Allogeneic hematopoietic cell transplant for hairy cell leukemia: EBMT experience.

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Hairy cell leukemia (HCL) is a rare indolent B-cell neoplasm accounting for 2% of leukemias, with an estimated incidence of <1 case per 100,000 population.[1] Purine analogs such as cladribine and pentostatin are potent agents in HCL with complete remission (CR) rates approaching 75-90% with monotherapy.[2,3] Despite these response rates, there is no evidence of cure and the majority of patients experience recurrence of the disease and require multiple treatments; repeated exposure to purine analogs yields lower response rates and shorter durations of remission.[2] Moreover, the distinct, variant subtype of HCL (HCLv) is more resistant to standard purine analogs,[4] so the median overall survival from diagnosis of patients with HCLv is 6-9 years compared to >25 years for those with classical HCL.[4-6] First-line chemoimmunotherapy, adding rituximab concurrently with or after treatment with a purine analog, improved CR rates with longer remission periods in both HCL and HCLv.[5,7,8] However, treatment for 'high-risk' patients and those with disease resistant to purine analogs remains challenging. Allogeneic hematopoietic cell transplant (allo-HCT) can potentially produce long-term remission in many diseases, including chronic leukemias; however, evidence to support the use of allo-HCT in refractory/multiple relapsed HCL has been limited to case reports only.[9]

Here we report an analysis of adult patients undergoing a first allo-HCT for HCL between 1996-2018, using either myeloablative or reduced-intensity conditioning defined by standard criteria. The Kaplan-Meier estimator was used to estimate overall survival and progression-free survival and the log-rank test was used to compare groups. The crude cumulative incidence estimator was used to estimate non-relapse mortality and relapse incidence within a competing risk setting. The crude cumulative incidence estimator was also used to estimate the cumulative incidence of acute graft-*versus*-host disease (GvHD) with death before acute GvHD as a competing event, as well as the cumulative incidence of chronic GvHD with death before chronic GvHD as a competing event. Events were artificially censored at 5 years except acute GvHD and death before acute GvHD, which were censored at 100 days after allo-HCT.

A total of 24 patients from 19 transplant centers were included in this study (Table 1). The median age at allo-HCT was 50 years (range, 32-68). The median number of lines of treatment and purine analogs prior to allo-HCT was six (range, 1-10) and two (range, 0-4), respectively. The median time from diagnosis to allo-HCT was 55.3 months (range, 1.6 months - 26.9 years). Details of prior lines of therapy were available for 11 patients (*Online Supplementary Table S1*). Six patients received rituximab, three in two lines of treatment. Three patients received BRAF inhibitors prior to allo-HCT. Disease status at allo-HCT (available for 20 patients) was reported as CR (n=7, 33%), partial remission (n=3, 14%), stable disease (n=5, 24%) and progressive/refractory disease (n=5, 24%). Among the 11 patients with details on prior treatment, 30% were refractory to the regimen preceding allo-HCT. Donor type was as follows: matched sibling (37%), syngeneic (4%), matched related (4%), mismatched related (4%), matched unrelated (29%), mismatched unrelated (17%) and unrelated, match unknown (4%). Myeloablative and reduced-intensity conditioning regimens were utilized in 59% and 41% of the patients, respectively. Eight patients (35%) received total-body irradiation as part of conditioning. Regarding stem cell source, peripheral blood was used in 22 patients (92%), bone marrow in one (4%) and cord blood in one (4%).

No follow-up data were available for two patients and hence further results are reported on 22 patients only. The cumulative incidence of grade 2-4 acute GvHD at day 100 was 15% (95% confidence interval [95% CI]: 0-31%). The cumulative incidence of chronic GvHD at 2 years was 47% (95% CI: 25-70%). Non-relapse mortality at day 100 was 14% (95% CI: 0-28%). The best overall response rate was 64% (95% CI: 41-83%) and the CR rate was 59% (95% CI: 36-79).

With a median follow-up after allo-HCT of 54.5 months (interquartile range: 15.4 - not reached), 5-year estimated non-relapse mortality, progression-free survival and overall survival rates were 26% (95% CI: 6-46%), 33% (95% CI: 9-56%) and 46% (95% CI: 22-70%), respectively (Figure 1A-C). The 5-year cumulative relapse incidence was 41% (95% CI: 17-66%). Causes of death were infection (in 36% of all deceased patients), multi-organ failure (27%), disease progression (18%), secondary malignancy (9%) and unknown (9%). The two patients with HCLv were alive and relapse free at the end of the reported follow-up (+12 and +20 months). The 2-year progression-free survival of patients transplanted in CR was 80% (95% CI: 45-100%) compared to 44% (95% CI: 16-72%) for those transplanted while not in CR (log-rank *P*=0.15). The 2-year progression-free survival of patients undergoing allo-HCT during 2010-2018 was 67% (95% CI: 40-94%), as compared to 53% (95% CI: 19-87%) for those transplanted between 1996-2009 (log-rank *P*=0.43).

Table 1. Patient, disease and transplantation characteristics.

Characteristics	
Total patients, N	24
Age at allo-HCT in years, median (IQR)	50.4 (46.6-55.6)
Patients' sex, Male, N (%) Female, N (%)	 17 (70.8) 7 (29.2)
Type of HCL Classical, N (%) Variant, N (%)	 22 (91.7) 2 (8.3)
Karnofsky status at allo-HCT ≥ 90, N (%) ≤ 80, N (%) Missing, N	 15 (75.0) 5 (25.0) 4
N of lines of any treatment Median (IQR) Missing, N	 6 (4.5-6) 13
N of lines of treatment including PA Median (IQR) Missing, N	 2 (1-2.5) 13
Any rituximab prior to allo-HCT No, N (%) Yes, N (%) Missing, N	 5 (45.5) 6 (54.5) 13
Any BRAF inhibitor prior to allo-HCT No, N (%) Yes, N (%) Missing, N	 8 (72.7) 3 (23.7) 13
Disease status at allo-HCT Complete remission, N (%) Partial remission, N (%) Stable disease, N (%) Primary refractory, N (%) Relapse/progression, N (%) Untreated, N (%) Missing, N	 7 (33.3) 3 (14.3) 5 (23.8) 1 (4.8) 4 (19.0) 1 (9.1) 3
Sensitivity at allo-HCT* Sensitive, N (%) Resistant, N (%) Missing, N	 7 (70.0) 3 (30.0) 14
Months from diagnosis to allo-HCT, median (IQR)	55.3 (8.1-116.9)
Year of allo-HCT 1996-1999, N (%) 2000-2009, N (%) 2010-2018, N (%)	 3 (12.5) 6 (25.0) 15 (62.5)
Conditioning regimen intensity Standard, N (%) Reduced, N (%) Missing, N	 13 (59.1) 9 (40.9) 2
TBI at allo-HCT No, N (%) Yes, N (%) Missing, N	 15 (65.2) 8 (34.8) 1

Allo-HCT: allogeneic hematopoietic cell transplant; IQR: interquartile range; HCL: hairy cell leukemia; PA: purine analogs; TBI: total body irradiation.
*Sensitivity of disease to last regimen given before first allo-HCT.

This study represents the largest one to date describing outcomes following allo-HCT for patients with HCL. Overall, allo-HCT produced long-term survival in a significant percentage of heavily pre-treated patients for whom many likely had limited options at that time. However, it is clear that a significant number of patients continued to experience recurrence and there was no plateau in progression-free survival in this cohort.

The treatment landscape for HCL has been revolutionized in the last decade with the availability of newer agents such as BRAF inhibitors and the anti-CD22 antibody-drug conjugate, moxetumomab pasudotox. Tiacci *et al.* reported response rates of 96-100% with vemurafenib monotherapy in relapsed/refractory HCL,[10] although the only modest CR rates (35-42%) and persistent minimal residual disease (MRD) even in CR, are likely reflected by the short progression-free survival of 19 months. More recently, Tiacci *et al.* demonstrated the beneficial impact of adding rituximab to vemurafenib.[11] A CR rate of 87% was reported, and 65% of patients achieved a negative MRD status with 78% of patients (85% among responders) remaining relapse-free at around 3 years. Another BRAF inhibitor, dabrafenib, in combination with a MEK inhibitor also produced a high CR rate of 65.5% and approximately half of these patients achieved MRD negativity.[12] Moxetumomab produced durable responses in 36% of patients, and 61% of patients who achieved CR remained in CR at 5 years.[13-15] Overall, 82% of patients who achieved CR were MRD negative, and the median duration of CR for those patients was >5 years. Supported by improvements in available therapeutics, the survival of patients with HCL diagnosed in the modern era has certainly improved.[16] Although many patients treated with the new agents remain positive for MRD, which is concerning for future disease progression, these treatments will undoubtedly reduce the number of patients who need to be considered for allo-HCT. However, challenges may remain, particularly in high-risk patients such as those with HCLv, who can display high rates of chemotherapy resistance (particularly with *TP53* mutation),[5] and those who are negative for the *BRAF*-V600E mutation, who have fewer treatment options. In selected high-risk patients the indication for allo-HCT should be considered with the utmost caution, balancing risks and potential benefits.

Several limitations of our study should be noted. These are related to the study's retrospective nature and cohort size which limit analysis exploring transplant-specific risk factors and improved allo-HCT strategies over time. Moreover, in this study we lacked an independent central review to confirm the diagnosis. The median time from diagnosis to allo-SCT was 55.3 months which is short considering the median progression-free survival of over 10 years following first-line purine analog monotherapy in HCL.[2] This may be due to selection of very aggressive

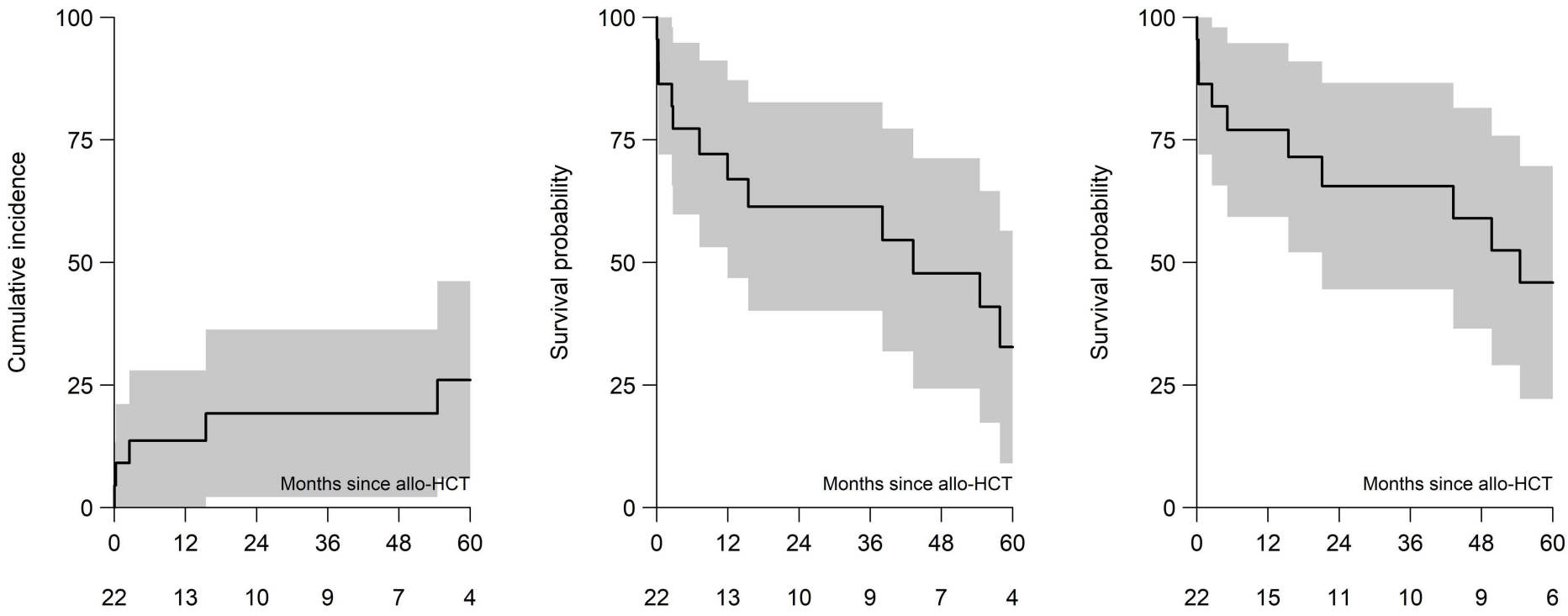

Figure 1. Outcomes after allogeneic hematopoietic cell transplantation in patients with hairy cell leukemia. (A) Cumulative incidence of non-relapse mortality. (B) Probability of progression-free survival. (C) Probability of overall survival. Numbers below the graph indicate the number of patients at risk. The shaded areas show the 95% confidence intervals.

cases such as IGHV4-34 unmutated HCL;[6] however, it also raises the possibility of misclassification between HCL and HCLv. Nevertheless, patients in this study received a median of six lines of treatment, which suggests that they had very aggressive HCL. Allo-HCT provided meaningful progression-free survival considering the number of treatments patients had required in a short period before allo-HCT, although it should be noted that the treatments patients received in this study do not reflect current standard treatment.

In conclusion, this study represents the largest reported evaluation of outcomes of allo-HCT for patients with HCL. In this heterogeneous cohort, allo-HCT produced meaningful response rates and durable remissions in some cases although, interestingly, there was no sign of a plateau in the progression-free survival, i.e. cure of HCL from allo-HCT. With the development of chimeric antigen receptor T-cell therapy and bispecific antibodies, these agents warrant evaluation for patients progressing following current standard treatments, including BRAF inhibitors and moxetumomab. The outcomes of allo-HCT in patients with HCL will provide references for future trials of novel agents.

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https://doi.org/10.3324/haematol.2022.281754

Received: September 4, 2022.
Accepted: December 12, 2022.
Early view: December 22, 2022.

Disclosures

No conflicts of interest to disclose.

Contributions

DC, OT, MvG, RJK and IYA designed the study; NZ, JM, JP, RPL JB, WK, DW, UP, IWB, FB, GH, AM, MM, MM, RR, JS, CVL, PJH and DM contributed data and reviewed the manuscript; LG analyzed the data; DC wrote the draft, and all the authors wrote and approved the manuscript.

Acknowledgments

The study was performed on behalf of the Chronic Malignancies Working Party of the EBMT. The authors would like to thank the contribution of the EBMT and CMWP data managers to this work.

Data-sharing statement

The data are not available for sharing.

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