Guidelines of the Belgian Hematology Society on the use of stem cell transplantation in lymphoproliferative diseases

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On behalf of the BHS lymphoma committee and the BHS transplantation committee***

SUMMARY

High-dose chemotherapy and autologous or allogeneic haematopoietic stem cell transplantation are widely used in the treatment of lymphoproliferative diseases. For chemo-sensitive relapsed lymphoma (Hodgkin's and non-Hodgkin's lymphoma) high-dose chemotherapy and autologous stem cell transplantation are generally accepted as a standard treatment. Emerging data exist for the use of haematopoietic stem cell transplantation in other disease stages for mantle cell lymphoma, follicular lymphoma and some T-cell lymphomas. The use of haematopoietic stem cell transplantation in other conditions is more controversial and remains a clinical option for selected patients or experimental within the framework of a clinical trial.
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INTRODUCTION

Myeloablative chemotherapy and autologous (ASCT) or allogeneic stem cell transplantation (allo-SCT) have been increasingly used during the last three decades and have been shown to be effective in many lymphoproliferative diseases (LPD) in different disease conditions.

In 2016, the European Group for Blood and Marrow Transplantation (EBMT) data base registered 8419 patients with an ASCT and 1893 with an allo-SCT in these diseases.

The following guidelines were written based on recent literature on adult transplantation procedures in LPD and published after discussion within the Belgian Hematology Society (BHS), with both the lymphoma and transplantation committee.

CATEGORISATION OF TRANSPLANT PROCEDURES

In accordance with the current EBMT classification system for transplant indications, we will classify haematopoietic stem cell transplantation (HSCT) as 'standard of care' (SC), 'clinical option' (CO), 'developmental' (D) or 'not generally recommended' (NGR).[1,2]

STANDARD OF CARE

This category includes indications that are well defined and generally supported by evidence derived from high quality clinical trials and/or observational studies. Obviously, this does not mean that an HSCT is the optimal therapy for every patient. Patient specific characteristics and the specific clinical circumstances should be taken into account.

CLINICAL OPTION

This category includes indications for which large clinical trials or observational studies are not available because the number of patients is low, and therefore randomised trials, for example, comparing conventional treatment with HSCT,

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are difficult to perform. However, data from small patient cohorts treated with HSCT show efficacy with an acceptable toxicity profile. HSCT is thus considered as a treatment option for individual patients after careful evaluation of risks and benefits, taking into account newly published data.

DEVELOPMENTAL

HSCT should only be considered in the context of a clinical trial. Additional research is necessary to define the role of HSCT.

NOT GENERALLY RECOMMENDED

Evidence and clinical practice do not support HSCT in this setting. This can include situations where the results of conventional treatment do not normally justify the additional toxicity of a HSCT, or situations where the chance of success is too small.

EVIDENCE GRADING

I. Evidence from at least one well-executed randomised clinical trial (RCT).
II. No evidence from RCTs, but evidence from at least one other well-executed cohort of case-controlled or uncontrolled clinical trial.
III. No evidence from well-executed clinical trials, only expert-opinion.

INDICATIONS FOR TRANSPLANTATION IN THE SPECIFIC DISEASE ENTITIES

1. T-CELL PATHOLOGY

The mature T-cell and natural killer (NK)-cell neoplasms comprise a group of rare and very heterogeneous lymphomas. The majority of these lymphomas is characterised by an aggressive clinical behaviour and dismal outcome. Here, we will discuss the most common subtypes: Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), angioimmunoblastic T-cell lymphoma (AITL), systemic anaplastic large cell lymphoma (ALCL, both ALK positive and ALK negative) and the extra-nodal NK/T-cell lymphoma (ENKTL).[3]

Peripheral T-cell lymphoma, not otherwise specified

PTCL, NOS responds poorly to conventional therapy, with an estimated 5-year overall survival (OS) of 25-40%.[3] RCTs with a head-to-head comparison of ASCT with chemotherapy alone are not available. To evaluate the efficacy of a dose-dense approach (CHOEP [cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone]-14 six times if <60 years, CHOP [cyclophosphamide, doxorubicin, vincristine and prednisone]-14 six times if >60 years) consolidated by upfront ASCT in complete (CR) or partial response (PR), the Nordic Lymphoma Group conducted a large prospective non-randomised phase II study (NLG-T-01) in untreated systemic PTCL (n=166, of which 62 were classified as having PTCL, NOS). Subtype-specific analysis of PTCL, NOS demonstrated a 5-year OS of 47% and progression-free survival (PFS) of 38%. This was the largest prospective phase II trial available of ASCT in first remission.[4] In the second largest prospective study of ASCT in CR1, containing 32 patients with a high-intermediate or high international prognostic index (IPI) score, poor outcomes with a 5-year OS of only 30% were noted.[5] The results of this study were updated in 2016 with a longer follow-up, and more patients (n=42) with an estimated 5-year OS of 44% and PFS of 39% were reported.[6] A recent Lymphoma Study Association (LYSA) initiated a large (PTCL, NOS: n=78) multicentric retrospective study, using both a multivariate proportional hazard model and propensity score matching to correct for selection bias, which did not support the use of ASCT upfront.[7] Given the results of chemotherapy, in trials, such as the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) trials, in which six cycles of CHOP or CHOEP resulted in a 3-year event-free survival (EFS) and OS of 41% and 54% respectively, there is only mixed evidence of level II to justify the use of consolidation with ASCT in CR1.[8] Therefore, a Belgian consensus on the role of ASCT in CR1 for PTCL, NOS could not be reached.

Allo-SCT is a potential curative option, but RCTs are needed to support this approach. The DSHNHL 2006-1A (AATT) protocol – in which younger patients with PTCL (excluding stage I with IPI 0) received a common induction with four cycles of CHOEP-14 and one cycle of DHAP, and were then randomised between BEAM (carmustine, etoposide, cytarabine and melphalan)/ASCT or allo-SCT after a full blood count (fludarabine 125 mg/m^2, busulfan 12 mg/kg, cyclophosphamide 120 mg/kg) – was prematurely stopped, based on an interim-analysis that estimated that it was highly unlikely that the primary objective, namely a 25% improvement of PFS at 3 years for allo-SCT, would be reached.

Overall, the disease status at the time of both ASCT and allo-SCT was a strong predictive marker for both PFS and OS in transplant patients. Several retrospective studies indicate a role for ASCT in relapsed, but chemo-sensitive disease. Yang *et al.* performed a multicentre retrospective study with 64 Korean patients treated with high-dose therapy (HDT)/ASCT after primary or salvage chemotherapy. The 3-year OS rate for patients in CR2 was 70.9%, compared to 50% for those in PR1. The achievement of CR at the time of transplantation was a more significant factor for predicting survival than transplant timing.[9] In a phase II prospective trial, reduced intensity conditioning (RIC) followed by allo-

TABLE 1. Transplant indications in T-cell lymphoma.

T-cell lymphoma	Autologous SCT	Allogeneic SCT
PTCL, NOS / AITL / ALK - ALCL		
CR1/PR1	CO/II	NGR/II
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II
ALK + ALCL		
CR1/PR1	CO if high-risk disease/II	NGR/III
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II
ENKTL		
CR1/PR1	NGR in limited - CO in advanced/II	NGR/III
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if Ch-S)/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II

SCT: stem cell transplantation, PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified, AITL: angioimmunoblastic T-cell lymphoma, ALK: anaplastic lymphoma kinase, ALCL: anaplastic large cell lymphoma, CR1: first complete response, PR1: first partial response, Ch-R: chemo-resistant, CO: clinical option, NGR: not generally recommended, SC: standard of care, ASCT: autologous stem cell transplantation, Ch-S: chemo-sensitive, ENKTL: extra-nodal NK/T-cell lymphoma.

SCT seemed feasible with low treatment-related mortality (TRM) in relapsing patients, with arguments for graft-versus-lymphoma (GVL) effect with a long-lasting response to donor lymphocyte infusion (DLI).[10]

Angioimmunoblastic T-cell lymphoma

AITL has a dismal prognosis with an estimated 5-year OS and PFS after intensive chemotherapy of 33% and 13% respectively.[11] There are no RCTs comparing chemotherapy alone with consolidation with HDT/ASCT in first line. The strongest evidence supporting HDT/ASCT in CR1 comes from the same Nordic study for which the subgroup analysis of 30 AITL patients demonstrated a 5-year PFS and OS of 49% and 52% respectively, with a low TRM (4% overall).[4] The EBMT executed the largest, but retrospective, study consisting of 146 patients with AITL. The 4-year PFS and OS after HDT/ASCT was 42% and 59% respectively, with the majority of patients receiving BEAM conditioning. Of note, the cumulative incidence of relapse at 4 years was 51%. However, patients who received a transplant during CR1 had a significantly superior PFS and OS compared to those in PR or with chemo-refractory disease. This study did not assess the differences in outcomes of patients in CR1, second or later CR.[12] In conclusion, ASCT might extend PFS with outcomes most optimal when the ASCT occurs in CR. In 2009, the EBMT published a retrospective study concerning the role of allo-SCT in AITL.[13] Forty-five patients, of which 34 patients had received two or more lines of chemotherapy, and 11 patients after prior ASCT, underwent an allo-SCT. Twenty-five patients underwent a myeloablative conditioning (MAC) for allo-SCT, and 20 underwent a RIC for allo-SCT. The cumulative incidence of TRM was rather high, up to 25% at 12 months (MAC=RIC). PFS and OS rates were 53% and 64% at 3 years and also here significantly better in chemotherapy-sensitive patients. Therefore, allo-SCT is a valid clinical option in the relapse setting.

Anaplastic large cell lymphoma

Because the disease is rare and no RCTs have been conducted, the evidence to guide treatment for patients with an ALCL is derived from only small prospective or retrospective trials and often without good identification of the *ALK* rearrangement status and without head-to-head comparison of chemotherapy-only strategies and HSCT.[3] The DSHNHL published promising results for patients with ALK-positive ALCL younger than 60 years (n=78) with the addition of etoposide to the standard CHOP regimen.[6] Six cycles of CHOEP in those patients resulted in a 3-year EFS of 91.2%. Although lower, the 3-year EFS for ALK-negative ALCL treated along the same strategy was 60.7%. Also impressive are the results of the small phase II trial concerning DA-EPOCH (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) in the frontline treatment of both ALK-positive (n=15) and ALK-negative (n=9) ALCL. At a median follow-up of 14 years, ALK-positive and -negative patients had EFS probabilities of 72% and 62.5% and OS probabilities of 87.5% and 78%, respectively.[14] These data make the benefit of an ASCT in CR1 more doubtful. For selected high-risk (IPI> or =3) patients with an ALK-positive ALCL and older than 40 years, some expert leaders suggest, without clear published evidence, a HDT/ASCT might be considered after a careful risk/benefit assessment and extensive discussion with the patient. The Nordic study assessed the role of HDT/ASCT in CR1 for ALK-negative ALCL. This subgroup (n=31) had a higher 5-year OS (70%) and PFS (61%) compared to PTCL, NOS and AITL.[4] However, others could not confirm these superior outcomes.[5] Therefore, also for ALK-negative ALCL, the currently available data do not support the use of ASCT in all patients in CR1. Some expert leaders consider ASCT only for high-risk patients.

Similarly, there are no RCTs assessing the benefit of ASCT or allo-SCT in patients with relapsed ALCL. Several retrospective trials suggest that patients with a chemo-sensitive relapse might benefit from a HSCT. In a large cohort of ASCT or allo-SCT recipients with PTCLs reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), a multivariate analysis showed that chemotherapy sensitivity and two or fewer lines of pre-transplantation therapy were prognostic of survival. Notably, for patients with ALCL (n=112), the 3-year OS and PFS for patients undergoing ASCT beyond CR1 were 65% and 50% respectively.[15] Because the relapse rate after transplantation remains high, treatment strategies involving therapies with novel agents such as brentuximab vedotin can be an alternative approach. Also, these new agents may serve as a bridge to allo-SCT.[16] Most expert opinion leaders only favour allo-SCT in those patients with multiple relapses or chemo-refractory disease.[3]

Extra-nodal natural killer/T-cell lymphoma

The historical overall prognosis of ENKTL was poor, with an expected 5-year OS of less than 20%. L-asparaginase-based regimens have been found to have a very high activity in ENKTL and are now included in standard first-line treatment.[3] Similarly to other subtypes, there are no RCTs available, comparing chemotherapy alone with consolidation by upfront ASCT. In the largest (n=62) retrospective study, induction chemotherapy (80% non-anthracycline-based) resulted in a CR rate of 61.3% before ASCT, with a post-transplant CR rate of 78%.[16] Patients with limited disease had a significantly better 3-year PFS (64.5% *vs* 40.1%) and OS (67.6% *vs* 52.3%) than those with advanced disease. These survival outcomes for limited stage are comparable to published chemo-radiotherapy alone outcomes, and most experts agree that upfront ASCT is of little value in limited stage ENKTL.[3] There is no consensus on the role of upfront ASCT for advanced disease, and there is no consensus on the ideal conditioning regimen (BEAM or other). In general, several studies showed that an ASCT in CR results in a better outcome than in PR or chemo-refractory setting.[3] Also in the relapsed setting, there are only retrospective series comparing ASCT with allo-SCT, all limited by the fact that patients undergoing allo-SCT often have a more advanced stage, more often have a high IPI risk and more often lack CR pre-transplantation. Most experts prefer ASCT in first relapse and consider allo-SCT in multiple relapsed disease or chemo-refractory ENKTL.[3]

2. B-CELL PATHOLOGY

Diffuse large B-cell lymphoma and high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements

Treatment of aggressive B-cell lymphomas is in evolution, since the biological and genetic heterogeneity becomes more and more elucidated. However, this complicates the interpretation of historical trials, investigating the role of ASCT in diffuse large B-cell lymphoma (DLBCL) but not addressing the cell of origin (COO) or more importantly MYC/BCL2/BCL6 expression or rearrangements.

A 2008 Cochrane meta-analysis included fifteen RCTs (and more than 3000 patients) and compared HDT/ASCT with no consolidation in first line. However, only four trials were conducted in the rituximab era, and subtypes were most often not studied. Thirteen out of fifteen showed higher CR rates, but there was no OS benefit for HDT/ASCT.[18] One recent American and two recent Italian studies randomised age-adjusted international prognostic index (aaIPI) inter-

TABLE 2. Transplant indications in aggressive B-cell lymphoma.

Diffuse large B-cell lymphoma	Autologous SCT	Allogeneic SCT
DLBCL, NOS		
CR1/PR1	NGR (CO if high IPI + slow response)/I(II)	NGR/III
Primary refractory (Ch-R)	NGR (CO)/II(III)	CO/II
First relapse	SC (if Ch-S)/I	CO/II
Later relapse	NGR/II (if prior ASCT)	CO/II
High-grade B-cell lymphoma, with rearrangements of *MYC* and *BCL2* and/or *BCL6*		
CR1/PR1	NGR/II	NGR/II
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II
Later relapse	NGR/II	CO/II
DEL (without rearrangements of *MYC* and *BCL2*)		
CR1/PR1	NGR/II	NGR/II
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC (if no prior ASCT and Ch-S)/II	CO/II
Later relapse	NGR/II	CO/II

DLBCL, NOS: diffuse large B-cell lymphoma, not otherwise specified, SCT: stem cell transplantation, CR1: first complete response, PR1: first partial response, NGR: not generally recommended, CO: clinical option, IPI: international prognostic index, SC: standard of care, Ch-S: chemo-sensitive, ASCT: autologous stem cell transplantation, DEL: double expressing lymphoma.

mediate-high and high-risk patients to either rituximab-chemotherapy alone or rituximab-chemotherapy followed by HDT/ASCT (high dose sequential schedule).[19-21] All three studies failed to show an improvement in OS. Two studies noted a significant difference in 2-year failure-free survival or PFS, whilst the other study showed identical 3-year EFS rates. Therefore, most opinion leaders now agree that consolidative ASCT is not generally recommended in CR1, even in patients defined as high-risk by clinical prognostic markers, such as (aa)IPI. However, this remains a controversial issue, and some experts argue that it can be a clinical option for high-risk patients with a slow response to first-line treatment. Therefore, the LNH2007-3B phase II trial investigated a fluorodeoxyglycose-PET driven consolidation strategy in newly diagnosed DBLCL with aaIPI 2 or 3.[22] PET2 and -4 double-negative patients continued with chemotherapy alone; PET2-positive/PET4-negative patients continued with two cycles of high-dose methotrexate and then HDT/ASCT. PET4-positive patients were mostly offered salvage treatment. Double-PET-negative patients obtained a 75% 4-year EFS and an 83% 4-year OS, which is comparable to historical LYSA trials in which all patients received upfront ASCT.[23] This suggests that clinically high risk patients with an early metabolic response can safely be given chemotherapy alone without impairment of disease control. Both PFS and OS of PET2-positive/PET4-negative patients who mostly received ASCT, were not significantly different from double-PET-negative chemo-treated patients. Same conclusions were made in the more recent phase III GAINED trial.[24] However, in both trials, there was no randomised comparison for the slow responders between ASCT and chemotherapy alone.

ASCT is clearly less effective in patients with chemo-refractory DLBCL. Patients with a Deauville score of 4 or 5 at the end of induction treatment have a significantly inferior prog-

nosis after ASCT. Recently, a 3-year PFS for patients with a Deauville 1-3 score was 64%, compared to 0% for Deauville 4, while the 3-year OS was 84% and 25%, respectively.[25]

Effective treatment of subgroups with a poorer outcome, notably activated B-cell DLBCL, double or triple hit lymphoma (DHL, or high grade B-cell lymphoma with translocations of *MYC* and *BCL2* [and *BCL6* for triple hit]) and double-expressing lymphomas (DEL; MYC and BCL2 protein over-expression) remains an unmet medical need. Whether upfront ASCT can improve outcomes of these biologically defined poor-risk groups is not well known. Considering the relative rarity (8-10%) of a DHL, most of the data available comes from retrospective studies or subgroup analyses of prospectively treated DLBCL cohorts. Moreover, many DHL/DEL patients have primary refractory disease. For patients achieving CR with front line therapy, one of the larger retrospective series (n=311) could not find a statistically significant difference in median OS between those who proceeded to ASCT and those who did not, although there was a trend towards improved OS post-ASCT.[26] Another recent large retrospective study (n=159) showed that for fit patients with DHL who achieved CR1, a consolidative ASCT was not associated with improved 3-year relapse-free survival (RFS; 75% *vs* 89%, p=0.12) or OS (85 *vs* 91%, p=0.74). Although non-randomised, the clinic-pathological characteristics between ASCT and non-ASCT patients in this trial were well matched.[27] In the South-West Oncology Group (SWOG) S9704 study, there was a trend towards an improvement in PFS after ASCT in first line for DEL, but this was not statistically significant (n=16).[28] Additional reports from small retrospective studies reviewed the role of consolidation strategies with either ASCT or allo-SCT, but no strong conclusions could be made due to heterogeneous induction regimens and patients' baseline characteristics and selection bias.[29]

For relapsed but chemo-sensitive patients, HDT/ASCT has been shown to improve outcome in RCTs.[30-32] In the pre-rituximab era, the PARMA trial clearly established HDT/ASCT consolidation as SC in relapsed patients with chemo-sensitive disease.[26] In the rituximab era, the CORAL trial confirmed the role of ASCT in this setting. Importantly, only 50% of all patients salvaged by R-ICE (rituximab combined with ifosfamide, carboplatin, etoposide) or R-DHAP (rituximab combined with dexamethasone, ara-C and cisplatin) achieved a PR or CR and was able to proceed to the ASCT. For those who underwent transplantation, the 3-year PFS was 53%. However, this trial also revealed that patients with early relapses (<12 months) after a rituximab-containing first-line treatment have a poor prognosis with a 3-year PFS of only 20%. The recently published registry of DLBCL with primary treatment failure (REFINE) study proposed a 3-factor prognostic score (primary progressive disease, *MYC* rearrangement, intermediate-high or high score following the enhanced National Comprehensive Cancer Network IPI (NCCN-IPI) for DLBCL patients treated in the rituximab era) model to identify a subgroup with an extremely poor prognosis (predicted 2-year OS of 13%) after ASCT.[33] The outcome of patients with a relapse/refractory DHL/DEL is extremely poor.[34] In a retrospective trial, the 4-year PFS and OS after ASCT in patients with DHL compared with non-DHL were 28% versus 57% (P=0.013) and 25% versus 61% (P=0.002), respectively. Patients with concurrent DEL and DHL had a PFS of 0% at 4 years.[35] In conclusion, ASCT is SC for chemo-sensitive relapsed DLBCL, but novel therapeutic approaches are needed for ultra-high risk subgroups. Moreover, long-term outcomes are not well described after ASCT in relapsed DLBCL. A recent report studying 2-year survivors of ASCT for relapsed/refractory DLBCL concluded that those patients have an excess late-mortality risk (standardised mortality ratio: 3.4) and experience different types of late complications such as secondary malignancies (61/781 patients).[36]

For heavily pre-treated patients or patients with refractory disease, and failure after ASCT, an allo-SCT remains the only curative option. Most studies agree that RIC allo-SCT can provide durable disease control.[37-39] A CIBMTR risk score model was developed to identify patients unlikely to benefit from allo-SCT and patients for whom relapse prevention strategies post-transplant should be strongly considered.[35] The three adverse prognostic factors were Karnofsky Performance Score <80 (4 points), ASCT to allo-SCT interval <1 year (2 points) and chemo-resistant disease at allo-SCT (5 points). This model classified patients into four groups: low-risk (0-2), intermediate-risk (2-5), high-risk (6-9) or very high-risk (11), predicting a 3-year PFS of 40%, 32%, 11% and 6% respectively. The role of allo-SCT in relapsed/refractory DHL/DEL is investigational. Studies on small series suggest that both DEL and DHL are also associated with dismal outcomes after allo-SCT due to early disease progression. Kawashima *et al*. noted a 2-year PFS rate of 27%, even if they selected patients with chemo-sensitive disease at allo-SCT.[40]

Follicular lymphoma

The role of HSCT for follicular lymphoma in the era of immunotherapy is not fully proven, and prospective RCTs are limited, most of them are from the pre-rituximab period. Four RCTs explored the role of HSCT for patients in CR1, none of which showed a survival benefit. The German Lymphoma Study Group compared interferon (IFN)-alpha maintenance with ASCT. Among 240 evaluable patients,

TABLE 3. Transplant indications in indolent B-cell lymphoma.

Follicular B-cell lymphoma	Autologous SCT	Allogeneic SCT
CR1/PR1	NGR (D for high risk m7-FLIPI)/I	NGR/I
Primary refractory (Ch-R)	NGR/III	CO/III
First relapse	SC /I	CO/II
Later relapse	SC (if no prior ASCT and Ch-S) /I	CO/II
Transformation to high grade	SC/II	CO/II
Waldenström macroglobulinaemia		
CR1/PR1	NGR/II	NGR/II
Primary refractory (Ch-R)	NGR/II	NGR/II
First relapse	CO/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II
Mantle cell lymphoma		
CR1/PR1	SC/I	CO(for high risk)/II
Primary refractory (Ch-R)	NGR/II	CO/II
First relapse	SC/II	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II

SCT: stem cell transplantation, CR1: first complete response, PR1: first partial response, Ch-R: chemo-resistant, NGR: not generally recommended, D: developmental, CO: clinical option, FLIPI: Follicular Lymphoma Prognostic Index, SC: standard of care, Ch-S: chemo-sensitive, ASCT: autologous stem cell transplantation.

there was a 5-year PFS of 64.7%, compared to 33.3% in the IFN group, without a difference in OS.[41] A French Groupe Ouest-Est d'Études des Leucémies Aigües et Autres Maladies du Sang (GOELAMS) trial investigated upfront HDT/ASCT compared to a CHOP-like chemotherapy regimen (CHVP) with IFN-alpha, with impact on PFS but not on OS, partially explained by an excess of secondary malignancies in the HSCT group.[42] Another French study from the Lymphoma Study Association (LYSA/GELA; GELF94) randomised 401 patients with untreated FL to CHVP plus IFN-alpha or CHOP plus HDT plus total body irradiation (TBI) plus ASCT.[43] After a median follow-up of 7.5 years, there was no difference in PFS and OS. These disappointing results were confirmed in a meta-analysis in 2012.[44]

More recently, a RCT compared the outcome of patients with HDT/ASCT or R-CHOP (rituximab combined with CHOP). This Italian trial could not show an OS benefit in either of the groups.[45] The occurrence of second malignancies including myelodysplastic syndromes and acute myeloid leukaemias generated a consensus against the use of ASCT in the upfront treatment of FL patients.

A small group of patients with FL (±20%), however, relapse within 24 months after initial treatment. When integrating the mutational status of seven genes available through next-generation sequencing with the clinical Follicular Lymphoma Prognostic Index (FLIPI) score (resulting in the so called m7-FLIPI), it is possible to identify one half of this high-risk group of patients (5-year failure-free survival of only 25%).[46] One would assume that intensive regimens with HSCT could influence this bad prognosis, but unfortunately insufficient data are available.

In a retrospective analysis from the CIBMTR-National Lymphocare Study (NLCS), it was clear that applying ASCT (within one year) in early relapsing patients was associated

with a better 5-year OS (73%) compared to 60% if conventional treatments were used.[47] For patients being in first or subsequent relapse (in the pre-rituximab era), the use of ASCT was considered as SC, based on the randomised CUP trial.[48] This study closed prematurely because of slow accrual after 140 of the 250 planned patients were included. Patients were treated with three cycles of a CHOP-like chemotherapy, followed by randomisation to high-dose chemo-radiotherapy (cyclophosphamide 2 x 60 mg/kg and TBI) or three more cycles of the initial standard chemotherapy. High-dose therapy and ASCT resulted in significantly better OS rates at four years of median follow-up: 71% when using unpurged autografts, 77% when using purged autografts in contrast to only 46% 4-year OS when using the conventional chemotherapy without ASCT.

There are five prospective, single-arm, phase II trials summarised by Hamadani and Horowitz evaluating the role of RIC allo-SCT in patients with FL.[49] Non-relapse mortality ranged from 15-35% and OS between 54-76 % at four years; one study reported a 78% OS at eleven years, all patients in that study had chemo-sensitive relapse before allo-SCT. These studies show a plateau in recurrence after 2-3 years but at a cost of 15-20% mortality and 50-55% graft-versus-host disease (GVHD), making this treatment modality difficult to use in unfit or older patients. So what treatment should be preferred for young, relapsed FL patients if a donor is available: ASCT or allo-SCT? Data from five registry studies comparing ASCT with allo-SCT are problematic: one study was prematurely stopped, one was in the pre-rituximab era, one was limited to grade 3A FL.[45] The two other trials did show a better 5-year PFS (57-58% *vs* 48-51%) but no 5-year OS benefit (66-67% *vs* 72-74%) for allo-SCT over ASCT.[50,51] The conclusion is that because of lack of data from RCTs, the use of allo-SCT should be restricted as a clinical option in well-selected patients or in the framework of a clinical trial.

The transformation of FL to a lymphoma of more aggressive histology bares a dismal prognosis (26% OS at five years), and the optimal treatment is not known. In a retrospective analysis from the Spanish Grupo Español de Linfomas y Transplante de Médula Osea (GELTAMO), the value of ASCT has been suggested.[52] This role for HSCT as a consolidation in the treatment of transformed FL is further established in the study by the Canadian BMT Group.[53] This group retrospectively analysed a multicentre cohort study of 172 patients with transformed FL, undergoing ASCT (97 patients), allo-SCT (22 patients) or a rituximab-based chemotherapy without transplantation. Five-year PFS after time of transformation was 46% for allo-SCT, 55% for ASCT and 40% for chemo-immunotherapy. Although this study comprises only a small number of patients, the conclusion stated that treatment with ASCT gave a significant better PFS and OS than treatment with allo-SCT or conventional treatment.

Waldenström's macroglobulinaemia

Waldenström's macroglobulinaemia (WM) has a relatively good prognosis (median OS of about eight years), and the median age is about 68 years. The recognition of some risk factors (age, anaemia, thrombocytopenia, high immunoglobulin M and high β2-microglobulin at diagnosis) and molecular markers such as MYD88 and CXCR4 allows tailoring treatment and selecting patients with poor prognosis. However, new molecules are introduced in the treatment of WM with fairly good results, making the indication for HSCT more questionable.

Small anecdotal studies in the pre-rituximab era suggested a possible benefit of ASCT when used upfront for high-risk patients with WM.[54]

With the use of agents such as rituximab and ibrutinib, this upfront modality has been questioned and should not be used outside a clinical trial.

In relapsed setting, ASCT is a clinical option in selected patients with early chemo-sensitive relapse, providing a PFS at five years of 44%. This excellent result worsens when ASCT is used after more than one treatment line, but even then this approach is successful in chemo-sensitive patients: the EBMT retrospective analysis of 158 patients (1/3 having had at least three lines of therapy) showed a PR or better in 84% of patients with a median EFS of four years and a median OS not reached at eight years.[55]

Because of the evidence of a relapse-free plateau after allo-SCT (5-year OS of 62-64%, PFS 49-56%), this treatment modality may be a clinical option based on the data from the CIBMTR, EBMT and others.[56-58] The timing of allo-SCT is unclear, but refractory disease should be avoided and high-risk patients (i.e., MYD88 negative) should be treated early.

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is characterised by a poor prognosis of around 4-6 years, even with new emerging therapies such as ibrutinib. Therefore, the use of HSCT in the upfront treatment gained a lot of interest.

The European MCL Network (EMCLN) conducted a RCT in 122 patients in first (partial or complete) remission, after a CHOP-like regimen. Patients were allocated to myeloablative radio-chemotherapy followed by ASCT or to IFN-alpha. The ASCT arm had a significant longer PFS of 39 months at three years, compared to 17 months for the IFN arm. OS was not significantly different yet, but there was a trend in favour of the ASCT arm.[59] The Nordic group published their

TABLE 4. Transplant indications in Hodgkin's lymphoma and CLL.

Hodgkin lymphoma	Autologous SCT	Allogeneic SCT
CR1/PR1	NGR (CO if PR1)/II	NGR (CO if PR1)/II
Primary refractory (Ch-R)	CO /II	CO/II
First relapse	SC/I	CO/II
Later relapse	CO (if no prior ASCT and Ch-S)/II	CO/II
CLL		
CR1/PR1	NGR/II	NGR/II
Primary refractory (Ch-R)	NGR/II	NGR (CO if high risk)/II
First relapse	NGR/II	NGR (CO if Bcl-2 first line)/II
Later relapse	NGR/II	CO/II
Richter's transformation	CO/II	CO/II

SCT: stem cell transplantation, CR1: first complete response, PR1: first partial response, Ch-R: chemo-resistant, NGR: not generally recommended, CO: clinical option, SC: standard of care, Ch-S: chemo-sensitive, ASCT: autologous stem cell transplantation, CLL: chronic lymphocytic leukaemia.

second MCL phase II trial evaluating maxi-R-CHOP and R-arabinoside (ARA-C) followed by ASCT: the 6-year EFS of 56% and 6-year OS of 70% were very promising, leading to further studies in the upfront setting.[60] An important next trial from the EMCLN was published in 2016: 455 patients were randomised to ASCT following R-CHOP or R-CHOP/R-DHAP.[61] Although the trial did not examine the value of ASCT directly, it showed the essential role of ARA-C and ASCT in the upfront setting with a median OS over seven years, much better than OS seen in historical series without ASCT. These favourable results were recently confirmed by others, both in the young patient population and in the elderly.[62-64] The value of ASCT after the R-hyper-CVAD (cyclophosphamide, vincristine, adriamycin and dexamethasone) regimen is unclear, with conflicting results from non-randomised trials but with OS beyond ten years.

There have been two prospective trials using allo-SCT upfront: the East German Study Group of Haematology and Oncology published two data sets of (only) 21 patients having allo-SCT after R-CHOP or R-CHOP/R-DHAP induction. CR rate at HSCT was 43%, 5-year OS was 73%.[65] The second trial on 25 patients using allo-SCT after at least a PR by standard induction R-CHOP/R-ARA-C and BEAM-Campath RIC, was only presented in abstract form. TRM was 8%, 2-year PFS 68% and 2-year OS was 80%.[66] Longer follow-up is needed to draw conclusions on the use of allo-SCT upfront.

Guidelines from the EBMT/EMCLN confirm the use of ASCT in first remission, but not allo-SCT in this indication, except perhaps for young patients with a very high risk profile, based on the MCL international prognostic index (MIPI) +Ki67 30% score. The role of ASCT or allo-SCT in later lines of treatment is more controversial, because of lack of RCTs. Allo-SCT can be offered as a clinical option after ASCT and chemo-sensitive relapse, following the same EBMT/EMCLN guidelines and based on retrospective data.[67] It remains to be seen if new molecules such as Bruton's tyrosine kinase inhibitors and BCL-2 inhibitors, very powerful alone or in combinations, will alter the place of transplantation in this disease entity.[68]

Hodgkin's lymphoma

Most patients with Hodgkin's lymphoma (HL) are nowadays cured with standard chemotherapy and the introduction of brentuximab vedotin (BV) or the PD-1 inhibitors – nivolumab frontline will probably impact positively on these cure rates. The role of upfront intensification and HSCT have therefore become even more questionable and current guidelines therefore outdated.[69]

Even in patients with high risk features (high Hasenclever risk score), upfront intensification with ASCT is not evidence-based.

KEY MESSAGES FOR CLINICAL PRACTICE

1. For relapsed but chemo-sensitive diffuse large B-cell lymphoma, autologous stem cell transplantation (ASCT) has been shown to improve outcome in randomised controlled trials. High-grade B-cell lymphoma with translocations of *MYC* and *BCL2* (and/or *BCL6*) remains an unmet medical need. In large retrospective series, consolidative ASCT in CR1 was not significantly related to a better progression-free survival and overall survival.
2. ASCT is a valuable option for both relapsing and transformed follicular lymphoma.
3. ASCT has an essential role in the upfront therapy of young patients with mantle cell lymphoma.
4. Despite novel agents, ASCT remains nowadays standard of care in eligible patients with relapsing Hodgkin's lymphoma or primary refractory disease sensitive to salvage treatment. Allogeneic stem cell transplantation should be used with extreme caution after PD-(L)1 inhibitors.
5. In peripheral T-cell lymphoma, only mixed evidence exist to justify ASCT in first remission: large randomised controlled trials are missing.
6. For chronic lymphocytic leukaemia, allogeneic stem cell transplantation has moved backwards due to emerging new molecules such as ibrutinib and venetoclax.
7. In general, reduced intensity conditioning is preferred over myeloablative conditioning before allogeneic stem cell transplantation for lymphomas, the main indication of the latter being multiple relapsed and chemo-refractory disease in fit patients.

If patients fail to achieve a CR with first-line treatment, second-line therapy and intensification with HSCT can be offered as a clinical option, with historically reported PFS of 40-45% and OS of 30-70%, but no RCTs are available. The absence of disease at the time of transplantation is an important prognostic factor. The impact of BV and PD-1 inhibitors as powerful salvage regimens are not fully known yet, but preliminary data on the use of BV and nivolumab as a pre-ASCT salvage regimen showed a remarkable 61% CR rate.[70]

Based on RCTs, ASCT is considered SC for patients who do relapse or who are refractory to first-line therapy but are sensitive to salvage treatment, curing 50% of them.[71,72] If patients have a high risk of residual HL after ASCT, the introduction of BV improves the 4-year PFS from 43% to 66%, as compared to placebo, shown in a recent phase III randomised AETHERA trial.[73]

With respect to allo-SCT, current practices are evolving rapidly, not only by the discussion on donor type (i.e. haplo-identical donors *vs* matched-related donors), but also by the definition of disease-sensitivity in view of the new drugs (BV and PD-1 inhibitors). Allo-SCT has been considered a clinical option for relapsed HL patients after ASCT, if the disease was chemo-sensitive.[74] Nowadays, chemotherapy and its effectiveness is less relevant at second relapse after ASCT because of the standard use of BV and PD-1 inhibitors in this indication. Preliminary data suggest that BV may improve the outcome of allo-SCT if used as a bridging modality to improve pre-transplant remission status, but recent retrospective analysis of the EBMT was less convincing.[75]

BV does not worsen acute or chronic GVHD, which seems more worrisome with the use of the PD-1 inhibitors: the increase of GVHD after PD-1 inhibitors is not very well understood. Specific recommendations of the use of PD-1 inhibitors in the context of allo-SCT are recently published.[76]

When HL is primary refractory without good response to salvage treatment, high-dose chemotherapy with ASCT or allo-SCT leads to remissions of short duration. It can be a clinical option for selected patients based on the studies of the French LYSA group and others.[77-79] Introducing BV and PD-1 inhibitors (inducing durable remissions even without consolidation HSCT) early, as salvage in primary chemo-refractory patients, is essential when proceeding to any type of HSCT in this indication.

Chronic lymphocytic leukaemia

New molecules such as ibrutinib, idelalisib and venetoclax, alone or combined with monoclonal antibodies, have changed the outcome for most patients with chronic lymphocytic leukaemia (CLL) dramatically.[80-82] Even in patients with high risk features (i.e., not achieving a response or relapsing within twelve months after purine analogue therapy; fludarabine resistant CLL, relapsing within 24 months after intensive therapy of purine analogue combinations ± ASCT, presence of TP53 or 17p deletion), these new molecules are able to abrogate their negative prognostic impact. Therefore, there is no place for ASCT anymore in this disease.[83]

Previously, allo-SCT, preferably with RIC, has been offered as a clinical option for young high-risk patients since this treatment was of curative potential and was said to be superior to other salvage regimens.[84,85] The 6-year OS was around 50-63%, but severe chronic GVHD was seen in about 48-56% of patients, largely responsible for the non-relapse mortality of around 20%.[86] Nowadays, although no randomised comparisons are available, the novel agents have challenged the role of allo-SCT in the upfront setting.[87,88] The American Society for BMT (ASBMT) has therefore updated the guidelines for CLL: all patients (also the high-risk category) should have received B-cell receptor pathway inhibitors such as ibrutinib first unless there are contraindications. Alternative options are idelalisib preferably combined with rituximab, or venetoclax. In case of a lack of response or at relapse after front-line therapy, a second-line therapy based on the new drugs should be used first. The optimal duration of treatment with these drugs as a bridge to allo-SCT remains an open question. An allo-SCT should be discussed at the first (if venetoclax has been used) or second relapse.[89]

Richter's or transformed CLL, especially the clonally-related DLBCL (median OS of about 14 months) which is a rare but dismal complication of CLL, poses an important challenge. The novel agents are not fully tested in this indication, but tend to have a short effect.

Anthracycline-based combination chemotherapy usually gives short lasting responses (median PFS of 10 months). Adding an intensive treatment modality upfront has been evaluated for possible improvement of these results. Non randomised data suggest that allo-SCT in patients in first CR or PR results in a 41-75% OS at 3 years.[90]

Based on a small EBMT survey of patients with Richter's transformation, there might be a clinical option for both ASCT and allo-SCT. Fifty-nine patients younger than 60 years old were registered. Thirty-four patients had received ASCT and 25 patients had received allo-SCT, with 36% being refractory to chemotherapy at HSCT. In allograft recipients, RIC allo-SCT was used in 72%. Three-year estimates of the probabilities of OS and RFS and the cumulative incidences of relapse and non-relapse mortality were 36%, 27%, 47% and 26% for allo-SCT and 59%, 45%, 43% and 12% for ASCT, respectively. Chemotherapy-sensitive disease and RIC were found to be associated with superior RFS after allo-SCT in a multivariate analysis.[90]

CONCLUSION

Stem cell transplantation in lymphoproliferative diseases has been proven SC by randomised clinical trials in only a few indications (relapsed DLBCL, HL, FL and in first line for young patients with MCL). In other indications, the value of transplantation is less clear and has been derived mostly from retrospective analysis. In some disease entities such as B-cell CLL, there is almost no place anymore for transplantation. The current national BHS guidelines, consensus statements of the BHS lymphoma committee and the BHS transplantation committee are in accordance with recent international guidelines anno 2018 and should help the haematologist in transplant-related decision-making. The development and incorporation of new drugs such as 'small-molecule drugs' and immunotherapies will continuously challenge the place of transplantation in the future.

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