Filgrastim for Cladribine-Induced Neutropenic Fever in Patients With Hairy Cell Leukemia

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Cladribine treatment of hairy cell leukemia (HCL) is complicated by neutropenic fever in 42% of patients despite documented infections being relatively uncommon. We performed a study of priming filgrastim followed by cladribine and then filgrastim again to determine if filgrastim would lead to a reduction of neutropenia and febrile episodes. Thirty-five patients received filgrastim and cladribine and were compared with 105 historic controls treated with cladribine alone. Cladribine was administered at 0.1 mg/kg/d by continuous infusion for 7 days. Filgrastim was administered at 5 μg/kg/d subcutaneously on days −3, −2, and −1 and then again after the completion of cladribine until the absolute neutrophil count (ANC) was ≥2 × 10^9/L on 2 consecutive days (days +8, +9, etc). After filgrastim priming, the median ANC increased from 0.9 × 10^9/L to 2.26 × 10^9/L (2.5-fold increase), and after cladribine, the median nadir ANC in the filgrastim-treated group was 0.53 × 10^9/L compared with 0.29 × 10^9/L among historic controls ($P = .04$). The median number of days to an ANC greater than 1.0 × 10^9/L was 9 days in the filgrastim-treated group versus 22 days among historic controls ($P < 10^{-5}$). The percentage of febrile patients, number of febrile days, and frequency of admissions for antibiotics were not statistically different in the two groups. Filgrastim regularly increases the ANC in patients with HCL and shortens the duration of severe neutropenia after cladribine. This phase II study, with comparison to historical controls, failed to detect any clinical advantage from the use of filgrastim and cladribine in the treatment of HCL. Accordingly, the routine adjunctive use of filgrastim with cladribine in the treatment of HCL cannot be recommended.

HAIRY CELL LEUKEMIA (HCL) is an uncommon chronic B-cell lymphoproliferative disorder whose defining features are the presence of mononuclear cells displaying cytoplasmic projections and the typical pattern of infiltration both in the bone marrow and spleen.[1] Single courses of cladribine (2-chlorodeoxyadenosine [2-CdA]; Leustatin; Ortho Biotech, Raritan, NJ), a purine nucleoside analog, induce complete and long-lasting remissions in the vast majority of HCL patients.[2-5] Of 349 evaluable patients treated at Scripps Clinic with a single course of cladribine administered at 0.1 mg/kg/d by continuous infusion for 7 days, the overall response rate was 98%, with 91% complete responses.[4] In this report from Scripps Clinic, the administration of cladribine to patients with HCL resulted in a high frequency of drug-induced severe neutropenia and neutropenic fever, although documented infections were relatively uncommon. After the administration of cladribine, 71% of patients experienced grade 4 neutropenia (absolute neutrophil count [ANC] $<0.5 \times 10^9$/L), and 42% of patients developed neutropenic fever that frequently resulted in the need for hospitalization, because these febrile patients are often ill-appearing, with chills, headache, myalgias, anorexia, and malaise. Nevertheless, only 13% of patients had documented viral or bacterial infections, and there were no acute fungal infections. The fever generally responded well to antipyretics such as acetaminophen and usually resolved within 3 to 5 days. A similar incidence of neutropenic fever has been documented in studies conducted with cladribine in patients with HCL at other institutions.[6-8]

The empiric institution of broad-spectrum antibiotics is the cornerstone of the initial management of chemotherapy-induced febrile neutropenic cancer patients. An ANC less than 0.5×10^9/L is considered the single most significant risk factor for infection.[9] The other factors that alter this risk include the magnitude of neutropenia, the duration of neutropenia, phagocyte function, the status of the patient's cellular and humoral immune system, alterations of physical defense barriers, and the patient's endogenous microflora.[10] There is a striking decrease in the incidence of infection when the neutrophil count increases from less than 0.1×10^9/L to greater than 0.5×10^9/L.[11]

Although documented infections in HCL patients after cladribine treatment are relatively infrequent, given the severity of the neutropenia and the pyrexia the standard of care in such patients is to initiate empiric broad spectrum intravenous antibiotics while extensive efforts are made to exclude infection. Considerable expense and inconvenience are thus incurred by these patients. Antibiotic-induced toxicity and nosocomial disease are potential risks. Although the precise mechanism of the neutropenic fever has not been defined, the release of interleukin-1, tumor necrosis factor-α, and other cytokines into the circulation during cell lysis or even occult infections may possibly play a significant role.

Recombinant human granulocyte colony-stimulating factor (G-CSF; filgrastim) has previously been shown to be safe in the treatment of neutropenia accompanying HCL and to regularly increase neutrophil counts.[12] Given that the fever universally occurs in the presence of severe neutropenia, it is reasonable to postulate that an agent capable of increasing granulocytes, such as filgrastim, would lead to a reduction in the number of these

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febrile episodes and thereby prevent unnecessary hospitalization, expense, and iatrogenic disease. Also, if the fever occurred in the absence of profound neutropenia, it would potentially mitigate against hospitalizing these patients. Accordingly, we performed a study of priming filgrastim followed by cladribine, and thereafter filgrastim, to evaluate this hypothesis and compared the results with those of historic controls.

MATERIALS AND METHODS

Eligibility criteria. Patients required a diagnosis of HCL based on the peripheral blood smear and bone marrow as reviewed by the hematopathologist at Scripps Clinic. In addition, they underwent a confirmatory peripheral blood immunophenotypic analysis (monoclonal antibodies against the B-cell antigens CD19, CD20, and CD22 were applied, and coexpression of CD11c, CD25, and CD103 was evaluated). Neutropenia (ANC $<1.0 \times 10^9$/L), anemia (hemoglobin <10 g/dL), thrombocytopenia (platelets $<100 \times 10^9$/L), symptomatic splenomegaly, rapidly progressive lymphocytosis, or repeated infections was required before administering cladribine treatment. There were no age restrictions. Patients were excluded if they had received treatment within 4 weeks of cladribine therapy, if they had an active infection, or if they had abnormal renal or hepatic functions. The study was approved by the Scripps Clinic Institutional Review Board and written informed consent was obtained.

Treatment plan. Patients were treated as outpatients using a computerized ambulatory drug delivery (CADD) portable infusion pump (Pharmacia Deltec, St Paul, MN) to deliver the cladribine after insertion of a peripherally inserted central venous (PICC) catheter. Cladribine was administered at a dose of 0.1 mg/kg/d by continuous intravenous infusion for 7 days. Filgrastim (Neupogen; Amgen, Thousand Oaks, CA) was administered to all patients at 5 μg/kg/d subcutaneously on days −3, −2, and −1 and then again after the completion of cladribine until an ANC $\geq 2 \times 10^9$/L was achieved on 2 consecutive days (days +8, +9, etc). Upon discontinuation of the filgrastim, if the ANC decreased to less than 1.0×10^9/L, then filgrastim treatment was restarted until the ANC was again $\geq 2 \times 10^9$/L on 2 consecutive days.

Acetaminophen (650 mg orally every 4 hours) could be taken by patients in the filgrastim-treated and historic control groups for a temperature greater than 38.5°C. Acetaminophen could not be taken on a prophylactic basis or when the temperature was less than 38.5°C. The use of aspirin or nonsteroidal anti-inflammatory agents was prohibited.

Patients were hospitalized to exclude infection and to receive broad spectrum intravenous antibiotics when fever (temperature >38.5°C) occurred in association with an ANC less than 1.0×10^9/L. Antibiotic selection was deferred to the treating physician. Antibiotics were discontinued if the cultures drawn remained negative, the patient had been afebrile for 24 hours, and the ANC was $\geq 0.5 \times 10^9$/L. If the patient remained afebrile off antibiotics, hospital discharge occurred after a further 24 hours of observation as an inpatient.

Patient evaluations. Before the initiation of filgrastim and cladribine, patients underwent a history and physical examination; a complete blood count with differential including neutrophil, lymphocyte, monocyte, and hairy cell counts; a 24-channel chemistry test, including renal and hepatic functions; bone marrow aspirate and biopsy; peripheral blood tartrate-resistant acid phosphatase (TRAP) stain; and a peripheral blood immunophenotypic analysis.

During filgrastim priming on days −3, −2, and −1, oral temperatures were taken three times daily at 8-hour intervals, and the complete blood count with differential was repeated on days −3 and 0. During cladribine therapy (days 0 to +7) and filgrastim (days +8, +9, etc) thereafter, the physical examination and oral temperature were recorded by the physician on days +3, +6, and +8 for outpatients and daily for hospitalized patients. Oral temperatures were recorded by the patient three times daily at 8-hour intervals and with the onset of suspicious symptoms, eg, subjective fever, chills, diaphoresis, etc. A complete blood count with differential was obtained daily during cladribine and at least twice weekly during filgrastim therapy in all patients. The 24-channel chemistry panel was repeated on days +3, +6, +8, and +10.

Toxicity. Toxicities were evaluated using standard criteria.[13]

Historical controls. The historic controls underwent the same evaluations and identical cladribine therapy as did the treated group, but received no neutrophil colony-stimulating factors. The historic control patients selected were consecutive patients with HCL treated with cladribine at the Scripps Clinic between April 1986 and January 1993. The hospitalization policies in the historic control patients and the filgrastim-treated group were identical.

Statistical considerations. Because HCL is a rare disease with only 600 new cases reported annually in the United States,[14] we accepted a phase II study design that favored accrual of a substantial number of HCL patients to expeditiously determine whether filgrastim, an expensive and potentially unnecessary intervention as an adjunct to cladribine treatment, results in clinical benefit. Because of the small number of patients available for study, we asked whether outcomes in unmatched, historical controls could provide a statistically valid comparison despite being neither randomized nor blinded.

Only a limited number of patients (n = 35) were treated with filgrastim in addition to cladribine; it was desired to compare outcomes in these patients with those of unmatched controls treated solely with cladribine, drawn consecutively from the Scripps Clinic database of HCL patients. One method of increasing the power of the experiment for detecting differences in outcomes is by increasing the number of controls relative to the filgrastim-treated group. Accordingly, an unbalanced design with unequal allocation of patients to the two cohorts was adopted. A 3:1 ratio of controls to filgrastim patients was chosen as the incremental gain in power that might have been realized by using even a greater ratio of controls to patients than 3:1 seemed marginal. Let e denote the effect size for any particular parameter to be compared, that is, $e = |\mu_1 - \mu_2| / \sigma$, where μ_1 denotes the mean of that parameter value in filgrastim + cladribine patients, μ_2 denotes the mean of that parameter value in cladribine patients, and σ denotes the common standard deviation in the two populations. Then, a sample size of 35 cladribine + filgrastim-treated patients and 105 cladribine controls would be sufficient to detect a clinically significant effect size of 0.4, 0.6, or 0.8 with a power of 0.53, 0.86, or 0.98, respectively, using a standard two-sided t-test at conventional α level $\alpha = .05$.[15]

Comparisons of univariate outcomes between the two groups were made with standard (parametric) t-tests and (nonparametric) Mann-Whitney tests for continuous outcomes and Fisher's exact test for discrete outcomes. Exploratory multivariate procedures were also undertaken but did not establish any other meaningful differences between the two groups. The results from the univariate nonparametric procedures are reported here, because the parametric results were quantitatively similar. Two-sided P values corresponding to the observed test statistics are given without correction for the multiplicity of tests performed.

RESULTS

Patient demographics. Thirty-five patients received filgrastim and cladribine and are compared with 105 historic control patients (Table 1) who received cladribine alone. The two groups were generally well balanced, with only spleen size and prior treatment demonstrating significant differences. There were more splenectomized patients among the historic controls ($P = .03$), and no historic control patients had received prior cladribine ($P < 10^{-4}$).

Table 1. Pretreatment Patient Characteristics

	Cladribine + Filgrastim (treated group)	Cladribine Alone (historic controls)	*P* Value
No. of patients	35	105	
Age (yr): median (range)	52 (34-75)	53 (28-77)	.57
Sex: males/females	31/4	81/24	.22
Pretreatment duration (mo)			
Median (range)	22 (1-193)	23 (1-192)	.59
Spleen size (%):			
Absent (splenectomized)	4 (11%)	35 (33%)	.03*
Nonpalpable	13 (37%)	16 (15%)	
1-2 fingerbreadths	5 (14%)	11 (10%)	
3-4 fingerbreadths	9 (26%)	24 (23%)	
>5 fingerbreadths	4 (11%)	16 (15%)	
Unknown	0	3 (3%)	
Prior Treatment (%):			
None	13 (37%)	41 (39%)	10^{-4}*
Splenectomy	0	16 (15%)	
Interferon	4 (11%)	27 (26%)	
Splenectomy/Interferon	0	19 (18%)	
Pentostatin/Interferon	0	2 (2%)	
Cladribine	12 (34%)	0	
Splenectomy/Interferon/Cladribine	3 (9%)	0	
Interferon/Cladribine	1 (3%)	0	
Other	2 (6%)	0	
Peripheral blood counts			
WBC ($\times 10^9$/L)			
Median (range)	2.3 (1.3-23.3)	3.4 (0.6-78.8)	.13
ANC ($\times 10^9$/L)			
Median (range)	0.9 (0.08-2.56)	0.9 (0.07-4.32)	.75
Hemoglobin (g/dL)			
Median (range)	13 (7.4-15.8)	11.9 (5.2-16.2)	.07
Platelets ($\times 10^9$/L)			
Median (range)	87 (34-187)	83 (19-468)	.83
Absolute hairy cell count ($\times 10^6$/L)			
Median (range)	83 (0-18,174)	164 (0-60,345)	.09

*Nominally significant at α level .05 ($P < .05$).

Blood counts after filgrastim priming and cladribine administration. The peripheral blood counts after filgrastim priming demonstrated that the median total leukocyte count increased from 2.3×10^9/L to 3.9×10^9/L, corresponding to an increase in the median ANC from 0.9×10^9/L to 2.26×10^9/L; this represents a 2.5-fold increase in the ANC (Table 2). No significant differences in the hemoglobin concentration or platelet counts were observed.

After the administration of cladribine in the filgrastim-treated group and among the historical controls, the median nadir total leukocyte count was 0.8×10^9/L and 0.6×10^9/L and the median nadir ANC was 0.53×10^9/L and 0.29×10^9/L ($P = .04$), respectively (Table 2). Again, no significant differences were observed in the median nadir hemoglobin concentration or platelet counts.

Toxicities—Duration of neutropenia, febrile episodes, and hospitalization. The median number of days to achievement of an ANC greater than 1.0×10^9/L was 9 days in the filgrastim-treated group versus 22 days among historic controls ($P < 10^{-5}$; Table 3). The median number of febrile days for all patients in the filgrastim-treated group was 1 day and was 3 days for only the febrile patients; the median number of febrile days for all patients in the historic controls was 3 days and was 6 days for only the febrile patients ($P = .21$ and $P = .17$, respectively). Additional information regarding the severity and duration of neutropenia observed and the proportion of febrile events that occurred in association with the different levels of neutropenia is also shown in Table 3. The number of patients at the different levels of nadir neutropenia and the number of days at these levels of neutropenia were statistically different between the filgrastim-treated group and the historic controls. The median number of hospital days, number of patients admitted, and number of days of intravenous and oral antibiotics were not statistically different in both groups. The mean number of admissions and the mean number of hospital days for neutropenic fever were 0.26 and 3.1 per patient in the filgrastim-treated group and 0.35 and 3.9 per patient in the historic controls, respectively.

The median time for the onset of fever in the filgrastim-treated group was on day +8 (range, day +1 to day +29) and in the historic controls was on day +7 (range, day +3 to day +32). Of the 19 febrile patients in the filgrastim-treated group, the median time for the onset of fever in 18 patients was on day +8 (range, day +1 to day +12); 1 patient experienced fever on day +29. Of the 47 febrile patients in the historic controls, the median time for the onset of fever in 44 patients was on day +7

Table 2. Peripheral Blood Counts After Filgrastim Priming and Cladribine Therapy

	Filgrastim + Cladribine	Cladribine Alone	*P* Value
Peak counts after filgrastim priming (day 0)			
WBC ($\times 10^9$/L)			
Median (range)	3.9 (1.6-64.5)		
ANC ($\times 10^9$/L)			
Median (range)	2.26 (0.18-29.03)		
Hemoglobin (g/dL)			
Median (range)	12.4 (6.8-15.7)		
Platelets ($\times 10^9$/L)			
Median (range)	82 (23-162)		
Absolute hairy cell count ($\times 10^6$/L)			
Median (range)	80 (0-32,250)		
Nadir counts after cladribine			
WBC ($\times 10^9$/L)			
Median (range)	0.8 (0-1.8)	0.6 (0-7.1)	.15
ANC ($\times 10^9$/L)			
Median (range)	0.53 (0-1.8)	0.29 (0-1.96)	.04*
Hemoglobin (g/dL)			
Median (range)	10.2 (3.7-15.2)	9.2 (4.8-14.3)	.12
Platelets ($\times 10^9$/L)			
Median (range)	64 (16-130)	68 (3-359)	.33

*Nominally significant at α level .05 ($P < .05$).

(range, day +3 to day +13); 3 patients experienced fevers on days +18, +28, and +32. Thus, the fevers tended to occur early on after cladribine therapy, when patients in both groups were at their neutrophil nadirs and were unaffected by the shorter duration of neutropenia in the filgrastim-treated group. This likely explains why the hospitalization rate was not significantly different between the two groups, because the incidence of fevers was similar.

Among the 11 patients in the filgrastim-treated group requiring hospitalization, 1 patient was admitted twice for fever and 2 patients were admitted for PICC-related complications (1 with negative blood cultures and 1 patient with *Staphylococcus aureus* bacteremia). Among the 45 patients in the historic control group requiring hospitalization, 1 patient was readmitted for fever and 8 patients were admitted for nonfebrile indications (2 with dehydration, 1 with vasovagal syncope, 1 with severe thrombocytopenia [platelets, 3×10^9/L], 1 with pneumonia, and 3 with PICC-related coagulase-negative staphylococcus cellulitis in the absence of bacteremia).

The same peripheral blood and clinical parameters were evaluated for patients with a pretreatment ANC less than 1.0×10^9/L and for patients with a pretreatment ANC less than 0.5×10^9/L. For patients with a pretreatment ANC less than 1.0×10^9/L, the median nadir ANC after cladribine was 0.45×10^9/L in the filgrastim-treated group (n = 21) versus 0.14×10^9/L among historic controls (n = 61; $P = .024$), and the median number of days to achieve an ANC greater than 1.0×10^9/L in the filgrastim-treated group was 9 days versus 27 days among historic controls ($P < 10^{-4}$). For patients with a pretreatment ANC less than 0.5×10^9/L, the median nadir ANC after cladribine was 0.04×10^9/L in the filgrastim-treated group (n = 5) versus 0.06×10^9/L among historic controls (n = 23; $P = .47$), and the median number of days to achieve an ANC greater than 1.0×10^9/L in the filgrastim-treated group was 14 days versus 33 days among historic controls ($P = .054$). In both groups, the ANC increased after filgrastim priming, but there was no clear advantage compared with historic controls for both subgroups in terms of number of febrile patients, febrile days, patients admitted, or hospital days.

Responses. Of the 35 patients in the filgrastim-treated group, 28 (80%) obtained a complete response, 5 (14%) a partial response, 1 patient was a nonresponder, and 1 patient had no follow-up data. Of the 105 historical controls, 94 (90%) achieved a complete response, 7 (7%) achieved a partial response, 2 were nonresponders, and 2 were not evaluated for response; these response rates are comparable to those for the filgrastim-treated group ($P = .27$).

DISCUSSION

We have previously demonstrated that single courses of cladribine administered to patients with HCL induced complete and long-lasting responses in the vast majority of patients treated.[4] The major acute toxicity, occurring in 42% of patients, is neutropenic fever, with documented viral or bacterial infections occurring in 13%. Accordingly, we initiated this study to determine if filgrastim administered before (priming) and after cladribine would ameliorate the incidence and severity of neutropenic fever. The rationale for the incorporation of priming filgrastim was twofold: first to determine what effect filgrastim would have on the absolute neutrophil counts in patients with HCL, and second by increasing the neutrophil count before the administration of cladribine it would potentially have a favorable impact on nadir neutrophil counts. A potential hazard to this approach is that filgrastim-induced cycling of hematopoietic progenitor cells may increase their susceptibility to cytotoxic drugs, thus increasing rather than reducing the myelotoxicity of the cladribine.[16,17] For example, granulocyte-macrophage colony-stimulating factor (GM-SCF; sargramostim) priming in acute myeloid leukemia may have slowed the speed of postchemotherapy neutrophil recovery.[18,19]

Table 3. Neutropenia Duration, Febrile Episodes, and Hospitalizations for All Patients

	Filgrastim + Cladribine			Cladribine Alone			*P* Value
Days of filgrastim administration (including priming)							
Median (range)	10 (5-52)			N/A			
Days to ANC $>1.0 \times 10^9$/L							
Median (range)	9 (8-41)			22 (7-64)			$<10^{-5}$*
No. of febrile patients (%)	19/35 (54%)			47/105 (45%)			.43
No. of febrile days (all patients)							
Median (range)	1 (0-11)			3 (0-41)			.21
No. of febrile days (only febrile patients)							
Median (range)	3 (1-11)			6 (1-41)			.17
No. of patients with nadir ANC							
0 to 0.199×10^9/L	8			48			.008*
0.2 to 0.499×10^9/L	7			23			
0.5 to 0.999×10^9/L	14			14			
$\geq 1.0 \times 10^9$/L	6			20			
No. of patients at onset of fever with ANC (%)							
0 to 0.199×10^9/L	4 (21)			12 (26)			.258
0.2 to 0.499×10^9/L	2 (11)			14 (30)			
0.5 to 0.999×10^9/L	5 (26)			10 (21)			
$\geq 1.0 \times 10^9$/L	8 (42)			11 (23)			
	(19 total febrile patients)			(47 total febrile patients)			
	Mean	Median	Range	Mean	Median	Range	*P* Value
Fever duration according to ANC at onset (d)							
0 to 0.199×10^9/L	6.3	6.5	1-11	11.7	6	1-41	.544
0.2 to 0.499×10^9/L	3	3	3	5.5	5	1-14	.177
0.5 to 0.999×10^9/L	3.6	2	1-10	5.9	5.5	1-13	.221
$\geq 1.0 \times 10^9$/L	3.8	1	1-11	6.9	7	1-17	.137
No. of days with ANC (until day +37)							
0 to 0.199×10^9/L	2.2	0	0-36	4.2	0	0-33	.0294*
0.2 to 0.499×10^9/L	1.3	0	0-7	5.2	4	0-28	.0008*
0.5 to 0.999×10^9/L	2.6	2	0-9	8.0	7	0-36	.0004*
$\geq 1.0 \times 10^9$/L	30.9	34	0-37	19.6	18	0.37	.$<10^{-4}$*
No. of patients admitted (%)		11/35 (31%)			45/105 (43%)		.31
No. of hospital days							
Median (range)		9 (1-35)			7 (3-41)		.44
No. of IV antibiotic days (hospitalized patients)							
Median (range)		7 (1-35)			5 (2-31)		.96
No. of oral antibiotic days							
Median (range)		10 (1-28)			10 (1-31)		.45
		(11 patients)			(25 patients)		

*Nominally significant at α level .05 ($P < .05$).

In this report, priming filgrastim regularly increased the neutrophil count without stimulating the number of circulating hairy cells. The median nadir ANC in the filgrastim-treated patients was statistically greater than that of the historic control patients. After a median of 10 days of filgrastim administration (including priming filgrastim), the time for the ANC to exceed 1.0×10^9/L was decreased from 22 to 9 days; this advantage was greatest in patients with a pretreatment ANC less than 1.0×10^9/L. However, the number of febrile days and duration of fever in febrile patients, the number of patients hospitalized, and the number of hospital days were not significantly different. It is possible that the interpretation of results may have been weakened by the lack of a concurrent, randomized control group and by the fact that the number of study subjects and events were insufficient to detect subtle differences. These results could also have been influenced by there being more splenectomized patients among the historic controls and only patients in the filgrastim group had received prior cladribine therapy. In addition, the use of priming filgrastim could have had an overall deleterious effect in the filgrastim-treated group of patients. No Scripps Clinic patients have been treated only with post-cladribine filgrastim, making comparisons impossible. Nevertheless, the data support the conclusion that filgrastim use in HCL patients treated with cladribine has little or no effect on the febrile episodes, even though the degree and duration of neutropenia was reduced.

Given these results, the routine use of filgrastim cannot be recommended for all patients with HCL receiving cladribine. In those patients with a precarious medical status, it might be reasonable to consider the use of filgrastim so as to lessen the duration of severe neutropenia exposure. Because the presence of active infection was an exclusion criterion in this study, no conclusions can be drawn except that filgrastim does improve neutrophil counts, which may be of benefit in this clinical

circumstance. Cladribine is generally not administered in the presence of active infection given the myelosuppression and potent immunosuppressive properties of this purine nucleoside analog.[20-22]

It is indeed curious that multiple reports, with the exception of a single study,[7] have demonstrated a very low incidence of opportunistic infections after cladribine treatment of HCL, despite the severe neutropenia, monocytopenia, and T-cell immunosuppression that accompanies cladribine treatment.[4-6,8] Prior studies have demonstrated an association between failure of interferon-α generation by peripheral blood mononuclear cells and susceptibility to opportunistic intracellular infections. It has now been shown that cladribine-induced responses in HCL resulted in improved interferon-α generation by these mononuclear cells, which may lessen the risk of opportunistic infections.[23]

Very few studies have evaluated the role of neutrophil colony-stimulating factors in the treatment of HCL. In a prior report 10 years ago by Glaspy et al,[12] it was reported that, of 4 consecutive patients with HCL complicated by severe neutropenia, 3 patients significantly improved their neutrophil count, 2 patients had resolution of their infections, and 1 patient developed acute neutrophilic dermatosis (Sweet's syndrome). No patient developed Sweet's syndrome in the study reported here. A study conducted by Juliusson et al[24] in Sweden identified pretreatment anemia, bone marrow differential with a high percentage of hairy cells, and a low percentage of myelopoietic cells as predictive factors for the development of neutropenic fever in 102 patients undergoing infusional cladribine. In the 12 patients who received GM-CSF at 400 μg/d on days 1 through 21, GM-CSF did not improve neutropenia or febrile episodes.

We previously performed a double-blind, placebo-controlled study of pentoxifylline (400 mg orally 4 times daily for 10 days), a modulator of tumor necrosis factor-α and other cytokines, to determine whether the incidence of neutropenic fever would be reduced.[25] Although pentoxifylline treatment resulted in fewer febrile, hospital, and antibiotic therapy days than placebo, none achieved statistical significance except for the number of days in hospitalized patients. Until the pathogenesis of the fever that follows cladribine use is elucidated, it is unlikely that empiric therapeutic interventions will be successful.

In conclusion, filgrastim regularly increases the neutrophil count in patients with HCL and shortens the duration of severe neutropenia after cladribine, although the number of patients hospitalized and the number of hospital days were not significantly different in the two groups. There are multiple other trials both in hematopoietic and nonhematopoietic malignancies in which colony-stimulating factors resulted in reductions of the severity and duration of neutropenia but did not provide practical clinical benefits.[26,27] This phase II study, with comparison to historical controls, failed to detect any clinical advantage from the use of filgrastim with cladribine in the treatment of HCL. Accordingly, the routine use of filgrastim as an adjunct to treatment with cladribine cannot be recommended for HCL patients.

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