Impact of Alemtuzumab Therapy and Route of Administration in T-Prolymphocytic Leukemia: A Single-Center Experience

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Abstract

T-prolymphocytic leukemia is a rare neoplasm with available data restricted to small prospective trials and retrospective case series. In a consecutive cohort of 41 patients, we found that intravenous alemtuzumab was associated with survival advantage over other therapies, including subcutaneous alemtuzumab. Hematopoietic stem cell transplantation was feasible in a minority of potentially eligible patients.

Objective: We conducted a single-center retrospective analysis to determine the impact of the anti-CD52 monoclonal antibody alemtuzumab including route of administration compared to non-alemtuzumab-containing regimens in T-prolymphocytic leukemia (T-PLL). **Patients and Methods:** The study was a retrospective analysis of a consecutive cohort of adult patients diagnosed with T-PLL at Mayo Clinic Rochester from January 1, 1997, through September 30, 2014. **Results:** A total of 41 patients were diagnosed with T-PLL per the World Health Organization 2008 classification. The median age was 66 years, and 23 (56%) were male. After a median follow-up of 18 months (range, 0.4-66.1 months), 32 patients (78%) had died, with a median overall survival of 16.9 months. Approximately half the cohort was treated with alemtuzumab, almost exclusively after 2004. Median survival for patients receiving intravenous alemtuzumab-based therapy was 40.5 versus 10.3 months for all other therapies ($P = .0004$). A significant survival difference between intravenous versus subcutaneous alemtuzumab administration of 40.5 versus 13.7 months was noted ($P = .0014$). Only 4 (14%) of 28 patients aged < 70 years underwent hematopoietic stem cell transplantation, with a median survival after transplantation of 4 months. **Conclusion:** In this large series of T-PLL patients treated at a single tertiary-care center, we confirmed the prior observation of the superiority of intravenous alemtuzumab over other therapies. Hematopoietic stem cell transplantation was feasible in a minority of potentially eligible patients. Early transplant referral should be considered for all eligible patients.

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Introduction

T-prolymphocytic leukemia (T-PLL) is a mature lymphoid neoplasm associated with an aggressive course and a historical median survival of less than 1 year. It typically affects the elderly, with a median age at diagnosis of 65 years, and has a slight male predominance.[1] Presenting features include an elevated leukocyte count, lymphadenopathy, hepatosplenomegaly, and cutaneous lesions. The malignant cells appear to be postthymic in origin, expressing $CD2^+$, $CD3^+$, $CD5^+$, $CD7^+$, $CD4^+$, and/or $CD8^+$.[1] CD52 is frequently expressed with high density.[2] Recurrent karyotypic abnormalities are common, with the majority of cases demonstrating chromosome 14 aberrations, usually inv(14) or t(14;14) with breakpoints at 14q11.2 and 14q32.[3,4] Such rearrangements approximate the T-cell receptor alpha-delta (*TRAD*) locus to the T-cell lymphoma 1 (*TCL1*) gene, which is thought to induce overexpression and constitutive activation

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with resultant malignant transformation of leukemic T cells. A rare X;14 translocation between the *TRAD* locus and the mature T-cell proliferation 1 (*MTCP1*) gene has also been described.[5] Other cytogenetic and genetic abnormalities include trisomy 8, 11q deletion (including *ATM*), and abnormalities of chromosome 17 (including *TP53* deletion). Approximately one third incur activating mutations in the JAK1 or JAK3 nonreceptor tyrosine kinases.[6]

Responses to standard multiagent chemotherapy are typically limited and short lived.[7] The introduction of the monoclonal antibody alemtuzumab has improved response rates. The duration of remission remains suboptimal, and ultimately the majority of patients die of their disease. In previously untreated patients, alemtuzumab demonstrated an overall response rate of 90%, with the majority being complete responses.[8] In contrast to chronic lymphocytic leukemia, subcutaneous administration of alemtuzumab had inferior outcomes, and a pilot project comparing intravenous versus subcutaneous administration of the drug was prematurely terminated.[8] Currently, the best treatment approach is considered to be a combination of intravenous alemtuzumab therapy followed by hematopoietic stem cell transplantation (HSCT) in eligible patients.[7] Three registry-based databases reported the use of allogeneic HSCT.[9-11] Each was limited by a small number of patients and heterogenous treatments received. Furthermore, the proportion of T-PLL patients who were able to proceed to HSCT was not reported. Although HSCT may in fact offer longer-term effective disease control in a subset of patients with T-PLL, the value of HSCT in the management of all patients remains uncertain. Herein we report a retrospective analysis of alemtuzumab therapy and HSCT outcomes in 41 T-PLL patients seen at Mayo Clinic Rochester. Given the limited literature for this rare disease, we sought to study the impact of alemtuzumab therapy, including the mode of administration of the drug on disease outcomes.

Patients and Methods

This study was approved by the Mayo Clinic institutional review board in compliance with the declaration of Helsinki and federal regulation. The electronic medical record database at Mayo Clinic Rochester was queried for the terms T-prolymphocytic leukemia, prolymphocytic leukemia, T-PLL, and PLL from January 1, 1997, until September 30, 2014. All adult patients whose medical records contained 1 or more of these terms were manually reviewed. Patients meeting diagnostic criteria for T-PLL as per the World Health Organization 2008 classification were retained.[12] All relevant demographic, clinical, laboratory, and pathologic data were retrospectively extracted. All patients had undergone a bone marrow aspirate and trephine biopsy at the time of diagnosis.

Categorical variables were analyzed by Pearson's chi-square test, while continuous variables were analyzed by the Wilcoxon/Kruskal-Wallis test, with $P < .05$ considered statistically significant. Overall survival was estimated from the time of diagnosis until date of death or last documented contact. Patients alive at the last documented follow-up were censored. Survival analysis was performed by the Kaplan-Meier method. Differences between survival curves were evaluated by the log-rank test.

Results

Baseline Clinical and Laboratory Characteristics

From January 1997 to September 2014, a total of 41 patients with T-PLL were identified. The relevant baseline characteristics of these patients are listed in Table 1. The median age at diagnosis was 66 years (range, 32-85 years), and 23 (56%) were male. Twenty-eight patients (68%) presented with lymphadenopathy, including 7 (18%) with mediastinal adenopathy, 25 (61%) with hepatosplenomegaly, 4 (10%) with cutaneous infiltration, 2 (5%) with pericardial effusion, and 1 each with central nervous system or gastric involvement (3%). The median hemoglobin was 13.5 g/dL (range, 6.6-17.3 g/dL) with 20% < 12 g/dL, white blood cell count 26.25 × 10^9/L (range, 9.4-551 × 10^9/L) with 20% > 100 × 10^9/L, absolute lymphocyte count 17.1 × 10^9/L (range, 5.7-540 × 10^9/L) with 15% > 100 × 10^9/L, and platelet count 164 × 10^9/L (range, 5-299 × 10^9/L) with 20% < 100 × 10^9/L. Among evaluable patients, fluorescence in-situ hybridization analysis was positive for *TCL1* disruption in 27 (96%) of 28, trisomy 8 in 4 (40%) of 10, 11q22.3 deletion in 4 (67%) of 6, and 17p deletion in 2 (67%) of 3.

Induction Therapy and Outcomes

Patients were stratified according to therapy received, and no significant differences in baseline presenting features were noted (Table 2). The median number of therapies received was 2 (range, 0-4). Twenty patients (49%) received alemtuzumab-based therapy as first line, 13 administered as intravenous, 5 as subcutaneous injection, and 2 had unknown route of administration. Patients treated after 2004 exclusively received alemtuzumab therapy as a single agent or in combination therapy, with 1 patient before 2004 receiving alemtuzumab. First-line alemtuzumab was provided as the sole therapy in 17 patients and as combination therapy in 3 others (Table 3). Fifteen patients (37%) received non-alemtuzumab-based therapies as the first line, including purine analogs as single agents or in combination with alkylating agents and/or corticosteroids. Non-alemtuzumab-based therapy was heterogeneous based on physician preferences, and none of the regimens demonstrated a survival

Table 1 Patient Characteristics

Characteristic	Value
Age (years), median (range)	66 (32-85)
Gender, male/female	23/18
Presenting Features	
Lymphadenopathy	28 (68%)
Hepatosplenomegaly	25 (68%)
Cutaneous involvement	4 (10%)
White blood cell count (×10^9/L), median (range)	26.25 (9.4-551)
Hemoglobin (g/dL), median (range)	13.5 (6.6-17.3)
ALC (×10^9/L), median (range)	17.1 (5.7-540)
Platelets (×10^9/L), median (range)	164 (5-299)
Cytogenetic or FISH Aberrations	
Inv(14) or t(14;14)	27/28 (96%)
11q22.3 deletion	4/6 (67%)
TP53 deletion	2/3 (67%)
Trisomy 8	4/10 (40%)
Other	7/38 (18%)

Abbreviations: ALC, absolute lymphocyte count; FISH = fluorescence in-situ hybridization.