Despite improvements over the past decade in the overall survival of patients with indolent non-Hodgkin lymphomas, these lymphomas remain largely incurable with standard therapies. Immunochemotherapy with rituximab-based regimens has become a well-established standard of care in the primary and relapsed disease settings. The role of hematopoietic stem cell transplantation in indolent lymphoma has been defined by the adoption of this therapy largely in the relapse setting because randomized trials in the first-line setting have not shown survival advantages. Allogeneic stem cell transplantation has the possibility for cure because of the potential for immunologic graft-versus-host disease and lower rates of relapse for allograft over autograft recipients. Retrospective comparisons with observation or maintenance interferon (IFN). Although the median follow-up for these trials was reasonable when reported (ranging from 50 to 90 months), it was apparent that this generation of trials did not offer meaningful OS benefits to patients. The Gruppo Italiano Trapianto di Midollo Osseo/Intergruppo Italiano Linfomi (GITMO/IIL) reported a randomized study comparing high-dose sequential chemotherapy in the first-line setting, maintenance, and relapse settings, older reports of SCT in patients not exposed to rituximab are of limited value. The purpose of this review is to highlight relevant data regarding SCT in the treatment of iNHL.

SCT as consolidation of primary therapy

Trials in the pre-rituximab era randomly assigned patients to ASCT in comparisons with observation or maintenance interferon (IFN). The first-line randomized trials typically reported improvements in PFS that were not associated with OS advantages. Although the median follow-up for these trials was reasonable when reported (ranging from 50 to 90 months), it was apparent that this generation of first-line studies did not offer meaningful OS benefits to patients. The Gruppo Italiano Trapianto di Midollo Osseo/Intergruppo Italiano Linfomi (GITMO/IIL) reported a randomized study comparing high-dose sequential therapy (a treatment that incorporated rituximab with high doses of single-agent chemotherapy in a sequential fashion [R-HDS] followed...
by ASCT) with the standard treatment of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy. Although there was a significant benefit for the R-HDS strategy in event-free survival (the primary end point of the trial; 61% vs 28% with a median follow-up of 51 months; \( P < .001 \)), OS was similar at 81% for the R-DHS arm and 80% for the R-CHOP arm.

Given the available data, there is no rationale that supports ASCT as part of the primary treatment of FL outside a clinical trial. The data for allo-SCT in FL are essentially restricted to the relapse setting and, given the high NRM rate associated with this procedure, allografting has been reserved for later in the disease.

SCT in the relapsed or refractory setting

Grade of FL, transformation, and prognostic factors

SCT strategies are typically considered in the setting of relapsed or refractory disease. In certain patients, it may be important to exclude transformation to an aggressive histology NHL. This is typically a consideration in patients with clinical signs of transformation (eg, rapid change in performance status [PS] or rapid progression in a single disease site, hypercalcemia, lymphoma involvement in sites atypical for the known subtype of iNHL, or rapid change in serum lactate dehydrogenase), or patients who have progressed on treatment, including rituximab maintenance. Aggressive histology transformation of an indolent lymphoma often involves SCT as part of the management strategy, but there may be a rationale for favoring ASCT in this group of patients on the basis of the available data.

The grade of FL and type of transplant remain controversial. The National Comprehensive Cancer Network (NCCN) guidelines suggest treating grade 3 FL (FL3) as an aggressive NHL without a distinction between FL3 subtypes. This contrasts with the European Society for Medical Oncology guidelines, which specify that only FL grade 3B (FL3B) should be treated as an aggressive NHL. This point is relevant because the standard management of aggressive NHL would be ASCT (not allo-SCT) in the setting of chemotherapy-sensitive relapsed or refractory disease.

Comparative data regarding the grade of FL or the outcome of other subtypes of iNHL with SCT are limited. Older reviews have reported conflicting reviews, with 2 of 3 relevant series reporting results from the pre-rituximab era. Prior allograft series did not routinely distinguish the grade of FL. Investigators in Seattle reported no differences in the outcome of ASCT on the basis of the grade of FL in more than 200 patients. Similar results are available from City of Hope in a smaller series of 55 FL patients. In contrast, the Nebraska group reported inferior survival, risk of progression (hazard ratio [HR], 2.14), and treatment failure (HR, 1.97) in patients with FL3 (when compared with other grades of FL) in another series of more than 200 patients.

The Center for International Blood & Marrow Transplant Research (CIBMTR) reported a comparison of outcomes between FL3 and diffuse large B-cell lymphoma that showed improved survival for patients with FL3 (HR, 0.55). Recently, the CIBMTR reported 2 studies comparing outcomes in patients pretreated with rituximab with both ASCT and RIC allo-SCT in FL grades 1 and 2 (FL1 and FL2; \( n = 518 \)) populations or in the FL3 population (\( n = 197 \)). In the FL1 and FL2 patients, the OS was 74% in the ASCT cohort and 66% (\( P = .05 \)) in the RIC allo-SCT cohort. In the FL3 study, the OS was 59% in the ASCT cohort and 54% (\( P = .7 \)) in the RIC allo-SCT cohort. These registry reviews are limited because they did not have central pathology review to assess histologic grade of FL.

The FL International Prognostic Index (FLIPI) has been validated and studied in both the primary and relapse settings. It has also been evaluated in patients undergoing ASCT in whom it has been shown to have prognostic significance, with high-risk FLIPI scores leading to inferior post-ASCT outcomes. The role of FLIPI as a prognostic index in patients undergoing allo-SCT has not been examined in the recent large registry or collaborative reviews of allo-SCT.

Prognostic factors have also been studied with cohorts undergoing ASCT or allo-SCT. The results from recent larger series are summarized in Table 1. In general, poor Karnofsky PS of <50, chemotherapy-resistant disease, and older age (variably defined as >50 or >60 years) are consistent predictors of poor outcomes for most relevant time-to-event outcomes.

The available data suggests inferior survival in patients with FL3 undergoing SCT. Results with modern pathology and treatment strategies seem to be limited to a few reports. Additional data are awaited to further clarify this issue. Age (typically older than 50 years), poor PS, and chemotherapy-resistant disease along with high FLIPI scores tend to predict inferior outcomes after SCT.

Chemotherapy response before SCT

The goal of therapy before SCT is to provide disease and symptom control associated with an objective response to treatment. The randomized CUP trial in relapsed FL required patients to respond to chemotherapy before being randomly assigned to either of the autograft arms (one arm involving a purging strategy for the graft and the other arm unpurged) or to CHOP chemotherapy. In that study, 140 patients were randomly assigned with 89 patients (64%) meeting the criteria for random assignment (complete response or partial response on imaging with <20% involvement in bone marrow by B lymphocytes). It is important to note that the chemotherapy sensitivity criterion in the CUP trial is similar to that in the randomized Parma trial in aggressive NHL. Although investigators of aggressive NHL have performed prospective studies of salvage chemotherapy to better understand the larger denominator of patients being considered for potential SCT, data are largely unavailable about this broader patient group in iNHL.

In contrast to SCT data, many centers are more comfortable with less stringent response criteria for proceeding to transplant in iNHL as evidenced by the presence of 5% to 25% of patients in recent series of ASCT or allo-SCT having resistant disease.

In general, the available data indicate that the best outcomes after SCT are in patients who are chemotherapy sensitive before therapy, typically by computed tomography criteria. The first report of fluorodeoxyglucose positron emission tomography (FDG-PET) response assessment in FL before SCT was from a retrospective French series that reported inferior 3-year PFS for patients with a positive FDG-PET before ASCT (45.5% vs 72.6%; \( P = .039 \)). A larger CIBMTR study reported outcomes of patients with NHL (\( n = 336 \); FL, \( n = 104 \); diffuse large B-cell lymphoma, \( n = 85 \); mantle cell lymphoma, \( n = 69 \)) by FDG-PET scan, which was typically performed at a median of 1 month (range, 0.07 to 2.83 months) before transplant. Positive FDG-PET scans were reported in 47% of patients. At 3 years after SCT, relapse rates were higher in the PET-positive group (40% vs 26%; \( P = .007 \)) whereas PFS and OS were similar. A positive PET scan before SCT was found to be predictive for increased risk of relapse or progression (relative risk, 1.86), but not for mortality.

Outcomes of ASCT for iNHL

High-dose chemotherapy regimens. There is no clear gold standard ASCT high-dose chemotherapy regimen (the myeloablative regimen used before hematopoietic stem cell infusion) for iNHL.
Table 2 highlights several trials and provides the high-dose chemotherapy regimen used when it was available. RCTs have been performed in first-line and relapse settings and have used regimens such as cyclophosphamide with or without etoposide with total body irradiation (TBI) or carmustine, etoposide, cytarabine, and melphalan (BEAM).\textsuperscript{22-24} The randomized CUP trial (which accrued patients between 1993 and 1997) used cyclophosphamide and TBI.\textsuperscript{16} The European Society for Blood and Marrow Transplantation (EBMT) LYM1 trial used the BEAM regimen.\textsuperscript{49} The question of TBI in FL ASCT procedures was recently evaluated in an EBMT study comparing outcomes of TBI-containing regimens with BEAM.\textsuperscript{50} Both NRM (6% at 5 years and 10% at 10 years) and secondary malignancies (9.7% after TBI and 7.9% after BEAM; \(P = .19\)) were similar. Differences in relapse rates could not be identified in patients transplanted beyond first remission. In a CIBMTR review that evaluated high-dose therapy regimens in lymphoma (including HL), interactions between disease histology, high-dose therapy regimens, and outcome were noted.\textsuperscript{51} Cyclophosphamide, carmustine, and etoposide (CBV) was noted to have lower mortality in patients with FL if doses of carmustine were defined in the article as CBV\textsuperscript{low}.

Table 1. Poor prognostic factors in patients undergoing SCT for FL

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Type of SCT</th>
<th>KPS</th>
<th>TBI</th>
<th>Sex</th>
<th>Disease type</th>
<th>Treatment</th>
<th>Age (y)</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Nonrelapse mortality</td>
<td>RIC allo-SCT (vs ASCT)</td>
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<td></td>
<td></td>
<td></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>RIC allo-SCT (vs ASCT)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>ASCT (vs RIC allo-SCT)</td>
<td>Male</td>
<td>REF/untreated</td>
<td>RT</td>
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<td></td>
<td></td>
<td>39</td>
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<td></td>
<td>RIC (vs ASCT)</td>
<td>REF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
</tr>
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<tr>
<td>Progression-free survival</td>
<td>RIC allo-SCT (vs ASCT)</td>
<td>&lt;80</td>
<td>REF</td>
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<td>Yes</td>
<td>REF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39</td>
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</tbody>
</table>

KPS, Karnofsky performance status; REF, chemotherapy-resistant disease (resistant to therapy prior to SCT); RT, radiation therapy (prior to SCT); TBI, total body irradiation (as part of SCT high-dose therapy).

Table 2. Select outcomes of ASCT for relapsed or refractory FL

<table>
<thead>
<tr>
<th>Series</th>
<th>Reference</th>
<th>Arm</th>
<th>No. of patients</th>
<th>HDCT regimen</th>
<th>PFS/EFS (y)</th>
<th>PFS timepoint (y)</th>
<th>HR</th>
<th>P</th>
<th>OS (%)</th>
<th>OS timepoint (y)</th>
<th>P</th>
<th>Comment</th>
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<td>16</td>
<td>Chemotherapy</td>
<td>24</td>
<td>HDCT regimen</td>
<td>26</td>
<td>2</td>
<td>.003</td>
<td>46</td>
<td>4</td>
<td>.07</td>
<td>RCT, no rituximab</td>
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<tr>
<td></td>
<td></td>
<td>Unpurged</td>
<td>33</td>
<td>CY-TBI</td>
<td>58</td>
<td>71</td>
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<td></td>
<td></td>
<td>Purged</td>
<td>32</td>
<td>CY-TBI</td>
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<td>77</td>
<td></td>
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<tr>
<td>EBMT</td>
<td>49</td>
<td>Unpurged, no MR</td>
<td>70</td>
<td>BEAM</td>
<td>35.8</td>
<td>10</td>
<td>ND</td>
<td>10</td>
<td>RCT, no rituximab</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Purged, no MR</td>
<td>72</td>
<td>BEAM</td>
<td>38.7</td>
<td>ND</td>
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<tr>
<td></td>
<td></td>
<td>Unpurged, MR</td>
<td>69</td>
<td>BEAM</td>
<td>48.8</td>
<td>.98</td>
<td>ND</td>
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<tr>
<td></td>
<td></td>
<td>Purged, MR</td>
<td>69</td>
<td>BEAM</td>
<td>52.1</td>
<td>ND</td>
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<tr>
<td>EBMT</td>
<td>67</td>
<td>CR/PR1</td>
<td>131</td>
<td>BEAM or TBI-based</td>
<td>39</td>
<td>15</td>
<td>ND</td>
<td>15</td>
<td>Registry, no rituximab</td>
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<tr>
<td></td>
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<td>No CR/PR1</td>
<td>562</td>
<td>BEAM</td>
<td>26</td>
<td>44</td>
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<tr>
<td>Nebraska</td>
<td>36</td>
<td>CR/PR2+</td>
<td>121</td>
<td>CY-TBI</td>
<td>55</td>
<td>5</td>
<td>71</td>
<td>5</td>
<td>No rituximab</td>
<td></td>
<td></td>
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<tr>
<td>GELA/ GOELAMS</td>
<td>62</td>
<td>Chemotherapy</td>
<td>133</td>
<td>BEAM or TBI-based</td>
<td>39</td>
<td>3</td>
<td>.005</td>
<td>63</td>
<td>3</td>
<td>&lt;.001</td>
<td>Multicenter, prior rituximab in 40%</td>
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<tr>
<td></td>
<td></td>
<td>ASCT</td>
<td>42</td>
<td>BEAM or CY-TBI</td>
<td>73</td>
<td>92</td>
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<tr>
<td></td>
<td></td>
<td>NCCN</td>
<td>44</td>
<td>CR/PR2+</td>
<td>135</td>
<td>BEAM, CBV or TBI-based</td>
<td>57</td>
<td>3</td>
<td>87</td>
<td>3</td>
<td>Multicenter, prior rituximab in 100%</td>
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<tr>
<td>EBMT</td>
<td>53</td>
<td>CR/PR2+</td>
<td>726</td>
<td>BEAM, CY-TBI, Other</td>
<td>48</td>
<td>5</td>
<td>72</td>
<td>5</td>
<td>Registry, prior rituximab in 53%</td>
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<td>CIBMTR</td>
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<td>CR/PR2+</td>
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<td>BEAM, CY-TBI, Other</td>
<td>41</td>
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<td>74</td>
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<td>Registry, FL1 and FL2, prior rituximab in 100%</td>
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<td>CIBMTR</td>
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<td>CR/PR2+</td>
<td>136</td>
<td>BEAM, CY-TBI, Other</td>
<td>36</td>
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<td>59</td>
<td>5</td>
<td>Registry, FL3, prior rituximab in 100%</td>
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</table>

BEAM, carmustine, etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine, and etoposide; CR, complete response; CY, cyclophosphamide; EFS, event-free survival; HDCT, high-dose chemotherapy; MR, maintenance rituximab; ND, no differences; PR1, first partial response; PR2, second partial response; PR2+, beyond second partial response; R-BEAM, rituximab plus BEAM.
given every 2 months for 4 doses or observation in the post-ASCT setting. In vivo purging with rituximab had no effect on PFS at 10 years (48% vs 42%; HR, 0.80; P = .18). In contrast, rituximab maintenance demonstrated superior 10-year PFS over observation (54% vs 37%; HR, 0.66; P = .012). Ten-year OS was similar in the maintenance arms at 68% and 73% (P = not significant).

Although the EBMTR LYM1 trial is a large (n = 280), prospective RCT, the outcomes are difficult to extrapolate to current patients, given the routine use of rituximab in first-line treatment. Investigators from the NCCN reported a retrospective series of ASCT and allo-SCT recipients that had received prior rituximab. There was a mean of 1.4 prior rituximab chemotherapy exposures, with 27% of patients receiving a rituximab-based salvage regimen. Three-year failure-free survival and OS were 57% and 87%, respectively. Additional follow-up will be needed to determine whether durable remissions, such as those seen in the pre-rituximab institutional series from the St. Bartholomew’s/Dana-Farber Cancer Institute study that reported 57 of 122 patients in ongoing remission with a plateau in PFS and similar OS (51 vs 62 or 55%). That CIBMTR study highlighted the feasibility of cord blood transplantation but include a variety of hematologic malignancies, MUD allo-SCT has largely been adopted as a standard procedure with reasonable outcomes. A summary of some of the relevant series of allo-SCTs is provided in Table 2.

Allo-SCT regimens and outcomes in iNHL

Early relevant trials. Allo-SCT was performed in younger, higher-risk patients, but application in FL was limited because of concerns about high NRM. The first large registry study was published in 2003 and reported outcomes in the pre-rituximab era. Myeloablative allografts from matched siblings were compared with ASCT and reported higher NRM (30 vs 14 or 8%), lower relapse rates (21 vs 43 or 58%), and similar OS (51 vs 62 or 55%). That CIBMTR study highlighted the differences in patient populations (allograft recipients were younger but were also more likely to have higher disease burden, more prior therapies, and more chemotherapy-resistant disease before SCT) that make comparisons difficult.

There was no correlation between the development of graft-versus-host disease and lower rates of recurrence—an important point that reinforces the early contradictory information about GVL in iNHL. This observation was concordant with a larger International Blood and Marrow Transplant Research (IBMTR)/EBMT study that reported outcomes of indolent and aggressive NHL using older pathologic classification. In that study, there did not appear to be any reduction of relapse rate in the patients with low-grade lymphoma who were undergoing myeloablative allograft. The reduction in relapse rate was seen in patients that received purged autologous grafts. Similar to the van Besien et al study, the IBMTR/EBMT study is likely confounded by imbalances in the reported patient populations but it did not provide support for GVL in NHL. In contrast, data from studies that used donor lymphocyte infusion support the presence of GVL effect with disease response after cell infusion. Indirect evidence comes from the comparative studies of allo-SCT and ASCT that show reduced relapse rates discussed in “Comparative results of SCT strategies in iNHL.”

Subsequently, clinical practice that used allografting shifted away from myeloablative techniques toward RIC procedures. RIC allo-SCT has been shown to reduce early NRM and allows older patients to undergo transplantation with less toxicity. The most important early study of RIC allo-SCT in FL is a CIBMTR study that compares matched sibling RIC and myeloablative procedures in 208 patients with FL. That study reported similar NRM (28% vs 25%; P = .60), PFS (55% vs 67%; P = .07), and OS (62% vs 71%; P = .15) in patients evaluated 3 years after SCT. There were significant imbalances in the patient groups, with RIC recipients being more likely to be older, more heavily pretreated, and more likely to have received rituximab before SCT (45% vs 26%; P = .003). In multivariate analysis, there was a higher RR in RIC allo-SCT recipients (RR, 2.97; P = .04). The study also highlighted a major shift in clinical practice with less than 10% of allografts performed in 1997 being RIC procedures whereas in 2002, RIC techniques were used in more than 80% of reported allografts.

Results of matched unrelated donor and alternative donor strategies. Over this time period, there has been an increasing use of matched unrelated donors (MUDs) in an attempt to expand access to allograft procedures. The EBMT reported a large series of MUD allografts for FL with 131 RIC and 44 myeloablative procedures performed between 2000 and 2005. In that cohort, the NRM was 24% at day 100 after SCT and 33% at 1 year. The 3-year PFS was 47% with a rate of disease progression of 17% and OS of 51%. RIC regimens were associated with lower NRM leading to longer PFS and OS in multivariate analysis. Given these data and other data sets in hemato logic malignancies, MUD allo-SCT has largely been adopted as a standard procedure with reasonable outcomes. A summary of some of the relevant series of allo-SCTs is provided in Table 3.

Beyond the routine adoption of MUD transplants, alternative donor SCT has become an increasingly common procedure with demonstrated feasibility of haploidentical and umbilical cord transplantation. Larger series such as the Eurocord/EBMT review clearly highlight the feasibility of cord blood transplantation but include a variety of lymphoma histologies, which make any assessment of efficacy difficult. A published series of haploidentical transplant and posttransplantation cyclophosphamide highlighted feasibility in a small number of iNHL patients. The optimal alternative donor stem cell source continues to be a point of clinical equipoise, particularly given the results of recent trials from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).

Comparative results of SCT strategies in iNHL

Chemotherapy and ASCT. The randomized CUP trial in the pre-rituximab era was a prospective RCT comparing chemotherapy to both purified and unpurged ASCT. The trial was a 3-arm trial (chemotherapy, unpurged ASCT, and purified ASCT) originally designed to show an improvement in PFS for the individual transplant arms over chemotherapy as well as for the purging strategy over the unpurged transplant arm. Accrual was not completed, and although the trial shows statistically significant PFS advantages (HR, 0.33; P = .0037 for the 3-arm comparison), the comparison for OS did not reach statistical significance (HR, 0.43; P = .079). In a comparison of the combined ASCT arms with the chemotherapy arm, the HRs for PFS (0.30) and OS (0.40) were statistically significant. The interpretation of this study remains difficult today, given the lack of rituximab exposure and small sample size. ASCT became a standard in the relapse setting largely on the basis of nonrandomized evidence.
Table 3. Selected outcomes of allo-SCT for relapsed or refractory FL

<table>
<thead>
<tr>
<th>Series</th>
<th>Reference</th>
<th>Preparative regimen</th>
<th>No. of patients</th>
<th>MRD (%)</th>
<th>Prior rituximab</th>
<th>NRM (%)</th>
<th>NRM timepoint (y)</th>
<th>PFS/DFS (%)</th>
<th>PFS timepoint (y)</th>
<th>OS (%)</th>
<th>OS timepoint (y)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIBMTR</td>
<td>13</td>
<td>MA</td>
<td>176</td>
<td>100</td>
<td>NR</td>
<td>30</td>
<td>5</td>
<td>45%</td>
<td>5</td>
<td>51</td>
<td>5</td>
<td></td>
</tr>
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<td>120</td>
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<td>3</td>
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<td>62</td>
<td>3</td>
<td></td>
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<td>EBMNT</td>
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<td>RIC, ATG</td>
<td>46</td>
<td>100</td>
<td>NR</td>
<td>18</td>
<td>3</td>
<td>55</td>
<td>.015</td>
<td>70</td>
<td>3</td>
<td>NS</td>
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<td>EBMT</td>
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<td>RIC, alemtuzumab</td>
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<td>100</td>
<td>NR</td>
<td>18</td>
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<td>68</td>
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<td>RIC, no TCD</td>
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<td>67</td>
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<td>74</td>
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<td>Allo-SCT</td>
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<td>63</td>
<td>100</td>
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<tr>
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<td>RIC</td>
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<tr>
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ATG, antithymocyte globulin; MA, myeloablative; MRD, matched related donor; NR, not reported; NS, not significant; TCD, T-cell depletion.

After the adoption of rituximab-based treatment, investigators had an opportunity to revisit these questions. Unfortunately, the field continues to lack prospective RCTs. One of the few data sets evaluating ASCT or chemotherapy in the modern era was provided by French investigators treating FL patients who had received cyclophosphamide, doxorubicin, etoposide, and prednisone with interferon alfa (CHVP-I) with or without rituximab in the FL2000 study and who subsequently progressed after first-line chemotherapy. In 175 patients (70 having received rituximab-based treatment), there was an improvement in 3-year OS for those receiving ASCT (92%) vs those who did not (63%; $P = .0003$). The effect of ASCT remained significant in multivariate analysis for both event-free survival and OS. It is important to note that this was not an RCT but is one of the few studies that report comparative outcomes of ASCT in the current treatment era. There are no such comparative studies of allo-SCT and conventional therapy.

**ASCT and RIC allo-SCT.** Prospective comparison of ASCT and allo-SCT for relapsed or refractory FL is another important question, given the available data. This question was considered to be sufficiently important for the BMT CTN to open a prospective comparative study in this patient population. The design of this trial included assignment to the RIC allo-SCT arm if an HLA-matched sibling donor was available or to the ASCT arm if such a donor was not available. Unfortunately, the trial was closed after limited accrual ($n = 30$) over 18 months, and no firm recommendations can be made on the basis of data from this study.

Subsequently, several investigators have reported comparisons of ASCT with RIC allo-SCT. In contrast to prior studies, these studies report outcomes after prior rituximab exposure, which ensures that the data are relevant, given current treatment practices. An analysis from the NCCN Lymphoma Outcomes Project compared 48 patients who underwent allo-SCT with 136 patients who underwent ASCT. NRM remained inferior for allo-SCT at 3 years (24% vs 3%; $P < .0001$) whereas cumulative rates of relapse, progression, and/or transformation favored allo-SCT (16% vs 32%; $P = .03$). Three-year OS rates were superior in the ASCT patients (87% vs 61%; $P < .0001$).

**CIBMTR/EBMT** researchers recently reported their experience comparing RIC allo-SCT with ASCT in rituximab-treated FL in two separate articles. Five hundred eighteen patients with FL1 or FL2 underwent RIC allo-SCT or ASCT between 2000 and 2012. ASCT patients had more favorable NRM (5% vs 26%; $P < .001$) and OS (74% vs 66%; $P = .05$) although they experienced inferior rates of relapse and/or progression (54% vs 20%; $P < .0001$) and PFS (41% vs 58%; $P < .001$). A landmark analysis of patients alive and free of progression at 2 years after SCT did not demonstrate differences in NRM but did report higher risk of relapse (RR, 7.3; $P < .001$), inferior PFS (RR, 3.2; $P < .0001$), and inferior OS (RR, 2.1; $P = .04$). In the FL3 study, 197 patients who had received prior rituximab underwent SCT between 2000 and 2012. ASC patients had a more favorable NRM (4% vs 27%; $P < .001$), similar PFS (36% vs 51%; $P = .07$), and similar OS (59% vs 54%; $P = .7$) but had inferior relapse and/or progression rates (61% vs 20%; $P < .001$). In a similar analysis in those who survived beyond 2 years, ASC patients had inferior OS (RR, 3.6) than patients undergoing allo-SCT.

Interpretation of these studies warrants some caution. The RIC allo-SCT patients continue to be younger and typically have higher-risk features (more bone marrow involvement or chemotherapy-resistant disease at the time of SCT). Despite the application of modern RIC techniques, NRM remains a significant concern and the primary driver of patient outcome over the first 2 years after the procedure. Although relapse rates are typically lower for the allo-SCT cohorts, this does not translate into significant OS differences when comparing all patients. In patients who survive beyond 2 years (negating the majority of NRMs in allograft recipients), the benefits of lower relapse rates lead to clear advantages in these longer-term survivors. Although these observations are instructive in understanding the causes and timing of treatment failure, allo-SCT does not provide a clear advantage to the majority of these patients. In fact, short-term disadvantages in survival for allograft recipients are likely, given the significant differences in NRM favoring ASCT. However, it is important to note that the relapse rates in these series favor allo-SCT over ASCT and provide indirect evidence of GVL.

**Secondary malignancies after SCT.** In contrast to concerns about reporting efficacy and early toxicity outcomes in patients who have not received rituximab, late effects can be evaluated from historic series. The key late toxicity after SCT is the high rate of second cancers in SCT recipients. It is important to note that a baseline risk of second malignancies exists in FL patients as reported in a large review from the Surveillance, Epidemiology, and End Results (SEER) database. A recent meta-analysis from the Cochrane group did not demonstrate an increased risk of second malignancies in patients from the first-line RCTs of ASCT vs observation, although these data lack longer follow-up periods. An institutional review from the Dana-Farber Cancer Institute with a 12-year follow-up of patients undergoing ASCT as consolidation of primary therapy reported a second malignancy incidence of 28%. In these 27 patients, the malignancies included 10 cases of therapy-related myelodysplastic syndrome (T-MDS) or therapy-related acute myeloid leukemia (T-AML), 2 other hematologic malignancies, 9 solid tumors, and 10 nonmelanoma skin cancers. The cumulative incidence of second malignancy in a competing risk model was estimated to be 38% at 15 years.
The EBMT reported long-term follow-up of 693 ASCT patients with a median follow-up of more than 10 years for living patients.67 Sixty-four patients (9%) in this cohort developed a secondary malignancy with cumulative incidences of 2%, 5%, and 21% at 5, 10, and 15 years, respectively, for patients who received a transplant in their first complete response and with rates of 4%, 9%, and 15% for patients transplanted later in the disease course. In multivariate analysis, more than 2 prior lines of therapy, age of 45 years or older at the time of SCT, and TBI-containing regimens were associated with a greater risk of developing a second malignancy. The majority of the malignancies were T-MDS and T-AML.

Second malignancy rates in allo-SCT recipients are also significant. The recently published CIBMTR/EBMT studies comparing RIC allo-SCT with ASCT reported a 5-year cumulative incidence of second malignancies that was similar between the two groups (5% [ASCT] vs 8% [RIC allo-SCT]; \(P = .22\)).39 The 10-year cumulative incidence of second hematologic malignancies was 7% in ASCT recipients compared with 9% in allograft recipients. In the FL3 cohort, the 5-year cumulative incidence rates of secondary malignancies did not differ significantly between the groups (9% [ASCT] vs 9% [RIC allo-SCT]; \(P = .53\)).40 Secondary hematologic malignancies were seen only in the ASCT cohort (n = 4).

Second malignancy rates after SCT seem to be dependent on the type of transplant, the point at which SCT is used in the disease course, TBI-containing regimens in ASCT, and patient age. The rate of second malignancies (with only 5-year follow-up in recent study reports) seem comparable between RIC allo-SCT and ASCT strategies but seem to suggest higher rates of hematologic malignancies (typically T-MDS and T-AML) in ASCT patients.

The current issue for clinicians is to define the appropriate patients and time in the disease course for SCT. Given the benefit of rituximab-based therapies, patients with later recurrences after primary therapy (more than 2 years after completion) are more likely to respond to standard-dose therapies and achieve durable remissions, which would imply that this population may derive less benefit from an intensive strategy. The concept of using transplantation for high-risk disease is appealing (consensus guidelines for allo-SCT in chronic lymphocytic leukemia recommend allograft for 17p- or fludarabine-refractory disease),68,69 but clinicians have not identified particularly high-risk patient subgroups with the exception of those who experience early treatment failure. Rituximab-refractory patients have a PFS of approximately 10 to 12 months.70-72 A recent report from the National LymphoCare Study reports that patients who relapse within 2 years of completing treatment with R-CHOP have an inferior 5-year OS (50% vs 90%).73 A pragmatic approach to SCT was suggested by the EBMT in their consensus document.74 ASCT was suggested at first relapse in patients with a short first remission (or with a high-risk FLIPI score) or in subsequent chemotherapy-sensitive relapses. Allo-SCT was considered in patients with FL in relapse after ASCT but no recommendation was given regarding allo-SCT vs ASCT.

Decision-making becomes increasingly difficult with additional options now available for patients with relapsed or refractory iNHL. Clinical trials have been conducted in rituximab-refractory population as well as patients that are rituximab-refractory and alkylator-refractory.70,71 SCT may be appealing in these patient populations because of the possibility of long-term disease control and this may lead to an alternative treatment pathway in which novel non-SCT strategies can be considered.

Finally, it remains incumbent on clinicians in the SCT and lymphoma fields to continue to perform RCTs. Although multiple trials incorporating novel therapies in iNHL have been successfully accrued, SCT trials are limited and have not accrued well in iNHL. Unfortunately, the questions that are relevant in 2015 are very similar to questions asked more than 10 years ago. SCT remains a useful treatment for patients with iNHL, but careful study is required to optimize the role of this treatment in the era of immunochemotherapy.

Summary and conclusions

Although several RCTs of SCT have been performed, they have been limited to ASCT studies typically in the primary treatment setting. It is widely accepted that ASCT should no longer be performed routinely as consolidation of primary treatment, given the excellent results seen with primary immunochemotherapy.31,34 For relapsed or refractory disease, ASCT is likely to be clinicians’ preferred choice, given the low NRM of the procedure. Access to and feasibility of allo-SCT continues to improve through the use of RIC allo-SCT techniques and the use of alternative donors. However, efficacy remains a concern because the trials that compare the OS of allo-SCT recipients with that of ASCT recipients seem to yield similar results because of NRM. The appeal of allo-SCT remains the potential for cure through the GVH effect, although some patients can achieve prolonged remission after ASCT. The debate regarding ASCT vs allo-SCT remains an important research question, but the closure of the BMT CTN RCT may indicate that it will never be adequately answered.

References

5. Herold M, Haas A, Srock S, et al; East German Study Group Hematology and Oncology Study. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy...


The role of autologous and allogeneic stem cell transplantation in the management of indolent B-cell lymphoma

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