Outcome of patients with transformed indolent non-Hodgkin lymphoma referred for autologous stem-cell transplantation

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Background: The proportion of potentially eligible patients with transformed indolent non-Hodgkin lymphoma who undergo autologous stem-cell transplantation (ASCT) is unknown. There are limited data describing their outcome in the rituximab era.

Patients and methods: We reviewed 105 consecutive patients with biopsy-proven transformation referred to Princess Margaret Hospital for consideration of ASCT during 1996–2009. Patients received anthracycline or platinum-based chemotherapy with or without rituximab. Responders proceeded to stem-cell mobilization and ASCT.

Results: The median age at transformation was 54 (range 30–65) years. Patients received a median of two chemotherapy regimens for transformation, including rituximab in 39%. Fifty patients (48%) proceeded with ASCT and 55 (52%) did not, mainly due to progressive disease (n = 42). Three-year overall (OS) and progression-free survival (PFS) post-ASCT were 54% and 42%, respectively. Patients receiving rituximab with chemotherapy before transplant had a 3-year post-ASCT OS of 71% versus 47% in those who received chemotherapy alone (P = 0.046). Patients transplanted after 2004 had a 3-year post-ASCT OS of 69% versus 39% in those receiving ASCT earlier (P = 0.009).

Conclusions: About half of transplant-eligible patients with transformation are able to undergo ASCT. Outcomes following ASCT appear to have improved over recent years, although the role of rituximab in this patient population requires further evaluation.

Key words: autologous transplant, rituximab, transformed lymphoma

Introduction

Patients with indolent B-cell non-Hodgkin lymphomas have a risk of disease transformation into an aggressive histology lymphoma (TRIL) of ~2%–3% per year [1–4]. Patients with TRIL treated with combination chemotherapy have high rates of treatment failure as well as a poor median overall survival (OS) of 2–3 years [1–7].

In an attempt to improve outcomes, high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) has been used to treat selected patients with TRIL. In one prospective [8] and a number of retrospective [9–17] series, a significant proportion of patients treated with ASCT achieved long-term remissions. However, the patients reported in these studies are highly selected for younger age, otherwise good health, and sensitivity to chemotherapy.

The addition of rituximab to combination chemotherapy has improved outcomes for patients with indolent [18–23] and aggressive [24–27] B-cell lymphomas. Limited data suggest it has also improved outcomes for patients with TRIL [28, 29]. However, the effect of prior rituximab exposure for indolent lymphoma on the natural history of TRIL as well as response to systemic therapy, including ASCT, is also largely unknown.

The objective of this study was to determine the proportion of transplant-eligible patients with TRIL who were actually able to proceed with ASCT and their subsequent outcomes in a contemporary era in which rituximab is being increasingly integrated into the pre- and post-TRIL regimens for these patients.

Patients and methods

Patient population

This was a retrospective, single-center review of a prospectively collected computerized database and medical records of all transplant-eligible patients with TRIL consecutively referred to the Autologous Blood and Marrow Transplant Program at Princess Margaret Hospital between 1996...
and 2009. Additional data were collected from the electronic patient record, and supplemented with information from the referring oncologists and primary care physicians, as necessary.

Patients with biopsy-proven indolent B-cell non-Hodgkin lymphoma who developed transformation to aggressive histology B-cell non-Hodgkin lymphoma were included. Patients in whom the diagnosis of indolent lymphoma occurred simultaneously (i.e. discordant or composite histology) with that of transformation were excluded. Patients with an initial diagnosis of aggressive lymphoma who were diagnosed with indolent lymphoma at subsequent relapse were excluded.

Patients underwent staging investigations at the time of transformation with computed tomography (CT) scans of the chest, abdomen, and pelvis and with magnetic resonance imaging when appropriate, as well as bone marrow aspirate and biopsy. Gallium scans were recommended for patients with disease bulk >5 cm at relapse, but were not mandatory, and positron emission scans for staging or response assessment were not routinely carried out.

Chemotherapy and response assessment

Patients received combination chemotherapy to assess chemosensitivity before proceeding with stem-cell collection. Patients not previously exposed to anthracyclines were treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Patients previously treated with CHOP, or those who developed TRIL shortly after cyclophosphamide, vincristine, and prednisone for indolent disease were treated with platinum-based chemotherapy. Patients previously treated with anthracyclines and platinum were treated with alternate regimens, most commonly carbustine, etoposide, cytarabine, and melphalan (mini-BEAM). All patients had response evaluation upon completion of chemotherapy with physical examination and CT scans. Gallium scans and bone marrow biopsies were repeated if abnormal before initiating chemotherapy.

Response was defined as achieving a complete remission (CR), unconfirmed CR, or partial remission (PR), as per the 1999 International Working Group criteria [30]. Patients achieving at least a PR proceeded to stem-cell mobilization and ASCT.

Stem-cell collection, high-dose chemotherapy, and ASCT

Patients responding to chemotherapy underwent peripheral stem-cell mobilization with cyclophosphamide 2 g/m2 i.v. day 1, etoposide 200 mg/m2 i.v. days 1–3, and filgrastim 10 μg/kg/day s.c. starting on day 6 and continued until the completion of leukapheresis. If peripheral blood stem-cell collection was inadequate (<2.0 × 10^6 CD34+ cells/kg), either peripheral stem-cell mobilization with plerixafor or bone marrow harvest was carried out.

The high-dose chemotherapy regimen consisted of etoposide 60 mg/kg i.v. day −4 and melphalan 180 mg/m2 i.v. day −3 (with 1200 cGy TBI in six fractions for patients treated before 2001), followed by stem-cell infusion on day 0. Consolidative involved field radiotherapy (30–35 Gy in 20 fractions) was given 6–12 weeks post-ASCT to patients with bulky (>5 cm) disease before chemotherapy.

In patients not proceeding to ASCT, the primary reason was identified. All patients were followed on a frequent basis after completion of all treatments, including imaging studies at 3 months and 1-year post-transplantation, or sooner if clinically indicated.

Statistical methods

The primary end point of this study was OS, calculated from the date of ASCT to death from any cause or the last follow-up. Progression-free survival (PFS) was a secondary end point, calculated from the date of ASCT to progression, the last follow-up, or death from any cause. For patients not undergoing ASCT, OS was calculated from the date the decision was made not to proceed with ASCT, which in most instances occurred during clinical and radiologic reassessment after the most recent line of chemotherapy.

Outcomes and characteristics at diagnosis and relapse were compared using Fisher’s exact test for discrete variables, and the Wilcoxon rank-sum test for continuous variables. OS and PFS were estimated using the Kaplan–Meier method [31] and differences between groups were compared with the log-rank test. Data were analyzed with SAS (Version 9.2). This study was approved by the University Health Network Research Ethics Board.

Results

Patient characteristics

A total of 110 patients were identified, of which 5 had composite/discordant histology at diagnosis and were excluded. Therefore, 105 patients were analyzed. Table 1 shows the median age at initial diagnosis of indolent lymphoma was 50 years (range 28–63), and the most common indolent histology was follicular lymphoma in 96% cases. Patients received a median of one prior systemic regimen for indolent lymphoma (range 0–5), which included rituximab in 28 patients (27%). Radiotherapy was given to 28 patients (27%) as part of treatment for indolent disease.

The median age at transformation was 54 years (range 30–65), and the median time to transformation was 3.7 years (range 0.2–21.8). Diffuse large B-cell lymphoma was the most common aggressive histology, and 90% of patients had advanced stage at the time of transformation. Patients received a median of 2 chemotherapy regimens for TRIL (range 0–4). Patients received different chemotherapy regimens to assess chemosensitivity before ASCT; these included CHOP in 19 (18%), platinum in 66 (63%), and rituximab in 28 (27%) patients. The overall response rate (CR + PR) to the last regimen administered was 57%; 42 (40%) patients developed progressive disease (PD).

Patients not undergoing ASCT

Figure 1 shows that 50 (48%) patients proceeded with ASCT, and 55 (52%) did not because of PD (n = 39), inability to collect/mobilize stem cells (n = 4), or both (n = 3); death due to toxicity of chemotherapy (n = 1); and other reasons including comorbidity (n = 8).

In general, patient characteristics were similar in the patients who underwent ASCT when compared with those who did not (Table 1), with two exceptions. First, those who did not undergo ASCT received a greater number of systemic regimens for TRIL, although the use of rituximab was similar. Second, 42 (76%) patients not proceeding with ASCT developed PD following chemotherapy, compared with none of the patients who went on to ASCT (P < 0.001).

Four patients in whom an adequate autologous graft could not be collected proceeded with myeloablative allogeneic stem-cell transplantation (two matched sibling and two matched unrelated donors). One patient experienced disease progression before the allograft and died of progressive lymphoma.
Table 1. Patient characteristics at diagnosis of indolent and transformed lymphoma

<table>
<thead>
<tr>
<th>Characteristic at diagnosis of indolent lymphoma</th>
<th>Entire cohort (n = 105)</th>
<th>ASCT (n = 55)</th>
<th>No (n = 55)</th>
<th>Yes (n = 50)</th>
<th>P-value</th>
</tr>
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<td>Year of diagnosis</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>≤1989</td>
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<td>8 (15)</td>
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<td>1990–1999</td>
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<tr>
<td>≥2005</td>
<td>13 (12)</td>
<td></td>
<td>8 (15)</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
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<td></td>
<td>31 (56)</td>
<td>24 (48)</td>
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<td>Age at diagnosis</td>
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<td>28–63</td>
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<td>Indolent lymphoma histology</td>
<td>FL grade 1–3A</td>
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<td>99 (94)</td>
<td>52 (95)</td>
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<td></td>
<td>FL grade 3B</td>
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<td>1 (2)</td>
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<td></td>
<td>MZL</td>
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<td>2 (2)</td>
<td>1 (2)</td>
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<td></td>
<td>LPL/WM</td>
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<td>1 (2)</td>
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<td></td>
<td>SLL/CLL</td>
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<td>1 (1)</td>
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<td>41 (39)</td>
<td>20 (36)</td>
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<td>27 (26)</td>
<td>13 (24)</td>
<td>14 (28)</td>
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<td></td>
<td>18 (17)</td>
<td>12 (22)</td>
<td>6 (12)</td>
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<td>Rituximab</td>
<td>28 (27)</td>
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<td>13 (24)</td>
<td>15 (30)</td>
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</tr>
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<td>Radiotherapy</td>
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<td></td>
<td>16 (29)</td>
<td>12 (24)</td>
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Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic at diagnosis of transformation</th>
<th>Entire cohort (n = 105)</th>
<th>ASCT (n = 55)</th>
<th>No (n = 55)</th>
<th>Yes (n = 50)</th>
<th>P-value</th>
</tr>
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<tr>
<td>Years from diagnosis to TRIL</td>
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<td></td>
<td>3.7</td>
<td>3.7</td>
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<td>Range 0.2–21.8</td>
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<td>0.4–21.8</td>
<td>0.2–19.7</td>
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<tr>
<td>Transformation histology</td>
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<td></td>
<td>99 (94)</td>
<td>54 (98)</td>
<td>0.270</td>
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<td>DLBCL t(8;14) and t(14;18)</td>
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<td>1 (2)</td>
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<td></td>
<td>Burkitt lymphoma</td>
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<td>2 (2)</td>
<td>0 (1)</td>
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<tr>
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<td>Hodgkin lymphoma</td>
<td></td>
<td>1 (1)</td>
<td>0 (1)</td>
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<td></td>
<td>Advanced stage</td>
<td></td>
<td>94 (90)</td>
<td>52 (95)</td>
<td>0.111</td>
</tr>
<tr>
<td></td>
<td>Elevated LDHα</td>
<td></td>
<td>44/66 (67)</td>
<td>22/31 (71)</td>
<td>0.603</td>
</tr>
<tr>
<td></td>
<td>IPI ≥3α</td>
<td></td>
<td>4/66 (6)</td>
<td>1/31 (3)</td>
<td>0.616</td>
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<tr>
<td>Lines of chemotherapy for TRIL</td>
<td>Median 2</td>
<td></td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0.013</td>
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<td>1–4</td>
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<td></td>
<td>1</td>
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<td>45 (43)</td>
<td>16 (29)</td>
<td>29 (58)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td></td>
<td>42 (40)</td>
<td>24 (44)</td>
<td>18 (36)</td>
</tr>
<tr>
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<td></td>
<td>17 (16)</td>
<td>14 (25)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Rituximab administration</td>
<td>With any line of chemo</td>
<td></td>
<td>41 (39)</td>
<td>22 (40)</td>
<td>19 (38)</td>
</tr>
<tr>
<td></td>
<td>With last line of chemo</td>
<td></td>
<td>28 (27)</td>
<td>12 (22)</td>
<td>16 (32)</td>
</tr>
<tr>
<td></td>
<td>With more than one line</td>
<td></td>
<td>10 (10)</td>
<td>5 (9)</td>
<td>5 (10)</td>
</tr>
<tr>
<td></td>
<td>Response to last line of chemo</td>
<td></td>
<td>10 (10)</td>
<td>5 (9)</td>
<td>5 (10)</td>
</tr>
</tbody>
</table>

*Number of patients/total number of patients with data.

FL, follicular lymphoma; MZL, marginal zone lymphoma; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia; SLL, small lymphocytic lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; ASCT, autologous stem-cell transplantation; TRIL, transformation into an aggressive histology lymphoma; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Figure 1. Management of patients with transformation into an aggressive histology lymphoma (TRIL).

Allogeneic stem-cell transplantation 4 inability to mobilize/collect stem cells
1 age ≥65
1 myelodysplastic syndrome
1 death from toxicity of salvage chemotherapy
1 poor performance status and age >60
1 advanced alpha1 antitrypsin deficiency

55 (52%) did not proceed with ASCT

105 patients with TRIL receiving salvage chemotherapy

50 (48%) proceeded with ASCT
6 months after transplant. The other three patients achieved CR following allogeneic stem-cell transplantation; two remain alive and free of lymphoma, whereas the other died of veno-occlusive disease.

patients undergoing ASCT
For the 50 patients who underwent ASCT, the median time from diagnosis to TRIL was 3.7 years (range 0.2–19.7), and the median time from TRIL to ASCT was 6 months (range 3–35). The majority patients presented with diffuse large B-cell lymphoma (94%), and had advanced stage at transformation (84%), whereas 22 (63%) had an elevated LDH. At the time of consideration for ASCT, the most recent chemotherapy regimens included CHOP in 11 (22%), platinum in 33 (66%), and mini-BEAM in 4 (8%) patients. These regimens were rituximab-containing in 16 (32%) patients. Subsequently, 48 (96%) patients were transplanted in CR/PR, and 2 (4%) were transplanted in stable disease. The intensive therapy regimen included TBI in seven patients (14%). Peripheral blood stem cells were collected and reinfused in 46 (92%) patients, whereas 4 (8%) required bone marrow stem-cell harvesting.

outcomes and causes of death
With a median follow-up of 3.3 years (range 3 months–8.3 years) for all living patients, the 3-year OS for the entire cohort was 36% [standard error (SE) 5%]. Figure 2 shows that among the non-transplanted patients, those with PD (n = 42) had 3-year OS of 7% (SE 4%), whereas those not transplanted for other reasons (n = 13) had 3-year OS of 65% (SE 14%), with \( P < 0.001 \). The latter was similar to that of patients undergoing ASCT (3-year OS 54%, SE 7%, \( P = 0.330 \)).

Following ASCT, 3-year post-transplant OS and PFS were 54% (SE 7%) and 42% (SE 7%), respectively. Patients transplanted after 2004 had improved 3-year OS (69% versus 39%, \( P = 0.009 \)) as shown in Figure 3, although differences in 3-year PFS (54% versus 27%, \( P = 0.077 \)) were not statistically significant.

Patients who received minimal therapy (0–1 lines of chemotherapy) for TRIL before ASCT experienced improved survival compared with those who received two or more lines of chemotherapy (3-year OS 50% versus 25%, \( P = 0.005 \)). Additionally, those receiving minimal chemotherapy for TRIL were more likely to proceed with ASCT compared with the more pretreated patients (58% versus 31%, \( P = 0.006 \)). However, in the 50 patients who underwent ASCT, the number of lines of therapy pre-ASCT did not impact OS (3-year OS 54%, SE 7%, \( P = 0.330 \)).

Deaths were described as early (\( \leq 100 \) days) or late (>100 days) [10]. There were 24 deaths in the 50 patients treated with ASCT: 3 were early (1 sepsis during ASCT and 2 PD), and 21 were late (1 acute myeloid leukemia, 1 engraftment failure, 19 PD). Therefore, transplant-related mortality was 2% at 100 days, and 6% at 3 years. Among the 13 patients not treated with ASCT for reasons other than PD, there were 2 early deaths (1 toxicity of salvage GDP chemotherapy, 1 PD), 1 late death (PD), and 1 death from veno-occlusive disease early after allogeneic transplantation. No other cases of myelodysplastic syndrome or acute myeloid leukemia have been diagnosed in living patients. Data regarding second malignancies in living patients are not available.

usage and influence of rituximab
In the entire cohort, 28 (27%) patients had received rituximab for treatment of indolent lymphoma before TRIL (Table 1). Exposure to rituximab for indolent lymphoma had no effect on time to TRIL or stage at TRIL. Exposure to rituximab for indolent lymphoma did not affect OS after transformation (\( P = 0.293 \)) or patients’ ability to proceed with ASCT (\( P = 0.388 \)), although the number of patients in our series is small and the power to detect a difference in effect of rituximab on survival and transplant rate is low.

Forty-one (39%) patients received rituximab-containing chemotherapy for TRIL. Of these, 15 (37%) had previously received rituximab for indolent lymphoma. There was no
difference in the number and type of systemic regimens between patients who received post-transformation rituximab and those who did not. Twenty-eight (27%) patients received rituximab with their last line of chemotherapy before ASCT, with similar use between transplanted and non-transplanted patients (P = 0.274). Ten (10%) patients received rituximab-containing chemotherapy for TRIL more than once. Post-ASCT maintenance rituximab was not used.

In the 50 patients who underwent ASCT, post-transplant OS was not affected by exposure to rituximab for indolent (P = 0.250) lymphoma. On the other hand, patients who received rituximab with the last line of chemotherapy before ASCT experienced improved 3-year post-transplant OS compared with those who did not (71% versus 47%, P = 0.046), as shown in Figure 4. The addition of rituximab did not affect response or relapse rates after ASCT.

discussion

About half of transplant-eligible patients with transformed lymphoma receiving chemotherapy at our center did not proceed with ASCT. The main reason was disease progression while on chemotherapy, followed by the inability to mobilize and collect adequate peripheral blood stem cells. Our results confirm that patients undergoing ASCT are highly selected for a number of factors in addition to chemosensitivity and indicate that the published studies including patients treated with ASCT [8–17] are limited by selection bias.

Our findings are consistent with a recently published Norwegian prospective phase II study of 47 consecutive patients with TRIL receiving chemotherapy between 1999 and 2004; 17 (36%) did not proceed with ASCT because of failure to achieve CR/PR to chemotherapy (n = 13), inability to collect stem cells (n = 2), poor performance status (n = 1), and bulky residual disease (n = 1) [8]. In an earlier retrospective cohort study of 56 patients with transformed follicular lymphoma referred to St Bartholomew’s Hospital between 1985 and 1996, 37 (66%) were ineligible for ASCT on the basis of age >60 years (n = 18), inadequate response to or progression after chemotherapy (n = 16), inability to collect stem cells (n = 2), and poor performance status (n = 1) [14]. The other ASCT series do not include the denominator of potentially eligible patients from which the outcome of ASCT is derived [9–13, 15–17].

In the present study, the 13 patients who did not proceed with ASCT for reasons other than PD had a 3-year OS of 65%, an outcome similar to that of patients who underwent ASCT, for whom 3-year OS was 54% (P = 0.330). Even though this is a small, heterogeneous subgroup and the comparison is not randomized and subject to selection bias, the similarity in outcomes suggests that chemotherapy intensification may not be necessary in all patients with TRIL who do not progress on chemotherapy. However, a prospective randomized trial evaluating this question is unlikely to occur.

Outcomes observed after ASCT are comparable with those reported by other investigators [8–17], including the observation that patients who receive minimal chemotherapy for TRIL pre-ASCT experience improved outcomes [7, 8, 28]. Outcomes were also improved in patients transplanted after 2004 (3-year OS 69% and PFS 54%) compared with those transplanted before this time and with those reported in older studies [9, 10, 13–15]. The main difference between these two eras is the use of pre- and post-TRIL rituximab after 2004, although it is possible that other factors account for improved outcomes after ASCT in more recent years, including the use of ASCT earlier in patients’ disease course, improved supportive care around ASCT, more palliative treatment options after relapse, and shorter length of follow-up.

We report outcomes for a contemporary transplant era in which rituximab is part of routine management of patients with B-cell non-Hodgkin’s lymphomas before and after TRIL. In the current study, patients undergoing ASCT who had received rituximab with their most recent line of chemotherapy experienced improved outcomes following transplantation. In a larger report of stem-cell transplantation for TRIL by the Canadian Blood and Marrow Transplant Group, the addition of rituximab to chemotherapy improved both 5-year OS (63% versus 42%, P = 0.012) and PFS (56% versus 37%, P = 0.003) in the subgroup of 217 patients with TRIL undergoing ASCT [17]. Other series suggest that the addition of rituximab to chemotherapy also improves outcomes in patients with TRIL, including those not undergoing ASCT [28, 29, 32].

Prospective studies in relapsed/refractory de novo diffuse large B-cell lymphoma suggest rituximab plays a significant role as part of salvage therapy for patients who are rituximab-naive. In the HOVON-44 study of 225 patients with relapsed/refractory diffuse large B-cell lymphoma, most of whom had never received rituximab, those randomized to receive rituximab with chemotherapy experienced significantly higher response rates and ability to proceed with ASCT, as well as EFS, PFS, and OS than those treated with chemotherapy alone [33]. Additionally, in the CORAL study, 396 patients received rituximab and platinum-containing chemotherapy for relapsed/refractory diffuse large B-cell lymphoma. Those who had previously received rituximab with first-line chemotherapy

Figure 4. Post-autologous stem-cell transplantation (ASCT) overall survival (OS) by addition of rituximab to the last line of pre-ASCT chemotherapy (n = 50).
(85%) experienced lower response rates, ability to proceed with ASCT, EFS, and OS compared with rituximab-naive patients [34].

The main strength of the current study is the ability to capture and assess all patients with TRIL consecutively referred for consideration of ASCT. Even though this is a single-institution study, there was a homogeneous pattern of practice, particularly around response assessment before and after ASCT, as well as the actual delivery of high-dose chemotherapy and ASCT. Limitations include a retrospective study design as well as a relatively small sample size, despite this being the largest experience of salvage therapy for TRIL reported in the literature.

In summary, patients with TRIL who undergo ASCT are highly selected for a number of factors in addition to age, fitness, and response to systemic therapy. Outcomes following ASCT appear to have improved over the last 5 years, although the role of rituximab in this patient population requires further evaluation. Although ASCT remains standard treatment for patients with TRIL, the timing of the intervention and the identification of patients who may not benefit from ASCT (beyond those with chemoresistant disease) need to be defined by careful, prospective study.

disclosure

The authors have declared no conflicts of interest.

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Long-term clinical and molecular remissions in patients with follicular lymphoma following high-dose therapy and autologous stem cell transplantation

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Background: Long-term clinical and molecular remissions in patients with follicular lymphoma (FL) following high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) have been evaluated in only a few studies. Results are especially limited for second-line HDT with BEAM (BCNU, etoposide, cytarabine and melphalan).

Patients and methods: Sixty patients with FL received ASCT in our institution (18 first-line with total body irradiation and cyclophosphamide, 34 second-line with BEAM and 8 ≥third-line with BEAM). In the case of long-term remission (>6 years; N = 17), peripheral blood was tested for minimal residual disease by t(14;18)- and IGH-PCR.

Results: Ten-year overall survival, progression-free survival and freedom from progression (FFP) after first-line ASCT were 79%, 57% and 64% after second-line ASCT 41%, 35% and 42%, respectively. Prognostic factors for FFP were treatment line and FLIPI (Follicular Lymphoma International Prognostic Index). Ten-year FFP for second-line ASCT and low-risk FLIPI was 57%, intermediate risk 37% and high risk 33%. No relapses occurred after 6 years following ASCT. Sixteen patients developed sustained long-term clinical and molecular remissions of up to 17.5 years.

Conclusion: Sustained long-term clinical and molecular remissions can be achieved following ASCT, including HDT with BEAM in second line.

Key words: autologous stem-cell transplantation, follicular lymphoma, long-term remission, MRO, relapse, secondary malignancies

Introduction

High-dose therapy (HDT) with autologous stem cell transplantation (ASCT) is known as an effective therapy which can achieve long-term remissions in a significant proportion of patients with disseminated follicular lymphoma (FL). However, a considerable number of patients relapse after ASCT. So its role in the management of patients remains controversial [1–14]. Up to now, only a few long-term molecular remissions (over 10 years) were described, mostly after total body irradiation (TBI) and high-dose cyclophosphamide [15–18]. This high-dose protocol is under debate because of an increased rate of secondary acute myeloid leukaemia and myelodysplastic syndrome (MDS) [8, 9]. No sufficient data regarding long-term molecular remissions after high-dose chemotherapy with BEAM (BCNU, etoposide, cytarabine and melphalan) are available, a protocol causing less secondary malignancies [9]. Long-term follow-up is frequently difficult,