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Comparison of Survival in Patients with T-cell Lymphoma after Autologous and Allogeneic Stem Cell Transplantation as a Frontline Strategy or in Relapsed Disease

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Abstract

We studied the roles of autologous (A) and allogeneic (allo) stem cell transplantation (SCT) in the treatment of 134 patients with T-cell lymphoma (TCL) at our center. Frontline SCT: Fifty-eight patients were studied. The 4-year overall survival (OS) rates for the ASCT (n=47; median age, 49 years) and alloSCT (n=11; median age, 55 years) groups were 76% and 54%, respectively (P > .05). The 4-year OS rates for first complete remission (CR1) patients were 84% and 83%, respectively. SCT for relapsed disease: Seventy-six patients were studied (41 with ASCT, and 35 with alloSCT). The 4-year OS rates were 50% and 36% for ASCT and alloSCT patients with chemosensitive disease, respectively (P > .05). Those who were in CR2 and CR3 had 4-year OS rates of 59% and 53%, respectively. Similar results were also observed in patients with refractory disease (29% and 35%, respectively). These data suggest that a pre-SCT CR is associated with improved outcomes in TCL patients after SCT. Considering the 84% 4-year OS rates in CR1 patients, SCT should be considered as a treatment option in TCL patients.© 2015 American Society for Blood and Marrow Transplantation.

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patients and the unpredictable responses in patients with relapsed disease, we favor the use of ASCT as consolidation therapy after CR1. AlloSCT did not result in a superior outcome compared with ASCT.

**Keywords**

Stem cell transplantation; T cell; lymphoma

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**INTRODUCTION**

T-cell lymphomas (TCLs) are a heterogeneous group of neoplasms that represent 15% of non-Hodgkin’s lymphomas.\(^1,2\) They are more resistant to conventional chemotherapy than are B-cell lymphomas, and patients have an inferior outcome, with the exception of patients with anaplastic kinase (ALK)-positive large-cell lymphoma (ALCL).\(^3\) Treatment with newly developed agents results in improved responses,\(^4-6\) but relapse is common, especially in patients with advanced and recurrent disease. High-dose chemotherapy, followed by autologous\(^7-12\) (A) or allogeneic\(^13-17\) (allo) hematopoietic stem cell transplantation (SCT), is often considered for patients with TCL; however, which approach is more effective is not clear. The results are further confounded by changes in lymphoma classification schemes over the past 2 decades,\(^18\) and the development of prognostic markers and scores for TCL patients.\(^19,20\)

The results of several phase II trials have suggested that alloSCT leads to improved outcomes.\(^13-16\) However, the rarity and diversity of TCLs and the evolving classification schemes have made it challenging to conduct randomized controlled studies. To determine the role of SCT in the management of TCL, we analyzed transplantation results at our cancer center. We compared the results of ASCT and alloSCT with patient and disease characteristics, such as remission status, and histological disease type.

**PATIENTS AND METHODS**

**Patient Population and Synopsis of Transplantation Strategy**

This study included all patients with TCL who had been treated in sequential phase II ASCT or alloSCT protocols at The University of Texas MD Anderson Cancer Center (Houston, Texas) between 1990 and 2009. The eligibility criteria included a Zubrod performance status score of ≤2 and no uncontrolled active infection or symptomatic organ dysfunction.

From the mid-1990s to 2002, newly diagnosed TCL patients were treated with alternating triple therapy with ASHAP (doxorubicin, methylprednisolone, cytosine arabinoside, and cisplatin), MBACOS (bleomycin, doxorubicin, cyclophosphamide, vincristine, methylprednisolone, and methotrexate), and MINE (mesna, ifosfamide, mitoxantrone, and etoposide), followed by ASCT.\(^21\) In a subsequent trial, Hyper-CVAD (hyper-fractionated cyclophosphamide, daunorubicin, vincristine, and dexamethasone, alternating with methotrexate and cytarabine) was used as induction chemotherapy.\(^21\) After 2002, patients were referred for transplantation if they did not experience a complete remission after treatment with hyper-CVAD or novel agents such as pralatrexate, romidepsin, and
brentuximab. The pattern of referral was also dependent on whether patients were being treated by physicians in the lymphoma department at our center or by those outside MD Anderson (the latter group mainly received induction chemotherapy with CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]). AlloSCT was reserved for patients with resistant or relapsed disease, if a suitable donor was available.

All eligible patients had a biopsy-proven diagnosis of TCL, as determined by histological and immunophenotypical analyses and defined according to the current classification system at the time of biopsy. Possible diagnoses were updated using the current version of the World Health Organization classification system. Patients with primary cutaneous TCL and ALK-positive ALCL were excluded. Two patients with ALCL with unknown ALK status were grouped with ALK-negative patients. The protocols and analysis were approved by the MD Anderson institutional review board, and informed consent had been obtained from all patients. Standard definitions were used to assess disease response. \(^{22}\) The International Prognostic Index (IPI) scores were calculated according to published methods.\(^ {19}\)

**Statistical Analysis**

The primary endpoints were overall survival (OS) and progression-free survival (PFS) rates. Actuarial OS and PFS rates were estimated using the Kaplan-Meier method. OS was estimated from the time of transplantation to death or last follow-up, and PFS was estimated from the time of SCT to disease progression, death, or last follow-up. Outcomes according to transplantation type (alloSCT vs ASCT) were compared in univariate analysis using Cox’s proportional hazards regression analysis. The comparison was stratified according to disease status at transplantation. Patient and SCT characteristics were compared using chi-square and Fisher’s exact tests for categorical variables and the Wilcoxon rank-sum test for continuous variables. Statistical significance was defined at the .05 level, and all \( P \) values were 2-sided. The statistical analyses were performed using STATA 9.0 software (StataCorp, College Station, Texas).

**RESULTS**

**Patients**

The study group was composed of 134 TCL patients: 88 ASCT and 46 alloSCT. Fifty-eight (43%) patients underwent SCT (47 ASCT and 11 alloSCT) as frontline consolidation therapy during their first remission, and 76 (57%) underwent SCT (41 ASCT and 35 alloSCT) for relapsed disease. Patients’ pre-SCT characteristics and demographic data are summarized in Tables 1 and 2.

The conditioning regimen consisted of BEAM (carmustine, etoposide, cytarabine, and melphalan) or carmustine, etoposide, cytarabine plus cyclophosphamide in 87% of ASCT patients. The remaining patients received busulfan-containing regimens. The conditioning regimens for alloSCT varied in intensity. Thirteen (28%) patients underwent non-myeloablative fludarabine and cyclophosphamide conditioning, and 6 (13%) and 27 (59%) underwent melphalan, fludarabine, and BEAM conditioning, respectively.
Twenty-seven (59%) of the 46 alloSCT patients received transplants from human histocompatible antigen-matched siblings, 12 (26%) from matched unrelated donors, and 7 (15%) from mismatched donors.

**Frontline SCT for TCL**

Forty-seven patients underwent ASCT. AlloSCT was used as a frontline strategy in 11 patients with a first complete remission (CR1) or primary induction failure (PIF)/CR (n=44), or with resistance to frontline conventional chemotherapy but a partial response (PR) to salvage treatment (PIF/PR, n =14). Patients’ characteristics are listed in Table 1. Most patients (85% of ASCT and 91% of alloSCT) underwent transplantations after year 2000. PTCL-NOS and AITL were the dominant histological types in both the ASCT (72%) and alloSCT (63%) groups. The median follow-up durations among survivors in the ASCT and alloSCT groups were 35 months (range, 3–145 months) and 45 months (range, 9–90 months), respectively. The 4-year OS and PFS rates for ASCT patients were 76% (95% confidence interval [CI]: 56%–88%) and 56% (95% CI: 34%–71%), respectively. These rates were not statistically significantly different from the alloSCT group, where the 4-year OS and PFS rates were 54% and 34%, respectively.

Similar results were also observed ASCT and alloSCT when patients were grouped by CR1/PIF CR and PIF/PR. The 4-year OS rates for ASCT and alloSCT were 84% and 83%, respectively (P = .6) (Figure 1A). The 4-year PFS rates were 61% and 67% (P = .8). Patients with PIF/PR had inferior outcomes to those of the CR1/PTR CR patients. However, the results were not statistically significant between the ASCT and alloSCT groups, where the 4-year OS rates were 44% and 20% (P = .1) (Figure 1B), and the 4-year PFS rates were 33% and 0% (P = .08). We did not discern any differences in outcome between the most common TCL subtypes included (PTCL-NOS, AITL and ALCL) (Figure 1C).

**SCT for Relapsed TCL**

Seventy-six TCL patients underwent ASCT (n= 41) and alloSCT (n=35). Patients’ characteristics are listed in Table 2. Only 3% of alloSCT patients were older than 60 years compared to 37% in the ASCT group (P<.05). The proportion of patients with IPI>1, elevated LDH, and refractory disease (not responding to chemotherapy) before SCT was not statistically different between the 2 groups. The 4-year OS rates for ASCT and alloSCT were 50% and 36%, respectively (P < .05). The 4-year PFS rate did not statistically significantly differ (38% and 28%) between the 2 groups. Patients with relapsed sensitive disease experienced a tendency towards a higher 4-year OS rate than did alloSCT patients (P = .06) (Figure 2A) but not a higher PFS rate. The same trends were observed when survival estimates were compared according to disease status (CR2/3 vs PR) in patients with relapse-sensitive disease. Those who were in CR2/CR3 had a 4-year OS of 59% after ASCT and 53% after alloSCT. Relapse-sensitive patients with a PR before SCT had 4-year OS rates of 55% and 22% after ASCT and alloSCT, respectively.

Although inferior outcomes were observed after transplantation in patients with relapsed and refractory TCL than in those with chemosensitive disease, the results were not statistically significant between ASCT and alloSCT. The corresponding 4-year OS estimates were 29%
and 35%, respectively ($P = .6$) (Figure 2B), and the 4-year PFS rates were 25% and 18% ($P = .4$). We were not able to discern statistically significant differences in OS in major histological types included (Figure 3), nor were we able to detect any differences in outcome by era of relapse (before or after the year 2000).

**Graft-Versus-Lymphoma after AlloSCT in TCL**

The conditioning regimens for alloSCT varied in intensity. However, more patients were in CR1 or CR2/CR3 in the non-myeloablative group (63%) than in the reduced-intensity group (50%) ($P = .3$). A graft-versus-lymphoma effect was directly manifested by the responses to donor lymphocyte infusion (DLI) in 4 TCL patients with recurrent disease after alloSCT: 2 PTCL, 1 AITL, and 1 subcutaneous panniculitis-like TCL. These patients remained in continuous CR after 14+, 36+, 44+, and 48+ months. We also observed a continuous CR in 4 (2 ALCL and 2 PTCL) of 8 patients who underwent alloSCT after not experiencing a durable response to ASCT. These patients were last followed up at 12+, 17+, 21+, and 216+ months after SCT. The graft-versus-lymphoma effect, however, did not translate into improved survival, in part because of increased toxicity in the alloSCT group. Indeed, the 4-year non-relapse mortality rate was significantly higher in alloSCT than in ASCT patients (40% and 17%, respectively; $P < .001$).

**DISCUSSION**

We previously reported encouraging results for TCL patients treated with ASCT. This follow-up report represents the largest single-institution study of ASCT and alloSCT in TCL patients published to date. Although there is an inherent selection bias in any retrospective study, we demonstrated a 4-year OS rate of 84% and PFS rate of 61% in TCL patients who underwent ASCT as consolidation therapy after experiencing a CR to conventional induction chemotherapy. Good results were also observed after ASCT in relapsed-sensitive disease of CR2/CR3 with a 4-year OS rate of 59%. Despite responses to DLIs in selected patients with persistent low-volume disease after alloSCT, we found that alloSCT resulted in no survival benefits compared with ASCT for patients with frontline or relapsed disease, after stratifying by level of response status before SCT. The histological type of TCL was not associated with a significant difference in OS or PFS, thus confirming the findings of other studies.

We acknowledge that our study has several limitations. The time span of the transplantation covers 19-years. However, about two-thirds of patients underwent transplantation after the year 2000. In addition the proportion of patients who underwent transplantation before or after 2000 was similar for both ASCT and alloSCT. OS and PFS were measured from date of the transplantation rather than from the date of first treatment, as into clinical trials. In addition, prognostic factors at the time of diagnosis rather than at SCT are missing, as many patients were diagnosed and underwent initial treatments outside MD Anderson. Several retrospective studies have shed light on the role of ASCT in TCL patients. The OS rates in these studies ranged from 50% to 70%. As in our study, chemosensitivity and SCT in CR1 were important determinants of outcome. A few prospective trials have also reported encouraging results, with 3-year OS rates of 40% to 73%. In all studies, however, a
significant proportion of patients (25% to 59%) could not undergo SCT because of a poor response to induction chemotherapy; this was an important bias in studies that evaluated the role of SCT.

The role of SCT in relapsed disease is less controversial, as it appears to be essential to improve survival rates. A study reported a median OS duration of 5 months in patients who were not eligible for a SCT procedure. However, the treatment of relapsed TCL remains challenging. These unsatisfactory results for ASCT in TCL patients who do not experience a pre-SCT CR and a response to DLI provide a plausible rationale for using alloSCT as a therapeutic modality. A comparative analysis in our study did not reveal a superior outcome for alloSCT over ASCT after adjusting for disease status (frontline vs relapse) and prior response to conventional chemotherapy. Similar findings were recently reported by the Center for the International Blood and Marrow Transplant Research (CIBMTR). In that study, the outcomes in 115 patients with different histological types of TCL were compared to those in 126 patients who received an alloSCT; no statistically different in OS or PFS. Unlike our study, however, the CIBMTR report excluded patients who were older than age 60. In addition, ALK-positive ALCL histological types were included.

In conclusion, our results suggest that pre-SCT CR is required for a good outcome after SCT in patients with TCL and highlight the need for more effective induction chemotherapy for TCL patients. Considering the 84% 4-year OS rates in CR1 patients and the unpredictable responses in patients with relapsed disease, we favor the use of ASCT as consolidation therapy after CR1. In our study, we could not establish a superior outcome for alloSCT compared with ASCT for TCL patients.

Acknowledgements
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REFERENCES


$P$ value 0.1

Cumulative Proportion Surviving

Months Post Transplant

AUTO

ALLO

B
Figure 1.
A: OS rates in TCL patients treated with ASCT or alloSCT during the first complete remission.
B: OS rates in TCL patients treated with ASCT or alloSCT during PIF/PR.
C: OS rates after ASCT during the first complete remission, according to the most common histological types studied.
Figure 2.
A: OS rates after ASCT and alloSCT in patients with relapsed, chemosensitive TCL.
B: OS rates after ASCT and alloSCT in patients with relapsed, chemorefractory TCL.
Figure 3.
OS rates after ASCT in patients with relapsed, chemosensitive TCL according to the most common histological types studied.
Table 1

Frontline SCT for TCL: Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASCT</th>
<th>AlloSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>47</td>
<td>11</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>49 (18–75)</td>
<td>55 (47–62)</td>
</tr>
<tr>
<td>&gt;60 years, n (%)</td>
<td>9 (19)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>32 (68)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Histological type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-TCL</td>
<td>38 (81)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>24 (51)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>ALK-negative ALCL</td>
<td>4 (9)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>AITL</td>
<td>10 (21)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>EN-TCL</td>
<td>9 (19)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>NK-TCL</td>
<td>2 (4)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>HSTCL</td>
<td>6 (13)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>SPTCL</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CR1/PIF CR</td>
<td>38 (81)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>PIF/PR</td>
<td>9 (19)</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Transplantation before year 2000, n (%)</td>
<td>7 (15)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>IPI score &gt;1 at SCT, n (%)</td>
<td>5 (11)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Elevated LDH at SCT, n (%)</td>
<td>14 (30)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Marrow + at SCT, n (%)</td>
<td>2 (4)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Median prior chemotherapy regimens</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Related/unrelated donor</td>
<td>NA</td>
<td>8/3</td>
</tr>
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</table>

SCT, stem cell transplantation; TCL, T-cell lymphoma; ASCT, autologous SCT; alloSCT, allogeneic SCT; N-TCL, nodal TCL; PTCL-NOS, peripheral TCL—not otherwise specified; ALK, anaplastic Kinase; ALCL, anaplastic large-cell lymphoma; AITL, angioimmunoblastic TCL; EN-TCL, extranodal TCL; NK-TCL, natural killer TCL; HSTCL, hepatosplenic TCL; SPTCL, subcutaneous panniculitis-like TCL; CR1, first complete remission; PIF, primary induction failure; PR, partial remission; IPI, International Prognostic Index.
Table 2

SCT for Relapsed TCL: Patient and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
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</tr>
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<tr>
<td>No. of patients</td>
<td>41</td>
<td>35</td>
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<td>Median age, years (range)</td>
<td>56 (25–74)</td>
<td>43 (22–73)</td>
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<tr>
<td>&gt;60 years, n (%)</td>
<td>15 (37)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>24 (59)</td>
<td>21 (60)</td>
</tr>
<tr>
<td>Histological type, n (%)</td>
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<td></td>
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<tr>
<td>N-TCL</td>
<td>35 (85)</td>
<td>20 (57)</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>16 (39)</td>
<td>15 (43)</td>
</tr>
<tr>
<td>ALK-negative ALCL</td>
<td>14 (34)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>AITL</td>
<td>5 (12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>EN-TCL</td>
<td>6 (15)</td>
<td>15 (43)</td>
</tr>
<tr>
<td>NK-TCL</td>
<td>4 (10)</td>
<td>9 (26)</td>
</tr>
<tr>
<td>HSTCL</td>
<td>0 (0)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>SPTCL</td>
<td>1 (2)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>EALT</td>
<td>1 (2)</td>
<td>3 (9)</td>
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<tr>
<td>Relapse sensitive</td>
<td>31 (76)</td>
<td>18 (51)</td>
</tr>
<tr>
<td>Relapse refractory</td>
<td>10 (24)</td>
<td>17 (49)</td>
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<tr>
<td>Transplantations before 2000, n (%)</td>
<td>15 (37)</td>
<td>13 (37)</td>
</tr>
<tr>
<td>Median time to SCT, months (range)</td>
<td>20 (7–113)</td>
<td>17 (2–135)</td>
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<td>IPI score &gt;1 at SCT, n (%)</td>
<td>9 (22)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Elevated LDH at SCT, n (%)</td>
<td>11 (28)</td>
<td>11 (33)</td>
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<tr>
<td>Marrow + at SCT, n (%)</td>
<td>1 (2)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Median prior chemotherapy regimens</td>
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</tr>
<tr>
<td>Related/MUD/MM donor</td>
<td>NA</td>
<td>19/9/7</td>
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