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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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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. For frontline SCT, 58 patients were studied. The 4-year overall survival (OS) rates for 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. For SCT for relapsed disease, 76 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 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.

INTRODUCTION

T cell lymphomas (TCLs) are a heterogeneous group of neoplasms that represent 15% of non-Hodgkin lymphomas [1,2]. TLCs are more resistant to conventional chemotherapy than are B cell lymphomas, and patients have an inferior outcome, with the exception of patients with anaplastic lymphoma kinase (ALK)-positive anaplastic 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 (A) [7-12] or allogeneic (allo) [13-17] 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.

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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, TX) between 1990 and 2009. The

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eligibility criteria included a Zubrod performance status score ≤ 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 (hyperfractionated 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 also depended on whether patients were 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 was obtained from all patients. Standard definitions were used to assess disease response [22]. The International Prognostic Index 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 versus 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. Statistical analyses were performed using STATA 9.0 software (StataCorp, College Station, TX).

RESULTS

Patients

The study group was composed of 134 TCL patients: 88 ASCT and 46 alloSCT. Fifty-eight patients (43%) 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 patients (28%) underwent nonmyeloablative fludarabine and cyclophosphamide conditioning and 6 (13%) and 27 (59%) underwent melphalan and fludarabine and BEAM conditioning, respectively. Of the 46 alloSCT patients, 27 (59%) 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. Peripheral TCL not otherwise specified (PTCL-NOS) and angioimmunoblastic TCL (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 to 145) and 45 months (range, 9 to 90), respectively. The 4-year OS and PFS rates for ASCT patients were 76% (95% confidence interval [CI], 56% to 88%) and 56%

Table 1
Frontline SCT for TCL: Patient and Disease Characteristics

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

N-TCL indicates nodal TCL; EN-TCL, extranodal TCL; NK-TCL, natural killer TCL; HSTCL, hepatosplenic TCL; SPTCL, subcutaneous panniculitis-like TCL; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Table 2
SCT for Relapsed TCL: Patient and Disease Characteristics

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

EALT indicates enteropathy-associated TCL; MUD, matched unrelated; MM, mismatched.