Allogeneic transplantation in lymphoma: current status

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Manuscript received December 21, 2006.
Manuscript accepted September 1, 2007.

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ABSTRACT

Allogeneic transplantation of hematopoietic stem cells (allo-SCT) is being increasingly used to treat patients with lymphoma. We describe current results of allo-SCT in patients with Hodgkin's disease, indolent lymphoma including Waldenström's disease, and aggressive lymphoma including mantle cell lymphoma and mature T-cell lymphomas. A Graft-vs.-Lymphoma (GvL) effect is present in most entities as evidenced by the generally lower relapse rates after allo-SCT and the results of donor lymphocyte infusions. Slowly proliferating diseases like chronic lymphocytic leukemia, indolent lymphomas, and some T-cell lymphomas are particularly sensitive to the effects of allogeneic T-cells while patients with Hodgkin's disease and aggressive lymphoma may need vigorous debulking before allo-SCT to achieve optimal results. Although reduced-intensity conditioning has lowered transplant-related mortality in most and improved survival in some sub-entities, relapse rates in patients with Hodgkin's disease and aggressive B-cell lymphomas, as well as in patients with heavily pre-treated and refractory lymphoma, remain high and further improvement is undoubtedly needed. Large prospective studies in well-defined entities are necessary to further clarify the role of allo-SCT in lymphoma.

Key words: allogeneic stem cell transplantation, Hodgkin's lymphoma, follicular lymphoma, aggressive lymphoma.

Haematologica 2007; 92:1533-1548. DOI: 10.3324/haematol.11185

Compared to the number of autologous transplants, few patients with lymphoma have undergone allogeneic transplantation of hematopoietic stem cells (allo-SCT). This is probably due to the higher median age at diagnosis, the increasing number of conventional treatment options, and the success of high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT). However, one of the major obstacles was the unfavorable outcome of allo-SCT in patients with lymphoma reported in all early series. Specifically, transplant-related mortality (TRM) had been devastatingly high and together with the relatively high relapse rates had resulted in poor progression-free survival (PFS) and overall survival (OS). Nonetheless, relapse rates after allo-SCT compared favorably with those after ASCT in most instances and gave rise to speculations that there may be a graft-vs.-lymphoma effect similar to what had been described as the graft-vs.-leukemia effect in the early 1980s.[1,2] Reduced-intensity conditioning (RIC) became clinical practice in the second half of the last decade and fed strong hopes of decreasing the high TRM. It has certainly been a major factor in the constant rise in the number of patients undergoing allo-SCT for lymphoma in recent years (Figure 1).

Assessment of the results of allo-SCT in lymphoma is problematic for a number of reasons. Over the past two decades, the histologic classification system for malignant lymphomas has been changed from the Working Formulation[3] (mostly used in the US) or the Kiel classification[4] (most popular in some European countries) to the R.E.A.L.[5] and the current WHO classification.[6] This not only makes it difficult to compare treatment results for diseases represented in all classification systems (because diagnostic criteria actually changed with increasing sophistication of available methodology) but also brought about the birth of new entities like mantle cell lymphoma which

previously had been hidden within other categories. Discussion of allo-SCT for lymphoma should also consider that many series include relatively low patient numbers and most reports group sub-entities together in a way that would be unacceptable to most lymphoma experts. This report addresses the most frequent entities of Hodgkin's lymphoma (HL), aggressive lymphoma, and indolent lymphoma where current knowledge indicates that results are sufficiently stable to justify separate presentation. We also briefly discuss mantle cell lymphoma, T-cell lymphoma, and Waldenström's disease but do not believe that existing data really allow a definition of the role of allo-SCT in these entities. It was felt that the scarcity of data with respect to the very aggressive lymphoblastic or BURKITT lymphomas did not justify separate consideration. Chronic lymphocytic leukemia (CLL) can be seen as a leukemic lymphoma and might therefore also have been included in this review. We chose not to address CLL because the nature of the disease and the selection criteria for candidates for allo-SCT clearly differ from other lymphomas. Furthermore, extensive reviews of how to treat CLL in general[7] and which CLL patients might benefit from allo-SCT[8] have recently been published.

Besides summarizing the results of allo-SCT after both myeloablative conditioning and RIC, this review focuses on the most relevant questions which will decide on the future of allo-SCT in lymphoma: firstly, what is the evidence to support the existence of a graft-vs.-lymphoma effect? and secondly, is there any data demonstrating that RIC has indeed reduced TRM and improved PFS or OS? Only positive answers to these questions warrant further efforts to fine-tune the interaction between conditioning regimen, graft, and the method of graft-vs-host disease (GvHD) prevention in order to optimize results after allo-SCT. On the other hand, there are good reasons to believe that the increasing efficacy of modern first-line therapy will leave behind lymphoma patients largely refractory to standard chemo- and antibody therapy at the time of relapse. It is for these patients that alternative treatment options such as allo-SCT will remain important in the future.

Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is highly responsive to conventional chemotherapy (CT). Close to 90% of patients even with advanced disease are cured with modern CT sometimes followed by irradiation.[9,10] Patients who prove refractory to or relapse after first-line therapy, do significantly worse. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) is the standard of care for medically fit patients with relapsed HL.[11,12] The results of HDT/ASCT, however, vary significantly depending on a number of prognostic factors the most important of which are the time interval between first-line treatment and relapse, the clinical stage at relapse, and the sensitivity of the tumor

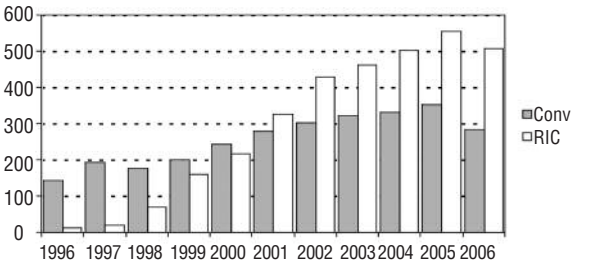

Figure 1. Numbers of allogeneic transplants in lymphoma following conventional vs. reduced intensity conditioning in Europe. Results from the European Group for Blood and Marrow Transplantation (EBMT) Lymphoma Working Party registry (with permission). Conv: conventional, myeloablative conditioning: RIC: reduced-intensity conditioning.

to salvage chemotherapy.[13-17] For example, approximately 70% of patients with late first relapse can be salvaged by HDT/ASCT whereas not more than 40% of patients suffering from early first relapse are rescued by this modality.[12] Only 20-35% of patients with refractory HL may achieve long-term survival after HDT/ASCT.[18-21] Therefore, although HDT/ASCT may cure a significant proportion of patients with relapsed or refractory HL, subsets of patients carry a high risk of failure and are candidates for more experimental procedures such as allo-SCT.

Myeloablative conditioning and allo-SCT in Hodgkin's lymphoma

The first reports on allo-SCT in patients with HL appeared in the mid 1980s.[22,23] Patient numbers were low and a realistic evaluation of the therapeutic potential of allo-SCT was not possible. Two larger registry-based studies published in 1996 gave disappointing results. Gajewski *et al.* analyzed 100 HL patients allografted from HLA-identical siblings and reported to the International Bone Marrow Transplant Registry (IBMTR).[24] The 3-year-rates for OS, disease free survival (DFS), and the probability of relapse were 21%, 15%, and 65%, respectively. The major problems after transplantation were persistent/recurrent disease or respiratory complications which accounted for 35% and 51% of deaths. A case-matched analysis including 45 allografts and 45 autografts reported to the European Group for Blood and Marrow Transplantation (EBMT) was performed by Milpied and co-workers.[25] They did not find significant differences in actuarial probabilities of OS, PFS, and relapse rates between allo-SCT and ASCT (25%, 15%, 61% vs. 37%, 24%, 61%, respectively). The actuarial TRM at 4 years was significantly higher for allografts than for autografts (48% vs. 27%, p=0.04). Acute GvHD ≥ grade II was associated with a significantly lower risk of relapse but also with a lower survival rate.

A number of reports confirmed the registry data: allo-SCT resulted in lower relapse rates but significantly higher toxicity with no improvement over HDT/ASCT

when PFS or OS were considered.[26-29] Although the poor results after myeloablative conditioning could at least partly be explained by the very poor-risk features of many individuals included in these early studies, the high procedure-related morbidity and mortality prevented the widespread use of allo-SCT. No major studies on allo-SCT after myeloablative conditioning have been published in the past decade.

Reduced-intensity conditioning and allo-SCT in Hodgkin's lymphoma

The largest cohort of patients treated with RIC/allo-SCT in HL was recently reported by the EBMT Lymphoma Working Party[30] and included 374 patients from 153 centres. Median age at transplantation was 31 years and 55% of patients were male. Patients had undergone a median of four lines of prior therapy, 77% of patients had failed HDT/ASCT. At the time of allo-SCT, 21% of patients were in CR, 39% had chemosensitive disease, and 40% had chemoresistant disease or untested relapse. Two hundred and thirty-four patients (63%) were allografted from a matched sibling donor, 112 (30%) from a matched unrelated donor (MUD), and 28 from a mismatched donor (7%). Grade II-IV acute GvHD (aGVHD) was reported in 27% of patients, chronic GvHD (cGVHD) in 42% of patients at risk. With a median follow-up of 25 months, 186 patients (50%) remained alive. The 100-day TRM was 12% but increased to 21% at one, and 23% at three years. It was significantly worse for patients with poor performance status and chemoresistant disease at transplantation. At 1, 3, and 5 years following transplantation, 39%, 48%, and 60% of patients had experienced relapse or progression of their disease. OS at 2 years after transplantation was 40%, PFS was 29% and significantly worse for patients with chemoresistant disease ($p< 0.001$) (Figure 2A-D). The development of chronic GVHD was associated with a higher TRM and a trend to lower relapse rate but had no impact on PFS or OS. In a landmark analysis the development of either acute or chronic GVHD within 9 months post transplant was associated with a significantly lower relapse rate (RR 1.8; CI 1.0-3.4) The MD Anderson Cancer Center (MDACC) recently updated their experience[31] on 40 patients allografted after fludarabine-based conditioning regimens (fludarabine/cyclophosphamide, n=14 or fludara-

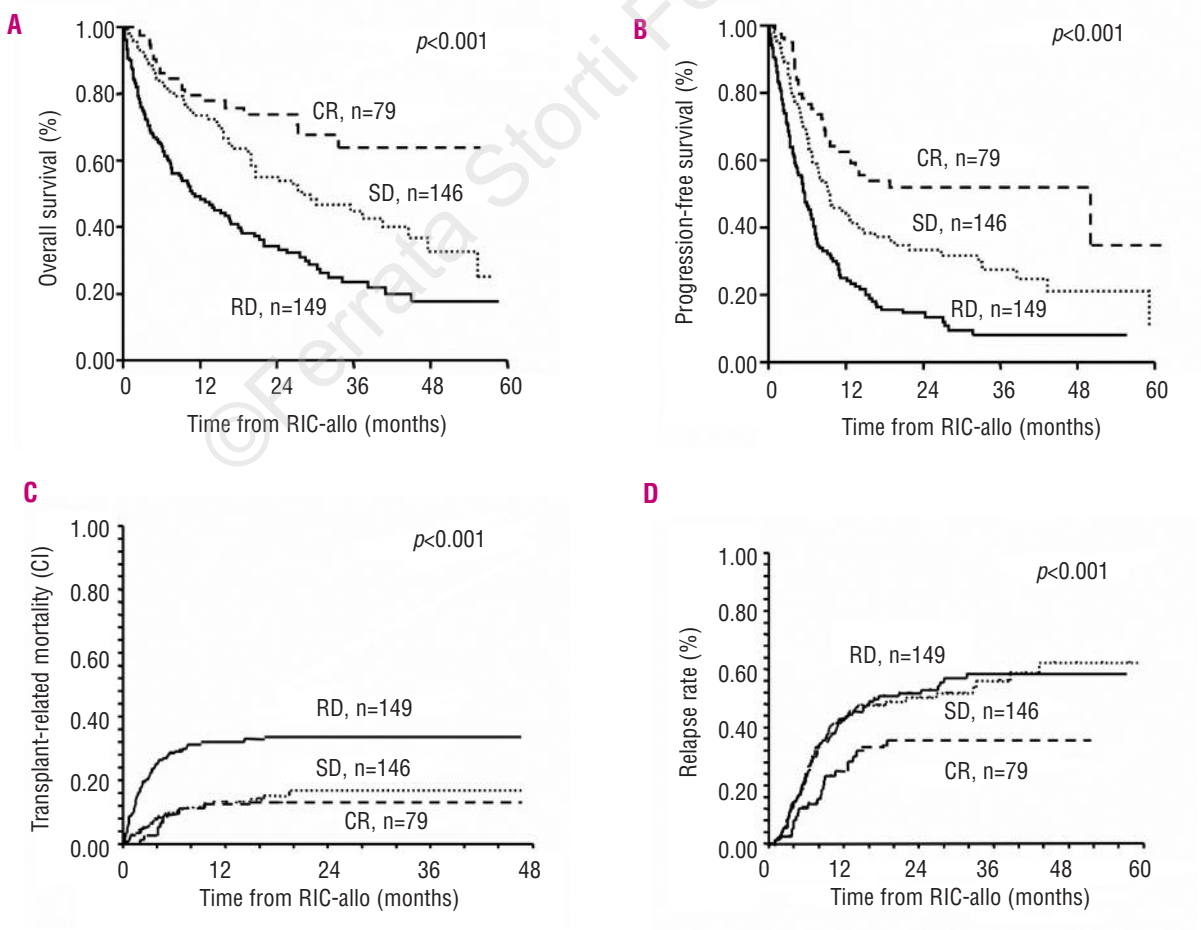

Figure 2. Reduced intensity allogeneic stem cell transplantation for relapsed or refractory Hodgkin's lymphoma. Results from the EBMT Lymphoma Working Party. Impact of chemosensitivity before transplantation on overall survival (A), progression free survival (B) transplant related mortality (C), and relapse rate (D) (with permission).

bine/melphalan, n=26) from HLA-identical siblings (n=20) or matched unrelated donors (MUDs) (n=20). The median age was 31 years. The median number of chemotherapy regimens received prior to allo-SCT was five. Thirty patients (75%) had received both radiotherapy (RT) and ASCT prior to allo-SCT. Disease status at transplantation was refractory (n=14) or sensitive relapse (n=26). Day 100 and 18-month TRM were 5% and 22%, respectively, for the whole group. The cumulative incidences of grade II-IV aGvHD and cGvHD were 38% and 69%, respectively. There was a trend for a lower relapse rate in patients developing acute or chronic GvHD. However, this was not statistically significant. Twenty-four patients (60%) were alive (14 patients in complete remission) with a median follow-up of 13 months. Patients conditioned with fludarabine and melphalan had a better OS (73% vs. 39%, p=0.03) and showed a trend towards better PFS (37% vs. 21%, p=0.2) compared to those receiving fludarabine and cyclophosphamide.

Forty patients with relapsed or refractory HL treated with the combination of fludarabine (150 mg/m^2) and melphalan (140 mg/m^2) have been presented by the Spanish group.[32] Twenty-one patients (53%) had received >2 lines of chemotherapy, 23 patients (58%) had been irradiated, and 29 patients (73%) had failed a previous ASCT. Twenty patients were allografted in resistant relapse, 38 patients received hematopoietic cells from an HLA identical sibling. One-year TRM was 25%. Acute GvHD developed in 18 patients (45%) and cGvHD in 17 (45%) out of the 31 evaluable patients. Extensive cGvHD was associated with a trend to a lower relapse rate (71% vs. 44% at 24 months, p=0.07). The response rate three months after RIC/allo-SCT was 67%. Eleven patients received donor lymphocyte infusions (DLIs) for relapse or persistent disease. Six patients (54%) responded (3 CR, 3 PR). OS and PFS were 48% and 32% at 2 years, respectively. Refractoriness to salvage chemotherapy was the only adverse prognostic factor for both OS and PFS. For patients who had failed an autograft, results were surprisingly good if relapse had occurred >12 months after ASCT. The respective 2-year OS and PFS were 75% and 70%. Investigators from Seattle reported their results for 27 HL patients with a median age of 37 years.[33] Eighteen patients had a matched related donor and 9 an unrelated donor. The patients had received 2 Gy total body irradiation (TBI) alone (n=7) or in combination with fludarabine (90 mg/m^2). Immunosuppression consisted of MMF and CsA. All patients were heavily pretreated with a median of five prior regimens administered. Twenty-four patients had failed a previous ASCT. Prior to RIC 5 patients were in CR, 11 in PR, 4 had relapsed disease, and 7 had refractory disease. The overall incidence of grade II, III, and IV aGvHD was 33%, 15%, and 4%, respectively. The incidence of extensive cGvHD was

Table 1. Clinical characteristics of patients with relapsed or refractory Hodgkin's lymphoma treated with reduced intensity conditioning prior to allogeneic stem cell transplantation.

	Burroughs et al., BBMT 2004	*Anderlini et al., BMT 2005*	*Peggs et al., Lancet 2005*	*Alvarez et al., BBMT 2006*
No. of patients	27	40	49	40
Sex (M:F)	–	–	25 / 24	24/16
Age: median (range) in years	37 (21-65)	31 (18-58)	32	31 (16-53)
previous lines of CT:median (range)	5 (2-9)	5 (2-9)	5 (3 - 8)	4 (2-6)
Prior RT (%)	25 (92)	30 (75)	–	23 (58)
Prior ASCT (%)	24 (89)	30 (75)	44 (89)	29 (73)
Dx to RIC-allo [median (range)] in mos.	–	23 (9-145)	58 (7 - 178)	37 (11-300)
ASCT to RIC-allo [median (range)] in mos.	16 (2-78)	–	–	17 (4-146)
Disease status at allo-RIC (sensitive/refractory)	20/7	26/14	36/13	20/20
Type of donor (Rel / UD)	18/9	20/20	31/18	38/2

M: male; F: female; CT: chemotherapy; RT: radiotherapy; ASCT: autologous stem cell transplantation; Dx: diagnosis; RIC-allo: reduced intensity allogeneic stem cell transplantation; Rel: related donor; UD: unrelated donor.

Table 2. Clinical outcome after reduced intensity conditioning and allogeneic stem cell transplantation in relapsed Hodgkin's lymphoma.

	Burroughs et al., BBMT 2004	*Anderlini et al., BMT 2005*	*Peggs et al., Lancet 2005*	*Alvarez et al., BBMT 2006*
AGVHD (grades II-IV)	47% (MSD)/55% (UD)	38%	16%	45%
cGVHD	50% (MSD)/60% (UD)	69%	14%	45%
100-day TRM	7%	5%	4.1%	12%
1-year TRM	35%	22% (18 mos.)	16% (2-year)	25%
PFS	11% (MSD)/35% (UD) (1-year)	55% (18 mos.)	32% (4-year)	32% (2-year)
OS	39% (MSD)/75% (UD) (1-year)	32% (18 mos.)	56% (4-year)	48% (2-year)
RR	–	55% (18 mos.)	43%	–

aGvHD: acute graft versus host disease; cGvHD: chronic graft versus host disease; TRM: transplant related mortality; PFS: progression-free survival; OS: overall survival; RR: relapse rate; MSD: matched sibling donors; UD: unrelated donors.

55% at 1 year. Day 100 and 1 year TRM were 7% and 35%, respectively. One year OS, PFS and relapse incidence were 51%, 18% and 47%, respectively. A recent update on 35 patients reported a 3-year OS of 35% and PFS of only 8%.[34] Peggs *et al.* explored the effects of *in vivo* T-cell depletion with alemtuzumab followed by fludarabine (150 mg/m^2) and melphalan (140 mg/m^2) in multiply relapsed patients. Ninety percent of patients had failed a previous autograft.[35] At transplant, 8 patients were in CR, 25 patients were in PR, one patient was in untested relapse, and 15 patients had refractory disease. Thirty-one patients were allografted from a matched related and 18 from unrelated donors. All patients engrafted, grade II-IV aGvHD occurred in 16% of patients, 14% developed cGvHD. Nineteen patients received DLIs for progression (n=16) or mixed chimerism (n=3). Nine patients (56%) showed a response (8 complete, one partial) which was significantly associated with acute and/or extensive cGvHD. Non-relapse mortality was 16% at 730 days (7% for patients who had related donors and 34% for those with unrelated donors, p=0.02). Projected 4-year OS and PFS were 56% and 39%, respectively. Clinical characteristics and outcome of these studies are summarized in Tables 1 and 2. No definitive information is available with respect to the best conditioning protocol or the impact of *in vivo* T-cell depletion. Results from a retrospective comparison of 67 patients with HL undergoing RIC/allo-SCT from sibling donors included in 2 prospective studies seem to indicate that the addition of alemtuzumab to RIC significantly reduces GvHD without showing a negative impact on relapse following allo-SCT (manuscript submitted).

Comparison of myeloablative and reduced-intensity conditioning in Hodgkin's lymphoma

The EBMT Working Party Lymphoma performed the only analysis reported so far which compares outcomes after reduced-intensity or myeloablative conditioning and allo-SCT in patients with lymphoma.[36] Ninety-seven patients with HL were allografted after RIC and 93 patients were allografted after a conventional preparative regimen. Age and disease characteristics at diagnosis and disease status at transplantation were similar in both

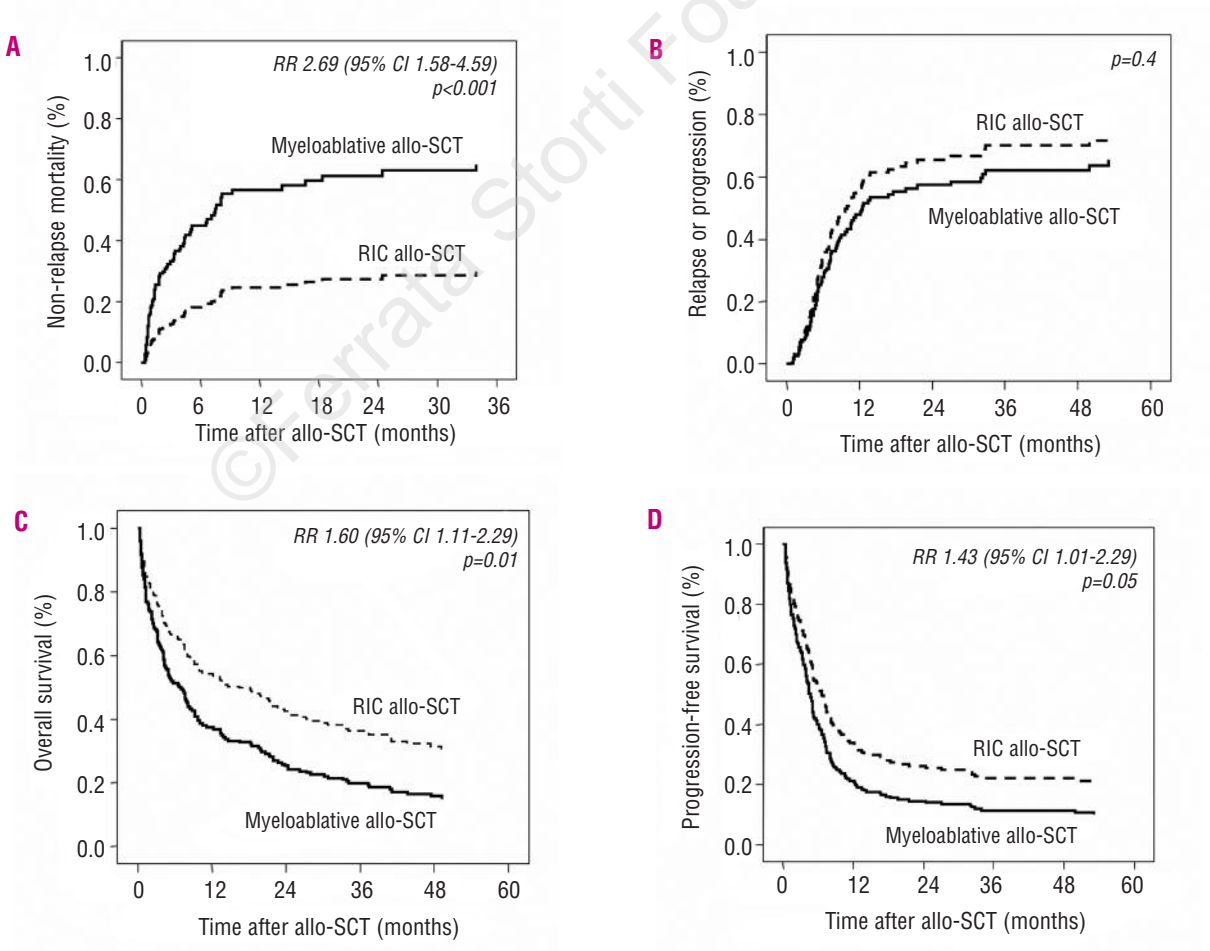

Figure 3. Comparison of outcomes between reduced intensity allogeneic stem cell transplantation and conventional allogeneic stem cell transplantation in patients with relapsed or refractory Hodgkin's lymphoma. A retrospective analysis of the Lymphoma working Party of the EBMT (with permission).

groups of patients. However, a previous ASCT was more frequent in the RIC group (61% vs. 44%, $p<0.03$) as was the use of peripheral blood stem cells (85% vs. 60%, $p<0.001$). After a median follow-up of 53 months OS was significantly better in patients after RIC compared with classical conditioning (OS at 3 years 34% vs. 22%, $p=0.01$) while PFS did not differ (17% vs. 19%, $p=0.3$). The use of myeloablative conditioning (RR 1.6, $p=0.005$), a donor other than an HLA-identical sibling or a MUD (RR 1.8, $p=0.01$), a previously failed ASCT (RR 1.5, $p=0.02$), and refractory disease at transplantation (RR 1.7, $p=0.003$) were independent risk factors for OS. Non-relapse mortality at 3 months and one year, respectively, was 32% and 52% in the standard group, compared with 15% and 27% in the RIC group ($p=0.001$), with classical conditioning and refractory disease being significant risk factors in the multivariate analysis. Disease progression and the incidences of acute or cGvHD were not significantly different. Main results are summarized in Figure 3A-D.

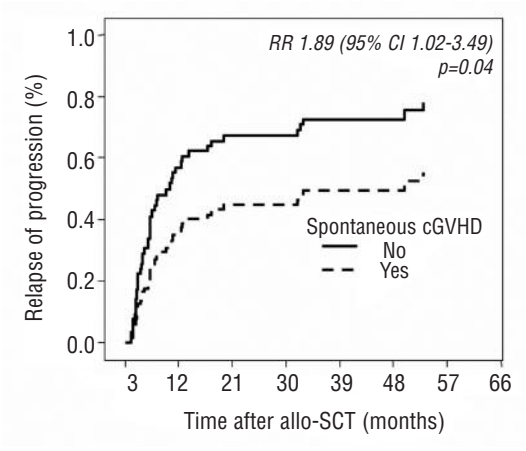

Figure 4. Comparison of relapse rates after reduced intensity allogeneic stem cell transplantation in patients developing or not developing cGvHD (*with permission of EBMT*).

Graft-versus-Hodgkin's effect

Relapse rates remain much too high after both myeloablative or reduced-intensity conditioning and allo-SCT but seem lower than after ASCT in most series. Patients with HL developing overt acute and/or cGvHD were reported to show lower relapse rates than patients without GvHD in most but not all series (Figure 4). Evidence of a graft-vs.-HL effect should also come from data showing that HL patients relapsing after RIC/allo-SCT respond to DLIs. In most smaller series, 30-50% of patients were reported to achieve a complete or partial remission after DLI[31,32,35,37] but follow-up was short and a significant proportion of patients had received chemotherapy prior to DLI. A retrospective analysis performed by the EBMT[30] reported on 85 patients who received DLI for treatment of persistent or progressive disease (n=71), mixed chimerism, or as part of a pre-emptive strategy to prevent relapse (n=14). Half of the patients had received a T-cell depleted graft, 33% of patients achieved a CR or PR, 8% had a brief response, and 8% had stable disease at last assessment. These and other data suggest that a graft-vs-HL effect does exist, particularly in patients who were exposed to in vivo T-cell depletion.[35] Recent data from Seattle, however, show that the relapse rates after minimal conditioning with 2 Gy TBI with or without fludarabine in patients with HL were especially high and it therefore seems unwise to rely exclusively on the GvHL effect.[34]

Indications for allo-SCT in Hodgkin's lymphoma

Allo-SCT remains an experimental modality to treat relapsed or refractory HL. The recent EBMT data suggests using some form of RIC in most cases because the significant decrease in TRM also resulted in better OS. The optimal conditioning regimen, however, remains controversial although minimal conditioning with regimens using 2 Gy of TBI (with or without fludarabine) seem less advisable and more intense conditioning may be necessary to improve results.[34] Given this, allo-SCT in patients with HL should only be performed within prospective clinical trials such as the HD-R Allo trial currently run by the Working Party Lymphoma of the EBMT (*www.EBMT.org*). Patients refractory to first-line therapy, patients in early first relapse with additional poor prognostic features, patients with multiple relapses, and those who failed a prior ASCT are all eligible for this trial.

Indolent lymphoma

Studies on indolent B-cell lymphoma usually include follicular lymphoma (FL), marginal zone lymphoma (MZL) including mucosa-associated lymphoid tissue lymphoma (MALT lymphoma), and lymphoplasmocytic lymphoma (LPL, formerly immunocytoma).[38] Since the WHO classification became effective only recently and histologic subtyping was not carried out or was not reported for the majority of published series on allo-SCT, separate analyses for most sub-entities are impossible. As FL comprises more than 80% of the indolent lymphomas, the terms FL, indolent lymphoma, and low grade lymphoma will be used largely synonymously. Waldenström's macroglobulinemia will be considered separately because some encouraging data on allo-SCT in this frequently chemoresistant disease are available. Chronic lymphocytic leukemia (CLL) and its aleukemic variant small lymphocytic lymphoma (SLL) may also be regarded as indolent B-cell lymphoma. With respect to allogeneic transplantation, however, CLL seems to behave differently from other indolent lymphomas and results have always been reported separately. Therefore, we decided not to include CLL in this manuscript.

Most investigators agree that only FL patients with symptomatic disease should be treated immediately. Various chemotherapy programs in combination with

Table 3. Selected studies on allogeneic SCT after reduced-intensity conditioning in follicular lymphoma.

	EBMT[53]	*Houston*[54]	*UK Collab. Group*[55]	*Nottingham*[56]	*Milan*[57]	*Seattle*[58]
Design	registry analysis	single center	multicenter	multicenter	multicenter	single center
n	52*	47	41*	28*	53*	45
TCD†	in part	no	yes	yes	no	no
RIC regimen	various	Flu/CY +/- CD20	Flu/Mel	BEAM	Flu/CY/TT	FLU/TBI2
TRM	31% (2 yrs.)	11% (2 yrs.)	11% (3 yrs.)	16% (2 yrs.)	18% (3yrs.)	34%
Survival	65% (2 yrs.)	88% (2 yrs.)	73% (3 yrs.)	74% (2 yrs.)	66% (3yrs.)	100% (2yrs.)
Relapse rate	21% (2 yrs.)	3% (2 yrs.)	44% (5 yrs.)	10% (2 yrs.)	n.r.	15% (2yrs.)
Late relapses (> 2 yrs.)	0	0	3	0	0	n.a.
Follow-up (mos.)	9	34 (3-72)	36 (18-60)	17 (1-67)	31 (6-70)	24 (2-45)

**"low-grade" lymphoma; †in-vivo alemtuzumab; BEAM: carmustine, etoposide, ara-C, melphalan; CD20: rituximab; CY: cyclophosphamide; Flu: fludarabine; Mel: melphalan; n.r.: not reported; SLL: small lymphocytic lymphoma; TBI2: total body irradiation 2Gy; TCD: T cell depletion; TRM: transplant-related mortality; TT: thiotepa.*

rituximab have recently been recommended for first-line therapy.[39-41] There is no general agreement which chemotherapy is best and whether HDT/ASCT should be part of first-line therapy. Maintenance therapy with rituximab seems to further improve outcome.[42,43] For patients with relapsed disease, a number of alternative drugs usually administered in combination with rituximab have been recommended.[44] Experience with allo-SCT concentrates on patients with multiply relapsed disease many of whom failed a previous autograft.

Myeloablative conditioning and allo-SCT in indolent lymphoma

Up to the late 1990s, only a few younger patients with advanced or refractory FL had undergone allo-SCT. These transplants had been performed after myeloablative conditioning, mainly TBI and high-dose cyclophosphamide. Results of classical allo-SCT in FL as in other lymphomas showed excessive transplant-related mortality (TRM) which in some series surpassed 40%.[45-48] In 2003, both the EBMT and the IBMTR/ABMT registries published large series comparing allogeneic transplantation after myeloablative conditioning to ASCT in follicular (low grade) lymphoma.[29,49] The EBMT reported on 231 patients (median age 42 years) who had received a transplant mostly from an HLA-identical sibling donor (84%). Twenty percent of patients were in first or later CR, 60% had chemosensitive disease, and 20% had chemoresistant disease at the time of transplantation. The actuarial OS at 4 years was 51%, the actuarial procedure-related mortality was 38%. Multivariate analysis showed that only the disease status at transplant and age significantly influenced OS and relapse rate. No formal analysis with respect to a correlation of GvHD and GvL was possible because detailed data on GvHD were missing. The plateau seen in the survival curves after allo-SCT for patients with low-grade NHL, however, suggested the existence of a graft-vs.-lymphoma effect which prevented the late relapses regularly seen after HDT/ASCT. The study from IBMTR compared outcomes in 176 patients with FL who had undergone allo-SCT from an HLA-identical sibling after myeloablative conditioning with 728 patients who had received ASCT using purged or unpurged grafts. Similar to the EBMT report, better disease control after allo-SCT was offset by its high TRM (30% at 5 years) resulting in an actuarial OS of 51% at 5 years. Again, the lack of late recurrences in the allogeneic group (only 2% beyond 1 year) suggested the existence of a GvL effect and a potential for cure after allo-SCT. Similar observations were made in single center or registry studies.[50-52] The recent study from Japan reported on 38 patients with indolent lymphoma (37 patients had FL) and reported a 2-year OS of 57% with no relapses seen beyond 2 years after transplantation.

Allo-SCT after reduced-intensity conditioning in indolent lymphoma

The results of major series reported so far are summarized in Table 3.[53-58] The early retrospective analysis from EBMT which reported on RIC followed by allo-SCT in different lymphoma subtypes showed favorable results in indolent lymphoma.[54] Progression rates for 52 patients with low grade NHL most of whom had received fludarabine-containing RIC or BEAM ± alemtuzumab were surprisingly low (~20%) and resulted in OS of 65% at 2 years while TRM at 2 years still exceeded 30% and remained unsatisfactory. A recent survey on RIC/allo-SCT from Japan[59] reported on 45 patients and confirmed the excellent results in low grade NHL. OS was 79%, PFS at 3 years was 83% for patients with sensitive disease and still 64% for patients with refractory disease. A total of 9 patients had died at the time of publication, 8 patients (18%) from transplant-related causes (mostly GvHD and infection).

Reports from the MDACC[54] as well as the prospective British studies[55,56] which both used alemtuzumab for *in vivo* T-cell depletion suggested that RIC might be able to clearly reduce the toxicity of allo-SCT, as 3-year TRM for low-grade lymphoma patients was 10%, 11%, and 16%, respectively, in these trials. All three reports confirmed the favorable OS and PFS after RIC/allo-SCT. In the BEAM trial,[59] however, TRM was high for patients who had previously undergone HDT/ASCT. An adverse effect of prior ASCT on TRM was also observed in patients

older than 55 years who had been allografted after RIC consisting of fludarabine, cyclophosphamide, and thiotepa.[57]

Given that there is no difference between sibling and MUD transplants in related diseases such as CLL,[60] the therapeutic potential of MUD transplants should be at least equivalent to that of family transplants also in FL. This assumption is supported by a recent EBMT analysis. Avivi et al. reported on 125 patients with FL and found that RIC significantly reduced TRM and improved PFS (60% vs. 39%) and OS (61% vs. 44%) if compared to myeloablative conditioning.[61]

Allo-SCT in Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM) is a rare B-cell neoplasia characterized by proliferation of IgM-producing plasmacytic lymphocytes. Though generally indolent, the course of the disease can also be aggressive with a median overall survival of less than 5 years.[62] Conventional therapy based on alkylating agents, purine analogues, and antibodies can achieve temporary remissions,[63] but curative treatment is not available. HDT/ASCT has been studied in WM and suggests that this approach is effective but not curative.[64-67] Only six cases of allo-SCT for WM had been reported until 2003, when data became available from the Société Francaise de Greffe de Moelle.[67] Ten patients had undergone allo-SCT, 9 of them after myeloablative conditioning. Outcome was excellent for patients with chemo-sensitive disease with a 4-year PFS rate of more than 80%, whilst refractory patients had a poor outcome. TRM was 40%, but 3 out of 4 patients dying from treatment-related causes also showed disease progression prior to death. Recently, the CIBMTR reported a registry analysis on 26 patients with WM who had been allografted after myeloablative (81%) or non-myeloablative conditioning (19%) from matched related (85%) or unrelated donors (15%). The vast majority of patients (67%) had refractory or uncontrolled disease at transplant. TRM was high with 40%, and the 3-year relapse rate was similar to that of 10 autologous patients analyzed in parallel (29% vs. 24%), translating into 3-year PFS and OS after allo-SCT of 31% and 46%, respectively.[65] Recently, Kyriakou *et al.* studied 106 patients with WM who received an allo-SCT and were reported to EBMT. Median age at transplantation was 49 years, patients had failed a median of 3 previous treatment lines. Nineteen patients (18%) had failed an autograft. At Allo-SCT, 10 patients (10%) were in CR≤2, 35 (33%) in PR1, 29 (27%) in PR≥2 and 32 (30%) had relapsed or refractory disease. Seventy-nine patients (74%) were allografted from an HLA-identical sibling donor, 18 (17%) from a MUD and 9 from other donors. Conventional conditioning protocols (CT) were used in 44 (41%) patients and reduced intensity conditioning (RIC) regimens in 62 (59%) patients. The incidence of relapse at 3 years was 12% after CT and 25% after RIC. Thirty-five patients died, 5 from disease progression and 30 from non-relapse mortality, with an incidence of NRM of 33% after CT and 30% after RIC at 3 years. PFS rates were 54% after CT and 44% after RIC at 3 years, OS was 59% after CT and 66% after RIC.

Graft-vs-lymphoma effect in indolent lymphoma

All major studies referred to above indicate that a strong graft-vs.-FL effect does exist. Compared to other lymphoma entities, the relapse rates after RIC/allo-SCT have been particularly low, suggesting that slowly progressing disorders like FL may be most receptive to the immunologic effects of expanding allogeneic T-cells. A comparison of the results of allogeneic and autologous

Table 4. Myeloablative conditioning and allogeneic transplantation in aggressive lymphoma.

	Kim[50]	*Dhedin*[87]	*Doocey*[88]	*Juckett*[89]	*Glass*[90]
Patient number (aggressive histologies)	233 (111) median age 31 years	73 (73) median age 35 years	44 (44) median age 40 years	37 (21) median age 30 years	32 (32)
Aggressive histology	DLBCL (n=44), PTCLu (n=22), NK/T (n=19), ALCL (n=7), MCL (n=5), other (n=14)	WF D-H (n=57) incl. 9 pts with T-NHL, ALCL Ki-1 pos. (n=13), other (n=3)	DLBCL (n=23), transformed (n=16), PTCL (n=5)	WF E-J	DLBCL (n=14), FL grade 3 (n=3), blastic MCL (n=3), PTCL (n=7), HD (n=5)
Refractory disease	45%	37%	20%	29%	59%
Conditioning/ GVHD-Prophylaxis	BI/CY/± ETO, Tother CsA/MTX	Myeloablative cond. (mostly TBI-based) CsA / MTX, ex-vivo TCD in 8 patients	TBI / CY ± ETO CsA / MTX	TBI / CY / Ara-C / PRED CsA + ex-vivo TCD	Fludarabine, Busulfan (12mg/kg), Cy (120mg/kg) CsA / Tacrolimus + MMF
Outcome (for aggressive histologies only)	TRM 42%, OS 42% at 2 years	TRM 44%, OS 41% at 5 years, PFS 40% at 5 years	TRM 25% at 1 year, OS 48%, EFS 43% at 5 years	TRM 43%, OS 29% at 39 months, PFS 33% at 5 years	TRM 37% at 1year, OS 44% at 2 years, PFS 39% at 2 years

transplantation gave remarkable differences in relapse rates (mostly >30% in favor of allo-SCT).[29,49] Compelling evidence highlighting the capacity of donor T-cells to control FL comes from the results of DLIs reported in this entity. Four out of 7 patients with low grade NHL reported by Morris *et al*. responded,[55] 8 out of 13 patients from 16 centers in the UK[67] showed complete responses and 2 additional patients receiving pre-emptive DLIs remained in CR. The most recent report from Nottingham reported 3 out of 4 complete responses after DLIs for FL.[68]

Indications for allo-SCT in indolent lymphoma

Given the indolent course of most FL and the availability of new treatment options such as, for example, bendamustine,[69] rituximab[39-41] and radiolabeled antibodies[70] to name just a few, it becomes clear that allo-SCT should be reserved for patients with poor-risk features. As prognostic factors based on the biology of FL are not yet available,[71] the prognosis of FL is best evaluated by the Follicular Lymphoma International Prognostic Index (FLIPI).[72] Since the course of FL may be highly variable even within the FLIPI high-risk group, and less toxic treatment options including ABMT[73] exist, upfront allo-SCT is not indicated. Allo-SCT should be seriously considered, however, in patients who are refractory to first-line therapy or failed at least two lines of standard treatment, such as immunochemotherapy (rituximab plus CHOP or other multi-agent chemotherapy) and an autograft. The low TRM rates reported suggest using RIC prior to allo-SCT and it may be worthwhile studying RIC/allo-SCT earlier in the course of disease in younger patients. As in other lymphoma subtypes, prospective studies addressing specific procedural questions as well as comparing RIC/allo-SCT to other modalities need to be performed.

Aggressive lymphoma

The following histologic sub-entities are considered to show a clinically aggressive behavior: follicular lymphoma grade III, diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, Burkitt-like lymphoma (B-cell lymphomas), mantle cell lymphoma, and all subtypes of mature T-cell lymphomas.[38] The German High-Grade Lymphoma Study Group also includes primary effusion lymphoma, intravasal B-cell lymphoma and aggressive marginal zone lymphoma in their studies. Other study groups or centers may use other in/exclusion criteria which can make comparison of results difficult. First-line treatment for younger patients with aggressive lymphoma typically consists of 6-8 courses of R-CHOP or CHOP-like regimens given every 2 or 3 weeks.[74-77] While close to 100% of patients with DLBCL and IPI 0-1 survive long-term after such therapy,[76] patients with other histologic subtypes or higher IPI have less favorable outcomes. Younger high-risk patients (age-adjusted IPI 2-3) often receive HDT/ASCT,[78-82] increasingly in combination with rituximab.[83,84] Patients relapsing after or resistant to first-line therapy have a very poor prognosis especially if the relapse occurs early (<12 months) after primary therapy.[85,86] These patients along with those failing multiple treatment modalities, including an autograft, are candidates for allo-SCT.

Myeloablative conditioning and allo-SCT in aggressive lymphoma

Table 5. Reduced-intensity conditioning and allogeneic transplantation in aggressive lymphoma

	Robinson[53]	*Kusumi*[59]	*Morris*[55]	*Spitzer*[112]	*Corradini*[96]
Patient number (aggressive histologies)	188 (62) median age 43 yrs	112 (58) median age 50 yrs	37 (37) median age 48 yrs	20	17 41 yrs
Aggressive histology	DLBCL, ALCL, LBL, PTCL, other	DLBCL (n=27), transformed (n=4), PTCL (n=11), Mantle cell (n=8), NK (n=4), ALC (n=4)	DLBCL (n=22), transformed (n=11), PTCL (n=4)	DLBCL (n=20)	PTCL (n=17)
Refractory disease	21%	43%	22%	85%	12%
Conditioning/GVHD -Prophylaxis	various fludarabine-based RIC in-vivo TCD in approx. 50% of patients* + CsA ± MTX	FLU + BUS (CY, MEL) in most cases *in vivo* TCD (ATG) in 13% of cases, CsA + MTX or CsA alone in most cases	FLU + MEL alemtuzumab + CsA	Reduced intensity cond. in-vivo TCD (ATG, anti-CD2) + CsA	FLU + TT CsA + MTX
Outcome (for aggressive histologies only) months	TRM 37% at 2 yrs, OS 47% at 2 yrs, PFS 13% at 2 yrs EFS 64% at 3 yrs	TRM 33%, OS 48% at 3 yrs, PFS 56% for sensitive disease, 30% for refractory dis. at 3 yrs	TRM 38% at 3 yrs, OS 34% at 3 yrs,	TRM 0% d100, OS: NA, EFS 34% at 3 yrs	TRM 6% at 2 yrs, OS 81% at 3 yrs, EFS 25% at 13-52

A recent EBMT survey compared allo-SCT with HDT/ASCT: 255 high-grade NHL patients (median age: 27 years) showed an OS of 41% at 4 years and disease recurrences were rare after the first year post-transplant. About one third of patients died of TRM. The relapse rate was lower after allo-SCT than after ASCT. Data regarding the role of acute and chronic GvHD in decreasing the relapse incidence were inconclusive.[29]

Other studies with more than 30 patients who underwent myeloablative conditioning and allogeneic transplantation for aggressive lymphomas are summarized in Table 4.[59,87-90] A recent publication from Japan[50] included 111 patients with DLBCL (n=44), PTCLu (n=22), extranodal NK /T-cell lymphoma (n=19), ALCL (n=7), and mantle-cell lymphoma (n=5). Eighty-three percent of patients had received a TBI-containing conditioning regimen and GvHD-prophylaxis consisted of CsA and MTX in 88% of patients. Approximately 20% of patients had a MUD, two-thirds were transplanted from an HLA-identical sibling. Grade II to IV acute GvHD occurred in 39% of patients, 42% of patients died of TRM. The major causes of death were infection, interstitial pneumonitis, GvHD, VOD, and heart failure. OS at 2 years was 42% with no obvious differences for patients with DLBCL, NK-/T-cell lymphoma or any other subtype except for PTCL patients who showed an OS of approximately 70% at 5 years. However, since numbers were low, differences were not significant. The multivariate analysis on risk factors for OS performed by Kim *et al*. showed that chemoresistant disease, a prior autograft, and prior RT were significant adverse prognostic factors. The other smaller studies summarized in Table 4 mostly support the Japanese data. Ratanatharathorn *et al*. performed a prospective comparative trial which included 31 patients who received an allograft after preparation mostly with 12 Gy TBI and cyclophosphamide (1.8 g/m^2 × 4 days) and 35 patients who received a purged autograft after the same myeloablative conditioning.[91] Priority for allogeneic BMT was given to patients aged ≥55 years who had a compatible sibling donor. The vast majority of study patients suffered from intermediate or high grade NHL (52/66 patients). The probability of disease progression was 69% in the ASCT and 20% in the allo-SCT group (p=0.001). Probably because of low patient numbers, there was no significant difference in PFS (p=0.21) although the absolute difference in PFS was more than 20% (although with wide confidence intervals) after a median follow-up of 14 months (47% after allo-SCT, 24% after ASCT). TRM was significantly higher after allo-SCT (12 non-lymphoma deaths after allo-SCT, four after ASCT).

Reduced-intensity conditioning and allo-SCT in aggressive lymphoma

RIC has also been used in aggressive lymphoma. Most series suffer from low patient numbers, heterogeneous patient characteristics, differing conditioning protocols and GvHD prophylaxis, and short follow-up. The largest studies are summarized in Table 5. The EBMT study published in 2002 included 62 patients with high-grade histologies.[53] Twenty-one percent of patients had chemoresistant disease at the time of transplantation, conditioning consisted of fludarabine plus cyclophosphamide or melphalan, or the BEAM regimen in most cases. Unfortunately, the results for patients conditioned with or without alemtuzumab were not reported separately. This may partly explain the very high relapse rate of 79% at 2 years. TRM was no lower than after myeloablative conditioning (37% at two years). Therefore, PFS was as low as 13% at 2 years. Recently, the EBMT updated results in 118 patients with unrelated donors.[92] Patients suffered from diffuse large B-cell lymphoma, 52% were grafted after RIC. Two year NRM was significantly lower in patients submitted to RIC: 19% vs. 39%. Patients with chemosensitive disease undergoing RIC/allo-SCT had an improved PFS and OS (41% and 50%, respectively). PFS of patients transplanted with refractory disease remained poor (25% at 2 years). Therefore, while acceptable results are achieved for patients with sensitive disease, results in refractory patients remain poor. Kusumi *et al*.[59] reported on 58 patients with aggressive histologies who received RIC including *in vivo* T-cell depletion with ATG in approximately 10% of patients. Results were much better than in the EBMT series with PFS of 56% in chemo-sensitive and 30% in chemo-resistant disease at three years. Morris *et al*. reported on 37 patients with either primary aggressive or transformed lymphoma who received RIC (fludarabine, melphalan) and *in vivo* T-cell depletion with alemtuzumab. In these patients, both relapse rate (52% at three years) and TRM (38%) were high. As a result, PFS at three years was no better than 34%.[55] Relapse rates and TRM in patients with aggressive B-cell lymphomas seem high after myeloablative and non-myeloablative conditioning.

T-cell lymphomas

Ten to 15% of all lymphomas carry a T-cell phenotype. While immature T-cell lymphomas are treated on leukemia protocols, the mature, peripheral T-cell lymphomas are usually being treated with chemotherapy regimens typically used for DLBCL. Results of such treatment, however, are generally poor[93] and new strategies are undoubtedly needed. Among others, HDT/ASCT is increasingly used as part of first-line therapy.[94,95] Reports on allo-SCT in T-cell lymphoma have been encouraging.[96,97] The largest series by Corradini *et al*.[96] reported on 17 patients with a median age of 14 years, of whom 8 patients had failed an autograft. The estimated 3-year OS and PFS rates were 81% and 64%, respectively. TRM at 2 years was 6% and DLI induced a response in 2 patients progressing after allografting.

Wulf et al. reported on 10 patients with relapsed or primary progressive T-cell lymphoma.[97] Patients received salvage therapy consisting of alemtuzumab with or without chemotherapy and received RIC (fludarabine, busulfan, cyclophosphamide) followed by allo-SCT. With a median follow-up of seven months 7 patients remained alive, 6 in complete remission. Surprisingly good results were also reported by Kim *et al.*[50] and Kusumi *et al.*[59]

Mantle cell lymphoma

Few data are available on the results of myeloablative conditioning and allo-SCT for mantle cell lymphoma. The largest series from MDACC, EBMT, and Baltimore reported on 16, 22, and 19 patients with MCL, respectively.[98-100] OS was > 50% at 2 or 3 years and indicated a potential role for allo-SCT in this disease. The outcome of MCL patients reported in the early EBMT study on RIC/allo-SCT was disappointing.[53] Twenty-two patients showed an OS of 13% at 2 years. Both the progression rate (100% at 2 years!) and TRM (82% at 2 years) were devastatingly high. An update from the EBMT on 180 patients with MCL (median age 52 years, 2 lines of prior therapy, 78 patients had failed a previous autograft) was slightly more encouraging.[98] At transplant, 30 patients had been in CR, 97 patients presented with chemosensitive disease, and 27 patients had resistant disease. Conditioning was performed with fludarabine-based regimens in 50%, low-dose TBI in 29%, BEAM-Campath in 9%, and a variety of other RIC in 11% of patients. Thirty-four of the donors were unrelated. With a median follow-up of one year, the 1-yr and 5-yr OS was 54% and 31%, respectively. TRM was 13% and 32% at 100 days and 1 year, respectively. The relapse rate was 26% at 1 year, and 29% at 4 years. Patients with chemoresistant disease had a significantly higher relapse rate and worse OS than patients with chemosensitive disease. PFS was 19% for patients with resistant and 45% for patients with sensitive disease (p=0.007). Smaller, single center series show more encouraging results. The 10 patients transplanted by Morris *et al.*[55] showed an estimated actual PFS rate of 40% and TRM was 20% at 3 years. It may be possible to substantially improve results in mantle cell lymphoma by integrating rituximab into the conditioning or giving it as maintenance as originally proposed in the autologous setting. Khouri et al. treated 18 patients (16 with chemosensitive disease) with RIC.[101] Thirteen of these patients received conditioning with fludarabine, cyclophosphamide, and rituximab (375 mg/m^2 given on day -13; 1,000 mg/m^2 given on day -6, day +1, and day +8). The estimated 3-yr-OS rate and current PFS rate were 86% (CI 53-96%) and 82% (CI 65-99%), respectively. It remains to be seen if these extremely positive results will be confirmed by others and what may have been the role of high doses of rituximab given before and after the transplant. A recent study on HDT/ASCT emphasizes the important role of rituximab in mantle cell lymphoma, demonstrating a significant improvement in EFS when rituximab was added to the conditioning regimen.[102]

Graft-versus-lymphoma effect in aggressive histologies

While the existence of a GvL effect in indolent lymphoma is well established, it continues to be a matter of debate for patients with aggressive NHL. The high TRM seen in earlier series made the detection of any GvL effect difficult if not impossible. Nonetheless, relapse rates after allo-SCT have generally been lower than after ASCT.[29] There is no general agreement, however, as to whether this is the consequence of a GvL effect or merely reflects the transfer of a tumor-free graft as proposed by a study from IBMTR and EBMT which compared the outcomes of syngeneic, allogeneic, and autologous transplants for different lymphoma entities. For patients with intermediate and high grade NHL, progression rates after syngeneic and allogeneic transplantation were virtually identical while progression after autologous transplants was significantly higher.[103] High progression rates after RIC raised doubts about the existence of a clinically meaningful GvL effect, at least in patients with poor-risk features and chemoresistant disease. On the other hand, a relatively large study from Japan which reported the outcome of unrelated donor transplants showed a correlation of grades II-IV acute GvHD with a reduced probability of disease progression.[104] However, no specific analysis of patients with aggressive NHL is provided.

The only prospective study comparing allo-SCT with HDT/ASCT showed a significantly lower relapse rate after allo-SCT.[91] T-cell depletion of the graft has been shown to have a negative impact particularly on patients with aggressive lymphoma.[105,106] Both observations support the clinical importance of the GvL effect. Occasional responses (including complete responses) to DLI in patients with aggressive lymphoma have been reported.[107,108,55] Other investigators, however, failed to observe significant effects of DLI in this entity.[67] Altogether, some observations support the existence of a clinically relevant GvL effect in aggressive lymphoma while others do not. Certainly, successful tumor debulking prior to allo-SCT seems to be far more important in aggressive lymphomas than in other histologies. Patients with high tumor load do not seem to be suitable candidates for allo-SCT because the unfavorable effector (T-cell) to target (tumor) cell ratio in patients with these fast growing lymphomas obviously prevents the graft-versus-lymphoma effect to become clinically relevant. Results of allogeneic transplantation after RIC in patients with T-cell lymphomas are surprisingly good. These lymphomas seem especially receptive to the anti-tumor effects of donor T-cells. The low relapse rates and high rates of PFS reported[96,97] need confirmation in larger, prospective studies.

Indications for allo-SCT in aggressive lymphomas

A substantial fraction of patients with aggressive NHL and high-risk disease may achieve long lasting remissions after initial immunochemotherapy. Even after relapse, patients with aggressive lymphoma can be successfully treated with HDT/ASCT, which offered a 40% chance of long-term DFS in the pre-rituximab era. Allo-SCT may be considered in patients who i) relapse after previous HDT/ASCT; ii) relapse early (within 1 year) after primary therapy; or iii) present with primary refractory disease. The situation is different in patients with mantle cell or T-cell lymphoma where responses to conventional first-line therapy are less favorable and patients with refractory or relapsed disease are hardly cured by any salvage therapy including anti-B- or anti-T-cell antibodies. In these disorders early RIC/allo-SCT may be indicated. An international trial comparing HDT/ASCT with RIC/allo-SCT after brief conventional therapy for T-cell lymphomas will commence next year.

Conclusions

Allo-SCT for patients with lymphoma was first performed in the mid-1980s. The high TRM seen after myeloablative conditioning discouraged a broader interest in this approach and made further research difficult. The generally lower relapse rates after allo-SCT, the association of GvHD with reduced relapse rates, the increase of relapse rates after *ex vivo* or *in vivo* T-cell depletion, and the frequent responses to DLIs all support the existence of a graft-vs.-lymphoma effect. However, further data analysis supports the view that not all lymphomas are created equal. While slowly proliferating diseases like CLL and follicular lymphoma seem particularly sensitive targets for allogeneic T-cells, results of allo-SCT in aggressive B-cell lymphomas and HL have been less convincing. Patients carrying these latter diseases obviously need vigorous debulking of their tumor prior to conditioning to allow incoming donor T-cells to grow and mature before a highly unfavorable effector to target cell ratio prevents the development of a clinically meaningful graft-vs.-lymphoma effect. Reduced-intensity conditioning fueled a renaissance of allo-SCT as treatment of lymphoma because the lower TRM expected was highly attractive for a patient population where TRM after myeloablative conditioning had, in many instances, exceeded 50%. While TRM has decreased after RIC, relapse rates which frequently remain in the order of 50% are still far from satisfactory, and new strategies must be developed to tackle this problem. Among others, HDT/ASCT followed by RIC/allo-SCT[109] or the use of more disease-specific though less toxic preparatory regimens, including the use of naked[110] or radiolabeled antibodies,[111] may be helpful. Only prospective studies enrolling sufficient numbers of patients with distinct lymphoma subtypes will advance the field and answer those questions we need to address to help our patients survive.

Authors' contributions

All authors contributed equally to this paper.

Conflict of Interest

The authors reported no potential conflicts of interest.

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