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REVIEW

The role of allogeneic haematopoietic progenitor cell transplantation in patients with diffuse large B-cell non-Hodgkin lymphomas (DLBCL)

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Despite the undoubted improvement in the prognosis of patients with diffuse large B-cell lymphomas (DLBCLs) with the addition of rituximab in the front-line treatment, a significant proportion of patients still relapse. Salvage immune-chemotherapy followed by high-dose therapy with autologous haematopoietic cell transplantation (auto-HCT) remains the treatment of choice for such patients, especially in those who demonstrate chemosensitive disease. In recent years, allogeneic haematopoietic cell transplantation (allo-HCT) has increasingly been used for patients who are resistant to salvage treatment or relapse after an auto-HCT. Strategies using reduced intensity conditioning regimens have allowed application of this approach to a broader range of patients. PFS is up to 55% with a risk of relapse up to 80% depending on different studies. In multivariate analysis, several factors have been associated with favourable outcome including chemosensitivity of the disease, younger age and Karnofsky performance status at the time of the transplant being the strongest ones. DLIs have shown to induce durable responses in relapsed or progressed disease; however, its role remains controversial as the results are inferior to the responses seen in other haematological malignancies. More recently, the addition of MoAbs in the non-myeloablative conditioning regimens has shown encouraging results. In conclusion, allo-HCT is a feasible option in selective patients with chemosensitive DBCL, as it reduces the risk of relapse; however, this is achieved at the cost of significant non-relapse mortality.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin lymphoma (NHL) corresponding to 30–40% of cases in adults.[1] In the Western world, the incidence of DLBCL is ~7 cases per 100 000. Although classified as a single entity by the World Health Organization (WHO),[2] DLBCL is characterised by significant heterogeneity with variation in molecular pathogenesis, clinical behaviour, response to therapy and long-term survival. The median age of presentation is 64 years and thus more aggressive approaches to treatment may not be suitable for a proportion of patients.

At the present time, conventional chemotherapy with CHO(E)P–R (CY, doxorubicin, VCR, and prednisone, rituximab), is considered standard first-line treatment for the majority of patients with DLBCL. This can produce long-term remission in ~60% of patients.[3–5] For fit patients with DLBCL who either fail to achieve CR or relapse after initial treatment, the standard approach is salvage immune-chemotherapy followed by high-dose therapy with autologous haematopoietic progenitor cell transplantation (auto-HCT).[6] This approach is most effective in those with chemosensitive disease[7] and is associated with prolonged survival in ~40% of patients.[8,9] However, patients who relapse within 12 months of initial treatment with a rituximab-containing regimen and those who are resistant to salvage treatment or relapse after an auto-HCT have a poor prognosis with a median survival of less than a year.[10,11] Allogeneic haematopoietic progenitor cell transplantation (allo-HCT) increasingly has been used as salvage treatment for these patients. Potential advantages of allo-HCT are the use of a tumour-free graft and an immune-mediated graft versus lymphoma effect (GvL). Here, we review the published data surrounding allo-HCT in patients with DLBCL.

THE GRAFT VERSUS LYMPHOMA EFFECT

DLI

In indolent lymphomas, the reported lower relapse rates after allo-HCT than after auto-HCT,[12,13] and the high response rates after DLI in patients experiencing relapse after allo-HCT,[14,15] have been attributed to a GvL effect. In contrast, the efficacy of this phenomenon is less well described in patients with aggressive lymphomas such as DLBCL.

Although an earlier retrospective matched-pair analysis from the European Group for Blood and Bone Marrow Transplantation (EBMT) registry[12] reported that allo-HCT was associated with a lower relapse rate than auto-HCT suggesting evidence for a GvL effect in patients with aggressive lymphomas, this was not clearly demonstrated by two subsequent studies.[16,17] However, although

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neither of these studies demonstrated a significant difference in risk of relapse or disease progression between the transplant strategies, the allo-HCT recipients were more likely to have high-risk features such as higher stage, more prior chemotherapy regimens and resistant disease.[16,17] On the contrary, some other studies suggested a potential GVL effect, however, at a cost of greater non-relapse mortality (NRM) compared with the autologous setting.[18–20]

The data to suggest that DLI can facilitate response in relapsed DLBCL after allo-HCT is limited, with a small number of patients having been included in reported studies. In the study by Morris *et al.*,[21] only three of nine patients with high-grade NHL responded to DLI compared with 6 of 10 patients with low-grade NHL. Bishop *et al.*[22] reported the outcomes of 15 patients with DLBCL who were either not in CR or relapsed after allo-HCT. Eleven patients were treated with either withdrawal of immunosuppressive drugs ($n=10$) or a DLI ($n=1$) alone, while four patients received chemotherapy with DLI to reduce tumour bulk. Nine out of the 15 patients (60%) responded (8 CR, 1 PR), while six responses succeeded after withdrawal of immunosuppression alone. Six patients were alive and in CR at the end of the study with median OS of 68 months (range: 42–83+ months). In a study by Thomson *et al.*,[23] 12 patients received DLIs +/− chemoimmunotherapy for relapse, and five patients obtained durable remissions, giving current PFS and OS rates at 4 years of 48 and 47%, respectively. Similar results have been reported in other studies particularly for patients with late relapses (>100 days).[24] The above findings suggest that GvL is not as strong as in other haematological disorders such as CML, but nevertheless evident in ~30–40% of patients.

ALLO-HCT WITH MYELOABLATIVE CONDITIONING REGIMEN

Myeloablative allo-HCT (MAC) is generally now recommended only for younger patients (that is, <50 years) without severe comorbitities. Aksentijevich *et al.*[17] retrospectively analysed the outcome of 45 patients with relapsed DLBCL (median age: 36 years) who underwent allo-HCT at Johns Hopkins University between 1985–2001. The majority (71%) of patients had chemoresistant disease at the time of allo-HCT and all patients had HLA-matched-related donors. The conditioning regimen consisted of TBI plus Cy (TBI/Cy) in 38% patients, Bu plus Cy (Bu/Cy) in 49%, and Bu/Cy plus Etoposide (Bu/Cy/VP-16) in 13% of patients, with T-cell depletion in all. At 3 years, the OS rate was 24%, event-free survival (EFS) 19%, and the treatment-related mortality (TRM) was 51%. For patients with chemosensitive disease, the OS at 3 years was 52% compared with 12% for patients with chemoresistant disease ($P<0.001$). Multivariate analysis revealed that chemonsensitivity was the most significant factor predicting risk of relapse.

The Center for International Blood and Marrow Transplant Research/National Marrow Donor Program (CIBMTR/NMDP) analysed the outcomes of 283 NHL patients who underwent unrelated donor allo-HCT between 1991 and 2004.[25] This study included 73 (26%) patients with DLBCL histology. The day 100 probability of death for the entire group of NHL patients from all causes was 39%, and TRM increased to 52% at 5 years. Patients with DLBCL were at higher risk of treatment failure than those with follicular or peripheral T-cell lymphoma. The failure was attributed to both increased TRM or disease recurrence.

Other studies with >20 DLBCL patients who received allo-HCT with myeloablative conditioning regimen are summarised in Table 1.[16,17,25–28] The majority of the studies conclude that MAC allo-HCT is effective as salvage treatment in only a small subset of 'younger patients' with relapsed DLBCL. However, its association with both a high TRM and relapse rates results in a survival benefit for only 25% of these patients.

Table 1. Allogeneic haematopoietic progenitor cell transplantation with myeloablative regimen (MAC) in the treatment of relapsed DLBCL

Study authors (reference)	*No. pts (DLBCL)*	*Age (median)*	*Status at allo-HCT (%)*	*Donor type (%)*	*Conditioning regimen TBI-based*	*TRM (%)*	*PFS/EFS (%)*	*RR (%)*	*OS (%)*	*aGVHD grades II–IV (%)*	*Extensive cGVHD (%)*
[a]Doocey *et al.*[26]	44 (23)	40 years (19–56 years)	Sens (80) Res (20)	MRD (75) MUD (25)	95%	25 at 1 year	36 at 5 years	39 at 5 years	39 at 5 years	52	54
[a]Kim *et al.*[27]	233 (44)	31 years (15–59 years)	Sens (55) Res (45)	MRD (74) MUD (26)	83%	42	36 at 5 years	21	42 at 2 years	39	29
Aksentijevich *et al.*[17]	(45)	36 years (18–59 years)	Sens (29) Res (71)	MRD (100)	49%	51	19 at 3 years	55 at 3 years	24 at 3 years	38	24
[a]Van Besien *et al.*[25]	283 (73)	37 years (2–65 years)	Sens (62) Res (38)	WMD (54) PMD (39) MMD (6)	84%	52 at 5 years	22 at 5 years	26 at 5 years	24 at 5 years	25 (III–IV)	32 at 5 years
Lazarus *et al.*[16]	(79)	46 years (21–59 years)	Sens (58) Res (42)	MRD (100)	52%	45 at 5 years	22 at 5 years	33 at 5 years	22 at 5 years	42	26 at 5 years
[a]Freytes *et al.*[29]	114 (52)[b]	34 years (15–65 years)	Sens (56) Res (44)	MRD (61) HSD (14) Unrelated (25)	39%	25 at 5 years	5 at 5 years	70 at 5 years	24 at 5 years	29	13 at 5 years
Van Kampen *et al.*[28]	(37)	43 years (18–66 years)	Sens (74) Res (26)	MRD (71) MUD (29)	54%	41 at 3 years	42 at 3 earsy	30 at 3 years	52 at 3 years	33	17 at 3 years

Abbreviations: aGVHD = acute GVHD; cGVHD = chronic GVHD; DLBCL = diffuse large B-cell lymphomas; EFS = event-free survival; HCT = haematopoietic cell transplantation; HSD = haploidentical sibling donor; MMD = mismatched donor; MRD = matched-related donor ; MUD = matched-unrelated donor; PMD = partially matched donor; Pts = patients; Res = chemoresistant; RR = relapse rate; Sens = chemosensitive; TRM = treatment-related mortality; WMD = well-matched donor. [a]These studies are not restricted only to DLBCL but include various histologically aggressive lymphomas as well. [b]Intermediate grade and high-grade non-Hodgkin lymphomas according to Working Formulation.

In addition, MAC allo-HCT has been used as salvage therapy for DLBCL patients who relapse after auto-HCT. The International Bone Marrow Transplant Registry (IBMTR) reported the outcome of MAC allo-HCT after auto-HCT failure[29] in 114 patients with NHL ($n = 79$) and Hodgkin lymphoma. The majority of NHL patients suffered from intermediate or high-grade NHL (52/79 patients). Median age at transplantation was 34 years and 40% of patients received graft from unrelated or haploidentical donors. Five-year probabilities of OS and DFS were 24 and 5%, respectively, for the entire group of patients. TRM was relatively low (22%), despite the high proportion of alternative donors. TBI in NHL patients was associated with favourable outcome as the ones who received non-TBI regimes had a threefold increased rate of disease progression. Similarly, patients with NHL who received non-TBI conditioning had a two-fold increased mortality compared with patients who received TBI. The authors concluded that MAC allo-HCT is feasible for selected young lymphoma patients who relapse after auto-HCT and can result in prolonged survival for a small proportion. They also concluded that the patients most likely to benefit from this strategy were those with disease responsiveness at the time of allo-HCT, good performance status and HLA-matched-related donors.

More recently, the European Group for Blood and Bone Marrow Transplantation (EBMT) reported the results of 101 patients with DLBCL who relapsed after auto-HCT and treated (74% with chemosensitive disease) with an allo-SCT.[28] MAC regimens were used in 37 patients and consisted of TBI-based regimen in 54% of patients. The use of MAC regimens was associated with a trend to higher NRM and lower relapse rates compared with reduced-intensity conditioning (RIC) regimens with no differences in PFS and OS. A limitation of this study is the small number of patients and limited follow-up of those treated with this approach.

ALLO-HCT WITH NON-MYELOABLATIVE OR RIC

The use of RIC and non-myeloablative conditioning regimens was introduced >20 years ago with the aim of reducing TRM while maintaining a GvL effect. This allowed the extension of allo-HCT to older patients or those with comorbidities and patients whose disease had progressed or relapsed after auto-HCT.[30,31] Although an early EBMT registry study reported disappointing outcomes for patients with high-grade NHL who underwent RIC allo-HCT with high rates of relapse (79% at 2 years),[32] recent trials in DLBCL have demonstrated the efficacy of this approach mainly in patients with chemosensitive disease[23,28,32–36] (Table 2).

A consortium of institutions led by the Seattle group reported their experience of allografting patients with DLBCL who failed (75%) or were ineligible for auto-HCT.[34] Thirty-one patients with DLBCL and one patient with Burkitt lymphoma underwent allo-HCT from HLA-matched siblings and unrelated donors following conditioning of 2 Gy TBI with or without fludarabine. GVHD prophylaxis consisted of cyclosporine or tacrolimus combined with mycophenolate mofetil. The median age was 52 years (range: 18–67 years). At the time of transplantation, 44% of patients were in CR, 28% were in PR, and 28% had chemorefractory disease. The 3-year cumulative incidence of NRM was 25%. With a median follow-up of 45 months, 3-year estimated OS, PFS and relapse rate were 45%, 35 and 41%, respectively. The authors concluded that RIC allo-HCT can produce long-term DFS in patients with chemosensitive relapsed DLBCL who had failed or were ineligible for autologous HCT. Nevertheless, cGVHD remains a real challenge with this protocol as $>40\%$ of patients develop extensive cGVHD.

In an effort to reduce the incidence of GVHD, alemtuzumab (anti-CD52 MoAb) has been added into RIC regimens. A United Kingdom Collaborative Group study reported the outcomes of alemtuzumab–fludarabine–melphalan (FMC) conditioning regimen in 48 relapsed DLBCL ($n = 30$) or DLBCL transformed from FL

Table 2. Selected studies on reduced intensity conditioning regimen (RIC) allogeneic haematopoietic progenitor cell transplantation in patients with relapsed DLBCL

Study authors (reference)	*No. pts (DLBCL)*	*Median age, years*	*Prior AHCT (n)*	*Donor type (n)*	*Conditioning regimen*	*NRM (%)*	*PFS/EFS (%)*	*RR (%)*	*OS (%)*	*aGVHD grades II–IV (%)*	*Extensive cGVHD (%)*
[a]Robinson *et al.*[32]	(62)	43	32		FLU based- no TBI	30 at 1 year	13 at 2 years	79 at 2 years	47 at 2 years	24	9
[a]Corradini *et al.*[33]	170 (31)	51	34		FLU/CY + THIOTEPA	15 at 3 years	54 at 3 years	31 at 3 years	69 at 3 years	35	52
Rezvani *et al.*[34]	(33)	52	24	MRD(21) MUD(8) MMUD(3)	FLU + TBI(2 Gy) (29) TBI (2 Gy) alone (3)	25 at 3 earsy	35 at 3 years	41 at 3 years	45 at 3 years	53	44
[a]Thomson *et al.*[23]	(48)	46	34	MRD(30)	FLU + MEL + CA	32 at 4 years	48 at 4 years	33 at 2 years	47 at 4 years	17	13
Sirvent *et al.*[35]	(68)	48	54	MRD(56)	FLU based-no TBI (50) FLU based + TBI (2 Gy) (17)	23 at 1 year	44 at 2 years	41 at 2 years	49 at 2 years	39	41
Van Kampen R *et al.*[28]	(64)	54	64		FLU based-no TBI (46) CY + THIOTEPA (7) Other non-TBI- based (3) FLU + low-dose TBI (5) Other TBI based (3)	20 at 3 years	42 at 3 years	30 at 3 years	52 at 3 years	33	17
[a]Warlick *et al.*[36]	123 (27)	57		MRD(25) MMRD (2)	TBI(2 Gy) + FLU + Cy ± ATG	22 (at 1 year)	45 (at 4 years)	32 at 4 years	58 at 4 years	38	50

Abbreviations: ATG = anti-thymocyte globulin; CA = campath; DLBCL = diffuse large B-cell lymphoma; FLU = fludarabine; HCT = haematopoietic cell transplantation; MEL = melphalan; MMUD = mismatched-unrelated donor; MRD = matched-related donor; MUD = matched-unrelated donor; NRM = non-relapse mortality; RR = relapse risk. [a]These studies are not restricted only to DLBCL but include various histologically aggressive lymphomas as well.

($n = 18$).[23] Patients had a median of five prior therapies, including auto-HCT in 69%. The median age was 46 years (range: 23–64 years) and 38% of patients had matched or mismatched-unrelated donors. At the time of transplantation, 19% of patients were in CR, 64% were in PR, and the remainder had chemorefractory disease. Only 17% of patients developed grades II–IV acute GVHD, with 13% experiencing extensive chronic GVHD. Four-year estimated NRM was 32% and relapse risk was 33%. After a median follow-up of 52 months, OS and PFS at 4 years were 47 and 48%, respectively. Chemosensitive disease before allo-HCT was associated with better outcome.

More recently, the French Society of Marrow Transplantation and Cellular Therapy reported outcomes of 68 patients with relapsed DLBCL.[35] In this study, patients had a median of two prior therapies, 79% had received prior auto-HCT, and 82% had HLA-identical sibling donor. Before transplantation, 47% of patients were in CR, 34% were in PR and 19% had stable or in progressive disease. Conditioning regimens were fludarabine-based and were mostly combined, either with other chemotherapy drugs (50 patients, 74%) or with 2 Gy TBI (17 patients, 25%). Acute GVHD grades II–IV occurred in 39% of patients, while among the 58 patients who survived for >100 days, chronic GVHD developed in 41%. The 1-year cumulative incidence of NRM was 23%. With a median follow-up of 49 months, estimated 2-year OS, PFS, and cumulative incidence of relapse were 49, 44 and 41%, respectively. As reported previously, patients transplanted in CR had a significantly longer PFS and lower relapse rate than patients transplanted in PR or stable or progressive disease.

Finally, van Kampen *et al.*[28] reported the results of 64 DLBCL patients (median age of 54 years) who relapsed after auto-HCT and subsequently underwent RIC allo-HCT. The conditioning regimen consisted of fludarabine-based combinations in 86% of patients. Acute GVHD grades II–IV was observed in 33% and extensive cGVHD in 17% recipients. The cumulative incidences of NRM and relapse were 20 and 30%, respectively, at 3 years. After a median follow-up of 3 years, the probabilities of OS and PFS were 52.2% and 41.7%, respectively. Recipients of a RIC allo-HCT had a lower NRM at 3 years (20 versus 41% $P = 0.05$) than DLBCL patients who underwent MAC allo-HCT ($n = 37$) in the same study. However, the recipients of RIC allo-HCT had less favourable pretransplantation characteristics and a reduction in NRM did not translate into an improved PFS and OS because of the higher relapse rate observed in this cohort. This observation duplicated that of an earlier retrospective comparison of outcomes of NHL patients who underwent a RIC or MAC allo-HCT.[37] Rodriguez *et al.*[37] reported that patients with intermediate-grade B-cell NHL who underwent RIC allo-HCT had a statistically significantly higher 2-year relapse rate compared with MAC recipient (44 versus 12%, $P = 0.02$). The risk of 2-year NRM was not different (28% for RIC versus 38% for MAC, $P = 0.4$). Similarly, there were no statistically significant differences in OS and PFS. The decision of whether to adopt a MAC regimen or a RIC regimen remains unclear and prospective clinical trials are needed in order to address this point.

Overall, the results of these studies do support a role for RIC allo-HCT in heavily pretreated DLBCL patients especially for those who have experienced relapse after auto-HCT. However, patients with chemorefractory disease at the time of transplantation are unlikely to benefit from this strategy. Longer follow-up is needed to clarify the competing risks of relapse and chronic GVHD and their impact on OS and quality of life.

PROGNOSTIC FACTORS FOR OUTCOME AFTER ALLO-SCT IN PATIENTS WITH DLBCL

Several studies have attempted to clarify the prognostic significance of various factors in patients with primary refractory or relapsed DLBCL who underwent allo-HCT[16,17,25–28,34,35] (Table 3).

Most of the studies consistently report that chemorefractoriness to salvage chemotherapy is a strong adverse prognostic factor for survival. Aksentijevich *et al.*[17] reported that the 3-year OS and PFS for patients with chemosensitive disease were 52 and 53%, respectively, compared with 12 and 6%, respectively, for patients with chemorefractory disease after MAC allo-HCT. The improved survival in chemosensitive patients has also been reported after RIC allo-HCT.[34,35] Inferior survival (PFS and OS) of chemorefractory patients were observed in the retrospective study of allo-HCT (MAC and RIC) recipients relapsing after auto-HCT performed by the EBMT, although these were not statistically significant on multivariate analysis.[28] Increased recipient age (>40–50 years) has been correlated with inferior OS,[16,17,25] higher NRM[16,28] and inferior PFS[16] after myeloablative conditioning.

Acute GVHD grades III–IV has also been shown as independent adverse prognostic factor for OS in two studies,[26,35] while the absence of chronic GVHD was inversely correlated with OS by the French group.[35]

Finally, other factors with negative impact on OS and/or PFS are increased LDH on diagnosis,[28] Karnofsky performance score (KPS) <90,[16,25] and time to relapse after auto-HCT <12 months[28] (Table 3). Interestingly, all studies except one[27] have found that prior auto-HCT does not have a negative impact on OS.

In terms of TRM, most studies have shown that chemorefractory disease, increased recipient age (>40 years old), and KPS <90 constitute independent negative prognostic factors as shown in Table 3. In addition, Kim *et al.*[27] reported that prior auto-HCT and chronic GVHD were associated with higher TRM, while in another study by Doocey *et al.*[26] aGVHD grades III–IV was also correlated with higher TRM. Finally, the EBMT study revealed that time to relapse after auto-HCT <12 months and BM as source of stem cells were associated with increased TRM.[28]

For relapse/progression, disease status is an important variable, as chemorefractory disease before allo-HCT is the strongest adverse prognostic factor.[6–17,25,28,34,35] Other factors that have been associated with increased risk of relapse are increased age (>40 years old),[16,17] relapse occurring <12 months after initial treatment,[26] and use of other sources of stem cells than peripheral blood stem cells (PBSC).[35] Interestingly, no study to date has revealed any association of cGVHD with risk of relapse, possibly reflecting a minor role of immunological mechanism in the response of DLBCL patients to allo-HCT.

THE ROLE OF ANTI-CD20 MOABS

Rituximab

Introduction of anti-CD20 antibody (rituximab) was a landmark step in the therapeutic approach to patients with B-cell NHL. Rituximab is a chimeric mouse/human MoAb that targets B-cell antigen CD20.

Combination with standard chemotherapy (CHOP or CHOP-like regimes) significantly improves response rates, DFS and OS of patients with DLBCL.[3,4] Moreover, several studies have shown that the addition of rituximab to salvage chemotherapy prior to auto-HCT has been associated with superior DFS and OS, as recently reviewed by Mounier and Gisselbrecht,[11] and Rodrigues *et al.*[38] Of concern is the inferior response to rituximab-containing salvage regimens described in patients after prior rituximab treatment.[10]

In the setting of allogeneic transplantation, the use of rituximab in conjunction with RIC regimens has been suggested. Treatment with rituximab pretransplant, by targeting host B-cells, may potentially prevent the presentation of recipient antigens to donor T cells, thereby potentially decreasing the risk of acute GVHD for patients undergoing allo-HCT. The CIBMTR group tested this hypothesis by comparing the outcomes of 435 B-cell NHL patients (DLBCL; $n = 91$) who underwent allo-HCT: This study included 179 patients who received rituximab within 6 months of

Table 3. Adverse prognostic factors for TRM, EFS/PFS, progression/relapse and OS on multivariate analysis for patients with DLBCL who treated with allo-HCT

Study authors (reference)	*TRM*	*EFS/PFS*	*Progression/relapse*	*OS*
Aksentijevitc *et al.*[17]		Chemoresistant disease	Chemoresistant disease Age > 40 years	Chemoresistant disease Age > 40 years Stage at diagnosis
[a]Van Besien *et al.*[25]	Age > 40 years DLBCL subtype KPS < 90	KPS < 90 DLBCL subtype Chemoresistant disease	Chemoresistant disease	Age > 40 years KPS < 90 Chemoresistant disease
Lazarus *et al.*[16]	Age > 50 years KPS < 90 Chemoresistant disease Transplants < 2001	Age > 50 years Chemoresistant disease Transplants < 2001	Age > 50 years Chemoresistant disease	Age > 50 years KPS < 90 Res Transplants < 2001
[a]Doocey *et al.*[26]	aGVHD grades III–IV	aGVHD grades III–IV	Relapse < 12 months after initial treatment	aGVHD grades III–IV
[a]Kim *et al.*[27]	Chemoresistant disease Prior auto-HCT Cgvhd			Chemoresistant disease Prior auto-HCT Prior radiotherapy
Van Kampen *et al.*[28]	Age > 45,years Time to relapse after auto-HCT < 12 months BM as source of stem cells Chemoresistant disease	High LDH at diagnosis Time to relapse after auto-HCT < 12 months BM as source of stem cells	Chemoresistant disease	Time to relapse after auto-HCT < 12 months High LDH a diagnosis
Rezvani *et al.*[34]			Chemoresistant disease	Chemoresistant disease 1–3 lines prior treatment
Sirvent *et al.*[35]		Not in CR at allo-HCT	Not in CR at allo-HCT No PBSC as source of stem cells	aGVHD grades III–IV Absence of cGVHD

Abbreviations: aGVHD = acute GVHD; auto-HCT = autologous haematopoietic cell transplantation; cGVHD = chronic GVHD; DLBCL = diffuse large B-cell lymphoma; EFS = event-free survival; KPS = Karnofky performance status; PBSC = peripheral blood stem cells; TRM = treatment-related mortality. [a]These studies are not restricted only to DLBCL but include various histologically aggressive lymphomas as well.

allo-HCT (RTX cohort) and 256 patients who did not (No-RTX cohort). The RTX cohort had a significantly lower incidence of aGVHD grades II–IV, and lower TRM. There was no difference in the risk of chronic GVHD. PFS and OS were significantly improved in the RTX cohort.[39] Moreover, it can be hypothesised that in patients treated with rituximab as a part of the preparative regimen[40] additional depletion of B cells in the stem cell graft, may be associated with greater GVHD protection as suggested by the animal model[41] and in the report by Iori *et al.*[42] However, this hypothesis remains to be confirmed by prospective clinical trials. Finally, rituximab has been used for the treatment of steroid refractory chronic GVHD allowing steroid tapering while concomitantly achieving at least partial control of the disease.[43,44]

Immunoconjugates

The development of anti-CD20 radioimmunoconjugates such as ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab has facilitated the delivery of therapeutic doses of radiation to the tumour cells that express the CD20 antigen restricting side effects from non-diseased tissue injury. Several studies have shown that the use of ^{90}Y-ibritumomab tiuxetan or ^{131}I-tositumomab in combination with high-dose chemotherapy and auto-HCT have no detectable effect on engraftment and has a toxicity profile similar to that of conventional conditioning regimens.[45–47] Gopal *et al.*[48] recently reported the results of a prospective phase II study evaluating a conditioning regimen of ^{90}Y-ibritumomab tiuxetan with fludarabine and low-dose TBI in 40 high risk B-cell NHL patients who underwent allo-HCT with persistent disease at the time of transplantation. This study included 14 patients (35%) with DLBCL, 8 patients (20%) with mantle cell NHL and 18 patients (45%) with indolent NHL. The median age of patients was 58 years (range: 29–69 years) who had received a median of six prior therapies. Chemosensitive disease was detected in only 15% of patients, while 43% of patients had bulky disease, and 85% of patients had comorbitity score $\geqslant 1$. Early responses at 3 months after allo-HCT were observed in 24 (60%, 14CR/CR unconfirmed, 10PR) patients, including 59% with chemoresistant disease and 59% with bulky disease. Interestingly, in patients with DLBCL, early responses were seen in 38% (all CR) and none of them have experienced disease progression during a median follow-up of 1.1 years (range: 0.7–3.7). The estimated 30-month OS, PFS and NRM were 54.1, 31.1 and 15.9%, respectively. The authors concluded that the addition of ^{90}Y-ibritumomab tiuxetan to RIC regimen allo-HCT is safe and yields early responses and prolonged disease control in a subset of the highest risk B-NHL patients. In a more recent report by Bethge *et al.*,[49] a total of 20 patients enrolled in a multicenter phase II dose escalation study of radioimmunotherapy (RIT) using yttrium-90-ibritumomab tiuxetan at two dose levels (22 and 30 MBq/kg) in 10 patients, combined with reduced intensity conditioning (RIC) using fludarabine, melphalan and alemtuzumab followed by allo- HCT from either matched-related ($n = 5$) or matched-unrelated donors ($n = 15$). Thirteen patients had DLBCL. All patients were high risk with relapsed/refractory disease or relapse after preceding autologous HCT. The cumulative incidence of non-relapse mortality was 30%. Kaplan–Meier estimated 3-year OS and EFS were 20% for both dose levels. The authors concluded that dose escalation of RIT and combined use with RIC is feasible with no additional toxicity due to dose escalation.

CONCLUSIONS AND FUTURE DIRECTIONS

Current published data suggest that allo-HCT, mainly with RIC regimens, is an effective and potentially curative therapeutic option for a subset of DLBCL patients with refractory disease or relapsed disease after auto-HCT. Figures 1a and b outline a simple algorithm on how these patients should be managed using either a MAC or RIC transplant as part of front-line treatment or with relapsed disease after an autologous PBSCT. The cutoff age of 50 years in patients without preceding auto-HCT or 40 for the ones who have failed a previous auto-HCS is arbitrary and consideration

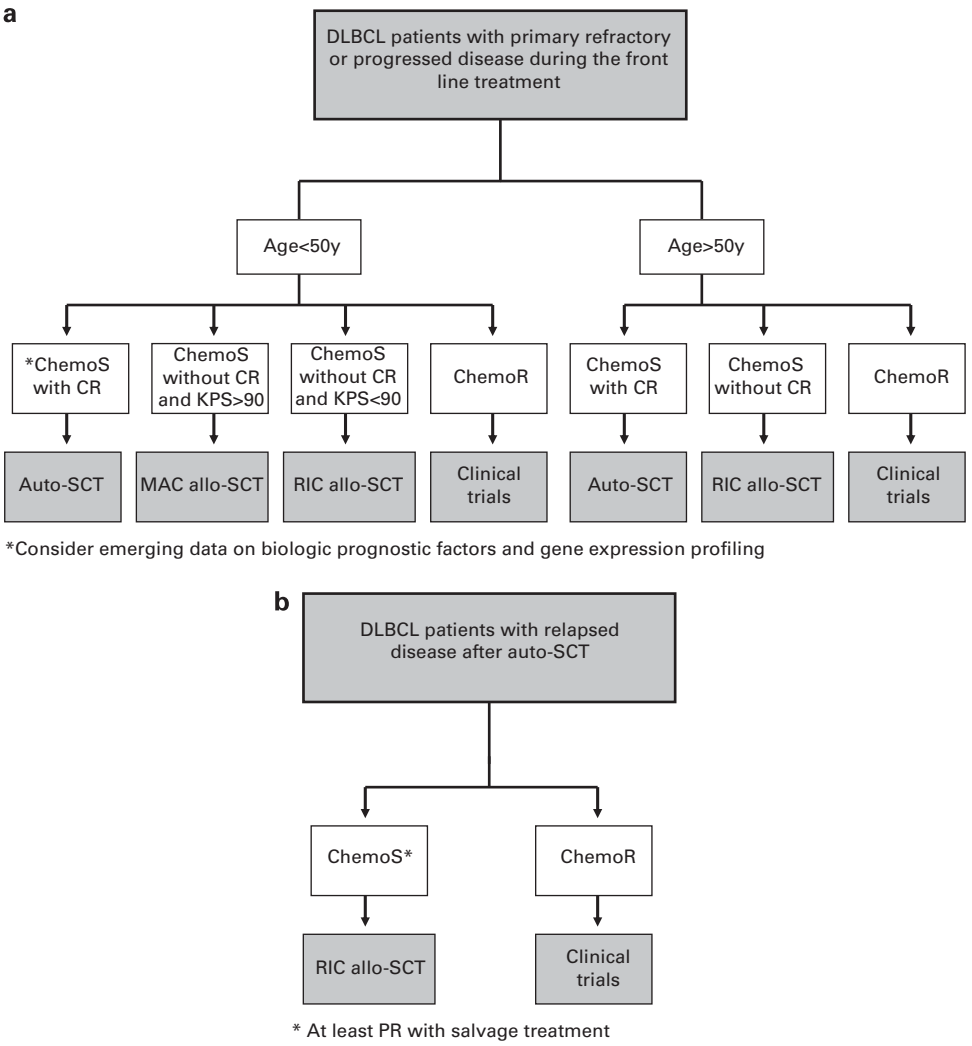

Figure 1. Transplant algorithm in patients with DLBCL as front-line treatment (**a**) and with relapsed disease post-auto-SCT (**b**).

has to be given more to the biological rather the chronological age when the physician has to choose between a RIC and a MAC transplant. However, most centers have opted not to offer myeloablative approaches to patients above the age of 50 irrespective of the performance status of the patient. As it is becoming increasingly apparent that certain subtypes such as MYC rearrangements carry bad prognosis independently from the known prognostic factors and regardless of the type of the treatment,[50] new approaches should be explored. Patients for example with relapsed responsive disease and MYC mutations who might have been offered an autologous transplantation up till now, might become candidates for more aggressive upfront treatments including an allogeneic transplantation.

The majority of the published data suggest that chemosensitive disease at the time of the transplant remains the strongest factor for favourable outcome. Patients with primary resistant disease or refractory relapse have a dismal outcome and other strategies should be identified. The use of immunoradiotherapy prior to the transplant might benefit a small fraction of patients with refractory disease; however, as there is no enough data to support such approaches, patients should be treated as part of clinical trials.

GVL constitutes one of the rationales for considering allogeneic transplantation. Possible mechanisms and interventions that potentially might enhance GVL effect should be explored. The use of DLI in this setting has been associated with less successful outcome compared with other haematological malignancies; however, the lack of data makes interpretation even more difficult. Further studies will be required especially using DLI preemptively in both chemosensitive and refractory disease to assess potentially efficacy, identifying group of patients that might benefit by this approach.

The use of novel clinical prognostic factors and biomarkers combined with functional imaging techniques such as PET scan for the assessment of response to treatment might help to identify earlier a subpopulation of patients that might benefit from allo-HCT. The CORAL study has clearly demonstrated that the cell of origin (COO) remains a major and independent factor in relapsed/refractory DLBCL[51] and therefore consideration should be given in allografting aggressive forms earlier in the course of the disease. Growing knowledge of the prognostic value of the cell of origin leads investigators to test new agents targeting key molecular pathways critical to B-cell growth. Several agents such as new MoAbs, antibody drug conjugates, immunomodulating agents, proteosome inhibitors, PI3K pathway inhibitors, HDAC inhibitors, kinase inhibitors, JAK/STAT pathway inhibitors, Toll-like receptor agonists, inhibitors of heat shock proteins and molecules targeting angiogenesis are in early or late phase of clinical trials having produced encouraging results (as reviewed by Foon *et al.*[52]). Potentially some of these new agents as monotherapy or in combination with conventional chemotherapy might provide

additional clinical benefit and act as a bridge towards a successful transplant.

The use of different conditioning regimes across different centers makes comparison difficult as none of the studies has ever succeeded to demonstrate superiority of one regime over another. The ideal conditioning should combine good anti-lymphoma effect with low TRM, potentially enhanced GVL effect and reduced risk of relapse. We may be far away from being able to identify such an effective conditioning; however, the incorporation of immuno-radiotherapy in conditioning regimes might be a step ahead. As more data will be becoming available from phase II studies, more patients will possibly be given the opportunity to receive an allogeneic transplant either as part of standard treatment or under a clinical trial.

Advances in unrelated donor selection including high-resolution HLA typing have resulted in major improvements in the outcome of matched-unrelated donor transplants.

The use of alternative donor transplants such as cord and haploidentical is now increasingly considered and recent novel conditioning regimes incorporating lymphocytes prior or simultaneously to the infusion of stem cells may be proven to be more effective in the future for the treatment of these aggressive lymphomas.

Another key investigational goal to improve outcome after transplant has been the effort to incorporate therapies after the transplant in the form of maintenance therapy. This concept has currently been applied in other haematological malignancies such as AML and it is something that should also be considered in aggressive lymphomas with agents such as rituximab, lenalidomide, bortezomib and other novel ones.

In conclusion, as the morbidity and mortality of allogeneic transplant continues to improve, more patients with DBCL who fail to respond to first-line treatment or to autologous SCT (in CR1 or relapsed disease), might be candidates for allogeneic procedures.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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