LYMPHOID NEOPLASIA

Autologous stem cell transplantation for enteropathy-associated T-cell lymphoma: a retrospective study by the EBMT

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Key Points

- ASCT provides long-term remission in the majority of EATL patients transplanted in first complete or partial remission.
- ASCT should be considered in transplant-eligible EATL patients.

Enteropathy-associated T-cell lymphoma (EATL) is a rare subtype of peripheral T-cell lymphomas with a poor prognosis. Autologous stem cell transplantation (ASCT) was retrospectively evaluated as a consolidation or salvage strategy for EATL. The analysis included 44 patients who received ASCT for EATL between 2000 and 2010. Thirty-one patients (70%) were in first complete or partial remission at the time of the ASCT. With a median follow-up of 46 months, relapse incidence, progression-free survival, and overall survival were 39%, 54%, and 59% at 4 years, respectively, with only one relapse occurring beyond 18 months posttransplant. There was a trend for better survival in patients transplanted in first complete or partial remission at 4 years (66% vs 36%; $P = .062$). ASCT is feasible in selected patients with EATL and can yield durable disease control in a significant proportion of the patients. (*Blood*. 2013;121(13):2529-2532)

Introduction

Enteropathy-associated T-cell lymphoma (EATL) is a rare type of systemic peripheral T-cell lymphoma (PTCL). According to the International PTCL Project, EATL comprises 5.4% of all T-cell lymphomas.[1] The prognosis of EATL has been considered to be poor.[2-5] The median survival of 62 patients identified in the International PTCL Project was only 10 months.[1]

Apart from a few anecdotal case series,[6-8] autologous stem cell transplantation (ASCT) has been evaluated in a prospective series of 26 EATL patients, of whom 14 proceeded to ASCT after first-line chemotherapy.[9] The recently published phase II study of the Nordic Lymphoma Group included 21 EATL patients, of whom 14 received ASCT.[10]

To explore the feasibility and efficacy of ASCT as a consolidation or salvage strategy in this lymphoma type within a larger sample size, a retrospective registry study (LWP-2010-*R*-07/2011/-*R*-05) was undertaken by the EBMT Lymphoma Working Party.

Study design

The objective of this registry analysis was to study the outcome and prognostic factors of ASCT as a consolidation or salvage strategy for EATL. The primary endpoints were overall survival (OS) and progression-free survival (PFS). Eligible patients were aged 18 years or more who had undergone ASCT for EATL between 2000 and 2010 and were registered in the EBMT database. Centers reporting patients to the registry meeting these inclusion criteria were contacted to provide additional data, including potential history of celiac disease, first-line therapy, high-dose regimen used, as well as updated follow-up data. Also, submission of a written histopathology report fitting with a diagnosis of EATL was mandatory for inclusion of the patients into the final analysis set.

Patient, disease, treatment, and transplant characteristics were compared between groups using χ^2 test or Fisher's exact test for categorical variables and *t* test or Mann-Whitney U-test for continuous variables.

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Table 1. Patient and transplant characteristics of 44 EATL patients receiving ASCT in 2000-2010

Gender, n (%)	
Female	20 (45)
Male	24 (55)
Age, median (range), y	54 (35-72)
History of celiac disease, n (%)	25 (57)
Disease stage at dx (Ann Arbor), n (%)	
I	9 (20)
II	14 (32)
IV	19 (43)
Data missing	2 (5)
B-symptoms at dx, n (%)	22 (54)
Initial therapy	
CHOP	18 (43)
CHOP/IVE/MTX	4 (9)*
CHOEP	4 (9)
ACVBP	3 (7)
IVE	3 (7)
Other/unknown	12 (27)
Antibody included	2 (5)
No. of treatment lines before ASCT, n (%)	
1	19 (46)
2	15 (34)
>2	4 (9)
Data missing	4 (9)
Time from dx to ASCT, median (range), mo	6 (3-32)†
Disease status at transplant, n (%)	
CR or PR1	31 (70)
More advanced	13 (30)‡
High-dose regimen, n (%)	
BEAM	36 (82)
TBI	4 (9)
Stem cell source PB, n (%)	44 (100)

ACVBP, doxorubicin-cyclophosphamide-vindesine-bleomycin-prednisone; BEAM, carmustine-etoposide-cytosine arabinoside-melphalan; CHOEP, cyclophosphamide-doxorubicin-vincristine-etoposide-prednisone; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; CR, complete remission; dx, diagnosis; IVE, ifosfamide-etoposide-epirubicin; MTX, methotrexate; PB, peripheral blood; PR, partial remission; TBI, total body irradiation.

*Methotrexate included in initial therapy in 8 patients.

†Median time 6 months (3-14) in patients transplanted in the first CR or PR and 12 months (4-32) in patients transplanted with more advanced disease status ($P = .0036$).

‡Sensitive relapse in 3 patients, unspecified relapse in 2 patients, CR2 in 3 patients, unspecified CR in 1 patient, and PR >1 in 2 patients.

The main outcomes analyzed in the study were OS, PFS, relapse incidence, and nonrelapse mortality (NRM). OS was defined as the time from transplantation to death from any cause; surviving patients were censored at the time of last follow-up. PFS was defined as the time from transplantation to relapse, disease progression, or death from any cause. NRM was defined as death with no evidence of relapse or progression of lymphoma at any time after ASCT.

The probabilities for OS and PFS were estimated from the time of ASCT using a Kaplan-Meier product-limit estimate and were compared by the log-rank test in univariate analysis. Estimates of NRM and relapse or progression were calculated using cumulative incidence rates to accommodate competing risks and were compared by Gray's test. Due to a limited number of patients, no multivariate analyses were attempted.

Results and discussion

The initial search identified a total of 137 patients meeting the eligibility criteria. Complete complementary and follow-up data including a written histopathology report were received for 54 patients (39%). Of these, 10 patients were excluded either because of another type of T-cell lymphoma as an underlying disease or due to a lack of confirmation by the histopathology report. The data set for final analysis thus included 44 patients (supplemental Data; supplemental Figure 1). The main patient and transplant-related characteristics of these patients are summarized in Table 1. These characteristics were compared with excluded patients (supplemental Data; supplemental Table 1).

Three patients died due to transplant-related causes (infection in all 3), translating into a NRM of 7% at 2 years (Figure 1A). The median follow-up for the living patients was 46 months (2-108) from ASCT. The relapse incidence was 39% at 4 years with only a single relapse occurring after 18 months (Figure 1A). PFS and OS were 54% and 59% at 4 years, respectively (Figure 1B). A trend toward better OS was observed in patients transplanted in complete remission (CR)1/partial remission (PR)1 (66%, 95% confidence interval = 51% to 86% vs 36%, 95% confidence interval = 14% to 96% at 4 years; $P = .062$) (Figure 1C).

Although patients with a history of celiac disease had superior PFS (71% vs 33% at 4 years; $P = .02$) and a trend for better OS (71% vs 45%; $P = .052$), no significant survival difference in favor of celiac disease remained if only patients in first complete or partial remission were considered. Similarly, age, gender, disease stage, B-symptoms at diagnosis, or high-dose regimen used were not associated with significant PFS or OS differences.

The main characteristics and outcome data of the 44 patients included into the final analyses were compared with those of 93 patients without sufficient information for full analysis. The excluded patients had a significantly longer time from diagnosis to ASCT and a much shorter follow-up (supplemental Data; supplemental Table 1) and significantly worse survival (supplemental Data; supplemental Figures 2 and 3). Possible explanations for these outcome disadvantages could be misdiagnosis, center effect, or just a shorter follow-up.

In this study, the survival curves showed a plateau, suggesting that ASCT could be a curative approach in the majority of EATL patients who receive high-dose therapy in first CR or PR. The OS of 66% observed in patients transplanted in first CR or PR is about the same as OS of 68% at 5 years observed in the UK study in patients who completed the whole treatment schedule including ASCT.[9]

Course and treatment after relapse following ASCT were not addressed in this study. However, considering that the PFS and OS curves were almost superimposable, one might conclude that relapse treatment after ASCT was largely ineffective.

This study has some important limitations. It included only patients who had actually received ASCT. Patients receiving autotransplants are highly selected in regard to performance status, age, and chemotherapy responsiveness of the lymphoma. However, it can be concluded that patients with EATL who do manage to proceed to ASCT have treatment outcomes that are comparable with other types of PTCL.[10-14] It is difficult to estimate the proportion of all EATL patients amenable to intensive therapies, but at least one-half of the patients aged <70 years may be considered for standard-dose chemotherapy. If they respond to therapy, their performance status may improve, thus allowing subsequent ASCT.

Although optimal first-line therapy in PTCL in general and specifically for EATL still needs to be defined, this study in the largest cohort of patients analyzed to date shows that ASCT is feasible in patients with EATL and may be followed in a significant proportion of patients with long-term disease control. This provides

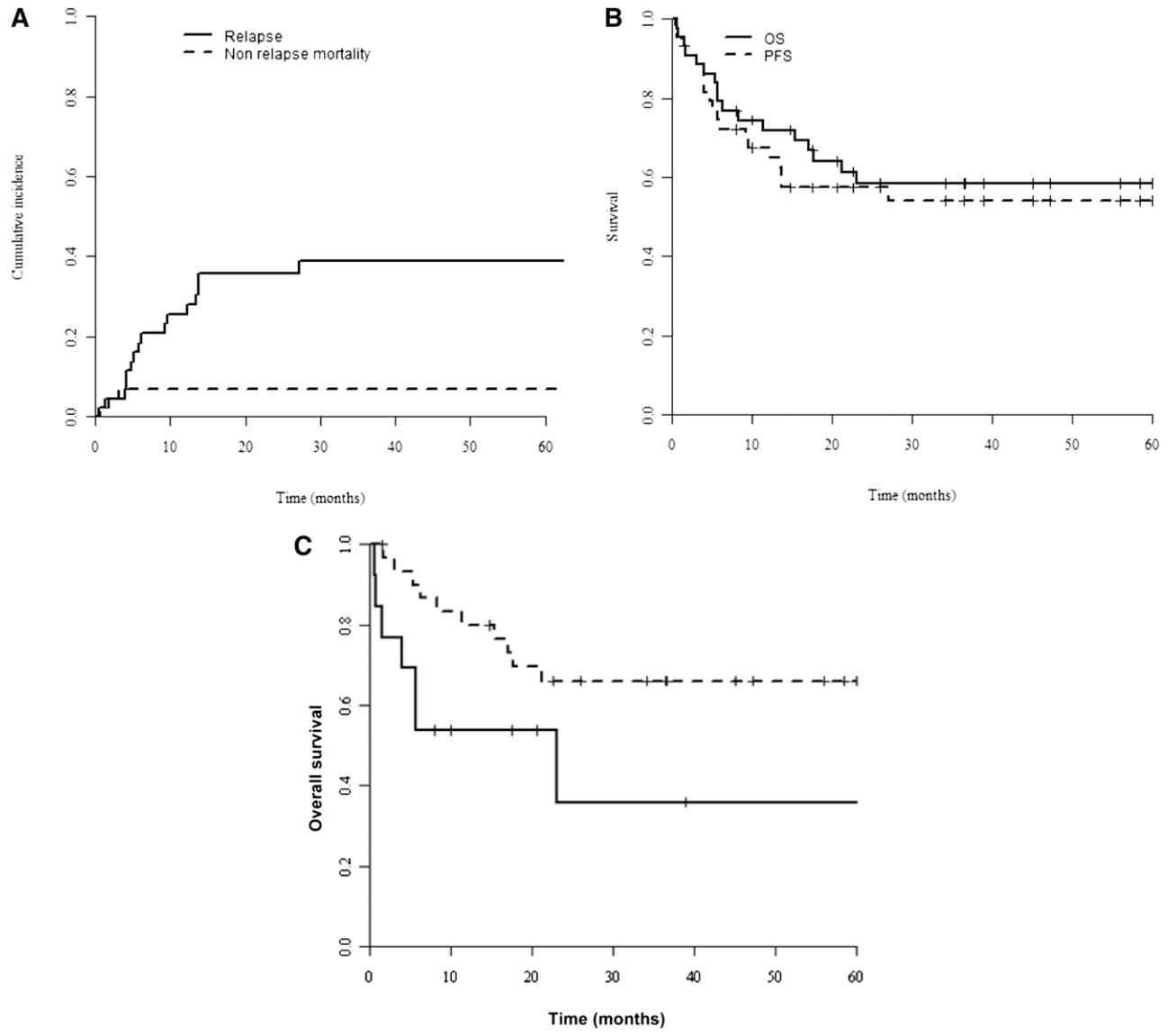

Figure 1. (A) NRM and relapse incidence among 44 EATL patients after ASCT. (B) PFS and OS in 44 EATL patients after ASCT. (C) OS of patients with EATL according to disease status at the time of ASCT. Dotted line: patients transplanted in CR1 or PR1; solid line: patients transplanted in other disease status. $P = .062$. CR, complete remission; PR, partial remission.

a basis for prospective intent-to-treat studies to conclusively demonstrate that ASCT can improve the hitherto dismal outlook of this disease.

Authorship

Contribution: E.J. proposed the study, interpreted the data, and wrote the manuscript; A.S. and P.D. helped in interpreting data and writing the manuscript; A.B. was responsible for statistical analysis; H.F. and J.-J.L. were study coordinators; and P.J., A.R., A.H., M.A.D., W.B., P.B., K.C., C.C., C.R., J.F., G.S., F.K., and P.D. reported updated patient data and read and commented on the manuscript. Additional colleagues reporting data to the study are listed in the Appendix below. All authors proofread the manuscript and agreed on the data presented.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Jian-Jian Luan died on December 26, 2010.

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Appendix: study group members

In addition to the authors listed, the following colleagues reported data on individual patients into this study and are thankfully acknowledged.

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References

1. Delabie J, Holte H, Vose JM, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. *Blood.* 2011; 118(1):148-155.
2. Gale J, Simmonds PD, Mead GM, et al. Enteropathy-type intestinal T-cell lymphoma: clinical features and treatment of 31 patients in a single center. *J Clin Oncol.* 2000;18(4):795-803.
3. Daum S, Ullrich R, Heise W, et al. Intestinal non-Hodgkin's lymphoma: a multicenter prospective clinical study from the German Study Group on Intestinal non-Hodgkin's Lymphoma. *J Clin Oncol.* 2003;21(14):2740-2746.
4. Al-Toma A, Verbeek WH, Hadithi M, et al. Survival in refractory coeliac disease and enteropathy-associated T-cell lymphoma: retrospective evaluation of single-centre experience. *Gut.* 2007; 56(10):1373-1378.
5. Di Sabatino A, Biagi F, Gobbi PG, et al. How I treat enteropathy-associated T-cell lymphoma. *Blood.* 2012;119(11):2458-2468.
6. Jantunen E, Juvonen E, Wiklund T, et al. High-dose therapy supported by autologous stem cell transplantation in patients with enteropathy-associated T-cell lymphoma. *Leuk Lymphoma.* 2003;44(12):2163-2164.
7. Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. *Br J Haematol.* 2007;136(1):111-113.
8. Al-Toma A, Verbeek WH, Visser OJ, et al. Disappointing outcome of autologous stem cell transplantation for enteropathy-associated T-cell lymphoma. *Dig Liver Dis.* 2007;39(7):634-641.
9. Sieniawski M, Angamuthu N, Boyd K, et al. Evaluation of enteropathy-associated T-cell lymphoma comparing standard therapies with a novel regimen including autologous stem cell transplantation. *Blood.* 2010;115(18):3664-3670.
10. d'Amore F, Relander T, Lauritzsen GF, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. *J Clin Oncol.* 2012;30(25):3093-3099.
11. Kyriakou C, Canals C, Goldstone A, et al; Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. High-dose therapy and autologous stem-cell transplantation in angioimmunoblastic lymphoma: complete remission at transplantation is the major determinant of Outcome-Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol.* 2008;26(2): 218-224.
12. Chen AI, McMillan A, Negrin RS, et al. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. *Biol Blood Marrow Transplant.* 2008;14(7):741-747.
13. Nickelsen M, Ziepert M, Zeynalova S, et al. High-dose CHOP plus etoposide (MegaCHOEP) in T-cell lymphoma: a comparative analysis of patients treated within trials of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). *Ann Oncol.* 2009;20(12): 1977-1984.
14. Reimer P, Rüdiger T, Geissinger E, et al. Autologous stem-cell transplantation as first-line therapy in peripheral T-cell lymphomas: results of a prospective multicenter study. *J Clin Oncol.* 2009;27(1):106-113.