Long-Term Outcomes of Hairy Cell Leukemia Treated With Purine Analogs: A Comparison With the General Population

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Abstract

Hairy cell leukemia (HCL) is a rare hematologic malignancy with high response rates and long progression-free survival (PFS) after treatment with purine nucleoside analogs (PNAs; Pentostatin/Cladribine). However, treatment is not curative, and subsequent treatment at relapse is often required. Rechallenge with a purine analog is commonly implemented despite limited data regarding the efficacy of this approach. We retrospectively analyzed 61 consecutive patients with HCL diagnosed between 1995 and 2013 at Cleveland Clinic. Median follow-up was 72 months (3-193). Cladribine as first-line therapy was administered to 59 patients (97%). Overall response rate (ORR) was 97%, with 78% of patients achieving complete remission (CR). PFS after response was significantly improved for patients who achieved CR compared with those with a partial remission (PR) (5-year PFS 71% vs. 39%, respectively [$P = .004$]). Of the 19 patients who relapsed, 12 received PNAs as second-line treatment with an ORR (83%) comparable to what these patients had with first-line treatment (ORR 92%). Overall survival of all 61 patients was excellent and superior to that of age-, sex-, and race-matched controls from the general population, possibly due to selection bias. In an analysis of a larger cohort of unselected patients in the Surveillance, Epidemiology, and End Results (SEER) database, we found that mortality rates for patients with HCL were similar to those of the general population approximately 5 years after diagnosis. These data confirm the excellent prognosis for patients with HCL after first- and second-line PNA therapy.

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Introduction

Hairy cell leukemia (HCL) is an uncommon indolent B-cell lymphoproliferative disorder first described by Bouroncle et al[1] in 1958 as "leukemic reticuloendotheliosis" in their report on 26 patients. The molecular pathogenesis of HCL is associated with a point mutation in the signaling protein BRAF (V600E) in nearly all cases, leading to constitutive cell proliferation signaling.[2] Clinically, HCL is characterized by pancytopenia, splenomegaly, and immunosuppression. Initial reports on outcomes of this disease showed a median survival of 4 years.[3] Treatment options were limited until the introduction of α-interferon, which produced meaningful rates of complete remission (CR) and partial remission (PR).[4] Introduction of the purine nucleoside analogs (PNAs) pentostatin and 2-chlordeoxyadenosine (2CDA, Cladribine) significantly improved outcomes of HCL.[5,6] Early reports using PNAs demonstrated CR rates of 80% to 90% with pentostatin and cladribine and 10-year overall survival (OS) rates of approximately 90%.[7-9] Comparative studies showed no difference in outcomes using pentostatin versus cladribine.[10-12] Because many patients ultimately relapse, rechallenge with PNAs has frequently been used, although data supporting this practice are limited. We therefore conducted a retrospective analysis of outcomes after first and subsequent lines of treatment of patients with HCL who were treated at a single institution to provide insight into the long-term management of

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Table 1 Patient Demographics

	At Diagnosis	At First Line	At Second Line
Median age (range), y	54 (31–80)		
No. male/female (%)	50/11 (82%/18%)		
Smoking history, n			
Current smokers (average pack years)	3 (24)		
Former smokers (average pack years)	25 (25)		
Never-smokers	31		
Unknown	2		
Medical comorbidities (>1 is possible)	n (%)		
Hypertension	21 (34)		
Hyperlipidemia	7 (11)		
Diabetes mellitus	7 (11)		
Coronary artery disease	5 (8)		
Atrial fibrillation	2 (3)		
None	34 (56)		
Laboratory and Clinical findings	n = 42-59[a]	n = 42-59	n = 12-17
Median hemoglobin, g/dL (range)	11.3 (4.0-15.2)	11.4 (6.4-15.2)	12.3 (8.1-15.2)
Median white blood cell count, k/μL (range)	2.4 (0.3-27.0)	2.5 (0.3-27.0)	2.3 (1.4-15.8)
Median absolute neutrophil count, k/μL (range)	825 (0-2840)	720 (0-2810)	1255 (590-2900)
Median platelet, k/μL (range)	79 (7-367)	72 (7-184)	103 (49-215)
Median lactate dehydrogenase, U/L (range)	172 (114-315)	166 (18-346)	206 (134-402)
Splenomegaly, n (%)	31/49 (63.3)		

[a]Range provided due to the presence of missing laboratory values.

these patients, particularly in the relapsed setting. In addition, we compared the OS of these patients with HCL and those captured in the Surveillance, Epidemiology and End Results (SEER) database with age- and sex-matched controls from the general population.

Methods

Patients

Patients diagnosed with HCL at the Cleveland Clinic Taussig Cancer Institute were identified through a search of the anatomic pathology database (CoPath). The diagnosis of HCL was made by expert hematopathologic review of bone marrow, peripheral blood, and/or spleen samples, including flow cytometry, per World Health Organization criteria.[13,14] Data from patients ≥ 18 years of age diagnosed from 1995 to 2013 and having adequate medical records were included in the study, approved by the Cleveland Clinic institutional review board. Baseline laboratory studies (hemoglobin, white blood cell count, absolute neutrophil count [ANC], platelet count, and lactate dehydrogenase levels) were obtained at diagnosis and just before first- and second-line treatments. In addition, we collected data on smoking status and medical comorbidities.

Treatment

First-line treatment was defined as the initial therapy administered following diagnosis; any additional therapeutic interventions within 60 days were counted part of first-line therapy. Cladribine was administered either at 0.1 mg/kg/d by continuous intravenous (IV) infusion for 7 days (n = 55); 0.14 mg/kg/d IV over 2 hours for 5 days (n = 3); or 5.6 mg/m^2 IV over 2 hours daily for 5 days (n = 1). Second-line treatment was defined as any treatment administered after 60 days from first-line treatment.

Response Evaluation

Responses were determined using standard response criteria.[15,16] Unconfirmed CR (CRu) was assigned to patients who had normalization of their peripheral counts; however, did not have a bone marrow biopsy performed to confirm response. Progression for patients who achieved CR/CRu was defined as appearance of cytopenias and/or evidence of HCL in peripheral blood or bone marrow. Progression after PR was defined as worsening cytopenias with > 50% increase in hairy cells in peripheral blood.

Statistical Analysis and Outcomes

Secondary malignancy and progression after start of first-line therapy were estimated using cumulative incidence methodology; OS and progression-free survival (PFS) were estimated using Kaplan-Meier analysis. Among patients who responded to first-line therapy, progression after the date of first response was compared for patients who achieved CR versus PR using the Gray test; OS and PFS were compared using the log-rank test. Among patients treated with PNAs in the second-line setting, OS was estimated from the start of second-line therapy. Secondary malignancies excluded skin squamous and basal cell carcinomas.

Comparison With US Population Data

Survival from an age-sex-race–matched US population was obtained from standardized actuarial tables in the National Vital