



**AUTOLOGOUS AND ALLOGENEIC STEM
CELL TRANSPLANTATION FOR
AGGRESSIVE AND HIGHLY-AGGRESSIVE
NON-HODGKIN LYMPHOMA**

**D. A. Stewart MD, FRCPC
Head, Division of Hematology and Hematological Malignancies,
Foothills Medical Center
Professor of Medicine,
University of Calgary**

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AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

General Considerations

Eligibility Criteria

Criteria to determine eligibility of lymphoma patients for Hematopoietic Stem Cell Transplantation (SCT) are not based upon high levels of evidence, and therefore, vary somewhat between transplant centres. In general, the following factors are taken into account when considering eligibility for SCT:

- 1) Age \leq 70 years,
- 2) Adequate performance status (KPS 70-100% or ECOG 0-2),
- 3) Chemosensitive lymphoma without active secondary spread to the CNS (parenchymal brain, leptomeninges),
- 4) Adequate major organ function (LVEF \geq 50%, PFTs [FVC, FEV1, DLCO] $>$ 60% predicted, creatinine $<$ 150 μ mol/L, ALT $<$ 2 x ULN, Bilirubin $<$ 2 x ULN, no evidence cirrhosis),
- 5) Ability to give informed consent,
- 6) No serious active infections (HIV, TB, HBsAg, active bacterial/fungal disease), and
- 7) Able to collect adequate stem cell graft (for autologous SCT $>$ 2 $\times 10^6$ CD34+ cells/kg free of tumor contamination, usually possible only with baseline blood platelet count $>$ 100 and WBC $>$ 3.0, and prior radiotherapy $<$ 30% marrow).¹

Absence of any one of these factors does not constitute an absolute contraindication to HDCT/ASCT, and successful outcomes have been reported in a variety of poor prognosis settings, even HIV infection.^{2,3} It is widely accepted, however, as the number of unmet eligibility criteria increases, the likelihood of a poor outcome from SCT also increases. For example, the Center for International Blood and Marrow Transplant Research (CIBMTR) compared the clinical outcomes of 805 older (age \geq 55 years) NHL patients with 1949 younger NHL patients ($<$ 55 years) receiving ASCT during 1990-2000. The study concluded that ASCT in older NHL patients is feasible, but most disease-related outcomes are statistically inferior to younger patients.^{4,5} For example, in multivariate analysis, while adjusting for patient-, disease-, and treatment-related variables, older patients with aggressive histologies were 1.86 times (95% CI 1.43-2.43, $P <$.001) more likely than younger patients to experience treatment-related mortality (TRM).⁵

Diffuse Large B-Cell Lymphoma

Indications and Outcomes

Diffuse Large B-cell Lymphoma (DLBCL) accounts for approximately 1/3 of all lymphomas, and represents the majority of patients treated in SCT studies for aggressive lymphoma.⁶ High dose chemotherapy (HDCT) and autologous SCT (ASCT) has been standard therapy for chemosensitive relapsed/refractory DLBCL ever since the results of the PARMA study were published more than a decade ago.⁷ The PARMA study is the only randomized controlled trial (RCT) of high dose versus conventional dose salvage chemotherapy for relapsed, chemosensitive NHL, and demonstrated a significant failure-free (51% vs 12%) and overall (OS) survival (53% vs 32%) advantage for high dose BEAC (BCNU, etoposide, cytarabine, cyclophosphamide) and ASCT over standard-dose DHAP. This was found despite the fact that not all patients allocated to the HDCT arm of the trial actually received HDCT, and many patients in the control arm eventually underwent HDCT/ASCT at the time of second disease progression.

The major prognostic factors for outcome of relapsed DLBCL include the time to relapse, IPI risk factors, and chemosensitivity. In the PARMA study, time to relapse <1 year was associated with a 40% response to DHAP, and only 13% 8 year OS.⁸ Costa and colleagues reported median overall survival of only 5 months for patients with both a time to relapse <18months as well as IPI=3-5, suggesting that these poor prognosis patients should not be subjected to ASCT.⁹ Hamlin and colleagues reported that the salvage age-adjusted IPI predicts outcome of relapsed DLBCL with PFS rates of approximately 69%, 46%, 25% for chemosensitive relapsed DLBCL patients with scores of 0, 1, and 2-3, respectively.¹⁰ More recently, in the first interim analysis of 200 patients treated in the CORAL study (R-ICE Versus R-DHAP in Relapsed DLBCL Patients, Followed by ASCT +/- Maintenance Rituximab) reported by Gisselbrecht and colleagues, factors associated with response to salvage therapy were refractory disease or relapse within 12 months (52% vs. 88%), IPI 2-3 (54% vs 77%), and relapse after prior rituximab (54% vs 82%).¹¹ DLBCL subtypes and extranodal presentations seem to be of less importance for those patients who prove chemosensitivity and undergo ASCT. For example, Kuruvilla and colleagues compared outcomes of 37 relapsed/refractory primary mediastinal DLBCL (PMLCL) patients with those of 143 other DLBCL patients. The overall response rate to salvage chemotherapy (25% vs. 48%, p = 0.01) and 2-year OS after diagnosis of relapse/refractory disease (15% vs. 34%, p = 0.018) was inferior in PMLCL patients, but the 2-year post-ASCT OS (67% PMLCL vs. 53%, p = 0.78) and PFS (57% PMLCL vs. 36%, p = 0.64) were similar.¹² Finally, the combination of IPI and PET/CT assessment of chemosensitivity may provide even greater predictive ability. Schot and colleagues reported the use of FDG-PET after 2 cycles salvage DHAP-VIM chemotherapy in 101 patients (78 Aggressive NHL [53 DLBCL], 23 HL), of whom 80 were chemosensitive and 77 eventually had ASCT.¹³ For NHL, the 2 year FFS was 67%, 56%, 26%, and 12% for aaIPI 0, 1, 2, 3, respectively. The 2 year FFS by PET response to salvage DHAP-VIM was 72% for CR, 38% for PR and 10% for NR. The two factors

were combined by assigning 0 points for CR, 1 point for PR, and 2 points for NR on PET imaging. The 2 year FFS rates were 82%, 58%, 24% and 5% for patients with a combined risk score of 0-1, 2, 3, and 4-5 points, respectively.¹³ Using evidence from the above studies, it is therefore, probable that relapsed DLBCL patients can be appropriately excluded from ASCT if they have 3, and possibly even 2 of the following adverse prognostic factors: 1) time to relapse of <12months, 2) relapse aaIPI scores of 2-3, and 3) chemoresistance as defined as lack of at least a PR to salvage chemotherapy.

No RCT has been conducted to evaluate potential benefit of HDCT/ASCT for patients with chemoresistant relapsed/refractory large cell lymphoma (i.e. patients who do not respond to second-line chemotherapy) or for patients who have experienced failure of more than one prior chemotherapy regimen. Retrospective reports, however, suggest only low rates of long-term progression-free survival (PFS) following HDCT for these poor prognosis patients. As such, in many transplant centres, ASCT is not offered in these settings.

Conflicting results have been reported from RCTs evaluating first remission-consolidation with HDCT/ASCT for aggressive NHL.¹⁴ Many studies were negative, while a few have shown significant PFS benefits from HDCT. Criticisms of these studies, however, are numerous. Many studies had inadequate statistical power, most did not use the age-adjusted IPI as an eligibility or stratification criterion, and they were heterogeneous with respect to histological subtypes, choice of standard and HDCT regimens, and timing of HDCT relative to number of induction chemotherapy cycles. Some studies used a non-conventional, intensive chemotherapy “control arm”. These studies reported that up to 40% of patients in the HDCT arm never received the assigned HDCT, often due to an inadequate response to abbreviated induction chemotherapy prior to planned HDCT/ASCT. The use of abbreviated induction therapy followed by a single HDCT/ASCT is not considered a viable strategy for future trials. Greb and colleagues performed a systematic meta-analysis searching the Cochrane Library, MEDLINE and other databases (1/1990 to 1/2005) for studies that evaluated the efficacy of front-line HDCT relative to conventional chemotherapy in aggressive NHL.¹⁵ Fifteen RCTs including 2728 patients were identified. The results of this meta-analysis demonstrated that HDCT does not improve OS (HR 1.05, 95% CI 0.92-1.19) or EFS (HR 0.92, 95% CI 0.80-1.05) compared with conventional chemotherapy for all patients included in these studies, if one does not consider IPI risk score, or type of “conventional” chemotherapy. However, subgroup analysis for OS indicated different effects (p=0.032) for good (HR 1.46, 95% CI 1.02-2.09) and poor risk (HR 0.95, 95% CI 0.81-1.11) patients. Funnel plot heterogeneity excluded the GELA LNH 93-3 study wherein the dose-intensity of the control arm exceeded that of the HDCT arm.¹⁶ Excluding this study, the meta-analysis demonstrated a significant benefit for HDCT over SDCT in terms of EFS (HR 0.78, 95%CI 0.65-0.94) and OS (HR 0.81, 95%CI 0.67-0.97) for patients with high intermediate or high risk IPI scores.

Despite this meta-analysis, upfront HDCT is still considered investigational. Recently, PFS and OS rates for DLBCL following standard dose therapy have improved by

approximately 15% with the addition of Rituximab to the CHOP regimen. Of interest, however, RCHOP has never been compared to CHOP in a RCT for poor prognosis DLBCL patients who were the target of prior HDCT RCTs; those who are under 60 years of age with 2-3 age-adjusted IPI risk factors. Potentially, a more definitive HDCT study has recently been completed by the American Intergroup and NCIC-CTG (LY.11), which enrolled aggressive histology NHL patients who had 2-3 age-adjusted IPI risk factors. In this study, patients who responded to 5 cycles of (R)CHOP chemotherapy were then randomized to one more (R)CHOP followed by HDCT/ASCT or to 3 more cycles of (R)CHOP. The study was adequately powered to definitively address the role of late first remission consolidation with HDCT/ASCT.

The other approach that is still worthy of study involves multiple cycles of high dose sequential induction chemotherapy as pioneered by groups in Italy and Germany.^{17,18} Such an approach, however, has significant feasibility issues for resource-constrained centres such as found in Canada. The study by Schmitz and colleagues suggest that early use of high dose induction may be necessary to improve DLBCL outcomes from HDCT/ASCT. In this study, 84 patients with aggressive lymphoma and elevated LDH levels were randomized to receive either 4 (Arm A) or 6 (Arm B) courses of cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (megaCHOEP). The last three treatment courses were supported by autologous peripheral blood stem cell transplantation. Although the total doses of cyclophosphamide and etoposide were comparable, the dose intensity during the first 3 treatment courses was planned to be 2.8-fold and 2.0-fold higher, respectively, for patients in Arm A. At 2 years, outcomes were superior for Arm A over Arm B for freedom from treatment failure (52.5% vs 23.1%, $p=0.02$) and overall survival (70% vs 46.2%, $p=0.037$). A final investigational approach involves early identification of patients who are unlikely to be cured by standard induction therapy through the use of interim response PET/CT imaging after 2-4 cycles of chemotherapy, and then treating unfavorable responders with immediate salvage HDCT/ASCT.¹⁹

Primary CNS Lymphoma

Conventional therapy for PCNSL involves high dose methotrexate-based induction, potentially followed by cranial radiation, although long term outcomes are poor, especially for patients over age 50 years or with poor performance status at diagnosis.^{20,21} In addition, high dose methotrexate followed by cranial radiation is associated with a high risk of dementia and neurotoxic death in patients over age 50-60 years.²² If patients refuse radiotherapy because of the concern regarding radiation-induced dementia, and fulfill standard eligibility for ASCT, they should be considered for high dose TBC chemotherapy (thiotepa, busulfan, cyclophosphamide) and autologous stem cell transplantation as part of their initial treatment, or at the time of first relapse following initial therapy since reports suggest long term progression free survival rates of 40-50% with this approach.^{23,24}

Choice of Re-induction Therapy prior to HDCT/SCT

Several salvage chemotherapy regimens exist for relapsed DLBCL, but RCT have not been performed to determine whether one regimen is superior to another.²⁵ Most regimens involve prolonged intravenous administration and therefore, require hospitalization. The GDP (gemcitabine 1g/m² IV days 1 and 8, dexamethasone 40mg p.o. days 1-4, cisplatin 75mg/m² IV day 1) regimen can easily be administered on an outpatient basis, and has been reported by the NCIC CTG to give 49% response rate in 51 patients with the relapsed/refractory NHL.²⁶ This is similar to other salvage chemotherapy options such as ICE or DHAP. The NCIC CTG LY12 trial is currently evaluating (R)DHAP versus (R)GDP for relapsed/refractory aggressive NHL, with responding patients proceeding to HDCT/ASCT and then to a second randomization between observation and rituximab consolidation therapy every 2 months for one year. The other RCT of salvage regimens for relapsed DLBCL, the CORAL study, thus far shows similar response rates and PFS rates for the RICE and RDHAP treatment arms.¹¹ There is some suggestion from phase II studies that intensive salvage therapy prior to HDCT/ASCT may improve OS rates, but this needs to be proven in well conducted RCT before wide adoption.^{27,28} Finally, Rituximab combined with salvage chemotherapy has been shown in a RCT and several historically controlled studies to improve post-ASCT outcomes relative to salvage chemotherapy alone.²⁹⁻³¹ The majority of this data involves patients who did not receive rituximab with their primary CHOP-like initial induction therapy prior to relapse. Nevertheless, rituximab is now commonly added to salvage therapy regimens, at least for patients who relapsed more than 6-12 months after completing initial RCHOP, or who never received rituximab with primary chemotherapy.

Stem Cell Source, Mobilization, and Purging

The preferred stem cell source for autologous SCT is apheresed mobilized peripheral blood stem cells, based upon small RCTs that demonstrated improved quality of life, shorter engraftment times, decreased blood and platelet transfusions, decreased hospital stays, and reduced costs relative to traditional bone marrow harvests.³²⁻³⁵ Chemotherapy (a salvage regimen or cyclophosphamide 2-4g/m²) plus G-CSF 5 mcg/kg/d (300mcg for body weight <60kg, 480 mcg for weight 60-90kg, and 600mcg for weight >90kg) is an acceptable standard method of stem cell mobilization.^{36,37} G-CSF doses 10-16 mcg/kg or the addition of stem cell factor have been shown to mobilize slightly more CD34+ cells into the blood, but this has not translated into superior engraftment times on average.^{38,39} Patients who are expected to mobilize CD34+ cells poorly may benefit from the use of intensive chemotherapy (eg. Cyclophosphamide 4.5 g/m² + etoposide 600 mg/m²) and G-CSF 5µg/kg bid as well as the possible addition of Stemgen 20µg/kg/d.^{40,41} Predictors of poor mobilization include: advancing age, prior treatment with chlorambucil, fludarabine, melphalan, radiotherapy to >25% of bone marrow, or repeated cycles of chemotherapy plus G-CSF within the past 6 months, as well as those with low blood platelet counts prior to mobilization treatment, or those who have experienced prior failure of stem cell mobilization.⁴²

ABMTR/EBMT data suggest a role for purging with extremely low relapse rates following syngeneic SCT, followed by higher relapse rates with purged autologous SCT and then significantly higher relapse rates with unpurged autologous SCT.⁴³ This data, however, is potentially biased, and randomized controlled trials evaluating ex-vivo autograft tumor purging techniques have not been reported in the setting of autologous transplantation for lymphoma. In addition, autograft purging results in stem cell loss and delays hematopoietic and immunological engraftment.⁴⁴⁻⁴⁶ Because of these facts, routine ex-vivo autograft purging is not recommended.

High Dose Therapy Regimen

The most common HDCT regimens used for lymphoma include: cyclophosphamide, etoposide, carmustine (CEB or CBV), carmustine, etoposide, cytarabine, melphalan (BEAM), fractionated total-body irradiation (fTBI) with cyclophosphamide (Cy) and possibly etoposide (VP-16) (CyTBI or VPCyTBI) and, Melphalan, etoposide with or without TBI (MeVPTBI). Randomized controlled trials comparing these regimens for lymphoma have not been conducted. Non-randomized retrospective studies suggest somewhat better efficacy and tolerability for BEAM over CBV or the TBI-containing regimens in the setting of aggressive lymphoma.⁴⁷⁻⁵⁰ For example, Salar and colleagues investigated the impact of the preparative regimens on the outcome of 395 patients with diffuse large cell lymphoma (DLCL), consecutively reported to the registry of the Spanish GEL/TAMO.⁵¹ Conditioning consisted of chemotherapy-only in 348 patients (BEAM, 164; BEAC, 145; and CBV, 39) and CyTBI in 47. Median times to engraftment and discharge were significantly shorter in the chemotherapy-only group, and early TRM was significantly higher with CyTBI. Overall survival of patients conditioned with BEAM or BEAC (58% (95% CI 50-66%)) was more favorable than with CBV (40% (95% CI 24-56%)), and significantly better than with CY-TBI (31% (95% CI 18-44%)), a finding that persisted in multivariate analysis. Other studies suggest that high TBI doses (>12Gy) or combinations of TBI and etoposide may increase the risk of secondary myelodysplasia/AML, and are to be discouraged.^{52,53} Perhaps the use of targeted TBI though radioimmunoconjugates will improve the efficacy while reducing toxicity of TBI, however, this has yet to be proven through RCTs.⁵⁴ Primary CNS Lymphoma requires chemotherapy agents that cross well through the blood brain barrier such as busulfan and thiotepa (eg. Thiotepa 600mg/m², Busulfan 9.6 mg/kg, Cyclophosphamide 4g/m²) rather than agents that penetrate poorly such as melphalan and etoposide.²³

Post-ASCT Therapy

G-CSF 5mcg/kg/d is generally given to all ASCT patients starting day +7 post-SCT until ANC >1.5 x 10⁹/L. This is based on randomized controlled trials showing improved neutrophil engraftment and shortened length of hospital stay compared to no G-CSF, as well as trials showing no significant benefit of using higher doses of G-CSF or starting G-CSF earlier post-SCT.⁵⁵⁻⁵⁸

Mantle Cell Lymphoma

Mantle-cell lymphoma (MCL) is characterized by poor prognosis with a median survival of only 3 to 5 years following conventional therapy, and little improvement in outcome when rituximab is added to conventional CHOP.^{59,60} In 1996, the European MCL Network initiated a randomized trial comparing consolidation with CyTBI/ASCT (TBI 12 Gy, cyclophosphamide 120 mg/kg) to a conventional α -interferon maintenance (6×10^6 IE IFN- α 3x weekly) for patients under 65 years of age who were in first remission after a CHOP-like induction regimen.⁶¹ A total of 232 previously untreated patients with advanced stage MCL were randomized upfront. Only 173 (76%) of 228 evaluable patients responded to initial induction chemotherapy, and 151 of these (87%) proceeded to the assigned consolidation therapy. Baseline characteristics were comparable in the per protocol as well as in the intent to treat (ITT) cohorts. By ITT, and after a median follow-up of 6.1 years, patients in the ASCT study arm experienced a significantly longer median time to treatment failure of 2.6 vs. 1.4 years ($p=0.0001$) as well as longer median OS of 7.5 vs. 5.3 years ($p = 0.031$).⁶¹ Accordingly, first-remission HDCT/ASCT represent the current therapeutic standard in younger MCL patients. The second Nordic MCL phase II trial in 160 patients suggests that HDCT/ASCT outcomes can possibly be improved upon by the addition of high dose Ara-C and Rituximab, with projected 6-year overall, event-free, and progression-free survival rates of 70, 56 and 66%, respectively, with no relapses occurring after 5 years.⁶² Other single centre reports suggest R-HyperCVAD induction followed by HDCT/ASCT may also a reasonable strategy, but confirmatory RCTs are lacking.⁶³ Because virtually all mantle cell lymphoma patients eventually relapse following autologous SCT, and relapse rates are known to be lower following allogeneic SCT, allogeneic SCT may be the preferred strategy for eligible patients in poor prognosis situations including 1st partial remission with several IPI risk factors or peripheral blood involvement at diagnosis, or patients in 1st relapse.⁶⁴⁻⁶⁶

Robinson and colleagues recently reported a large retrospective EBMT study of reduced intensity SCT (RIST) in MCL.⁶⁷ Between 1998 and 2006 279 patients with MCL received a RIST with 210 procedures performed after the year 2001. Patients had received a median of 3 lines (range 1-9) of prior therapy and 119 (43%) had undergone a previous autologous SCT. The median time from diagnosis to transplant was 30 months (range 3-161). Conditioning for RIST was achieved with fludarabine+alkylating agent in 66%, fludarabine+TBI in 13%, and a variety of other reduced intensity regimens in 20%. The 100 day, 1 year and 3 year non-relapse mortality rates were 13, 32 and 41% respectively. The Kaplan-Meier estimate of the PFS at 1 and 3 years was 49% and 29% respectively. PFS was significantly worse for patients with refractory disease (RR=2.2, $p<0.001$), poor PS (RR2.6, $p=0.005$) or those transplanted prior to 2002 (RR=1.5, $p=0.03$).

Peripheral T-Cell Lymphoma

In North America, peripheral T-cell lymphomas (PTCL) represent 5-10% of all lymphomas.⁶⁸ In terms of frequency, 75% of PTCL in North America are represented by

PCTL-NOS (34%), CD30+ anaplastic large cell lymphoma (24%, ALK+ 16%, ALK- 8%), and angioimmunoblastic (16%). With the exception of CD30+ anaplastic large cell lymphoma, PTCLs are associated with only 10-20% chance of long-term progression-free survival following conventional chemotherapy. Some small single centre reports of HDCT/ASCT for relapsed/refractory PTCL suggest poor PFS rates of only 10-20% (Chen AI, Smith SD.),^{69,70} while other reports, including larger transplant registry series, suggest outcomes similar to those for relapsed DLBCL (Feyler S., Kewalramani T, Song KW., Nickelsen M),⁷¹⁻⁷⁴ with uniformly superior outcomes for ALCL compared to other PTCLs.

Nickelsen and colleagues reported a retrospective analysis on 424 pts with mature T-cell lymphoma who have received HDCT/ASCT in EBMT centres between 2000 and 2005. Histological subtypes were ALCL=98, PTCLu=176, AITL=120, unknown=30. Median time from diagnosis to ASCT was 9 months (4-99), and median follow up for surviving pts was 36 months (0.4-99). Disease status was CR1 in 35%, chemosensitive disease worse than CR1 in 52%, and refractory disease 13%. Only 9% received TBI. At 3 years after ASCT non relapse mortality (NRM) was 7.4%, relapse rate (RR) was 43.1%, PFS was 49.5% and OS 62.3%. In multivariate COX analysis for PFS, refractory disease and chemosensitive disease worse than CR1 were significant adverse factors compared to CR1 (relative risk (RR) 3.2 and 1.7, respectively, $p < 0.001$ each) as was refractory disease compared to chemosensitive disease (including CR1; RR 1.9, $p = 0.004$). Other significant adverse factors were age at SCT > 60 years (RR 1.4, $p = 0.04$), poor performance status at ASCT (RR 2.1, $p = 0.046$) and PTCLu versus other subgroups (RR 1.4, $p = 0.02$).

In view of poor outcomes following conventional CHOP-like chemotherapy, many studies have investigated first-remission HDCT/ASCT for PTCL. Jantunen and colleagues reported a survey of 37 adult PTCL patients transplanted in Finland during 1990-2001 (PTCL-NOS=14, ALCL=14, other=9).⁷⁵ Disease status at the time of ASCT was CR/PR1 in 18 patients; CR/PR2 in 14 patients, and other in five patients. HDT consisted of either BEAC (N=22) or BEAM (N=15). The estimated 5-year OS was 54%. Patients with ALCL had superior OS when compared with other subtypes (85 vs 35%, $P = 0.007$). OS at 5 years was 63% in patients transplanted in CR/PR1 vs 45% in those transplanted in other disease status ($P = NS$). In contrast to these encouraging results, Reimer and colleagues reported a prospective multicenter study of 4-6 cycles of CHOP followed in responding patients by CyTBI/ASCT.⁷⁶ From June 2000 to April 2006, 83 patients were enrolled and 55 (66%) patients received ASCT. In an ITT analysis, the 3-year PFS rate was only 36%. Mercadal and colleagues reported results of a phase II study involving 41 patients with PTCL who received 6 cycles of intensive chemotherapy followed in responding patients by HDCT/ASCT.⁷⁷ Only 17 patients ultimately underwent ASCT, with 17 patients not achieving PR/CR, and 7 failing to mobilize stem cells. Overall, 4 year PFS was 30%, with similar outcome whether or not ASCT was performed. Rodríguez and colleagues reported 74 patients transplanted in first complete response (CR) from the Spanish Lymphoma and Autologous Transplantation Group cooperative group.⁷⁸ Eighty-eight percent presented advanced (III-IV) Ann Arbor stage; and 52% had high lactate dehydrogenase; 65% had two or three risk factors of the aaIPI.

The 5-year OS was 68% and PFS reached 63%. Kyriakou and colleagues from the EBMT reported a retrospective, multicenter study of 146 patients with angioimmunoblastic T cell lymphoma (AITL) who received ASCT.⁷⁹ The actuarial overall survival (OS) was 67% at 2 years and 59% at 4 years and the cumulative incidence of relapse was estimated at 40% and 51% at 2 and 4 years, respectively. The estimated 2 and 4 year PFS rates for patients who received their transplants in CR were 70% and 56%, compared to 42% and 30% for patients with chemotherapy-sensitive relapsed disease, and 23% at both time points for patients with chemotherapy-refractory disease. Available retrospective and phase II evidence, therefore, suggests that PTCL patients can benefit from HDCT/ASCT when used in the settings of chemosensitive relapse, or first remission consolidation.⁸⁰ RCTs evaluating treatments for these uncommon lymphomas are lacking, however.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma (LBL) is a rare, clinically aggressive neoplasm of the young that frequently involves the bone marrow (BM) and/or central nervous system.⁸¹ These patients require aggressive combination chemotherapy (similar to acute lymphoblastic leukemia therapy) with induction, consolidation, prophylactic intrathecal chemotherapy and either maintenance therapy or first remission autologous stem cell transplantation. Sweetenham and colleagues reported a prospective RCT comparing a first remission HDCT/ASCT to conventional-dose consolidation and postremission maintenance chemotherapy in adults with lymphoblastic lymphoma.⁸² In total, 119 patients entered the study from 37 centers. Of the 98 patients eligible for randomization, only 65 were randomized; 31 to ASCT and 34 to conventional therapy. Although the actuarial 3-year RFS rate was 24% vs 55% in favour of ASCT (hazards ratio = 0.55; 95%CI, 0.29 to 1.04; P =.065), the sample size was too small to demonstrate any effect on OS (45% vs 56%, P =.71). It can be concluded from low level evidence in this rare disease, that either induction therapy followed by first remission HDCT/ASCT or conventional ALL-type intensive induction/consolidation/maintenance chemotherapy with salvage SCT at relapse are reasonable approaches for LBL. Conditioning regimens typically include TBI based upon low level evidence from ALL studies suggesting TBI improves outcomes compared to Busulfan regimens. For example, Bunin and colleagues evaluated children <21 years with ALL undergoing allogeneic stem cell transplant (SCT) with either busulfan (Bu) or TBI, with etoposide 40 mg/kg and cyclophosphamide 120 mg/kg.⁸³ Randomization was stratified based upon duration of remission, remission status, and prior cranial irradiation. A total of only 43 patients were enrolled. At a median follow-up of 43 months, event-free survival (EFS) was 29% in the Bu arm and 58% in the TBI arm (P=0.03).⁸³

Because LBL is similar to acute lymphoblastic leukemia, some centers prefer allogeneic hematopoietic stem cell (SC) transplantation to autologous SC transplantation. The IBMTR and ABMTR databases were retrospectively analyzed for outcomes of LBL patients who underwent autologous (auto, n = 128) or HLA-identical sibling (allo, n = 76) SC transplantations from 1989 to 1998.⁸⁴ AlloSCT recipients had higher treatment-related mortality (TRM) at 6 months (18% versus 3%, P =.002), and this disadvantage

persisted at 1 and 5 years. Significantly lower relapse rates were observed in alloSCT recipients at 1 and 5 years (32% versus 46%, $P = .05$; and 34% versus 56%, $P = .004$, respectively), but no differences were noted in 5 year lymphoma-free survival rates (36% versus 39%, $P = .82$) or 5 year OS (44% versus 39%, $P = .47$) between alloSCT and autoSCT. Multivariate analyses to account for confounding factors confirmed these results. In summary, alloSC transplantation for LBL is associated with fewer relapses than with autoSC transplantation, but higher TRM offsets any potential survival benefit. Independent of SCT type, BM involvement at the time of transplantation and disease status more advanced than first complete remission were associated with inferior outcomes. In addition to this retrospective study, the EORTC ALL-3 trial evaluated the efficacy of alloSCT compared with that of autologous marrow transplantation and maintenance chemotherapy in 220 acute lymphoblastic leukemia and non-Hodgkin's lymphoma patients ≤ 50 years who reached CR.⁸⁵ Among these patients 184 patients started consolidation and were HLA typed; 68 had a donor and 116 had no sibling donor. The median follow-up was 9.5 years. AlloSCT was performed in 47 (68%) patients with a donor while autologous transplantation or maintenance chemotherapy was given to 84 (72%) patients without a sibling donor. The 6-year disease-free survival rate was similar in the groups with and without donor [38.2% (SE=5.9%) vs. 36.8% (SE=4.6%), hazard ratio 1.01, 95% CI 0.67-1.53]. Comparing the donor group with the no donor group, the former had a lower relapse incidence (38.2% vs. 56.3%, $p=0.001$), but a higher cumulative incidence of death in CR (23.5% vs. 6.9%, $p=0.0004$). The 6-year survival rates were similar [41.2% (SE=6.0%) vs. 38.8% (SE=4.6%)]. AlloSCT is, therefore, generally reserved for second-line therapy of relapsed/refractory LBL, whereas ASCT is considered a treatment option for first-remission consolidation in lieu of prolonged consolidation/maintenance therapy with complex conventional chemotherapy regimens.

Burkitt Lymphoma

True Burkitt lymphoma is rare, representing $<1\%$ of all lymphomas.⁸⁶ As such, treatments for this entity have not been evaluated in RCTs. Conventional primary induction therapy consists of intensive chemotherapy with CNS prophylaxis using regimens such as CODOX-M/IVAC.⁸⁷ SCT is generally reserved for recurrent disease or chemosensitive primary induction failures. There very little data on SCT for Burkitt lymphoma, and no evidence that allogeneic SCT is superior to autologous SCT for this disease. Therefore, patients with relapsed/refractory Burkitt lymphoma who fulfill standard eligibility criteria for autologous SCT indicated above, are usually treated with this approach. The largest series of Burkitt lymphoma patients undergoing SCT was reported by the EBMT in 1996 by Sweetenham and colleagues.⁸⁸ This study of 117 patients included Burkitt and Burkitt-like lymphomas in first remission ($n=70$) or relapse/refractory states ($n=47$). The 3 year OS rate following SCT was 72% for patients in first remission, 37% in chemosensitive relapse, and 7% for chemoresistant patients.

ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

Full Intensity (Myeloablative) Conditioning

As opposed to Autologous SCT, randomized controlled trials have never been performed to evaluate the role of allogeneic SCT for aggressive lymphoma. Available retrospective data is very difficult to interpret due to alterations in lymphoma classification over the past 20 years and newly identified entities like mantle cell lymphoma were previously grouped with other NHL subtypes. In addition, most series have relatively low numbers of patients, who were very heterogeneous in terms of remission status, disease burden, amount and type of prior therapy. Finally, these patients have received a variety of conditioning and GVHD prophylactic regimens.

Retrospective studies that attempt to compare results of autologous and allogeneic SCT for lymphoma identify that patients treated with allogeneic SCT tend to have more advanced, heavily pre-treated disease, and more marrow involvement. Despite this selection bias, allogeneic SCT seems to result in lower relapse rates than autologous SCT for lymphoma.⁸⁹ This may be due to infusion of a tumor-free graft, induction of a graft versus tumor effect, the use of different types of high dose conditioning, or to subtle differences in patient selection that may result in slower progressive types of disease. For example, it is uncommon that aggressive lymphoma patients in second or third relapse would be considered candidates for an allogeneic SCT, therefore, those patients who actually receive this form of late salvage therapy must maintain excellent performance status, and generally maintain chemosensitive, low tumor burden disease. Large transplant registry data demonstrate that high 20-40% TRM from allogeneic SCT, unfortunately offsets the lower relapse rate, and 5year overall survival rates of 35-40% are not superior to those of autologous SCT for aggressive lymphoma.⁴³ These results seem to be fairly similar regardless of lymphoma subtype, with a little less than 1/3 dying from non-relapse mortality and similar proportion experiencing disease relapse, and a little more than 1/3 achieving long-term disease-free survival. Somewhat better results have occasionally been reported by single centres, studying small numbers of patients, but of course these reports are far less reliable. Results of allogeneic SCT for aggressive lymphoma after failure of prior autologous SCT are particularly poor; with 5 year PFS rates of <10%.⁹⁰

Reduced Intensity (Non-Myeloablative) Conditioning

Reduced intensity conditioning (RIC) allogeneic SCT is associated with approximately 10-15% lower TRM, but higher relapse rates compared to traditional full myeloablative allogeneic SCT.⁹¹ Since the beneficial treatment outcome of RIC allogeneic SCT relies upon an immunological graft versus tumor effect, this strategy is questionable for aggressive NHL, particularly for bulky, rapidly progressive disease situations. When these aggressive tumors are treated with RIC allogeneic SCT, the disease often progresses prior to the potential onset of GVHD. Although a few small series suggest brief responses of aggressive lymphoma to DLI or withdrawal of immune suppression post-alloSCT, a graft-versus-aggressive lymphoma effect has never clearly been demonstrated to confer long-term disease control.⁹² Successful tumor de-bulking prior to

allogeneic SCT seems to be far more important in aggressive lymphoma than in other histologies to create a favorable effector T-cell to target tumor cell ratio in patients with these fast growing lymphomas.

Despite theoretical concerns regarding RIC alloSCT for aggressive lymphoma, available non-randomized data suggests at least similar OS rates compared to myeloablative alloSCT. Sorror and colleagues compared outcomes among patients with lymphoma or chronic lymphocytic leukemia given either nonmyeloablative (n = 152) or myeloablative (n = 68) conditioning.⁹³ Outcomes were stratified by the SCT-specific comorbidity index. Patients in the nonmyeloablative group were older, had more previous treatment and more comorbidities, more frequently had unrelated donors, and more often had malignancy in remission compared with patients in the myeloablative group. Patients with indolent versus aggressive malignancies were equally distributed among both cohorts. For patients without comorbidities, even after adjustment for pretransplantation variables, no significant differences were observed between nonmyeloablative and myeloablative SCT cohorts in NRM, PFS or OS. In contrast, patients with comorbidities experienced lower NRM (P = .009) and better survival (P = .04) after nonmyeloablative conditioning. These differences became more significant (P < .001 and .007, respectively) after adjustment for other variables. Further, nonmyeloablative patients with comorbidities had favourable adjusted progression-free survival (P = .01) suggesting that patients with comorbidities should preferentially receive RIC alloSCT.

Cesar Freytes and colleagues recently described results of non-myeloablative allogeneic SCT for 267 B-cell NHL patients relapsing after autoHCT who were reported to the CIBMTR 1997-2006 (median follow-up 37 months).⁹⁴ Histological subtypes included DLBCL (56%), follicular (17%), mantle cell lymphoma (27%), and time from 1st to 2nd transplant was < 1 yr=21%, 1-2 ys=30%, > 2 yr=49%. In total, 63% were chemosensitive, 31% chemoresistant, and 6% untreated. The graft source was peripheral blood in 78%, and 90% involved unrelated donors. Outcome at 3 years included TRM=42%, progression=36%, and PFS=22%. Causes of death were NHL (29%), infection (19%), MOF (19%), GVHD (14%). There was a lower risk of relapse and death with KPS \geq 90%, >2yr between transplants, use of TBI, and CR at time of SCT.

Overall, full and reduced intensity allogeneic SCT for aggressive lymphoma requires further evaluation in well designed prospective RCTs before the true benefit and role can be fully understood. Only a few conclusions can be drawn based upon currently available data.

- 1) Relapse rates are lower after myeloablative allogeneic SCT than autologous SCT, although this difference is less than that reported for indolent lymphoma.
- 2) Treatment-related mortality rates are high, in the range of 20-40%.
- 3) Some patients who would otherwise have died from their lymphoma achieve long-term survival following allogeneic SCT, and therefore this treatment needs to be considered an option for motivated, well-informed, transplant-eligible patients who

are well enough to tolerate this intensive treatment, have relapsed non-bulky chemosensitive disease, and are not candidates for autologous SCT.

- 4) Data do not demonstrate any improvement in 5 year survival rates with allogeneic over autologous SCT for lymphoma, with the exception of relapsed lymphoblastic and mantle cell lymphomas.^{84,95} Patients with these subtypes who present with extensive blood/marrow disease should also be considered for allogeneic SCT in first remission.⁹⁶ Allogeneic SCT should also be considered in the situation when a patient is a candidate for an autologous SCT but an adequate autograft could not be collected for the patient. Occasionally, patients who relapse after a prior autologous SCT could be considered for an allogeneic SCT, especially for mantle cell or indolent lymphomas.

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