantly higher CR rate, event-free survival (EFS), and OS (Table 1). In 1998, Fermand et al. reported the results of a randomized trial of early ASCT versus ASCT performed after relapse(33). The OS was similar in both groups; however, the investigators favored early ASCT since it was associated with a shorter duration of chemotherapy and better quality of life. The survival advantage with high-dose melphalan therapy was later confirmed in another study by Child et al., where melphalan 200 mg/m$^2$ followed by ASCT was associated with significantly higher CR rate, OS and progression-free survival (PFS)(32). However, several subsequent randomized trials failed to show a convincing survival advantage for high-dose melphalan and ASCT over chemotherapy alone(34–36).

Recently, the landscape of myeloma treatment is changing rapidly due to the advent of novel agents. However, during the same time, the results of ASCT have also improved and the newer agents are being incorporated into the conditioning regimens, while post-transplant maintenance strategies are being devised(37). Until further conclusive data becomes available, ASCT remains the standard treatment of all newly diagnosed myeloma patients who are deemed fit to undergo high-dose therapy, in most treatment centers(37).

## Tandem autologous stem cell transplantation

Barlogie and colleagues pioneered a more intense approach and demonstrated the feasibility of tandem ASCT with melphalan 200 mg/m$^2$ for the first transplant and melphalan 140–200 mg/m$^2$ + TBI for the second ASCT(38). Tandem ASCT was associated with significantly

superior CR rate, EFS, and OS compared to chemotherapy alone (Table 2). In the Bologna 96 trial, Cavo and colleagues randomly assigned patients to single versus tandem ASCT. Statistically significant superior near-CR rate and EFS were seen with the tandem ASCT. Although there was no difference in OS between the two arms, the authors noticed that administration of a second ASCT and the use of novel agents for treating sequential relapses in up to 50% of patients assigned to receive single ASCT likely contributed to prolonged survival duration of the entire group(39). Furthermore, the authors noticed a trend toward improved OS in tandem ASCT arm in patients who failed to achieve near-CR after first ASCT. Recently, a meta-analysis of six randomized controlled trials concluded that, although the tandem ASCT was associated with statistically significantly better response rate; there was no survival benefit, while the treatment-related mortality (TRM) was higher with the tandem ASCT(40). Based on the currently available data, our approach is to collect the stem cells for two ASCT after two to four cycles of chemotherapy, after the patient achieves remission or at the time of maximum cytoreduction. A tandem ASCT is now offered in the setting of a clinical trial for patients who achieve less than very good partial response (VGPR) after the first ASCT.

## Melphalan dose intensity

Melphalan at the dose 200 mg/m$^2$ is the most widely used drug as preparative regimen for transplantation(27). This regimen was initially reported in 1992 by the Arkansas group based on administration of two equally divided daily doses(41). In a subsequent report, further dose escalation to melphalan 220 mg/m2 was studied; however, this was associated with higher incidence of grade IV mucositis (>60%), delayed platelet engraftment and cardiac arrhythmias(42). In the randomized Intergroupe Francophone du Myelome (IFM) 9502 trial, melphalan 200 mg/m$^2$ was compared with melphalan 140 mg/m $^2$ plus 8 Gy TBI before ASCT for newly diagnosed myeloma patients(43). Melphalan 200 mg/m$^2$ was associated with faster hematologic recovery, less transfusion requirement and shorter duration of hospitalization. While the EFS was similar, the 45-month survival was significantly superior in the melphalan 200 mg/m$^2$ arm (65.8% vs. 45.5%; p=.05). In another randomized trial, Palumbo et al.(44) compared two ASCTs after melphalan 200 mg/m$^2$ or melphalan 100 mg/m$^2$. The OS was similar; however, the median PFS was significantly better in the higher dose arm (31.4 vs. 26.2 months; P=.01). Median time to progression (TTP) was also longer with melphalan 200 mg/m$^2$ (34.3 vs. 27.0 months; P=.014).

Whether elderly patients, particularly those above age 70 should receive standard dose melphalan at 200 mg/m$^2$ or lower doses, remains unclear. In the IFM 99-06 study(45), where patients (65 to 75 years) were randomized to treatment with melphalan, prednisone, and thalidomide (MPT) versus MP versus tandem ASCT using melphalan 100 mg/m$^2$, PFS and OS were found to be significantly longer in the MPT arm. It is possible that melphalan 100 mg/m$^2$ dose was less than optimally effective before ASCT and might have compromised the treatment outcomes. On the other hand, Mayo Clinic group compared 33 patients ≥ 70 years undergoing high-dose melphalan at 200 mg/m$^2$ with a cohort of matched patients ≤ 65 years(46). Dose reduction to 140 mg/m$^2$ was required in 10 patients in the elderly group; however, there was no difference in the response rate compared to patients who received melphalan 200 mg/m$^2$. In another report, melphalan 200 mg/m$^2$ was

associated with excessive early mortality of 16% in patients ≥ 70 years old(47). We have previously reported that melphalan 200 mg/m$^2$ can be safely administered in patients more than 70 years old; however, the incidence of cardiac and gastrointestinal toxicity may be higher compared with intermediate-dose melphalan(48).

There is limited data on adjusting melphalan dose based on renal function. First, the Arkansas group showed that ASCT with high dose melphalan was feasible in patients with severe renal failure(49). Melphalan clearance was not significantly delayed in patients with renal insufficiency and melphalan was not detected in the dialysate of patients who underwent dialysis 6 hours after its infusion. The same group later reported that, although the EFS and OS were similar in patients with renal insufficiency who received melphalan 200 mg/m$^2$ or 140 mg/m$^2$; the gastrointestinal adverse effects, atrial dysrhythmias, pulmonary complication, and neurological complications were more frequent in the higher dose group(50). Thirty-eight patients on dialysis were dialyzed before melphalan infusion and dialysis dependence did not affect survival. A retrospective analysis of dialysis dependent patients and those without renal insufficiency who underwent ASCT with melphalan 100 mg/m2 and 200 mg/m2 did not reveal any significant difference in toxicity or survival(51). We have previously reported that melphalan 200 mg/m$^2$ may not be associated with an increase in toxicity or TRM, and renal function may actually improve after ASCT in a subset of patients(52).

Our current standard approach for ASCT in MM patients is to use melphalan 200 mg/m$^2$ except in those above age 70 and those with serum creatinine above 2.0 mg/dL or on hemodialysis, for whom a lower dose of melphalan is used (140mg/m$^2$), if the patient is otherwise eligible for transplantation. Targeting exposure to melphalan by using area under the curve (AUC) in the latter setting becomes particularly appealing as recently reported(53).

## Role of induction regimen

A strong association between maximal response after induction therapy and long-term outcome after ASCT has been shown(54, 55). Accordingly, the advent of novel anti-myeloma agents and their inclusion in induction regimens led to improved post-induction and post-transplant response rates compared to induction with VAD (vincristine/doxorubicin/dexamethasone) chemotherapy(56, 57). The combination of bortezomib, thalidomide, and dexamethasone (BTD) was found to further improve response rates compared to thalidomide and dexamethasone (TD)(58). Recently, in a randomized phase III trial, BTD was shown to be superior to TD and the combination of alkylator based chemotherapy and bortezomib in both response rates and PFS(59). CR was achieved post-induction in 35% of patients with BTD compared to 14% and 21% with TD and combination chemotherapy, respectively. The median PFS was also significantly longer with BTD at 56 months compared to < 36 months with others. Although whether these improvements in response rates and PFS would translate to OS is not clear, we recommend bortezomib-based induction regimens in MM patients eligible for ASCT.

### Combination with other agents

Combination of high-dose melphalan with TBI or other drugs has generally failed to improve survival and was frequently associated with additional hematologic and non-hematologic toxicity (31, 33–35, 60–62). However, as TRM continues to improve, it is conceivably possible that melphalan in combination, with busulfan for example, could eventually prove superior to melphalan alone. A study in this regard is ongoing at MDACC.

Incorporation of novel myeloma agents into MM conditioning regimens is promising. Recently, bortezomib and melphalan was combined in a phase II IFM trial(63) and results were compared to that in IFM 2005-01 trial (high-dose melphalan alone) in a matched control analysis(64). No toxic deaths were observed and the CR rate was significantly higher in the combination arm (35% vs. 11%; p=.001) regardless of the type of induction therapy used. We conducted a randomized phase II trial comparing pre-ASCT preparative regimen of ascorbic acid, arsenic trioxide, and high-dose melphalan, with and without bortezomib(65). The addition of bortezomib was safe and well tolerated; however, no significant improvement in the CR rate, PFS, or OS was seen. Inclusion of patients with more advanced disease probably contributed to a lack of clinical benefit noted in our study. Overall, the combination of melphalan and novel agents for pre-transplant conditioning appears safe and feasible, and is an area under intense investigation.

**Allogeneic stem cell transplantation for multiple myeloma—**Allo-SCT can potentially cure multiple myeloma by virtue of high-dose chemotherapy administration, absence of tumor contamination of the graft, and potential for a graft-versus-myeloma effect(66). The initial trials of allo-SCT for MM employed intense myeloablative conditioning regimens, mostly consisting of TBI and melphalan(67, 68). Despite long-term disease control in a relatively small number of patients, TRM was unacceptably high (>35%)(69). To overcome this barrier, reduced-intensity conditioning (RIC) regimens were developed, which resulted in marked reduction in early mortality at the expense of higher relapse rates(70).

In order to capitalize on the reduction of TRM with RIC allo-SCT, a strategy of planned ASCT followed by RIC allo-SCT was developed. Initial ASCT using melphalan 200 mg/m$^2$ followed by RIC allo-SCT using low-dose TBI or low-dose melphalan plus fludarabine was shown to be safe and also led to a 2-yr OS exceeding 70% in some studies(71–74). Based on these encouraging results, several prospective randomized trials were conducted, which compared tandem ASCT with planned ASCT followed by RIC allo-SCT(75–86) (Table 3). Overall, two randomized trials have shown that ASCT followed by RIC allo-SCT leads to superior PFS and OS(77, 80) and one randomized trial has shown a trend towards superior PFS with this approach(76). The majority of other randomized trials showed that, while allo-SCT is associated with superior CR rate, the PFS and OS were similar to that seen with tandem ASCT. The lack of superiority despite better response rate with allo-SCT can be at least partly attributed to a higher TRM with allo-SCT. Until further data becomes available, we do not recommend allo-SCT in MM patients outside of a clinical trial.

## AMYLOIDOSIS

High-dose melphalan therapy followed by ASCT is an effective treatment for immunoglobulin light chain (AL) amyloidosis. In a retrospective study including 701 consecutive new AL amyloidosis patients, 5-year OS of 312 patients who started stem cell mobilization was found to be 47%, while that of patients ineligible for ASCT was only 16%(87). TRM in first 100 days was 13%, mostly cardiac-related. Patients who received melphalan 200 mg/m$^2$ had better outcome compared with patients who received modified doses (100 or 140 mg/m$^2$), with 5-year OS rate 61% versus 41%, respectively (P<0.001). Similar results were seen in another large series where 421 patients received high-dose (55%) or modified dose (45%) of melphalan followed by ASCT(88). While the higher-dose melphalan may be more effective, the TRM was generally higher than that seen in myeloma patients. Consequently, a risk-adapted approach was evaluated in a phase II trial where 45 patients with newly diagnosed AL amyloidosis involving ≤2 organ systems were assigned to melphalan 100 mg/m$^2$, 140 mg/m$^2$, or 200 mg/m$^2$ stratified based on age, cardiac involvement, and renal function(89). Only 2 patients (4.4%) had deaths attributable to stem cell mobilization and/or transplant. Hematological response was seen in 63% with stable disease in another 37% patients. Twenty patients (44%) had improvement in their primary involved organ. No significant difference was seen in response rates for different melphalan doses suggesting dose adaptive approach may not be justified.

Melphalan plus dexamethasone is widely used as standard treatment for patients who are not candidates for ASCT(90). The response rate with this regimen, however, is low, and CR is generally achieved in < 20% of the patients(91, 92). The ASCT achieves the highest rates of response among the currently available regimens for the treatment of AL amyloidosis(93).However, one lingering question is whether the patients who are selected to undergo high-dose melphalan plus ASCT have inherently a better prognosis. In a Mayo Clinic study, the median survival of the patients who were eligible for ASCT, but were treated with standard chemotherapy was 42 months, which was better than the expected median survival for all patients with AL amyloidosis(94). The results were compared with a matched cohort of patients who underwent ASCT, and no difference in survival was seen. The authors concluded that the patients who were eligible for ASCT represented a good-risk population who might have had good outcomes with chemotherapy alone. However, in another report from the same group, 63 patients undergoing melphalan (100–200 mg/m$^2$) and ASCT were compared with 63 matched patients not receiving transplantation(95). The 4-year OS was significantly superior for ASCT (70% vs. 40%; P<0.001). There is only one randomized clinical trial in which high-dose melphalan followed by ASCT was compared to chemotherapy consisting of melphalan plus dexamethasone(96). One hundred patients were randomly assigned to each arm. After a median follow up of 3 years, the median OS was significantly superior in the melphalan plus dexamethasone arm (56.9 vs. 22.2 month; P=0.004). However, this trial was criticized for the high TRM of 24% with high-dose therapy, which was higher than expected at centers performing transplants for AL amyloidosis(97).

Following the footsteps of myeloma treatment, where intensifying treatment with tandem ASCT might improve response, Sanchorawala et al. conducted a prospective trial of tandem

courses of high-dose melphalan and ASCT(98). Hematologic CR was seen in 55% of patients after initial ASCT with TRM of 8% in first 100 days. A second course of high-dose melphalan was given to 17 patients who did not achieve CR after the initial treatment. The TRM was 6%, and 31% achieved a CR. Overall, on intention to treat analysis, CR rate was 56%. While these results are remarkable, only a few patients are usually fit enough to undergo such intense treatment.

Overall, we believe that ASCT has an important role in the treatment of AL amyloidosis; however, several important issues such as patient selection and melphalan dose intensity need to be addressed in prospective randomized trials.

## MYELOID MALIGNANCIES

Intravenous melphalan was initially evaluated in acute myeloid leukemia (AML) treatment in Europe. At ablative doses, melphalan, followed by ASCT or in combination with total body irradiation (TBI) for allo-SCT, was associated with long-term leukemia-free survival in more than half of AML patients in first complete remission (CR)(99, 100). High-dose melphalan with autologous stem cell support was also used for relapsed/refractory AML patients(101).

However, it was not until the pioneering work of the MD Anderson group using melphalan in combination with fludarabine (FM) when melphalan found a main stream role in allogeneic transplant conditioning for patients with AML(102, 103). Fludarabine was used with melphalan primarily due to its immunosuppressive effects(104) and synergy with alkylating agents through inhibition of DNA damage repair(105). In a retrospective analysis of 112 patients with AML (n=80) or high-risk myelodysplastic syndrome (MDS) (n=32) who underwent allo-SCT following FM conditioning at MDACC, the 2-year OS was 44% despite the presence of active disease in 82 patients at the time of transplantation(106). While the cumulative incidence of NRM for the whole cohort was 54% at last follow-up, it was 20% at 2 years among patients in CR at transplantation, demonstrating a relatively favorable toxicity profile. There was no difference in survival and risk of progression between patients who received 140 $mg/m^2$ and 180 $mg/m^2$ of melphalan as part of the conditioning regimen, thus 140mg/m2 remains to this day the standard dose for allogeneic transplantation.

To further improve regimen-related morbidity and mortality of the FM regimen, van Besien et al. incorporated alemtuzumab for GVHD prophylaxis in place of post-transplant methotrexate(107). Later, a retrospective comparison of AML/MDS patients who received FM conditioning regimen at the University of Chicago with alemtuzumab, and at our institution without alemtuzumab, demonstrated no difference in survival, NRM, or relapse rate between the two cohorts(108). However, GVHD incidences were significantly lower among patients who received alemtuzumab.

Reduced-intensity conditioning with FM may be a particularly good option for patients with primary myelofibrosis (PMF), since the average age at PMF diagnosis is approximately 60 years(109). Devine and colleagues were the first to report the use of FM140 in a small number of myelofibrosis patients(110). Further retrospective studies demonstrated long-term

disease-free survival in PMF patients after allo-SCT with FM conditioning(111, 112). We recently reported our experience in PMF patients with leukemic transformation(113). All patients who received FM conditioning engrafted and all JAK2V617F mutation-positive patients became negative on day 30 after transplant. Approximately half of the patients survived long term, suggesting that induction chemotherapy followed by allo-SCT with FM140 conditioning could be an effective strategy for patients with AML progressed from myelofibrosis (113).

Apart from fludarabine, melphalan was also combined with busulfan, carmustine, TBI, and clofarabine in conditioning of AML patients prior to transplantation (Table 4). Of those, clofarabine-melphalan combination is of particular interest. Clofarabine was designed to retain antitumor and immunosuppressive properties of fludarabine while providing an improved safety profile(114, 115). van Besien and colleagues recently published the results of their phase I–II study of clofarabine, melphalan and alemtuzumab conditioning in 82 patients with advanced hematological malignancies, of whom 43 had AML or MDS(116). All patients engrafted. The incidence of grade II–IV aGVHD and cGVHD were 22% and 5%. Among 74 patients who received 140 mg/m$^2$ of melphalan in the phase II part, NRM at day 100 and 1 year were 19% and 26%. One-year OS was 59%.

In summary, fludarabine-melphalan combination is an alternative to busulfan-based conditioning regimens in myeloid malignancies. Future studies should explore the combination with clofarabine to enhance its antitumor effects.

## LYMPHOID MALIGNANCIES

Although melphalan was not part of the conditioning regimen used in the groundbreaking study by Philip et al. which showed superior survival with ASCT over salvage chemotherapy in patients with chemosensitive relapsed/refractory lymphomas(117), it was subsequently incorporated into the probably most commonly used conditioning regimen for patients with lymphoma today, BEAM (carmustine, etoposide, arabinoside, melphalan at 140 mg/m$^2$). BEAM, designed in mid-80s(118, 119), was favored over BEAC (with cyclophosphamide) in most transplant centers due to its simpler treatment scheme. Mucositis is almost universal following BEAM chemotherapy, commonly requiring opioids and sometimes total parenteral nutrition(120–122). Still, BEAM is a fairly well-tolerated regimen with early NRM rates of less than 5%(122–125).

ASCT with BEAM is effective in treatment of both chemosensitive aggressive NHL and Hodgkin lymphoma (HL). Among relapsed/refractory aggressive chemosensitive NHL patients, long-term OS and PFS ranged between 56%–64% and 49%--51% after ASCT with BEAM conditioning(120, 122, 123). In retrospective analyses, BEAM was also observed to be effective in the treatment of anaplastic large cell lymphomas and angioimmunoblastic lymphomas(126, 127). As in NHL, BEAM is highly effective in patients with chemosensitive relapsed/refractory HL, with reported long-term OS and PFS rates of 56%–78% and 49%–69% 54 55(122, 125, 128, 129).

More recently, fotemustine and bendamustine were substituted for carmustine to improve the antitumor effect of BEAM regimen. In a prospective study including 84 relapsed/

refractory lymphoma patients who underwent ASCT with FEAM regimen (with fotemustine), 100 day NRM was 2% with 74 patients (88%) still alive after a median follow-up of 13 months(130). Meanwhile, in a similar study with BeEAM (with bendamustine instead of carmustine) which included 43 relapsed/refractory lymphoma patients, none of the patients died within 100 days of transplant. Thirty-five patients (81%) were still alive after a median follow-up of 18 months(131).

Melphalan was also used in combination with busulfan prior to ASCT for the treatment of lymphoid malignancies. First, Srivastava and colleagues demonstrated the feasibility of melphalan in combination with oral busulfan in 24 patients with a variety of malignancies(132). Recently, our group reported the results from a phase II trial of pharmacokinetics-guided intravenous busulfan and melphalan conditioning prior to ASCT for patients with advanced lymphoid malignancies(133). No grade IV regimen-related toxicity was observed. TRM at day 100 and 3 years were 1% and 3%. Among 49 and 12 patients with HD and NHL beyond first CR, 2-year OS rates were 85% and 67%.

To further improve its anti-tumor effect, our group incorporated gemcitabine into the i.v. busulfan and melphalan regimen (GemBuMel). In a retrospective comparison of 115 refractory HD patients who underwent ASCT with BEAM (n=26), busulfan-melphalan (n=38), and GemBuMel (n=51) conditioning during the same period of time, no treatment-related deaths were observed in any cohort. Patients who received GemBuMel had a significantly better OS and PFS despite having worse prognostic features(134).

Our group was also the first to demonstrate the feasibility of BEAM as a preparative regimen for allo-SCT from matched related donors in patients with NHL(135). Subsequently, its feasibility was shown in patients with matched unrelated donors and mismatched related donors with the addition of alemtuzumab in the conditioning regimen(136, 137). In a retrospective analysis of 65 lymphoma patients who relapsed or were ineligible for ASCT treated with allo-SCT with BEAM-alemtuzumab conditioning, Faulkner et al. reported a two-year NRM of 13% while primary graft failure occurred in 3 patients. Three-year OS was 63%.

Apart from BEAM, FM combination was also successfully implemented for conditioning of lymphoma patients prior to allo-SCT. After the report of a case with relapsed HL treated with allo-SCT using FM conditioning(138), Branson and colleagues reported on allo-SCT using FM140 in 38 patients with lymphoproliferative malignancies which relapsed after ASCT(139). At a median follow-up of 14 months, OS, PFS, and NRM were 53%, 50%, and 20%, respectively. Additionally, FM regimen with alemtuzumab was found to be effective in advanced CLL patients, with relatively low toxicity and a PFS of 45% at 2 years(140). Recently, Anderlini and colleagues reported our experience with allogeneic transplantation in HL patients with FM conditioning(141). Fifty-eight patients were treated with a day-100 TRM of 7%. OS at 2 years and last follow-up were 64% and 48%, despite the heavily treated cohort of patients. Table 5 summarizes the results from studies of allo-SCT with FM conditioning in lymphoma patients.

Melphalan has also been used as part of conditioning for patients with acute lymphoblastic leukemia (ALL) undergoing allo-SCT. Deconinck et al. reported on consolidation allo-SCT with an intensified conditioning of 12 Gy fractionated TBI, arabinoside 3 g/m2 for 8 doses, and melphalan 140 mg/m$^2$ in 42 high-risk ALL patients in CR1(142). All but one patient engrafted. OS and EFS at last follow-up were 45% and 40%, similar to those reported with other conditioning regimens not containing melphalan(143, 144). Reduced-intensity conditioning with FM140 was also investigated in a prospective trial in 37 patients with high-risk ALL in CR(145). All patients were engrafted with 16 and 21 (76%) developing grade II–IV acute GVHD and chronic GVHD, respectively. At 3 years, NRM, DFS, and OS were 18%, 63%, and 64%, demonstrating the feasibility of this regimen for patients with ALL.

BEAM conditioning is still the standard of care for ASCT in patients with lymphoid malignancies, while newer conditioning regimens are being explored. For allo-SCT, BEAM and FM regimens may be used successfully in place of TBI-based conditioning.

## ALTERNATIVE DONOR TRANSPLANTATION

Melphalan has been incorporated into multiple reduced-intensity conditioning regimens used in umbilical cord blood transplantation (UCBT)(146–148). Yuji and colleagues reported on 20 advanced lymphoma patients, of whom 12 had relapsed/refractory large B-cell lymphoma, who underwent single umbilical cord blood transplant (UCBT) with fludarabine 25 mg/m2 for 5 days, melphalan 80 mg/m2, and 4 Gy TBI. Only one patient developed primary graft failure. NRM at day 100 was relatively high at 41%, and OS and PFS at 1 year were both 50%. Recently, the Dana-Farber group reported an improved NRM with FM-ATG regimen and use of double umbilical cord blood units in 32 patients with advanced hematological malignancies(147). No primary graft failure was reported. Three and four patients experienced grade II–IV aGVHD and cGVHD. NRM at 100 days and 2 years were 13% and 34%. At 2 years, PFS and OS were 31% and 53%, demonstrating the safety and efficacy of this regimen.

Melphalan has also been used as part of conditioning before transplantation from haploidentical related donors (haploSCT). Lacerda and colleagues treated 14 patients with a regimen consisting of fludarabine, melphalan, thiotepa, cyclosporine, and rabbit ATG plus standard doses of CD34+ selected cells(149). All patients engrafted, 8 developed aGVHD and 6 survived long term. Subsequently, Bethge et al. used the fludarabine 150–200 mg/m2, melphalan 120 mg/m2 and thiotepa 10 mg/kg (FMT) regimen in 29 patients with hematological malignancies, of whom 23 had acute leukemia(150). Only one patient experienced primary graft failure. The regimen was well tolerated with no grade 4 toxicities. The 100-day NRM was 20% with deaths primarily due to infectious complications related to T-cell depletion. The incidence of grade II–IV aGVHD was 48%, and 1-year OS was 35%.

We have utilized FMT regimen prior to both UCBT and haploSCT(151),[187]. In a phase II trial, 28 patients with hematological malignancies, of whom 22 had AML/MDS, received FMT-ATG followed by CD34+ selected grafts from haploidentical related donors(152). Six patients failed to achieve primary engraftment and 5 later received second transplants. Of

these, 3 out of 4 tested patients were found to have anti-HLA antibodies. No grade III–IV aGVHD was observed and 4 patients developed cGVHD. NRM at 100 days and last follow-up were 18% and 40%, primarily due to infectious complications. OS at last follow-up was 18%. More recently, we presented our early results with haploSCT after FMT conditioning regimen using T-cell replete grafts and post-transplant cyclophosphamide(153). Primary engraftment was improved and achieved in 94% of patients, TRM at 100 days was only 9% and OS at 1 year was 66%, demonstrating improved early outcomes with use of T-cell replete grafts compared to T-cell depleted haploSCT after conditioning with the same regimen (FMT).

For alternative donor transplants, we believe melphalan remains the mainstay conditioning drug. For patients with low grade lymphoid malignancies and older patients with acute leukemia in remission, reduced doses of melphalan in combination with fludarabine and thiotepa can be used as an alternative to fludarabine-cyclophosphamide-TBI conditioning(154).

## FUTURE DIRECTIONS

In summary, since its discovery more than 50 years ago, melphalan use has been expanded to all forms of transplantation. As we move forward, this drug will likely to remain an essential component of pre-transplant preparative regimens for autologous and allogeneic stem-cell transplantation, and will probably continue to provide the framework for building newer and better conditioning regimens in the future. Improving the antitumor activity may prove effective by adding busulfan to the melphalan-based conditioning for lymphoid malignancies or by replacing fludarabine with clofarabine for allogeneic stem cell transplantation. Targeting mephalan dose based on area-under the curve, similar to busuflan, could be explored to maximize efficacy and minimize toxicity of this drug. Improving relapse rate could be also foreseen using cellular therapy after allogeneic stem-cell transplantation in patients conditioned with FM and alemtuzumab regimen, as patients develop minimal GVHD and immunosuppression can be tapered early post transplant.

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**Table 1**

Studies comparing high-dose melphalan and autologous stem cell transplantation with chemotherapy for multiple myeloma.

| Reference | N | Treatment | Response | EFS* | OS* | Notes |
|---|---|---|---|---|---|---|
| Attal et al.[39] | 200 | VMCP/BVAP vs. MEL 140 + TBI (8Gy) IFN-a maintenance until relapse | ASCT vs. chemo CR 22% vs. 5% VGPR 16% vs. 9% P<.001 | ASCT vs. chemo 27 vs. 18 mo P=0.01 | ASCT vs. chemo NR vs. 37.4 mo P=0.03 | |
| Child et al.[40] | 407 | BCAM vs. VMCP → Cy+G-CSF mobilization → MEL 200 IFN maintenance in both groups N=8 received TBI+MEL140 | ASCT vs. chemo CR-rate 44% vs. 8% P<0.001 PR-rate 42% vs. 40% P=0.72 | PFS ASCT vs. chemo 31.6 mo vs. 19.6 mo P<0.001 | ASCT vs. chemo 54.1 mo vs. 42.3 mo P=0.04 | 17% of patients in chemotherapy arm crossed over to ASCT arm, usually after disease progression, hence the actually survival benefit may be higher. |
| Fermand et al.[41] | 179 | VAMP vs. LomustineVP-16+Cy+Mel140+TBI (1,200 cGy) & ASCT IFN offered to both groups in remission | Early ASCT vs. chemo CR 18% vs. 5% | Early ASCT vs. chemo 39 mo vs. 13 mo | Early ASCT vs. chemo 64.6 mo vs. 64 mo P=0.92 | Late ASCT offered to chemotherapy group at progression or resistant disease after 6 cycles of VMCP. Distribution of periods spent without chemotherapy was longer in early ASCT group. |
| Blade et al.[42] | 186 | VBMCP/VBAD vs. MEL 200 or MEL 140+TBI (12Gy) Responding patients in both groups received maintenance with IFN + Dex until relapse | ASCT vs. chemo CR 30% vs. 11% P=0.002 | PFS ASCT vs. chemo 42 mo vs. 33 mo P=0.57 | ASCT vs. chemo 61 mo vs. 66 mo P=0.89 | Only patients with chemo-sensitive disease were enrolled. |
| Fermand et al.[43] | 190 | VMCP vs. CHOP+G-CSF for collection → VAMP → MEL200 or MEL140 + Bu | ASCT vs. chemo CR +MRD 36% vs. 19.8% | ASCT vs. chemo 25.3 mo vs. 18.7 mo P=0.07 | ASCT vs. chemo 47.8 mo vs. 47.6 mo P=0.91 | TwiSTT ASCT vs. chemo 25.1 mo vs. 16.6 mo P=0.033 |

| Reference | N | Treatment | Response | EFS* | OS* | Notes |
|---|---|---|---|---|---|---|
| | | IFN-a proposed to both arms | | | | |
| Barlogie et al.[44] | 516 | MEL140+TBI (12Gy) vs. VBMCP Responding patients randomized to IFN × 4 yrs vs. Obs | ASCT vs. chemo CR 11% vs. 11% | ASCT vs. chemo 17% vs. 14% | ASCT vs. chemo 38% vs. 38% | |

**Legend:**

V, vincristine; M, melphalan; C & Cy, cyclophosphamide; P, prednisone; B, carmustine (BCNU); A, adriamycin (H, hydroxydaunorubicin); IFN, interferon; MEL, melphalan; G-CSF, granulocyte colony-stimulating factor; TBI, total-body irradiation; IFN-a, interferon-alpha; Dex, dexamethasone; O, oncovin (vincristine); Bu, busulfan

ASCT, autologous stem cell transplantation; Chemo, chemotherapy; CR, complete remission; PFS, progression-free survival; MRD, minimal residual disease; TwiSTT; the period of time without symptoms, treatment, and treatment toxicity; EFS, event-free survival; OS, overall survival

*Median values

**Table 2**

Studies comparing single autologous stem cell transplantation with tandem autologous stem cell transplantation for multiple myeloma.

| Reference | N | Regimen | Response | EFS | OS | Comments |
|---|---|---|---|---|---|---|
| Barlogie et al.[46] | 123 | EDAP/MEL200 MEL200 or MEL140+TBI (1,125Gy) vs. chemo ᶜ IFN-a maintenance till relapse | ≥PR Tandem ASCT vs. chemo ᶜ 86% vs. 52% P=.0001 | Tandem ASCT vs. chemo ᶜ Median EFS 49 mo vs. 22 mo P=.0001 | Tandem ASCT vs. chemo ᶜ Median OS 62 mo vs. 48 mo P=.01 | Absence of abnormalities of chromosome 11q and 13 associated with significantly poor EFS and OS |
| Attal et al.[49] | 399 | MEL 140+TBI (8Gy) vs. (tandem arm) MEL140 then MEL140+TBI (8Gy) Both groups received IFN-a maintenance | CR+VGPR ᵍ Single vs. tandem 49% vs. 63% P=0.01 | At 7-yr Single vs. tandem 10% vs. 20% P=0.03 | At 7-yr Single vs. tandem 21% vs. 42% P=0.01 | Median time between 1st and 2nd ASCT was 2.5 months |
| Cavo et al.[50] | 321 | MEL200 vs. MEL200 MEL120+Bu IFN-a maintenance until relapse in both groups | Single vs. tandem nCR 33% vs. 47% P=0.008 | Single vs. tandem median EFS 23 mo vs. 35 mo P=0.001 | Single vs. tandem median OS 65 mo vs. 71m P=0.90 | Trend for improved OS in tandem ASCT arm in patients failing to achieve at least near CR after 1st ASCT. (7-yr rate 60% vs. 47%; P=0.10) |

**Legend:** E, etoposide; D, dexamethasone; C, cytarabine; P, cisplatin; MEL, melphalan; D, dexamethasone; IFN-a, interferon-alpha; TBI, total-body irradiation; Bu, busulfan EFS, event-free survival; OS, overall survival; CR, complete remission; nCR, near CR

ᶜ SWOG 8229 trial VMCP-VBAP & SWOG 8624 trial VMCP/VBAP vs. VMCPP/VBAPP vs. VAD (see Table 1 for details);

ᵍ In patients who actually received 1 or 2 ASCT

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**Table 3**

Randomized trials comparing tandem autologous stem cell transplantation with autologous followed by allogeneic stem cell transplantation in patients with multiple myeloma.

| Reference | N | Regimen | TRM | Response | PFS* | OS* | Comments |
|---|---|---|---|---|---|---|---|
| Garban et al.(75) | 284 | Initial ASCT MEL 200 Tandem ASCT MEL 200+Dex Or MEL 220+Dex+B-E8 Allo-SCT Bu-Flu-ATG | Tandem ASCT 5% Allo-SCT 10.9% | CR/VGPR Tandem ASCT 51% Allo-SCT 62.2% | EFS Tandem ASCT 30 months Allo-SCT 25 months P=0.56 | Tandem ASCT 41 months Allo-SCT 35 months P=0.27 | |
| Rosinol et al.(76) | 110 | Initial ASCT VBMCP/VBAD Tandem ASCT MEL 200 or CVB Allo-SCT Flu+Mel | Tandem ASCT 5% Allo-SCT 16% P=0.09 | CR Tandem ASCT 11% Allo-SCT 40% P=0.001 | Tandem ASCT 31 months Allo-SCT Not-reached P=0.08 | Tandem ASCT 58 months Allo-SCT Not-reached P=0.9 | Plateau in PFS seen in allo-SCT group |
| Bruno et al.(77) | 162 | Initial ASCT MEL 200 Tandem ASCT MEL 100 – 200 Allo-SCT TBI (200 cGy) | Tandem ASCT 2% at 2-year Allo-SCT 10% at 2-year P=0.09 | CR Tandem ASCT 26% Allo-SCT 55% P=0.004 | EFS Tandem ASCT 29 months Allo-SCT 35 months P=0.02 | Tandem ASCT 54 months Allo-SCT 80 months P=0.01 | On multivariate analysis allo-SCT was associated with longer EFS and OS |
| Björkstrand et al.(80) | 357 | Initial ASCT MEL 200 Tandem ASCT MEL 200 Allo-SCT Flu-TBI (2 Gy) | Tandem ASCT 4% at 5-year Allo-SCT 16% at 5-year P=<.001 | CR Tandem ASCT 41% Allo-SCT 51% P=0.020 | At 60-months Tandem ASCT 18% Allo-SCT 35% P=0.001 | At 60-months Tandem ASCT 58% Allo-SCT 65% P=0.006 | On intention-to-treat analysis of high-risk patients, allo-SCT was associated with longer PFS and OS |
| Krishnan et al.(84) | 710 | Initial ASCT MEL 200 Tandem ASCT MEL 200 (patients were then randomized to maintenance therapy with | Tandem ASCT 4% at 3-year Allo-SCT 11% at 3-year P=<.0001 | CR Tandem ASCT 45% Allo-SCT 58% P=0.007 | At 3-year Tandem ASCT 46% Allo-SCT 43% P=0.67 | At 3-year Tandem ASCT 80% Allo-SCT 77% P=0.191 | |

| Reference | N | Regimen | TRM | Response | PFS* | OS* | Comments |
|---|---|---|---|---|---|---|---|
| | | thalidomide+Dex or observation) Allo-SCT TBI (2 Gy) | | | | | |
| Lokhorst et al.(85) | 260 | Initial ASCT MEL 200 (followed by maintenance therapy with IFN or thalidomide. 3 patients received tandem ASCT) Allo-SCT TBI (2 Gy) | No donor 3% Donor available 16% P=<0.001 | CR No donor 37% Donor available 43% P=0.67 | At 6-year No donor 22% Donor available 28% P=0.17 | At 6-year No donor 55% Donor available 55% P=0.72 | Cumulative incidence of relapse at 6-year was significantly lower in patients with a donor versus no donor group (55% vs. 77%; P=0.005) |
| Knop et al.(86) | 199 | Initial ASCT MEL 200 Tandem ASCT MEL 200 Allo-SCT Flu+Mel+ATG (for unrelated donors) | - | CR Tandem ASCT 32% Allo-SCT 59% =0.003 | | At 3-yr Tandem ASCT 72% Allo-SCT 60% P=0.22 | |

**Legend:**

Bu, busulfan; Flu, fludarabine; ATG, anti-thymocyte globulin; Dex, dexamethasone; B-E8, Anti-IL6 antibody; VBMCP: vincristine, BCNU, melphalan, cyclophosphamide, prednisone VBAD: vincristine, BCNU, adriamycin, dexamethasone; CVB: cyclophosphamide, etoposide, BCNU; MEL, melphalan; TBI, total-body irradiation; IFN, interferon

ASCT, autologous stem cell transplantation; allo-SCT, allogeneic stem cell transplantation; TRM, treatment-related mortality; EFS, event-free survival; CR, complete remission; VGPR, very good partial remission; PFS, progression-free survival; OS, overall survival; * CR rate for tandem ASCT: CVB 3%, Mel 35%, P=<0.001

*Median PFS and OS, unless specified otherwise.

**Table 4**

Studies of allogeneic stem cell transplantation with melphalan containing preparative regimens in patients with acute myeloid leukemia/myelodysplastic syndrome (published 2000–2011)

| Author Publication year/type | Diagnosis and disease status | Median age (range) | MRD/MUD/mismatch | Preparative regimen* | GVHD prophylaxis | Primary graft failure (n) | GVHD incidence (acute, chronic)† | NRM ‡ | RI ‡ | PFS/OS‡ |
|---|---|---|---|---|---|---|---|---|---|---|
| de Lima, 2004/R (155) | 42 AML (10 in CR) 20 MDS | 54 (22–75) | 25/29/8 | FLU 100–150 mg/m2 + MEL 140–180 mg/m2 | TCR/CSA + MTX | 2 | 39%, 39% | 100d: 26% 3yr: 39% | NA | 3yr: 32% / NA |
| Malladi, 2004/R(156) | 12 AML (11 in CR) 4 MDS | 47 (27–66) | 16/0/0 | FLU 150 mg/m2 + MEL 140 mg/m2 | CSA + MTX | 1 | 47% (II–III), 46% | 4yr: 13% | LFU: 1 pt | 4yr: 79% / 79% |
| van Besien, 2005/P(107) | 41 AML (13 in CR) MDS (11) | 52 (17–71) | 23/22/7 | FLU 150 mg/m2 + MEL 140 mg/m2 + ALE 100 mg/m2 | TCR | 2 | 33%, 18% | 100d: 17% 2yr: 33% | 2yr: 40% | 2yr: 31% / 39% |
| Tauro, 2005/R(157) | 56 AML (42 in CR) MDS (20) | 52 (18–71) | 35/41/0 | FLU 150 mg/m2 + MEL 140 mg/m2 + ALE 50–100 mg/m2 | CSA | 4 | None (III–IV), 8 pts | 100d: 9% 1yr: 19% | LFU: 27 pts | 3yr: 37% / 41% |
| Nakamura, 2007/R(158) | 15 AML (8 in CR) MDS (28) | (30–71) | 19/20/4 | FLU 125 mg/m2 + MEL 140 mg/m2 | CSA + MMF (±MTX for MUDs) | None | 63%, 23 pts | 100d: 27% 2yr: 35% | 2yr: 16% | 2yr: 51% / 54% |
| Oran, 2007/R(106) | 82 AML (30 in CR) MDS (30) | 55 (22–74) | 53/59/0 | FLU 100–150 mg/m2 + MEL 140–180 mg/m2 ± GO 2–4 mg/m2 (16) ± ATG (31 with MUD) | TCR + MTX | 4 | 39%, 49% | LFU: 54% | 2yr: 25% | 2yr: NA / 44% |
| Small, 2007/P(159) § | 20 AML (1 in CR) (Total 43) | 46 (1–62) | 18/25/0 | BU (serum level of 600–900 ng/mL) + MEL135 mg/m2 ± ATG 30 mg/kg (MUDs) | TCR + MTX | 2 | 24%, 11 pts | LFU: 28% | LFU: 10 pts (AML pts) | 3yr: 13% / NA (AML pts) |
| de Lima, 2008/P(160) | 48 AML (3 in CR) MDS (4) | 53 (13–72) | 31/19/2 | FLU 120 mg/m2 + MEL 140 mg/m2 ± GO 2–6 mg/m2 + ATG (MUDs) | TCR + MTX | None | 42%, 52% | 100d: 13% 1yr: 29% | NA | 2yr: NA / 38% |

| Author Publication year/type | Diagnosis and disease status | Median age (range) | MRD/MUD/mismatch | Preparative regimen* | GVHD prophylaxis | Primary graft failure (n) | GVHD incidence (acute, chronic)† | NRM ‡ | RI ‡ | PFS/OS‡ |
|---|---|---|---|---|---|---|---|---|---|---|
| Marks, 2008/P(161) § | 58 AML (11 in CR) MDS (23) (Total 133) | 56 (24–74) | 68/59/6 | FLU 150 mg/m2 + BCNU 300–400 mg/m2 + MEL 110-140 mg/m2 ± ATG (MUDs) | CSA + MTX or MMF | 1 | 23%, 33% (ext) | 100d: 16% 5yr: 34% | NA | 3yr: 40% / 47% (AML/MDS pts) |
| Kirschbaum, 2011/P(162) | 16 AML (9 in CR) | 63 (31–66) | 8/8/0 | CLO 150–200 mg/m2 + MEL 100–140 mg/m2 | CSA + MMF or TCR + SRL | None | 4 pts, 5 pts | 100d: 2pts | LFU: 2 pts | LFU: 11 pts /12 pts |

**Legend:**

*Cumulative doses shown;

†Cumulative incidences of grade II–IV acute GVHD followed by limited & extensive chronic GVHD shown unless indicated. If incidence is not available, number of patients were shown;

‡Time points shown (d: day, yr: year) prior to incidence. If incidence not available, number of patients was shown;

§Study including patients with diagnoses other than AML and MDS.

Information given is applicable to the whole cohort unless indicated; R indicates retrospective; P, prospective; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CR, complete remission; MRD, matched related donor; MUD, matched unrelated donor; FLU, fludarabine; MEL, melphalan; ALE, alemtuzumab; GO, gemtuzumab ozogamicin; ATG, anti-thymocyte globulin; BU, busulfan; BCNU, carmustine; TCR, tacrolimus; CSA, cyclosporine A; MTX, methotrexate; MMF, mycophenolate mofetil; SRL, sirolimus; GVHD, graft-versus-host disease; NRM, non-relapse mortality; RI, relapse incidence; PFS, progression-free survival; OS, overall survival; LFU, last follow-up; ext, extensive chronic GVHD; pts, patients; NA, not available

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**Table 5**

Studies of allogeneic stem cell transplantation with fludarabine-melphalan conditioning in patients with lymphoid malignancies.

| Author Publication year/type | Diagnosis and disease status * | Median age (range) | MRD/MUD/ mismatch | Preparative regimen † | GVHD prophylaxis | Primary graft failure (n) | GVHD incidence (acute, chronic)‡ | NRM § | PFS/OS § |
|---|---|---|---|---|---|---|---|---|---|
| Branson, 2002/R(139) | 10 H-NHL, 1 L-NHL, 2 MCL, 12 HL, 1 CLL, 12 MM [38] | NA | 38/0/0 | FLU 150 mg/m2+ MEL 140 mg/m2 + ALE 100 mg | CSA +MTX | NA | None (III–IV), 5 pts | 100d: 8% 14mo: 20% | 14mo: 50% / 53% |
| Morris, 2004/R(163) | 37 H-NHL, 41 L-NHL, 10 MCL [37] | 48 (18–73) | 63/17/8 | FLU 150 mg/m2+ MEL 140 mg/m2 + ALE 100 mg | CSA | 1 pt | 13 pts, 6 pts | Early: 14 pts | 3yr: NA / 55% |
| Delgado, 2006/P(140) | 41 CLL [0] | 54 (37–67) | 24/13/4 | FLU 150 mg/m2+ MEL 140 mg/m2 + ALE 100 mg | CSA | None | 4 pts (III–IV), 13 pts | 100d: 5% 2yr: 26% | 2yr: 45% / 51% |
| Rodriguez, 2006/R(164) | 19 H-NHL, 16 L-NHL, 5 MCL [16] | NA | NA | FLU 125 mg/m2+ MEL 140 mg/m2 | NA | NA | 65%, 76% | 2yr: 28% | LFU: 40% / 53% |
| Thomson, 2009/P(165) | 48 DLBCL [34] | 46 (23–64) | 29/10/9 | FLU 150 mg/m2+ MEL 140 mg/m2 + ALE 100 mg | CSA | None | 8 pts, 9 pts | 4yr: 32% | 4yr: 48% / 47% |
| Alvarez, 2006/P(166) | 27 NS, 3 MC, 2 LD [29] | 31 (16–53) | 37/2/1 | FLU 150 mg/m2+ MEL 140 mg/m2 | CSA + MTX | 1 pt | 42%, 47% | 100d: 12.5% 1yr: 25% | 2yr: 32% / 48% |
| Peggs, 2007/R(167) | 57 NS, 5 MC, 5 LP [53] | 35 (19–56) | 67/0/0 | FLU 150 mg/m2+ MEL 140 mg/m2 ± ALE 100 mg | CSA ± MTX | 2 pts | 12 pts, 20 pts | NA | NA |
| Anderlini, 2008/R(141) | 58 HD [48] | 32 (19–59) | 25/33/0 | FLU 125 mg/m2+ MEL 140 mg/m2 + ATG | TCR + MTX | None | 28%, 73% | 100d: 7% 2yr: 15% | 2yr: 32% / 64% |

**Legend:**

* Number in brackets show the number of patients who previously had autologous stem cell transplantation;

† Cumulative doses shown;

‡ Cumulative incidences of grade II–IV acute GVHD followed by limited & extensive chronic GVHD shown unless indicated. If incidence is not available, number of patients were shown;

§ Time points shown (d: day, mo: month, yr: year) prior to incidence.

If incidence not available, number of patients was shown; R indicates retrospective; P, prospective; H-NHL, high- or intermediate-grade non-Hodgkin lymphoma; L-NHL, low-grade non-Hodgkin lymphoma; MCL, mantle cell lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; DLBCL, diffuse large B-cell lymphoma; NS, nodular sclerosing Hodgkin lymphoma; MC, mixed cellularity Hodgkin lymphoma; LD, lymphocyte depleted Hodgkin lymphoma; LP, lymphocyte predominant Hodgkin lymphoma; MRD, matched related donor; MUD, matched unrelated donor; FLU, fludarabine; MEL, melphalan; ALE, alemtuzumab; ATG, anti-thymocyte globulin; TCR, tacrolimus; CSA, cyclosporine A; MTX, methotrexate; GVHD, graft-versus-host disease; NRM, non-relapse mortality; PFS, progression-free survival; OS, overall survival; LFU, last follow-up; lim, limited chronic GVHD; ext, extensive chronic GVHD; pts, patients; NA, not available.