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Research paper

Allogeneic hematopoietic cell transplantation in T-cell prolymphocytic leukemia: A single-center experience

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ABSTRACT

Background: T- cell prolymphocytic leukemia (T- PLL) is a rare aggressive hematological malignancy. Alemtuzumab, an anti-CD52 humanized monoclonal antibody, is the treatment of choice for remission induction. Allogeneic hematopoietic cell transplantation (allo-HCT) has been described to induce durable remissions and improve survival, but data is limited.

Patients and methods: We evaluated clinical outcomes of 11 patients, median age of 56 (range, 43–71) years who underwent allo-HCT for T-PLL. The majority of cases were in the first complete remission (CR1 = 9, CR2 = 1, second partial response PR2 = 1) at time of allo-HCT. Myeloablative conditioning was the most commonly prescribed preparative regimen (n = 8, 73%) and tacrolimus plus sirolimus was most commonly prescribed regimen for graft-versus-host disease prophylaxis (n = 5, 46%).

Results: The median follow-up for surviving patients was 48 (range, 6–123) months. The 4-year progression-free survival (PFS) and overall survival (OS) were 45% (95% confidence interval (CI) = 13–78%) and 56% (95% CI = 24–89%), respectively. Cumulative incidence of non-relapse mortality (NRM) at 4-year post-transplantation was 34% (95%CI = 14–85%). The 4-year cumulative incidence of relapse/progression was 21% (95% CI = 6–71%).

Conclusion: Allo-HCT is an effective treatment for T-PLL. Patients must be evaluated for their candidacy for allo-HCT as soon as the diagnosis is confirmed. Efforts are needed to decrease NRM and relapse.

1. Introduction

T- cell prolymphocytic leukemia (T- PLL) is a rare aggressive malignancy, representing approximately 2% of mature lymphocytic leukemias in adults [1]. Patients typically present with lymphocytosis, hepatosplenomegaly, generalized lymphadenopathy and skin involvement. Rearrangement involving T-cell leukemia 1A (*TCL1*) gene on chromosome 14, is a relatively specific diagnostic marker for T-PLL, detected in 80% of patients which can serve as a diagnostic criterion [2]. Most patients with T-PLL have an aggressive clinical course with very limited survival despite aggressive treatment. In a series of 119 patients from M. D. Anderson Cancer Center, the reported median survival was 19 months [3].

Alemtuzumab, an anti-CD52 humanized monoclonal antibody, is the initial treatment of choice as CD52 is highly expressed in T-PLL. This treatment can yield complete remission (CR) rates of 60- 80%; however, relapses are commonly seen within a year [4,5]. Survival of patients with relapsed T-PLL is dismal and response rates to the second line therapy is limited and generally short lived [6]. Allogeneic hematopoietic cell transplantation (allo-HCT) has been reported to yield durable remissions, especially if offered after achieving a CR or at least a PR. A multi-institutional retrospective case series of 27 T-PLL patients, reported on behalf of the French Society for Stem Cell Transplantation (SFGM-TC), showed 3-year progression-free survival (PFS) and overall survival (OS) after allo-HCT of 26% and 36%, respectively [7]. Also, allo-HCT appears to improve survival when compared to observation alone after remission induction based on a retrospective series [8]. A larger series from the European Society for Blood and Marrow Transplantation (EBMT) reported 3-year OS of 21% in 41 allo-HCT recipients [9].

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Uncertainties still remain about optimal timing for allo-HCT. Herein, we performed a retrospective analysis of 11 patients who underwent allo-HCT for T-PLL at our center. We also reviewed literature assessing the role of allo-HCT in T-PLL and summarized studies reporting outcomes in ≥10 patients.

2. Patients and methods

Eleven patients received an allo-HCT for T-PLL between January 1, 2006 and February 29, 2016. All treated patients were consecutively enrolled. Eligible subjects were identified by electronic medical record search and pathology slides were independently reviewed by an experienced hematolopathologist for confirmation of the diagnosis. This study was approved by the Institutional Review Board of the University of South Florida and was conducted in accordance with the declaration of Helsinki.

2.1. Study objectives, definition of endpoints, and statistical methodology

The primary objective of this retrospective study was OS after allo-HCT for T-PLL. Secondary objectives were PFS, relapse/progression, and non-relapse mortality (NRM) post-allografting.

OS was defined as the time from allo-HCT (day 0) until death from any cause or last follow up date. PFS was defined as the time from HCT until disease relapse/progression or death or last follow up date. NRM was defined as cumulative incidence of death without evidence of disease relapse or progression. In the case of relapse incidence, NRM was considered a competing risk. Time-to-neutrophil engraftment was defined as the first of 3 consecutive days after achieving an absolute neutrophil count (ANC) of ≥500/μL. Time-to-platelet engraftment was defined as the first day with a platelet count of ≥20,000/μL or higher in the absence of platelets transfusion for 7 consecutive days. We defined CR at any stage of treatment as follows: no signs of organ infiltration or lymph node or spleen enlargement as per physical examination and imaging studies as well as a normalized absolute lymphocyte count (ALC) and lack of an aberrant T-cell population by a bone marrow biopsy with immunohistochemical evaluation and flow cytometry. PR was defined as decrease in the peripheral ALC by at least 50% from the level prior to therapy, reduction in previously enlarged nodes by at least 50% with no increase in the size of any single lymph node and no new enlarged lymph nodes. If enlarged prior to therapy, the spleen should have to be reduced in size by at least 50% to qualify as PR.

The baseline patient characteristics were summarized using descriptive statistics including mean, median, standard deviation and range for continuous variables and proportions and frequencies for categorical variables. Kaplan-Meier method was used to estimate the PFS and OS. Survival curves were compared using the Log-rank test. Fine and Gray competing risk regression model was used for incidence of relapse/progression and NRM [10]. P values were 2-sided and significance level was set at < 0.05. Ninety five percent (95%) confidence intervals (CIs) were provided for survival probabilities and/or cumulative incidences. Statistical analysis was performed using NCSS 11 (2016) (NCSS, LLC, Kaysville, UT, USA) statistical analysis software.

2.2. Literature review

We performed literature search for previously published data on allo-HCT outcomes in T-PLL. We searched PubMed, Embase, Cochrane library, Web of Science® for following key terms: "leukemia, prolymphocytic, t-cell"[MeSH Terms] OR t prolymphocytic leukemia OR t-pll OR t prolymphocytic lymphoma OR b-prolymphocytic leukemia OR b pll) AND ("Bone Marrow Purging"[Mesh] OR allogeneic bone marrow OR allogeneic bone marrow transplant OR allogeneic transplant OR allotransplant OR "stem cell transplantation"[MeSH Terms] OR stem cell transplant. Filters: Publication year- 1960–2017. This search resulted in 155 unique citations. The articles and abstracts were reviewed by the author (B.D.) We excluded the articles not describing T-PLL and allo-HCT outcomes (79), autologous HCT (4) and review articles (30). We also excluded articles with less than 10 T-PLL cases (29), duplicate publication (6) and insufficient information regarding allo-HCT outcomes (3). At the end, four articles were considered eligible and data are summarized in a Table 2.

3. Results

3.1. Baseline patient characteristics

The median age of patients was 56 (range, 43–71) years and the majority were of male gender (n = 7, 64%). Complete blood counts revealed evidence of absolute lymphocytosis with a median ALC of 11,000/μL (range, 9000–69,000) and bone marrow involvement at time of presentation in all patients. Two (18%) patients had splenomegaly and one (9%) had skin involvement at diagnosis. Seven (64%) had an abnormal karyotype and 5 patients (46%) had cytogenetic aberrations involving ≥5 chromosomes. Abnormalities on chromosome 8, 11 and 14 were the most frequently seen abnormalities. Abnormal fluorescent in-situ hybridization (FISH) for 14q11 rearrangements and deletion 11q22 were detected in 3 patients each.

Alemtuzumab was prescribed as single agent (n = 7, 64%) or in combination with chemotherapy (cladrabine −1 patient; fludarabine, cyclophosphamide, mitoxantrone- 1 patient) (n = 2, 18%) as first line treatment. In non-alemtuzumab group, 1 patient received chlorambucil and the other received denileukin diftitox. Responses to first-line treatment were as follows: CR1 in 9 (82%) and PR1 in 2 (18%) patients. At time of allo-HCT 9 patients were in CR1, one in CR2 and another in PR2. The majority patients had HCT comorbidity index (HCT-CI) of 0 (55%) or 1 (27%). Myeloablative conditioning (MAC) was used in 8 (73%) patients. Choice of conditioning regimen was based on institutional policies according to the patient age and co-morbidities. Donor source was Human Leukocyte Antigen (HLA) matched related (MRD) in 5, matched unrelated (MUD) in 3, mismatched unrelated (MMUD) donor in 2 and umbilical cord blood in 1 patient. Tacrolimus plus sirolimus was the most frequently used regimen for graft-versus-host disease (GVHD) prophylaxis. Table 1 summarizes patient disease- and treatment-related characteristics.

3.2. Outcomes after allo-HCT

3.2.1. Engraftment kinetics

Median time to neutrophil and platelet engraftment were 15 (range, 12–23) days and 14 (range, 11–26) days respectively.

3.2.2. Disease response

Nine patients who were in CR1/CR2 prior to allo-HCT maintained CR post-allo-HCT. One patient with PR2 before allo-HCT had disease progression on day 57.

3.2.3. Survival

Median follow up of surviving patients after allo-HCT was 48 (6–123) months. Median PFS and OS were 15 months (95% CI = 12–99) and 56 months (95% CI = 15–56). The 4-year PFS and OS were 45% (95% CI = 13–78%) and 57% (95% CI = 25–89%), respectively (Fig. 1).

We also conducted a subgroup analysis restricted to 9 patients who were in CR1 before allo-HCT. The 4-year PFS and OS were 50% (95% CI = 15–85%) and 62% (95% CI = 29–96%) respectively. The 4-year PFS and OS were similar between the patients who were in CR1 vs non-CR1 (i.e.-CR2, PR2) prior to allo-HCT. (PFS, Log-rank p = 0.82; OS, Log-rank p = 0.6) Ablative intensity of the allo-HCT regimen did not impact OS (HR for OS = 0.64, 95% CI = 0.09–4.47, *p*-0.76). We also looked at the patients who had ≥5 chromosomal abnormalities in the