Long-term disease-free survival in patients with angioimmunoblastic T-cell lymphoma after high-dose chemotherapy and autologous stem cell transplantation

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Background and Objectives. Patients with angioimmunoblastic T-cell lymphoma (AIL) have a poor prognosis with conventional treatment.

Design and Methods. We initiated an EBMT-based survey studying the impact of high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell transplantation in patients with AIL. Data on 29 patients, who were transplanted between 1992 and 1998 in 16 transplant centers, were collected on standardized documentation forms.

Results. The median age at transplantation was 53 years. HDCT was given as part of 1st-line therapy (N=14; 48%) or 2nd/3rd-line therapy (N=15; 52%). Regimens for the mobilization of peripheral blood stem cells (PBSC) included VIPE (N=7; 26%), DexaBEAM (N=6; 22%), CHOP-like regimens (N=6; 22%), other regimens (N=5; 19%) or alternatively growth factor alone (N=3; 11%). The median yield of PBSC was 3.8×10^6 $CD34^+$cells/kg. Two patients received autologous bone marrow. The HDCT consisted of BEAM-type regimens in 16 patients, ICE-type regimens in 7, and other regimens in 6 patients. There was one treatment-related death. The rate of complete remissions increased from 45% before HDCT to 76% after HDCT. As of January 2003, after a median observation time of living patients of 5 years (range 2.5 to 10 years), 14 patients have died (13 from progressive disease), and 15 patients are alive. The probability of 5-year overall and event-free survival was 44% (95% CI, 22% to 66%) and 37% (95% CI, 17% to 57%), respectively. Long-term disease-free survival was observed in patients transplanted during 1st-line treatment as well as in the context of 2nd/3rd-line therapy.

Interpretation and Conclusions. There is evidence that AIL is susceptible to high-dose chemotherapy. HDCT and autologous stem cell transplantation should be considered in selected patients with AIL.

Key words: angioimmunoblastic T-cell lymphoma, high-dose chemotherapy, autologous stem cell transplantation.

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Angioimmunoblastic T-cell-lymphoma (AIL) is one of the mature T-cell neoplasms defined in the REAL- and WHO-classifications.[1] Lymph node histology of this disease is characterized by a typical morphologic picture with effacement of the nodal architecture by a polymorphic inflammatory infiltrate containing small lymphocytes, large lymphoid blasts and follicular dendritic cells, as well as marked vascular proliferation. According to the *Non-Hodgkin's Lymphoma Classification Project* the frequency of AIL among cases referred to expert hematopathologists ranges between 1% and 2% of all non-Hodgkin´s lymphomas in Europe.[2] Although research on the etiology, pathophysiology and clinical behavior of AIL is hampered by its rarity and the difficulty in identifying the neoplastic cell population, considerable progress has been made during the last decade.[2] AIL was initially supposed to be the result of an abnormal immune reaction. However, due to the frequent finding of T-cell receptor gene rearrangements and distinct cytogenetic aberrations (trisomy 3 and/or 5), it is now clearly recognized that AIL is a malignant T-cell lymphoma.[4-6]

At presentation, 90% of patients with AIL have advanced disease and the median age at initial diagnosis is about 65 years.[7] AIL usually has a very aggressive course. However, as it is a rare disease there are no generally accepted treatment guidelines of proven effectiveness. Most clinicians choose intensive adriamycin-containing chemotherapy programs. However, the probability of 5-year event-free survival even after intensive chemotherapy is below 30%.[8-12]

Given the increasing experience in applying high-dose chemotherapy (HDCT) and autologous stem cell transplantation to improve the prognosis of patients with high-grade B-cell lymphomas, we asked whether HDCT may also be advantageous for selected patients with AIL. We, therefore, performed an international survey and retrospectively evaluated the clinical characteristics at initial diagnosis, treatment-strategies prior to HDCT, PBSC mobilization, status at transplantation, hematopoietic regeneration, response and long-term outcome of patients with AIL who had received HDCT.

Design and Methods

Data collection and selection of patients

In June 1999 272 EBMT bone marrow transplant centers were asked to contribute data to a survey on patients with AIL who had received high-dose chemotherapy and an autologous stem cell transplant. Uni-

form standardized questionnaires were sent to centers which wanted to participate. In September 2002 follow-up information was requested for every patient.

Definitions

The stage of disease was determined according to the Ann Arbor classification system.[13] The age-adjusted International Prognostic Factor Index for patients aged below 60 years was applied.[14] First-line treatment strategies were classified as follows: a strategy of *watch and wait* was defined by a minimum interval of one month between diagnosis and the onset of any specific treatment, including the administration of corticosteroids. A therapeutic trial of *corticosteroids without chemotherapy* had to last for a minimum of one month.

Complete remission (CR) was defined as total disappearance of all evidence of tumor; partial remission (PR) as a >50% reduction in the sum of the products of the longest diameters of measurable lesions; stable disease (SD) as no objective decrease in the tumor measurements qualifying as partial remission and no objective increase qualifying as progressive disease; progressive disease (PD) as a >25% increase of the product of the longest diameters of any measurable lesion or the appearance of new lesions. Relapse mortality after HDCT was defined as death related to progressive disease, whereas treatment-related mortality was defined as death from any other cause.

Statistical analysis

Data were analyzed as of January 2003. Survival probabilities were calculated according to the method of Kaplan and Meier. Overall survival was calculated from the date of transplantation to the date of death or the date of last follow-up. Event-free survival was taken from the date of transplantation until treatment failure or death from any cause. Patients with stable or progressive disease at first evaluation after HDCT were included in the calculation with an event-free survival of zero days.[15] The χ^2 test was used for the comparison of proportions and the log-rank test was used for the comparison of time-dependent events.

Results

Patients

Sixteen EBMT-centers reported data on 29 patients (Table 1). At inital diagnosis the median age of the patients was 51 years. Nineteen were male, 10 were female. At inital diagnosis only one patient (3%) had limited disease (Ann Arbor stage ≤ II) while 28 patients (97%) had stage III or IV disease.[13] According to the age-adjusted International Prognostic Factor Index (IPI) 79% of patients were at high intermediate or high risk.[14] Bone mar-

Table 1. Baseline characteristics at initial diagnosis.

Characteristics	
Median age at diagnosis (range) [yrs]	51 (20 to 59)
Median age at HSCT (range) [yrs]	53 (20 to 60)
Sex (male/female)	19 (65%)/10 (35%)
Diagnosis based on:	
detailed report (including immunophenotype)	15/29 (52%)
reference histology	8/29 (27%)
brief pathological report	6/29 (21%)
Ann Arbor stage (N=29)	
I	0 (0)
II	1 (3%)
III	9 (31%)
IV	19 (66%)
B-symptoms	20/29 (69%)
Elevated LDH	20/27 (74%)
ECOG (N=25)	
0	7 (28%)
1	6 (24%)
2	8 (32%)
3	3 (12%)
4	1 (4%)
Age-adjusted International Prognostic factor Index (N=24)	
low	0 (0%)
low intermediate	5 (21%)
high intermediate	8 (33%)
high	11 (46%)
Bone marrow involvement	12/29 (41%)
Any extranodal involvement	17/29 (59%)
liver	6/29 (21%)
lung	3/29 (10%)
skin	3/29 (10%)
intestine	2/29 (7%)
other	8/29 (27%)
Signs and symptoms	
pruritus	9/24 (37%)
skin rash	5/25 (20%)
arthralgia	3/24 (12%)
edema	5/25 (20%)
effusions	9/25 (36%)
Any autoimmune phenomena	10/29 (34%)
Cold agglutinins/cryoglobulins	6/29 (21%)
Coombs'-pos. AIHA	8/17 (47%)

Table 2. Results of 1st-line chemotherapy (N=29).

	Response
CHOP (N=16)	4×CR (25%) 8×PR (50%) 4×SD/PD (25%)
Intensive combination chemotherapies* (N=12)	5×CR (42%) 5×PR (42%) 2×SD/PD (16%)
Others (N=1)	1×CR (100%)

**ProMACE-CytaBOM: prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue;[16] COPBLAM-IMVP16: cyclophosphamide, vincristine, bleomycin, adriamycin, procarbazine, prednisone alternating with ifosfamide, methotrexate, etoposide;[8] VACOP-B: etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin;[26] CHOEP: CHOP combined with etoposide.[16]*

Table 3. Results of salvage chemotherapy at first relapse (N=15).

	Response
DexaBEAM (N=6)	3×CR (50%) 3×PR (50%)
CHOP (N=4)	1×CR (25%) 1×PR (25%) 2×SD/PD (50%)
DHAP ± Etoposide (N=2)	1×CR (50%) 1×PR (50%)
Others (N=3)	1×CR (33%) 2×PR (67%)

DexaBEAM: dexamethasone, BCNU, etoposide, cytarabine, melphalan;[17] CHOP: cyclophosphamide, vincristine, adriamycin, prednisolone;[16] DHAP: dexamethasone, cytarabine, cisplatin.[18,19]

Table 4. High-dose-chemotherapy regimens (N=29).

BEAM/BEAM-like	16 (56%)
ICE/ICE-like	7 (24%)
TBI/CY or BU/CY	3 (10%)
Others	3 (10%)

BEAM: BCNU, etoposide, cytarabin, melphalan;[17] TBI: total body irradiation; CY: cyclophosphamide; BU: busulfan.[22]

row was involved in 12 patients (41%). B-symptoms were present in 20 patients (69%). Lactate dehydrogenase (LDH) was elevated above the upper normal range in 20 of 27 patients (74%). Extranodal involvement was found in 17/29 patients (59%) in the following organs: liver (21%), lung (10%), skin (10%), and intestine (7%). Patients showed signs and symptoms known to be associated with a diagnosis of AIL, such as pruritus (37%), effusions (36%), skin rash (20%) and peripheral edema (20%) as predominant features. Autoimmune phenomena, such as Coombs'-positive hemolytic anemia or the presence of cold agglutinins or cryoglobulins, were diagnosed in 10 patients (34%).

Treatment prior to HDCT

First-line treatment consisted of chemotherapy in 22 patients (76%), while 4 patients (14%) received *corticosteroids without chemotherapy* and a *watch-and-wait* strategy was applied in 3 patients (10%). No patient received radiotherapy as first-line treatment. Sixteen patients (55%) received the CHOP regimen as first-line chemotherapy and in 12 patients (41%) more intensive chemotherapies were administered (Table 2).[8,16] First-line chemotherapy resulted in an overall response rate of 79% (34% CR and 45% PR). HDCT was administered as a part of first-line treatment in 14 (48%) patients.

Fifteen patients received HDCT as part of 2nd (N=10; 34%) or 3rd-line (N=5; 18%) treatment. In these patients the salvage chemotherapies at first relapse consisted of DexaBEAM (40%), CHOP (27%), DHAP ± etoposide (13%) and other regimens in 3 patients (Table 3). Salvage chemotherapy resulted in an overall response rate of 87% (40% CR and 47%PR).[17-19] Two patients (7%) received local radiotherapy as part of their 2nd line treatment. Five patients received HDCT as part of 3rd-line treatment after a variety of salvage chemotherapies.

Stem cell harvest

The autologous hematopoietic stem cell graft consisted of bone marrow in 2/29 (7%) patients, and of peripheral blood stem cells (PBSC) in 27/29 (93%) patients. Regimens used for PBSC mobilization were VIPE (7/27; 26%), DexaBEAM (6/27; 22%), CHOP-like (6/27; 22%), high-dose cyclophosphamide (4/27; 15%) and mitoxantrone/cytarabine (1/27; 4%) each in combination with granulocyte colony-stimulating factor (G-CSF) or G-CSF alone (3/27, 11%).[17,20] The stem cell products were unmanipulated in 19 patients (70%), while 8 patients (30%) received $CD34^+$ selected PBSC.

Conditioning regimens and HSCT

Patients received HDCT and HSCT between 1992 and 1998. At transplantation the median age was 53 years (range, 20 to 60 years). Conditioning prior to HSCT was carried out with BEAM or BEAM-like regimens in 16 patients (56%), ICE or ICE-like regimens in 7 patients (24%), TBI/CY or BU/CY in

Table 5. Response status before and after HDCT.

	N=29	*Prior HDCT*		*Max response after HDCT*	
First-line	14	CR	7	CR	12
		PR	6	PR	1
		NC/PD	1	NC/PD	1
Second-line	10	CR	4	CR	7
		PR	5	PR	2
		NC/PD	1	NC/PD	1
Third-line	5	CR	2	CR	3
		PR	0	PR	0
		NC/PD	3	NC/PD	2

3 patients (10%) and miscellaneous regimens in 3 patients (10%) (Table 4).[17,21,22] The mononuclear cell counts in the two patients who received autologous bone marrow, were 2.2 and 2.8×10^6 cells /kg body weight. PBSC products contained a median number of 3.8×10^6 CD34 cells/kg (range, 1.0 to 13.6×10^6 CD34 cells/kg). Supportive care after transplantation was provided according to differing protocols of each participating institution.

Hematologic regeneration

After transplantation all patients received growth factors to accelerate hematopoietic regeneration. Twenty-seven patients (93%) received G-CSF and two patients (7%) received granulocyte-macrophage colony-stimulating factor. Data on hematologic regeneration were missing in two patients and one patient died before platelet regeneration occurred. In the evaluable patients regeneration of granulocytes to > 0.5×10^9/L took a median of 11 days (range, 10 to 55 days) and regeneration of platelets to > 25×10^9/L took a median of 14 days (9 to 55 days).

Response to HDCT

Immediately before HDCT 13 patients (45%) were in CR, 11 patients (38%) in PR, and 5 patients (17%) had SD/PD (Table 5). After HDCT 22 patients (76%) were in CR, 3 patients (10%) in PR, and 4 patients (14%) had SD/PD. The CR rates after transplantation in patients who were treated with HDCT as part of first-line, 2nd-line and 3rd-line therapy were 86%, 70% and 60%, respectively (p=0.446). Of 5 patients with stable or progressive disease at transplantation four patients achieved a remission and one out of these four patients is still alive in continuous CR four years after transplantation.

Survival

Complete follow-up was available for 28 patients, while one patient was lost from follow-up 2 years after transplantation while in continuous CR. As of January 2003 after a median observation time of 5 years (range 2.5 to 10 years) in living patients, 14 patients had died and 15 were alive. Thirteen patients died due to relapse and one patient died from CMV-pneumonia 43 days after transplantation.

The 5-year probabilities of overall survival and of event-free survival (Figure 1) were 44% (95% CI, 22% to 66%) and 37% (95% CI, 17% to 57%), respectively. Of 22 patients who achieved a complete remission after HDCT, nine patients (41%) experienced a relapse and the 5-year probabilities of overall survival and event-free survival were 62% (95% CI, 48% to 86%) and 49% (95% CI, 24% to 74%), respectively. At last follow-up, five patients were in continuous CR for more than 5 years (range, 6 to 10 years after HSCT). The 5-year probabilities of overall and event-free survival in patients who were transplanted as first-line therapy compared to those who were transplanted as second- or third-line therapy were 60% and 37% compared to 44% and 39%, respectively (Figures 2 and 3). The 5-year probabilities of event-free survival according to the International Prognostic Factor Index were 60% (95% CI, 18% to 100%) for patients at low intermediate risk, 42% (95% CI, 3% to 81%) for patients at high intermediate risk and 25% (95% CI, 0% to 55%) for patients at high risk (log-rank, p=0.2572).

Discussion

Angioimmunoblastic T-cell lymphoma is a very rare disease. The median age at initial diagnosis is about 65 years and currently patients with AIL are generally considered to have a poor prognosis. Despite past reports on individual patients with benign disease courses, the reported median survival is 20 months and the 4-year probability of overall survival is only about 30%.[8-10,12] Patients with AIL are most often treated like patients with aggressive B-cell lymphoma. Data on second-line treatment strategies for patients with relapsed AIL are rare. However, there have been case reports on prolonged disease-free survival after HDCT and autologous stem cell transplantation in patients with relapsed AIL.[12,23,24] We, therefore, performed a survey in order to determine the feasibility and efficacy of HDCT in patients with AIL.

Indirect evidence that mobilization of PBSC in patients with AIL is comparable to mobilization in patients with more conventional diagnoses comes from the fact that PBSC harvest was successful in 9 patients transplanted at first relapse and in 5 patients transplanted at second relapse. Furthermore we did not receive reports on difficult or impossible stem cell mobilization in patients with AIL.

The potential of high-dose chemotherapy to

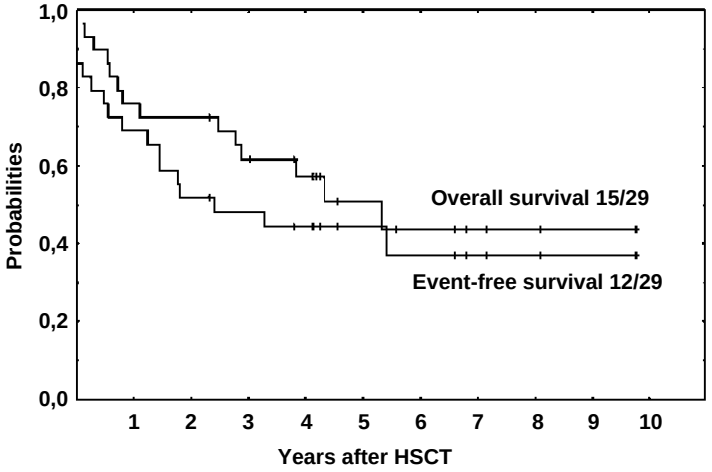

Figure 1. Overall and event-free survival. The probability of 5-year overall survival was 44% (95% CI 22% to 66%) and that of 5-year event-free survival was 37% (95% CI 17% to 57%).

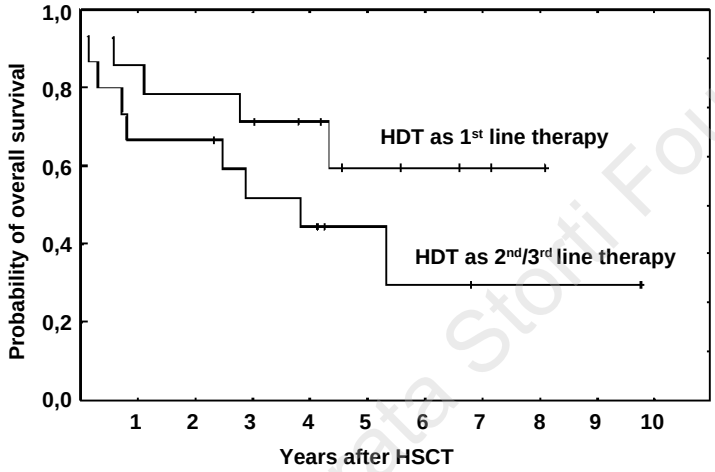

Figure 2. Overall survival according to treatment strategy. The probability of 5-year overall survival was 60% (95% CI 30% to 90%) for patients in whom HDCT was applied as 1st line therapy and 44% (95% CI 18% to 70%) in those in whom it was administered as 2nd / 3rd line therapy (log-rank, *p*=0.1699).

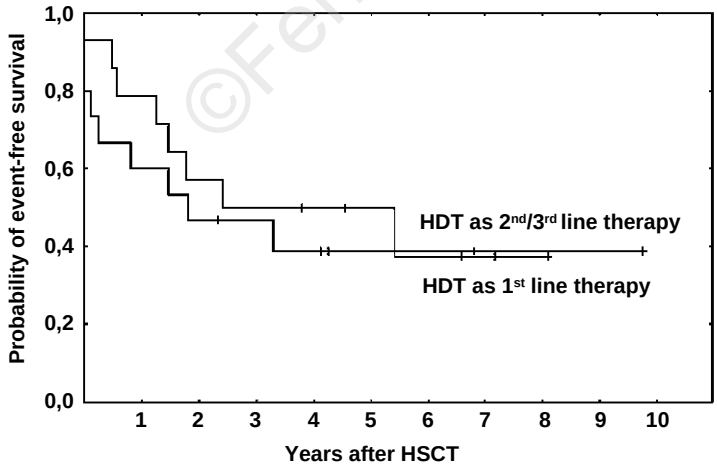

Figure 3. Event-free survival according to treatment strategy. The probability of EFS was 37% (95% CI 8% to 66%) for patients in whom HDCT was applied in 1st line therapy and 39% (95% CI 13% to 65%) in those in whom it was administered in more advanced disease (log-rank, *p*=0.6075).

increase the rate of complete remissions from 45% before HDCT to 76% after it is of special importance. Furthermore, the rate of relapse was very low in patients achieving a complete remission after HDCT. Among the 22 patients who achieved a complete remission after HDCT the 5-year probability of overall survival was 62% (95% CI, 48% to 86%). To date, five patients are in continuous complete remission with a follow-up of more than 5 years. These excellent results can be interpreted as a susceptibility of AIL to escalated doses of cytostatic agents and suggest that long-term event-free survival and cure can be achieved in selected patients with HDCT. Bearing in mind that half of the patients were transplanted in first or even second relapse, and that their median age was 53 years at HSCT, the 5-year overall survival probability of 44% for the whole group compares very favorably with published results, especially when comparing data on second-line treatment.[8,9,11]

Of 14 patients with AIL receiving second-line therapy, reported by Pautier *et al*. in 1999, only 3 patients obtained a durable second complete remission.[12] It is of interest that two of these three patients had received HDCT and autologous HSCT. In addition to reports on long-term disease-free survival after HDCT, there is evidence that the adverse prognostic influence of the T-phenotype in aggressive lymphoma could be overcome by dose-escalation strategies. Gisselbrecht *et al*. reported a 5-year overall survival rate of 41% in patients with a variety of aggressive lymphomas of T-phenotype. This compared with a rate of 53% in patients with lymphoma of B-phenotype (p=0.0004) included in the LNH87-trials of the *Groupe d'Etudes des Lymphomes de l'Adulte*.[11] However, for the subgroup of 16 patients with a T-phenotype who had received HDCT and autologous HSCT, he reported similar survival rates to those in patients with aggressive B-cell lymphoma. Rodriguez *et al*. retrospectively analyzed data on 36 patients with peripheral T-cell lymphoma (REAL classification) who had received HDCT and autologous HSCT after relapse and found a 3-year overall survival rate of 36%, similar to that in patients with relapsed B-cell lymphoma.[25] This observation was supported by retrospective data published by Blystad *et al*.[23] Blystad analyzed data on patients with aggressive lymphoma of T-cell phenotype who had received HDCT and autologous HSCT and found overall survival rates similar to those of B-cell lymphoma. Our data, therefore, fit within an emerging picture that the poor prognostic implication of T-phenotype in aggressive lymphoma can be overcome by HDCT.

However, our data must to be interpreted with caution. There is a systematic bias from including patients who had received HDCT. We do not have information on patients who should have received HDCT but failed salvage chemotherapy.

Future trials need to answer the question of whether HDCT and autologous HSCT should be applied as first-line strategy for patients with AIL. However, we observed long-term event-free survival even in patients transplanted in relapse. A conservative approach would, therefore, be to offer conventional treatment as first-line strategy and HDCT and autologous HSCT in first relapse.

In conclusion, HDCT and autologous HSCT in AIL as first-line or as a part of a salvage strategy induces a high remission rate and long-term event-free survival in selected patients. This observation argues in favor of a dose-response relationship in AIL. The option of HDCT should be offered to patients with relapsed AIL, eligible for intensive treatment strategies. Our data should encourage the inclusion of patients with AIL into ongoing prospective multicenter trials evaluating the role of HDCT.

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Contributions

WS had the original idea and designed the study. JS and DK participated in the conception of the study, collected the data, performed the statistical analysis and wrote the first draft of the article. SF, AR, WEB, YB, SB, DC, IM, HH, HEJ, EK, EM, DS, AC, WR, JP and DK applied high-dose chemotherapy and autologous stem cell transplantation, did the clinical assessment and follow-up of the patients. All the authors contributed to the interpretation and discussion of the data and revised the manuscript.

Disclosures

Conflict of interest: none

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, Editor-in-Chief. The final decision to accept this paper for publication was taken jointly by Professor Cazzola and the Editors. Manuscript received August 6, 2003; accepted October 2, 2003.

In the following paragraphs, Professor Cazzola summarizes the peer-review process and its outcomes.

What is already known on this topic

Patients with angioimmunoblastic T-cell lymphoma (AIL) have a poor prognosis with conventional treatment.

What this study adds

High-dose chemotherapy has been applied safely in patients with AIL and induced a high rate of complete remissions. Long-term disease-free survival was observed both in patients transplanted upfront and in relapsed disease. High-dose chemotherapy should, therefore, be considered in patients with relapsed AIL eligible for intensive treatment strategies.