Long-term outcome of allogeneic hematopoietic cell transplantation for T-cell prolymphocytic leukemia – a study on behalf of the Chronic Malignancies Working Party of the EBMT

T-cell prolymphocytic leukemia (T-PLL) is a rare subtype of an aggressive T-cell lymphoma[1] associated with poor outcomes.[2] Intravenous alemtuzumab is recommended as a first-line treatment[3] but with a high cumulative relapse incidence and short responses lasting between 3-11 months. We recently published data on autologous hematopoietic cell transplantation (HCT) which could be a consolidative option, although not curative.[4] Single-center[5,6] and registry studies[7-10] have found that allogeneic HCT was associated with both high toxicity and high relapse incidence despite being the only hope of cure. Such studies, however, have a follow-up of <5 years and concerns remain about long-term efficacy and tolerance. Here we provide an update on the long-term outcome after allogeneic HCT in patients with verified T-PLL diagnoses whose short-/medium-term outcomes were previously reported within two European Group for Blood and Marrow Transplantation (EBMT) Chronic Malignancies Working Party (CMWP) studies.[11,12] In this study the findings indicate that long-term survival in patients with T-PLL remains disappointingly poor, and allogeneic HCT appears to be curative in fewer than 20% of patients. This retrospective study was approved by the CMWP of the EBMT. We selected patients with verified T-PLL diagnoses undergoing allogeneic HCT between 1995 and 2012 from the EBMT registry who were described in two previous reports.[11,12] The primary endpoint of the study was overall survival, and secondary endpoints were relapse-free survival, relapse, and non-relapse mortality. This retrospective study was approved by the CMWP of the EBMT.

The patients' characteristics are reported in Table 1. Data on previous treatment lines were available for 46 patients, of whom 31 (67.4%) had received one line, nine (19.6%) had received two lines, and six (13.0%) had received three or more lines, including alemtuzumab in 91% of those treated (Figure 1). The median interval between initiation of first-line therapy and allogeneic HCT was 5.5 (interquartile range [IQR], 4.6-8.1) months. The median time between initiation of the last alemtuzumab protocol and allogeneic HCT was 5.0 (IQR, 4.2-6.6) months.

At the time of transplantation, 47.2% of patients were in complete response, 11.1% had progressive disease and the remainder had a partial response (33.3%) or stable disease (8.3%). Donors were mostly HLA-compatible, either related (45.5%) or unrelated (41.6%). Conditioning was myeloablative in 51.4% of cases and reduced intensity in 48.6%. Total body irradiation (TBI) was not used or delivered at a dose of <6 Gy in 46 (69.7%) patients and at a dose ≥6 Gy in 20 (30.3%) patients. The distribution of TBI among those given myeloablative and reduced intensity conditioning and the listing of conditioning are reported in *Online Supplementary Table S1*. *In vivo* T-cell depletion, mostly with antithymocyte globulin, was performed in 32 (56.1%) patients. The source of stem cells was peripheral blood in 66 (85.7%) cases. Graft-*versus*-host disease (GvHD) prophylaxis was conducted mostly with cyclosporine combined with a short course of methotrexate (47.3%) or with mycophenolate mofetil (21.8%) (Table 1).

With a median follow-up after allogeneic HCT of 12.5 (IQR, 6.0-14.4) years, the 6- and 10-year probabilities of overall survival were 29% (95% confidence interval [CI]: 18-39) and 21% (95% CI: 11-31), respectively, those of progression-free survival were 20% (95% CI: 10-29) and 9% (95% CI: 1-17), the 6- and 10-year cumulative incidences of relapse were 42% (95% CI: 31-54) and 46% (95% CI: 34-58) and the 6- and 10-year probabilities of non-relapse mortality were 38% (95% CI: 27-49) and 40% (95% CI: 28-51), respectively (Figure 2). Of note, relapse events occurred regularly throughout the whole duration of follow-up.

The cumulative incidence of acute GvHD was 27% (95% CI: 17-37) at day 100, including 15% (95% CI: 7-23) with grade III or higher. The cumulative incidence of chronic GvHD at 1 year was 39% (95% CI: 27-50), including 13% (95% CI: 5-21) with extensive disease (*Online Supplementary Figure S1*).

Half of the ten cases of secondary malignancies reported during follow-up were post-transplant lymphoproliferative disorder (N=5, all within the first 13 months after allogeneic HCT), two were skin tumors, one was pulmonary epidermoid carcinoma, one was 'other kidney tumor including renal cell carcinoma' and one was other, unspecified, carcinoma. The cumulative incidence of secondary malignancies increased from 9% (95% CI: 2-16%) at 2 years to 14% (95% CI: 6-23%) at 10 years.

Fifty-nine (76.6%) patients succumbed after allogeneic HCT. The cause of death, unknown for seven patients (11.9%), in the remaining cases was relapse/progression (N=23), infection (N=12), GvHD (N=8), secondary malignancy (N=3) or other (N=6). The 12 fatal infections were of bacterial (N=2), viral (N=2), fungal (N=2) or unreported origin (N=6). The

Table 1. Characteristics of the patients and their transplants.

Characteristics	Values
Total patients, N (%)	77 (100)
Patients' sex, N (%) Male Female	 54 (70.1) 23 (29.9)
Year of diagnosis, median (IQR)	2005 (2003-2007)
Age at diagnosis, years, median (IQR)	51.0 (46.7-58.6)
Lymphocyte count at diagnosis, x10^9/L, median (IQR); missing 58	44 (18-90)
Cytogenetics, N (%); missing 52 Normal karyotype Abnormal karyotype	 3 (12.0) 22 (88.0)
Age at allo-HCT, years, Median (IQR) Range <50, N (%) 50-60, N (%) ≥60, N (%)	 53.6 (47.6-59.6) 23.6-71.1 27 (35.1) 34 (44.2) 16 (20.8)
KPS at allo-HCT, N (%); missing 40 ≤80 90 or 100	 11 (29.7) 26 (70.3)
HCT-CI, N (%); missing 65 low risk (0) intermediate risk (1-2) high risk (≥3)	 7 (58.3) 3 (25.0) 2 (16.7)
Year of allo-HCT Median (IQR) <2005, N (%) ≥2005, N (%)	 2006 (2004-2008) 22 (28.6) 55 (71.4)
Interval diagnosis - allo-HCT, months, median (IQR)	10.5 (6.0-17.2)
Disease stage at allo-HCT, N (%); missing 5 Complete remission Partial remission Stable disease Relapse/progression	 34 (47.2) 24 (33.3) 6 (8.3) 8 (11.1)
N of previous lines of therapy, N (%); missing 31 1 2 ≥3	 31 (67.4) 9 (19.6) 6 (13.0)
Alemtuzumab before allo-HCT, N (%); missing 31	42 (91.3)
Auto-HCT before allo-HCT, N (%)	2 (2.6)
Donor type, N (%) Identical sibling Matched unrelated donor Mismatched unrelated donor UD, number of mismatches unknown	 35 (45.5) 32 (41.6) 6 (7.8) 4 (5.2)
Donor: female to male, N (%)	17 (22.1)
Donor age, years, median (IQR); missing 21	43.8 (32.8-52.6)
Stem cell source, N (%) Bone marrow Peripheral blood	 11 (14.3) 66 (85.7)
CMV serostatus, N (%); missing 25 Patient(-) / donor(-) Patient(-) / donor(+) Patient(+) / donor(-) Patient(+) / donor(+)	 14 (26.9) 6 (11.5) 14 (26.9) 18 (34.6)
T-cell depletion, N (%); missing 20 No Yes, *in vivo* Yes, *ex vivo*	 24 (42.1) 32 (56.1) 1 (1.8)
ATG given as conditioning at allo-HCT, N (%); missing 21	16 (28.6)
GvHD prophylaxis, N (%); missing 22 CsA+MTX CsA+MMF CsA alone Other	 26 (47.3) 12 (21.8) 8 (14.5) 8 (14.5)
N of infused CD34$^+$ cells, x10^6/kg body weight, median (IQR); missing 32	5.9 (3.9-7.5)

allo-HCT: allogeneic hematopoietic cell transplantation; ATG: antithymocyte globulin; auto-HCT: autologous hematopoietic cell transplantation; CMV: cytomegalovirus; CsA: cyclosporine A; HCT-CI: Hematopoietic Cell Transplantation Comorbidity Index; IQR: interquartile range; KPS: Karnofsky performance status; MMF: mycophenolate mofetil; MTX: methotrexate; UD: unrelated donor.

2-year cumulative incidence of progression-related death was 22% (95% CI: 13-31%), followed by infection-related death (13%, 95% CI: 6-21%), GvHD (10%, 95% CI: 4-17%) and other or unknown cause of death (5%, 95% CI: 0-10%). The 10-year cumulative incidence of death due to relapse/progression and infection reached 32% (95% CI: 21-43%) and 16% (95% CI: 8-43%), respectively. No other causes of death were reported between 2 and 10 years except for unknown/other causes of death amounting to a 10-year cumulative incidence of 15% (95% CI: 6-23%).

Univariable analyses revealed a significant association of three variables with better outcome: more favorable disease status at allogeneic HCT (complete response *vs*. no complete response), use of TBI (≥6 Gy *vs*. no TBI or <6 Gy) and later calendar year of transplantation (*Online Supplementary Table S2*). Exploratory multivariable analysis included those variables and, additionally, age at time of allogeneic HCT. Patients in complete response at allogeneic HCT and those receiving TBI ≥6 Gy showed significantly lower risk of relapse and longer progression-free and overall survival. Older age at allogeneic HCT was also associated with lower risk of relapse and longer progression-free survival. None of the analyzed factors was significantly associated with non-relapse mortality (*Online Supplementary Table S2*).

Results from this study rely on the same patients as previously published[11,12] but with substantially longer follow-up and confirm findings from previous reports in T-PLL[1,5-10] on the poor outcomes, highlighting that only a minority (10-

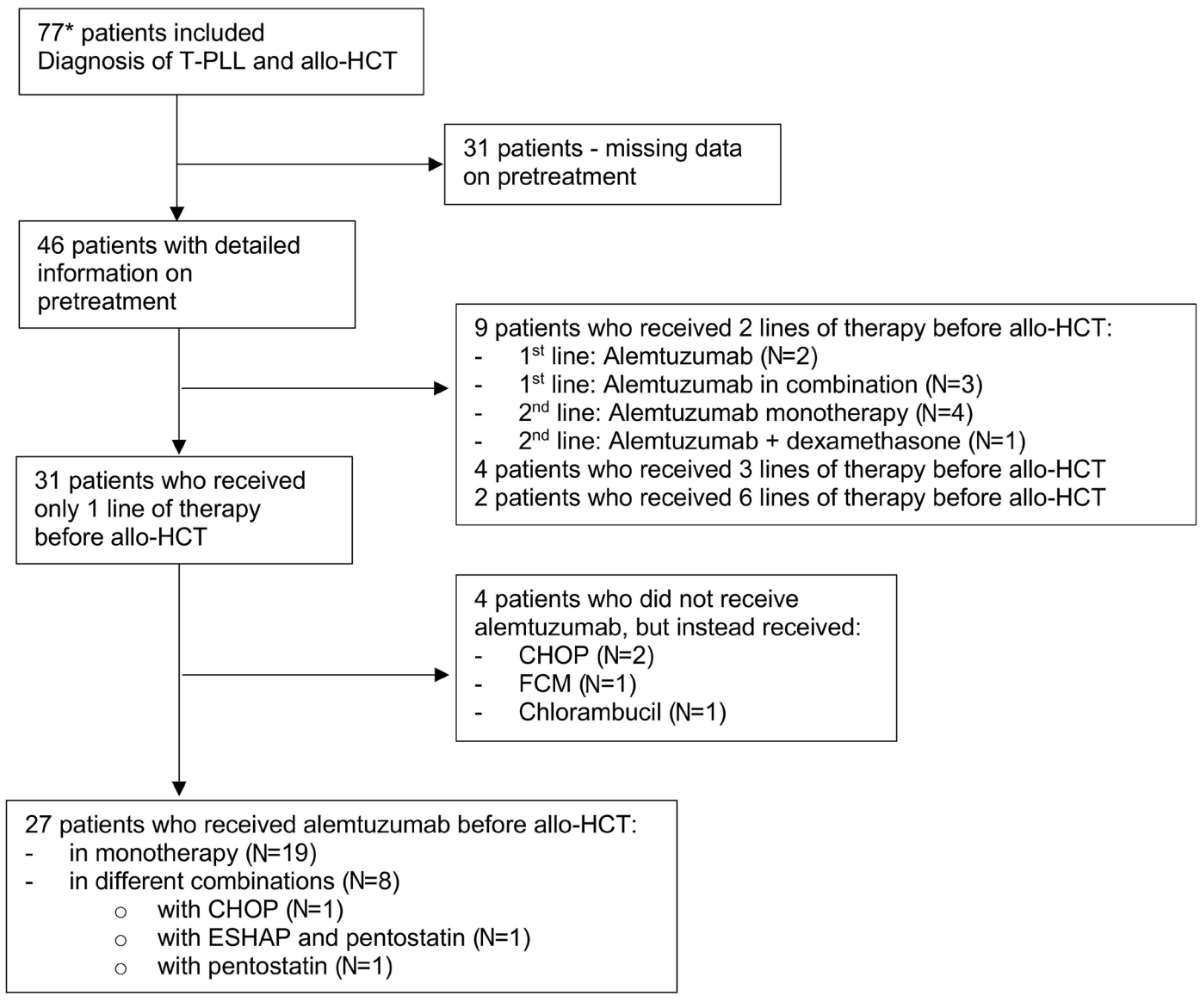

Figure 1. Flow diagram depicting the number of patients with different numbers of lines of therapy and different types of treatment before allogeneic hematopoietic cell transplantation. *One patient from a former retrospective study (Wiktor-Jedrzejczak W, Leukemia, 2012) was excluded (not T-cell prolymphocytic leukemia). allo-HCT: allogeneic hematopoietic cell transplantation; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; ESHAP: etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; FCM: fludarabine, cyclophosphamide, mitoxantrone); T-PLL: T-cell prolymphocytic leukemia.

20%) of T-PLL patients achieve long-term control of the disease, which offers hope of a cure. However, considering the absence of available alternatives such as fratricide-resistant chimeric antigen receptor T cells or bispecific antibodies, and given the natural poor prognosis, allogeneic HCT remains imperative in T-PLL treatment algorithms for eligible patients and should be optimized. Failures are related to the high cumulative incidence of relapse, above 40% at 6 years, and the high non-relapse mortality, which is also almost 40% at 6 years, with infectious complications prevailing. These relapses after a massive incidence within the first year continue steadily with very late occurrences, translating into a much higher cumulative incidence of relapse compared to that in other mature T-cell neoplasias, such as peripheral T-cell lymphoma.[13]

With the usual caveats, given the retrospective nature and small sample size, our data point to three potential ways of improving results. A positive evolution of practices in the management of infections could improve the results, which is suggested by the association of non-relapse mortality with calendar year of allogeneic HCT albeit not confirmed in multivariable analysis. The quality of disease control at transplantation appears crucial. Unlike peripheral T-cell lymphoma, for which the results of allogeneic HCT in partial response/stable disease remain acceptable, the probability of achieving long-term survival in patients not in complete response appears very low in T-PLL, with many patients experiencing both early and late relapses. Beyond alemtuzumab, it is essential to find new therapeutic approaches that can bridge patients successfully to allogeneic HCT. Choice of conditioning must be addressed. In line with the study by the Center for International Blood and Marrow Transplant Research (CIBMTR)[10] we did not find a benefit of myeloablative conditioning. However, applying the previously used cut-off,[11] we confirmed the benefit of at least 6 Gy TBI on the risk of relapse. This finding is in line with the findings of other studies of T-cell neoplasia, including acute lymphoblastic leukemia and peripheral T-cell lymphoma.[14,15]

A paradoxical result was the association of older age at allogeneic HCT with better progression-free survival and lower risk of relapse. We might hypothesize that older patients were selected based on stricter criteria for the

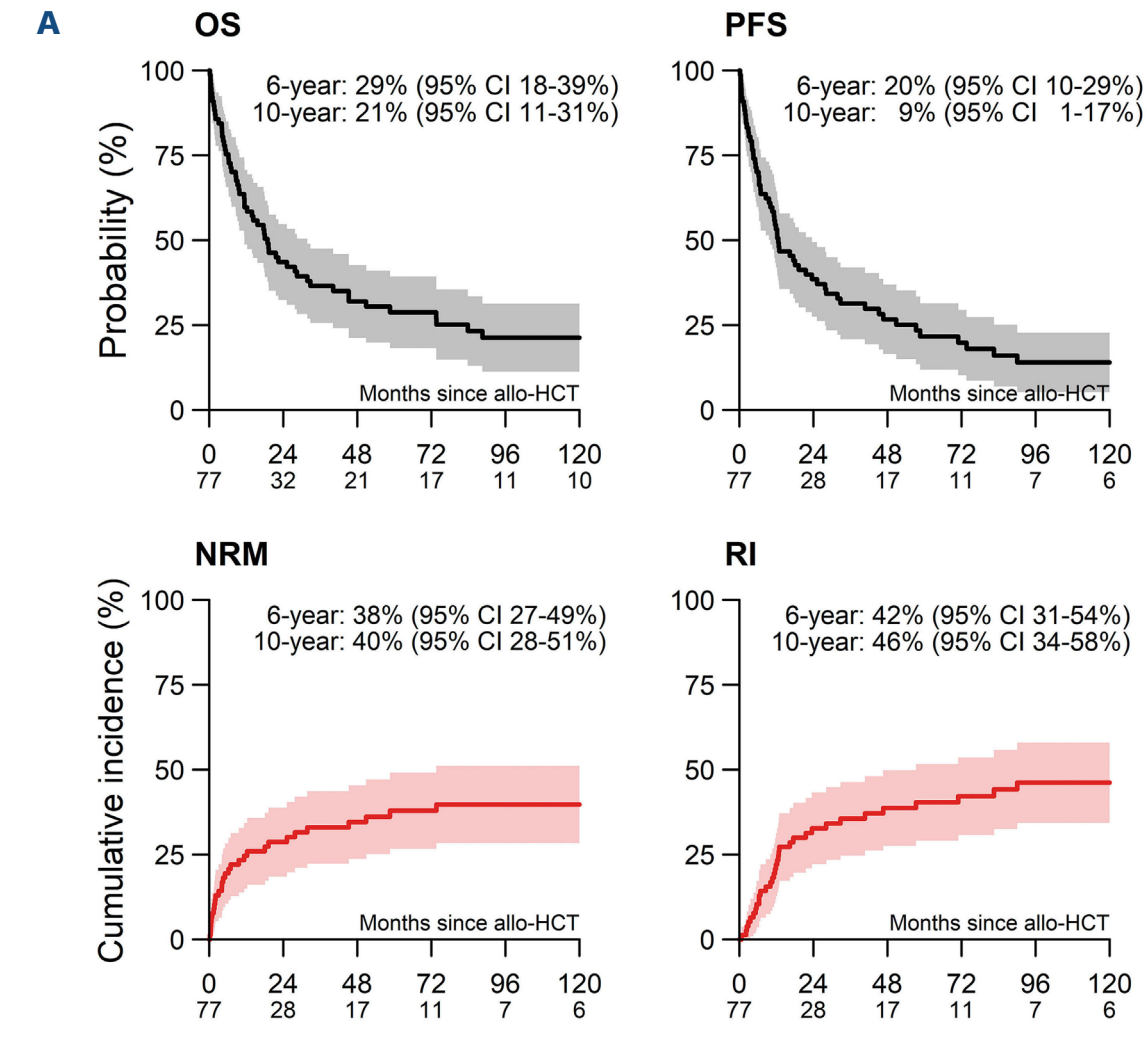

Figure 2. Outcomes after allogeneic hematopoietic cell transplantation for T-cell prolymphocytic leukemia. (A) Overall survival, progression-free survival, non-relapse mortality, and cumulative relapse incidence for all patients. (B) Overall survival, progression-free survival, non-relapse mortality, and cumulative relapse incidence for patients stratified by receipt of total body irradiation at a dose of ≥6 Gy. Numbers below the graphs show the number of patients at risk. Shaded areas show the 95% confidence intervals. allo-HCT: allogeneic hematopoietic cell transplantation; CI: confidence interval; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; RI: cumulative relapse incidence; TBI: total body irradiation.

absence of comorbidities compared to younger patients, or that the systematic use of reduced-intensity conditioning resulted in lower toxicity. However, unmeasured confounders may also have contributed to those findings.

An important question not addressed by this study is the potential role of pretransplant alemtuzumab in allogeneic HCT. In the CIBMTR study,[10] the authors did not analyze the impact of pretransplant alemtuzumab, however peri-transplant *in vivo* T-cell depletion strategies (with antithymocyte globulin and/or alemtuzumab) resulted in increased transplant-related mortality and inferior disease-free survival. Unlike in other mature T-cell neoplasias, alemtuzumab is essential in T-PLL, since it is the only drug enabling the achievement of a complete response in most patients. In chronic lymphocytic leukemia, the use of alemtuzumab has been associated with unfavorable outcomes of allogeneic HCT in both prospective and retrospective cohort studies. The risk of infection and higher non-relapse mortality could be among the main reasons. In addition, residual circulating alemtuzumab levels at the time of allogeneic HCT can be associated with a significant reduction in T-cell engraftment at day 100.[16] Thus, it could be concluded that the logically recommended alemtuzumab washout before allogeneic HCT, so as not to annihilate the graft-*versus*-leukemia effect, in fact allows the T-PLL to become progressive again at the time of the transplant. Despite its anti-neoplastic activity, alemtuzumab is not simple to use as a bridge and alternatives are warranted. The development of therapies specifically targeting CD7, which is almost constantly expressed by T-PLL cells, as well as TRBC1 could lead to the use of such therapies alone or as a bridge to allogeneic HCT.

Finally, there is evidence that T-PLL is less susceptible to graft-*versus*-leukemia effects than other lymphomas,[5] questioning the role of allogeneic HCT in general and emphasizing the need for more effective cellular therapies in T-PLL. Autologous HCT[4] could also be an option for a proportion of patients, although more data are needed to establish its place in the T-PLL treatment algorithm.

In conclusion, this long-term analysis suggests that if we want to continue doing allogeneic HCT for eligible T-PLL patients, we need to optimize our practices in terms of infectious risk management and novel bridges to transplantation. Incorporating at least intermediate-dose TBI into conditioning could become a recommendation if its value is confirmed in larger, more recent cohorts of patients.

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No conflicts of interest to disclose.

Contributions

JD-S, OT, LG, DML, LGAB, and LK were involved in study design, analysis and drafting the paper. All other co-authors contributed data to the study, critically revised the paper and approved the submitted and final versions.

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Data-sharing statement

The final analysis dataset will be available upon specific request to the Chronic Malignancies Working Party Chair.

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