Leukemia Research 83 (2019) 106171

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

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# Allogeneic stem cell transplant provides durable response in peripheral T-cell lymphoma

Peripheral T-cell lymphoma (PTCL), a group of heterogeneous lymphoid malignancies, is characterized by an aggressive disease course. Unlike B-cell lymphoma, the outcomes of anthracycline-containing regimen alone are not satisfactory with a 5-year overall survival (OS) around 30% [1]. Patients with advanced disease or a high International Prognostic Index (IPI) respond poorly or progress early following treatment. Autologous stem cell transplantation (autoSCT) as a consolidation therapy in first complete remission (CR) may provide long term remission rate between 34%–51% [2–5]. However, patients with second CR or refractory disease have dismal outcomes following autoSCT with a progression-free survival around 15–20% and 0%, respectively [6]. Approximately, 25–30% of patients experience disease relapse despite achieving complete response with autoSCT [7]. Moreover, patients with high-risk features such as chemo-refractory disease and extensive bone marrow involvement are unable to undergo autoSCT. Allogeneic stem cell transplantation (alloSCT) may overcome these adverse features and provide long term disease control via graft-versus-lymphoma effect [8]. Herein, we report long term outcomes of alloSCT in patients with high-risk PTCL.

We conducted a retrospective study of adult PTCL patients who underwent alloSCT between January 2005 and December 2017 at Karmanos Cancer Institute. Patients with prior autoSCT were included. This study was approved by the Wayne State University Institutional Review Board. This research work has been carried out in accordance with the code of ethics of the Declaration of Helsinki for experiments involving humans.

Demographic and transplant details for all patients were collected including age at transplant, sex, race, karnofsky performance score, donor type, HLA match, cytomegalovirus serotype status of donor/recipient, ABO match, conditioning regimen, graft versus host disease prophylaxis, and busulfan pharmacokinetics. Pre-transplant comorbidity index was calculated using HSCT-CI formula [9]. Disease status at transplant was determined as per Lugano classification [10]. All patients' records were reviewed to determine the extent of acute and chronic GVHD. Patients were followed till the last follow up or death.

Thymoglobulin at a total dose of 4.5 mg/kg was given in divided doses (day -3: 0.5 mg/kg; day -2: 1.5 mg/kg; and day -1: 2.5 mg/kg). Tacrolimus was administered intravenously (0.03 mg/kg/day) starting on day -3 and tapered starting around day +100 in the absence of active GVHD with a goal of tapering off completely by day +180. Oral MMF was initiated at 15 mg/kg twice daily from day -3 and stopped at day +30.

The objectives were to estimate OS, relapse rate, non-relapse mortality (NRM), and GVHD-free relapse-free survival (GRFS). Kaplan-Meier estimates were used to summarize the distributions of GRFS, RFS and OS. Univariable and multivariable Cox regression and sub distribution hazards regression models were for RFS/OS and relapse/NRM, respectively, to assess associations of two prior chosen predictors (disease status at transplant, and type of transplant).

Thirty-nine patients underwent alloSCT (Table 1). Histologic diagnoses included PTCL NOS (n = 16, 41%), angioimmunoblastic T-cell lymphoma (n = 8, 21%), anaplastic large cell lymphoma (ALK negative = 6, ALK positive = 1 and unknown = one, 21%), advanced cutaneous T-cell lymphoma (n = 3, 8%), hepatosplenic lymphoma (n = 2, 5%), and NK cell lymphoma (n = 2, 5%). Eighteen patients (47%) received three or more lines of prior therapies and 12 (31%) had prior autoSCT. Disease status at the time of alloSCT was following: CR (n = 16, 41%) (CR1 = 5, CR2 = 8 and CR3 = 3 patients), partial remission (n = 2, 5%), disease progression (n = 12, 31%) and refractory disease (n = 9, 23%). Patients with CR1 had following high-risk features: failed prior autoSCT (n = 2), hepatosplenic lymphoma (n = 1), CNS involvement (n = 1), and > 2 lines of prior therapies (n = 2). Bone marrow, extranodal and CNS disease were noted in 17 (44%), 17 (44%) and 5 (13%) patients, respectively. Twenty-one (54%) received matched related and 18 (46%) patients received unrelated donor alloSCT. Twenty-two (56%) received myeloablative (MAC) and 17 (44%) received reduced intensity conditioning (RIC) regimens.

The median times to neutrophil and platelet engraftment were 11 and 16 days, respectively. One-year cumulative incidences of grade III-IV acute and chronic extensive GVHD were 25.6% and 30.8%, respectively. Median follow-up for surviving patients was 3.3 years. Five-year OS, relapse-free survival and GRFS was 31.6%, 33.1% and 12.0%, respectively (Fig. 1).

No difference in OS was noted in patients receiving alloSCT beyond CR1 and following prior failed autoSCT (Figure S1). Fourteen patients were alive and in remission at the time of data analysis; of these, six had CR/PR, four had relapsed, and four had refractory disease at the time of alloSCT. The 5-year cumulative incidence of relapse was 23.1%. Disease status at alloSCT for the relapsed patients was CR/PR (n = 3), disease progression (n = 2), and refractory disease (n = 4). Out of nine patients who relapsed following alloSCT, three relapsed within 100 days, five relapsed between 100 days and 1-year, and one relapsed beyond 1-year. All nine patients with relapse died.

The 5-year cumulative incidence of NRM was 43.8%. No difference in NRM was noted between MAC and RIC regimens (p = 0.6). BEAM conditioning regimen, prior autoSCT, and > 2 lines of prior therapies were associated with numerically higher NRM, although it was not statistically significant. Similarly, numerically better OS, NRM and relapse rate was noted in patients who received two or less lines of therapy compared to > 2 lines of therapy prior to alloSCT (Figure S2). Five patients had CNS involvement. Two patients each received BEAM, and busulfan/fludarabine/TBI, while one had busulfan/fludarabine as conditioning regimen. One-year cumulative incidence rates of relapse, NRM, RFS and OS were 40%, 20%, 49% and 60%, respectively. Three

https://doi.org/10.1016/j.leukres.2019.106171
Received 25 March 2019
Available online 15 June 2019

**Table 1**
Baseline patient characteristics.

| | N = 39 |
|---|---|
| **Age at transplant (year) - median (range)** | 50 (21-67) |
| **Sex - no. (%)** | |
| Male | 25 (64) |
| Female | 14 (36) |
| **Race - no. (%)** | |
| Caucasian | 30 (77) |
| AA | 7 (18) |
| Others* | 2 (6) |
| **Subgroup - no. (%)** | |
| Peripheral T cell lymphoma, NOS | 16 (41) |
| Angioimmunoblastic T-cell Lymphoma | 8 (21) |
| Anaplastic T cell lymphoma | 8 (21) |
| Hepatosplenic T cell lymphoma | 2 (5) |
| Cutaneous T cell lymphoma | 3 (8) |
| NK cell lymphoma | 2 (5) |
| **Disease stage at diagnosis - no. (%)[a]** | |
| 2 | 7 (18) |
| 3 | 9 (23) |
| 4 | 22 (56) |
| **LDH at diagnosis - median (range)** | 400 (187-3636) |
| **Number of therapy prior to Allo-HSCT - median (range)** | 2 (1-5) |
| **Time to AlloHSCT from diagnosis, month – median (95% CI)[b]** | 14.5 (12.5-18.8) |
| **Prior auto transplant - no. (%)** | |
| Yes | 12 (31) |
| **Disease status at transplant - no. (%)** | |
| Complete Response^ | 16 (41) |
| Partial Response | 2 (5) |
| Disease Progression | 12 (31) |
| Refractory Disease | 9 (23) |
| **Stage at transplant - no. (%)[c]** | |
| 2 | 6 (15) |
| 3 | 10 (26) |
| 4 | 22 (56) |
| **Bone marrow involvement at transplant - no. (%)** | |
| Yes | 17 (44) |
| **CNS involvement at transplant - no. (%)** | |
| Yes | 5 (13) |
| **Extra nodal involvement at transplant - no. (%)** | |
| Yes | 17 (44) |
| **Admit KPS, % - median (range)** | 80 (50-100) |
| **Comorbidity index - median (range)** | 2 (2-9) |
| **Disease risk index - no. (%)** | |
| Intermediate | 4 (10) |
| High | 20 (51) |
| Very High | 15 (38) |
| **HLA mismatch - no. (%)** | |
| 8/8 | 29 (74) |
| 7/8 | 8 (21) |
| ≤6/8 | 2 (5) |
| **ABO mismatch - no. (%)[c]** | |
| Matched | 20 (51) |
| Major Mismatch | 8 (21) |
| Minor Mismatch | 7 (18) |
| Bidirectional | 2 (5) |
| **CMV serogroup status - no. (%)[d]** | |
| +/+ | 12 (31) |
| +/- | 6 (15) |
| -/+ | 5 (13) |
| -/- | 14 (36) |
| **Sex mismatch - no. (%)** | |
| M-M | 18 (46) |
| M-F | 7 (18) |
| F-M | 5 (13) |
| F-F | 6 (15) |
| **Type of transplant - no. (%)** | |
| Matched Related | 21 (54) |
| Matched Unrelated | 18 (46) |
| **Source of stem cell - no. (%)** | |
| Peripheral Blood | 37 (95) |
| Bone Marrow | 2 (5) |
| **Infused CD34, million/kg - median (range)** | 7.62 (2.04-24.7) |
| **Type of conditioning regimen - no. (%)** | |
| Reduced | 17 (44) |
| Full | 22 (56) |
| **Conditioning regimen - no. (%)** | |
| BEAM | 15 (38) |
| BU-FLU-TBI | 14 (36) |
| BU-FLU | 3 (8) |
| VP16-TBI | 2 (5) |
| CY-TBI | 2 (5) |
| Others (BU-CY, CY-FLU-TBI, CVB+/-R) | 3 (8) |
| **GVHD prophylaxis - no. (%)** | |
| Thymo-based[$] | 13 (33) |
| Non-thymo-based[#] | 26 (67) |

[a],Data are not available for one patient; [b], Data are not available for 3 patients; [c], Data are not available for one patient; [d], Data are not available for 2 patients; *, Others include one Asian.

out of 5 patients relapsed: PTCL NOS (n = 1) and NK cell lymphoma (n = 1) had skin relapses, and one PTCL NOS relapsed in lymph nodes. Four patients with CNS involvement deceased. Multivariable analysis was conducted by incorporating disease status at transplant and type of conditioning regimen as variables and these variables were not predictive of adverse OS, relapse, or NRM. Among 25 patients who died following alloSCT, common causes of death were disease relapse (32%), infection (20%), multiorgan failure (24%), and acute GVHD (12%).

In our study, approximately 31% of the patients were alive and free of disease following alloSCT at a median follow-up of 3.3 years. This is clinically meaningful considering the fact that the majority of patients on the study were heavily pretreated and had high risk disease. Our results corroborate the findings of previous retrospective studies showing durable long-term responses following alloSCT [11,12]. The CIBMTR study compared outcomes of autoSCT (n = 115) and alloSCT (n = 126) in systemic T-cell lymphoma patients and 3-year OS, NRM and RFS rates of alloSCT were 47%, 34%, and 37%, respectively [12]. RFS was lower in our study; however, NRM was much higher, which could have resulted in inferior survival. Our study included high risk subtypes of T-cell lymphoma like hepatosplenic lymphoma, cutaneous T-cell lymphoma and NK cell lymphoma. Moreover, our study cohort was older with a median age of 50 years and bone marrow and CNS involvement was greater than CIBMTR study. We think that these differences might have contributed to adverse NRM and survival. Interestingly, we observed findings that potentially indicate a graft-versus-lymphoma effect of alloSCT in PTCL. Firstly, we noticed plateauing of survival and relapse curves at 2 years following alloSCT indicating durable responses in a subset of patients; and secondly, relapse rates were not statistically different in patients who received RIC compared to MAC regimens, a finding similar to previously reported studies [13–15].

One of the intriguing findings of this study was higher NRM compared to young adult patients undergoing alloSCT for myeloid malignancies [16]. We believe that this difference is predominantly stemming from the fact that patients with PTCL undergoing alloSCT were frequently heavily pre-treated, had refractory disease and many of them had undergone prior autoSCT as well as experienced high rate of GVHD. It has been reported in a CIBMTR study that the patients who have received two or more lines of pre-transplant therapies, primary induction failure disease, and longer duration (> 12 months) between diagnosis to SCT experience higher NRM [12]. Similarly, presence of chemo-resistant disease at the time of alloSCT, development of higher grade III-IV aGVHD, and receipt of alloSCT following autoSCT are predictors of higher NRM [11,12,17]. This high NRM may offset the survival benefit offered by alloSCT in PTCL. Therefore, timing of alloSCT is crucial and early alloSCT may offer a greater OS benefit and less NRM in patients with high-risk features. Additionally, a number of patients experience a significant decline in their performance status and organ function after receiving multiple lines of therapies and therefore

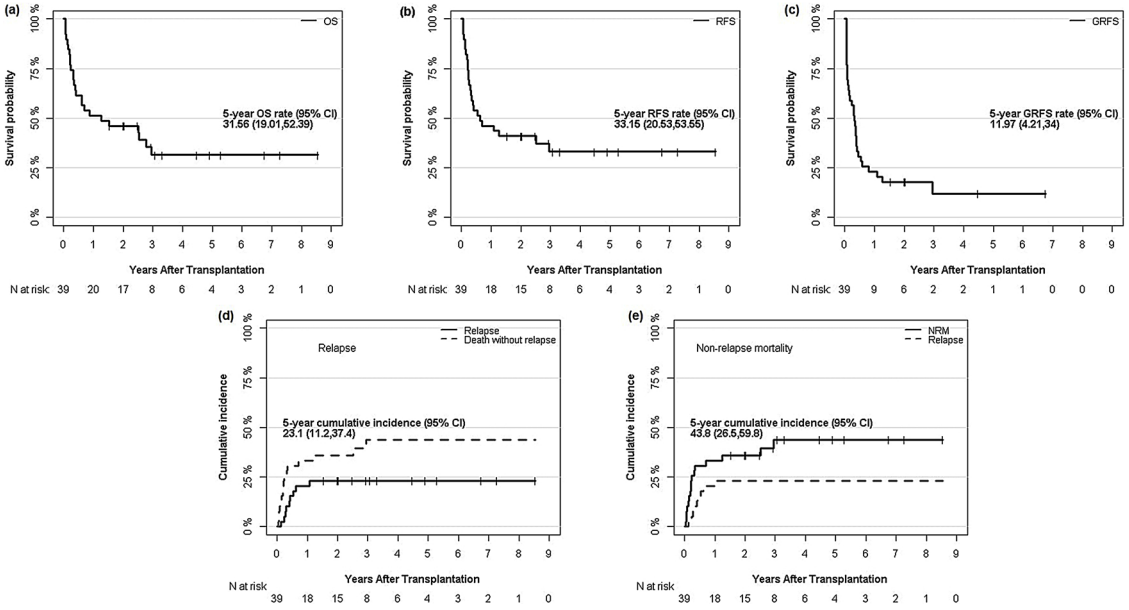


**Fig. 1.** (a–c) Kaplan-Meier survival curves for overall survival (OS), relapse-free survival (RFS), and GVHD-free/relapse-free survival (GRFS). NR stands for not reached. (d–e) Cumulative incidence curves for relapse and non-relapse mortality (NRM).

may not be able to undergo subsequent alloSCT. Accordingly, alloSCT offered earlier in the course of disease may render survival benefit to a higher number of patients. Moreover, the multivariate analysis did not show a statistically significant difference in survival between patients in CR and relapsed/refractory disease at the time of undergoing alloSCT. Therefore, we believe that patients with good performance status should be considered for alloSCT as soon as high-risk features such as chemo refractoriness or relapse have been identified. Finally, our experience shows that a subset of patients who failed autoSCT may be cured with alloSCT and therefore, these patients should be considered for alloSCT if they have good performance status and organ function. Similar results were echoed in a study by John Hopkins group, which did not observe any difference in PFS and OS in patients undergoing alloSCT in CR1 and beyond [13].

Given the retrospective nature of this study, the results should be interpreted with caution. Due to relatively small number of patients and heterogeneity of diagnoses, many factors did not achieve statistical significance. However, because of rarity of this diagnosis, randomized studies are difficult to conduct for this patient population and retrospective studies such as this one can support the use of alloSCT in high risk PTCL patients.

In conclusion, our study supports consideration of the use of alloSCT in high risk PTCL patients, although NRM is high. A proportion of patients appear to have durable response with alloSCT which suggests a potential graft-versus-lymphoma effect, but further studies are warranted.

## Declaration

We presented our study results at American Society of Hematology (ASH) annual meeting 2018. The abstract was published in Blood journal supplement issue in December 2018 and it is available online (Google scholar).

## Financial disclosure

The authors have no existing or potential financial conflict of interest to disclose. No funding was obtained.

## Contributions

1 Dipenkumar Modi: Conception and design of the study, or acquisition of data, or analysis and interpretation of data; Drafting the article or revising it critically for important intellectual content; Final approval of the version
2 Malini Surapaneni: acquisition of data, or analysis and interpretation of data; Final approval of the version
3 Seongho Kim: Conception and design of the study, or analysis and interpretation of data; Drafting the article or revising it critically for important intellectual content; Final approval of the version
4 Lois Ayash: Conception and design of the study, Final approval of the version
5 Asif Alavi: Conception and design of the study, Final approval of the version
6 Voravit Ratanatharathorn: Conception and design of the study, Final approval of the version
7 Abhinav Deol: Conception and design of the study, Final approval of the version
8 Joseph Uberti: Conception and design of the study, Drafting the article or revising it critically for important intellectual content; Final approval of the version

## Acknowledgements

None.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.106171.

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