Autologous hematopoietic cell transplantation for T-cell prolymphocytic leukemia: a retrospective study on behalf of the Chronic Malignancies Working Party of the EBMT

T-cell prolymphocytic leukemia (T-PLL) is a rare subtype of mature T-cell non-Hodgkin lymphoma[1,2] with poor prognosis. Recently, the first consensus criteria have been proposed by the T-PLL International Study Group (TPLL-ISG)[3] to allow a systematic approach to diagnosis, treatment, and response assessment.

Treatment of T-PLL is challenging. Alemtuzumab, an anti-CD52 monoclonal antibody, administered intravenously[4] is considered the mainstay of first-line treatment. Alemtuzumab is associated with objective response rates (ORR) over 90%, but with short duration of response and a progression-free survival (PFS) of between 8 and 11 months.[3] Therefore, despite the high ORR, it is recommended to offer consolidative treatment to all eligible patients. Allogeneic hematopoietic cell transplantation (allo-HCT) is considered the gold standard for this indication although it is associated with only modest long-term disease control.[5-7] Autologous hematopoietic cell transplantation (auto-HCT) is cited as a possible option[8,9] but this vague recommendation for auto-HCT is a result of extremely scarce data for this potential therapeutic choice.[10,11]

The current study aimed to study outcomes after auto-HCT using data from the European Group for Blood and Marrow Transplantation (EBMT), an organization comprising over 600 transplant centers, mainly from Europe. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time in order to report pseudonymized data. Patients diagnosed with T-PLL who underwent their first auto-HCT between 2000 and 2019 were selected for the study. Data to verify the diagnosis, as well as clarification on treatment pre- and post-auto-HCT and cause of death, were requested from participating centers. T-cell prolymphocytic leukemia was diagnosed based on the TPLL-ISG consensus criteria.[3] In our study, the diagnosis could be verified for patients for whom additional confirmatory data were provided by the participating centers.

The primary objective was to assess overall survival (OS). The secondary objectives were to examine PFS (the time between auto-HCT and relapse/progression of disease or death), relapse incidence (RI), non-relapse mortality (NRM), cause of death, incidence of second primary malignancies (SPM), and response to treatment. Response to treatment at day 100 was assessed according to TPLL-ISG recommendations.[3] We separately analyzed a subset of patients for whom data were available to ascertain that these were patients who obtained a response to first-line alemtuzumab and who proceeded to consolidation with auto-HCT (the post-alemtuzumab consolidation group). A second, smaller subset consisted of those patients in the post-alemtuzumab consolidation group who had received alemtuzumab as monotherapy (the post-alemtuzumab monotherapy consolidation group).

Median follow-up was calculated using the reverse Kaplan-Meier estimator. The Kaplan-Meier estimator was used for OS and PFS, and the crude cumulative incidence estimator was used for the competing events: RI together with NRM, and SPM. The log-rank test was used to assess differences between groups in OS and PFS, and Gray's test was used to assess differences in RI and NRM according to sex, age, disease status, and Karnofsky performance status, year of auto-HCT, total body irradiation (TBI), and number of pre-treatment lines. All statistical tests were two-sided and $P<0.05$ was considered statistically significant. All analyses were performed in R version 4.2.2 using 'survival', 'cmprsk', and 'prodlim' packages.

Forty-two patients were initially identified. Additional confirmatory data were obtained for 21 of these patients, among whom 19 fulfilled the diagnostic criteria for T-PLL. Two patients were excluded based on immunophenotype. Thus, 40 T-PLL patients from 31 centers form the "whole group" for this analysis (Table 1). In 25 of these 40 patients, detailed information on pretreatment was available (Figure 1). Twenty-four patients of these 25 (96%) had been exposed to alemtuzumab before auto-HCT. Twenty patients (80%) had received only one line of previous therapy.

In the 20 patients for whom auto-HCT was used as first-line consolidation, one patient received fludarabine and cyclophosphamide rather than alemtuzumab. Thus, the "post-alemtuzumab first-line consolidation group", as defined above, consisted of 19 patients, including 15 patients who received alemtuzumab as monotherapy (the "post-alemtuzumab monotherapy first-line consolidation group"). In these 15 patients, the median interval between start of first-line alemtuzumab and auto-HCT was 8.1 (interquartile range [IQR] 6.1-9.2) months.

Data on mobilization were available for 13 patients. Twelve (92%) patients required only one mobilization attempt, while one (8%) required 2 mobilization attempts. The first mobilization was performed solely with granulocyte colony stimulating factor (G-CSF) in 7 (54%) patients, with G-CSF and plerixafor in one (8%) patient. In other patients, hematopoietic cells were collected after chemotherapy and G-CSF, i.e., cyclophosphamide in 4 (31%) and DHAP in one

Table 1. Patients' and T-cell prolymphocytic leukemia characteristics at diagnosis and at auto-hematopoietic cell transplantation.

	Whole group	Post-alemtuzumab consolidation group	Post-alemtuzumab monotherapy consolidation group
	N (%)	N (%)	N (%)
Total	40 (100)	19 (100)	15 (100)
Sex			
Male	23 (58)	11 (58)	8 (53)
Female	17 (42)	8 (42)	7 (47)
Age at diagnosis in years, median (IQR)	61 (50.3-66.2)	64 (60-68)	65 (61-68)
Year of diagnosis, median (IQR)	2009 (2006-2013)	2012 (2007-2014)	2012 (2007-2015)
WBC count at diagnosis, x10^9/L, median, (IQR); 22 missing	56.6 (24-232.8)	62 (51-237)	58 (52-204)
Cytogenetics; 19 missing			
Normal karyotype	5 (24)	3 (21)	2 (18)
Abnormal karyotype	16 (76)	11 (79)	9 (82)
Specific abnormalities*			
abn14q23	9 (56)	6 (55)	4 (44)
abnXq28	2 (12.5)	2 (18)	1 (11)
neither abn14q23 nor abnXq28	5 (31)	4 (36)	4 (44)
abn11q22.3	4 (25)	2 (18)	1 (11)
complex karyotype	9 (56)	7 (64)	5 (56)
Age at auto-HCT in years, median (IQR)	62 (53-67)	66 (61-69)	66 (62-69)
<65	24 (60)	9 (47)	7 (47)
65-70	12 (30)	7 (37)	6 (40)
≥70	4 (10)	3 (16)	2 (13)
KPS at auto-HCT; 8 missing			
≤80	7 (22)	3 (16)	2 (13)
90 or 100	25 (78)	16 (84)	13 (87)
HCT-CI; 14 missing			
low risk, 0	14 (54)	8 (47)	6 (46)
intermediate risk, 1-2	5 (19)	3 (18)	2 (15)
high risk, ≥3	7 (27)	6 (35)	5 (38)
Year of auto-HCT			
Before 2010	17 (42)	6 (32)	5 (33)
2010-2019	23 (58)	13 (68)	10 (67)
Interval in months diagnosis – auto-HCT, median (IQR)	8.8 (6.4-17.7)	9 (7.3-16.9)	9.7 (7.7-16.9)
Disease stage at auto-HCT			
CR	27 (67)	11 (58)	9 (60)
PR	10 (25)	6 (32)	4 (27)
Stable disease	2 (5)	2 (10)	2 (13)
Relapse / progression	1 (3)		
N of previous lines of therapy; 15 missing			
1	20 (80)	19 (100)	15 (100)
2	5 (20)		
Alemtuzumab before auto-HCT; 15 missing	24 (96)	19 (100)	15 (100)
Months between start of the first pretreatment and auto-HCT, median (IQR); 15 missing	7.4 (6-11.8)	7.4 (6.1-9.2)	8.1 (6.1-9.2)

The characteristics are provided for all patients, for the subset of the post-alemtuzumab consolidation group of patients, and for the smallest subset of the post-alemtuzumab monotherapy consolidation group of patients (see Figure 1). Patient-, disease-, and transplant-related variables are expressed as median and interquartile range (IQR) for continuous variables and frequencies for categorical variables. *More than one category possible for each patient, hence percentages do not add up to 100%. (Percentage calculated as the percentage among patients with an abnormal karyotype). auto-HCT: autologous hematopoietic cell transplantation; CR: complete remission; HCT-CI: hematopoietic cell transplantation comorbidity index; IQR: interquartile range; KPS: Karnofsky performance status; N: number; PR: partial remission; WBC: white blood cells.

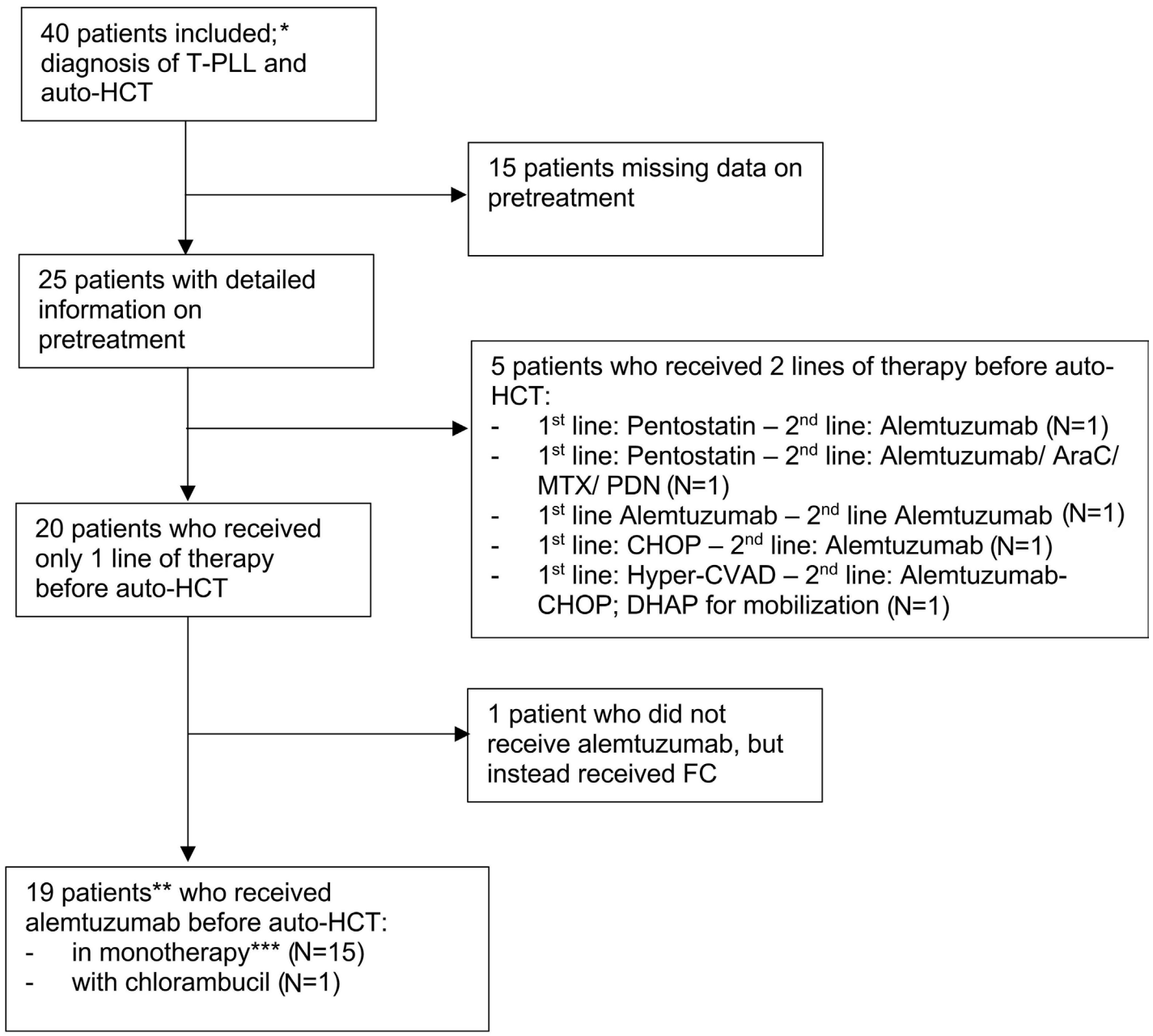

Figure 1. Flow diagram depicting the number of patients with different types of treatment before autologous hematopoietic cell transplantation. AraC: cytarabine; CHOP: cyclophosphamide/ doxorubicine/ vincristine/ prednisone; DHAP: dexamethasone/ cisplatin/ cytarabine; FC: fludarabine/ cyclophosphamide; Hyper-CVAD: cyclophosphamide/ doxorubicin/ vincristine/ dexamethasone; MTX: methotrexate; PDN: prednisone. *Whole group. **Post-alemtuzumab first-line consolidation group. ***Post-alemtuzumab monotherapy consolidation group. auto-HCT: autologous hematopoietic cell transplantation; N: number; T-PLL: T-cell prolymphocytic leukemia.

(8%). Median time to mobilization from the initiation of alemtuzumab treatment was 25 weeks (range, 15-81).

Information on conditioning was available for 37 patients. Most received chemotherapy-based conditioning: BEAM (N=22, 59%), BEAC (N=6, 16%), and FEAM (N=3, 8%). In 3 patients, alemtuzumab was incorporated into the conditioning regimen. Four (10%) patients received TBI (10.4-13 Gy). Engraftment was achieved in all evaluated patients.

For the whole group of evaluable patients (N=34), the ORR at 100 days post auto-HCT was 88% (95% Confidence Intervals [CI]: 72-97%). Importantly, 7 out of 34 patients (21%) improved their response after auto-HCT to complete remission (CR), while one (3%) partial remission (PR) patient experienced direct progression post transplantation.

With a median follow-up of 87.7 months (IQR, 41.7-89.9), the 4-year OS, PFS, cumulative RI, and NRM estimates were 34% (95% CI: 19-50%), 29% (95% CI: 14-44%), 66% (95% CI: 50-81%), and 5% (95% CI: 0-12%), respectively (Figure 2A-D).

For the post-alemtuzumab first-line consolidation group (N=19), the ORR at 100 days was 85% (95% CI: 65-96%). OS, PFS, and cumulative RI estimates after four years were: 39% (16-63%), 34% (11-56%), and 66% (44-89%), respectively; there was no NRM (Figure 2A-D) in this group.

For the post-alemtuzumab monotherapy consolidation group (N=15), the 4-year OS and PFS were 47% (95% CI: 21-72%) and 37% (95% CI: 11-63%), respectively. *Online Supplementary Table S1* shows probabilities of OS and PFS, and cumulative incidences of RI and NRM at two years after auto-HCT for the evaluated prognostic factors. None of these were significantly associated with analyzed outcomes in univariable analyses. Only 3 patients who died before relapse were observed during follow-up.

The most frequently reported cause of death among the 29 patients with data available on the cause of death

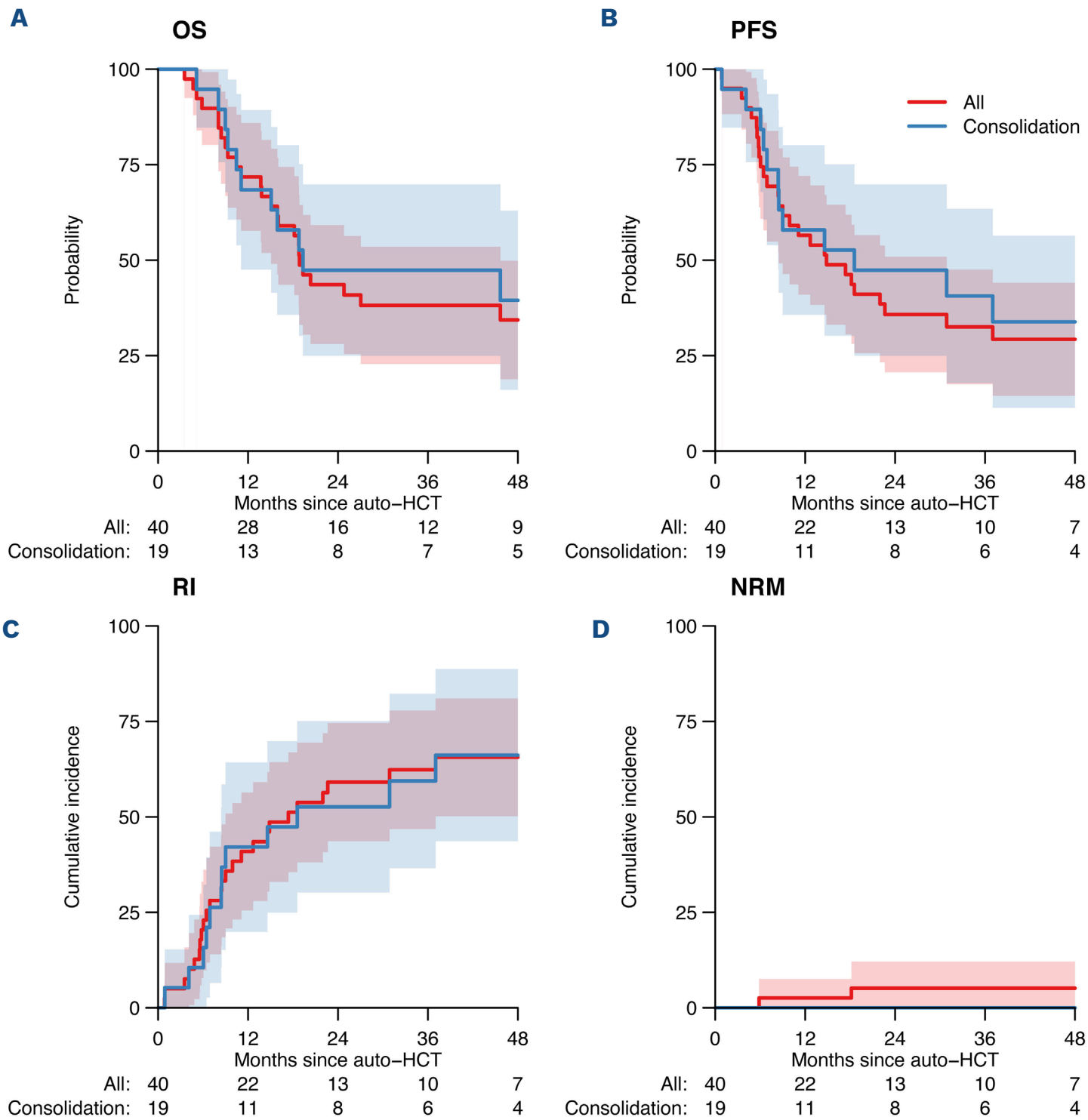

Figure 2. Outcome after autologous hematopoietic cell transplantation. (A) Overall survival (OS), (B) progression-free survival (PFS), (C) relapse incidence (RI), and (D) non-relapse mortality (NRM) of patients undergoing autologous hematopoietic cell transplantation (auto-HCT). Shaded areas represent 95% Confidence Intervals. Figures below the graph are the number of patients at risk. "Consolidation" patients (blue line) are patients with available detailed data receiving auto-HCT as a consolidation of response after first-line alemtuzumab (either in monotherapy or in combination). This group is a subset of "All" patients representing the whole group (red line). Hence the groups cannot be compared using a statistical test.

was relapse / progression (N=16), followed by infection (N=5), secondary malignancy (N=3), and other causes of death (N=5). In the whole group, 31 patients had data on SPM status available; the 4-year cumulative incidence of SPM was 19% (4-34%). Among the whole group of patients (N=40), there were 25 patients with data available on post-auto-HCT therapy. The cumulative incidence of having received post-auto-HCT treatment at four years was 73% (95% CI: 56-91%). Alemtuzumab was given in 62% of patients who had received post-auto-HCT therapy. In 7 patients, an allo-HCT was recorded after auto-HCT (*Online Supplementary Table S2*).

To summarize, this retrospective study analyzed the outcomes of 40 T-PLL patients treated with auto-HCT. Unfortunately, we were not able to answer the question as to why patients with T-PLL underwent auto-HCT instead of allo-HCT as it was not part of the data collection.

As a large majority of patients received BEAM-like conditioning regimens, the effect of TBI-based conditioning on outcome after auto-HCT cannot be assessed. Further research is needed to answer the question of the role of TBI in HCT for T-PLL. While it is well-known that T-PLL is refractory to conventional chemotherapy, it was surprising to find that high-dose chemotherapy followed by auto-HCT was effective

in T-PLL. ORR at +100 days for the whole group of evaluable patients post auto-HCT was 88%. Response after auto-HCT had improved to CR in 7 out of 34 (21%) evaluable patients. Among patients transplanted in CR, all patients retained their response after treatment. For the entire cohort, efficacy of this approach was highlighted but also showed that improvements were required; 4-year OS was 34%, 4-year PFS 29%, 4-year RI 66%, and 4-year NRM 5% (Figure 2). These are important findings, ensuring that, at least in the short term, auto-HCT appears safe and efficacious confirming its potential for future therapeutic strategies.

Relapse or progression constituted the most prevalent cause of death in the whole cohort of patients. The occurrence of SPM in T-PLL patients was surprisingly high with a 4-year cumulative incidence of SPM of 19% (but with wide Confidence Intervals). It cannot be verified whether this is the result of the T-PLL treatment, or an inherent feature of T-PLL. We were not able to find any information on SPM in T-PLL in papers published so far.[3,8,10,12,13] When compared to reported results of allo-HCT performed for T-PLL, the outcomes of auto-HCT seem to be comparable, or only slightly worse[5-7,14-15] (*Online Supplementary Table S3*).

Limitations of the study are those applicable to retrospective, registry-based studies, including missing data, lack of precise information on pre-treatment and diagnostic verification in all subjects. Nevertheless, this is the first study to report a significant number of patients, and it does suggest that high-dose therapy followed by auto-HCT is a valid therapeutic option in the treatment of T-PLL with acceptable efficacy and low toxicity. Even if it probably does not represent a curative strategy, until new approaches are found, auto-HCT can be proposed as consolidation to extend response duration, especially after alemtuzumab.

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Disclosures

No conflicts of interest to disclose.

Contributions

JDS, OT, LG, DML, IYA 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 final version.

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Data-sharing statement

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

Appendix

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References

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.
2. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375-2390.
3. Staber PB, Herling M, Bellido M, et al. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. Blood. 2019;134(14):1132-1143.
4. Dearden CE, Khot A, Else M, et al. Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route. Blood. 2011;118(22):5799-5802.
5. Wiktor-Jedrzejczak W, Drozd-Sokolowska J, Eikema DJ, et al. EBMT prospective observational study on allogeneic hematopoietic stem cell transplantation in T-prolymphocytic leukemia (T-PLL). Bone Marrow Transplant. 2019;54(9):1391-1398.
6. Wiktor-Jedrzejczak W, Dearden C, de Wreede L, et al. Hematopoietic stem cell transplantation in T-prolymphocytic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation and the Royal Marsden Consortium. Leukemia. 2012;26(5):972-976.
7. Murthy HS, Ahn KW, Estrada-Merly N, et al. Outcomes of allogeneic hematopoietic cell transplantation in T cell prolymphocytic leukemia: a contemporary analysis from the Center for International Blood and Marrow Transplant Research. Transplant Cell Ther. 2022;28(4):187.e10.
8. Dearden C. Management of prolymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2015;2015:361-367.
9. Horwitz SM, Ansell S, Ai WZ, et al. T-cell prolymphocytic leukemia (TPLL-1). In: T-Cell Lymphomas. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Version 1.2023. Jan 5, 2023. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf.
10. Dearden CE, Matutes E, Cazin B, et al. High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H. Blood. 2001;98(6):1721-1726.
11. Krishnan B, Else M, Tjonnfjord GE, et al. Stem cell transplantation after alemtuzumab in T-cell prolymphocytic leukaemia results in longer survival than after alemtuzumab alone: a multicentre retrospective study. Br J Haematol. 2010;149(6):907-910.
12. Jain P, Aoki E, Keating M, et al. Characteristics, outcomes, prognostic factors and treatment of patients with T-cell prolymphocytic leukemia (T-PLL). Ann Oncol. 2017;28(7):1554-1559.
13. Rose A, Zhang L, Jain AG, et al. Delineation of clinical course, outcomes, and prognostic factors in patients with T-cell prolymphocytic leukemia. Am J Hematol. 2023;98(6):913-921.
14. Guillaume T, Beguin Y, Tabrizi R, et al. Allogeneic hematopoietic stem cell transplantation for T-prolymphocytic leukemia: a report from the French society for stem cell transplantation (SFGM-TC). Eur J Haematol. 2015;94(3):265-269.
15. Yamasaki S, Nitta H, Kondo E, et al. Effect of allogeneic hematopoietic cell transplantation for patients with T-prolymphocytic leukemia: a retrospective study from the Adult Lymphoma Working Group of the Japan Society for Hematopoietic Cell Transplantation. Ann Hematol. 2019;98(9):2213-2220.