Reduced dose pentostatin for initial management of hairy cell leukemia patients who have active infection or risk of hemorrhage is safe and effective

Hairy cell leukemia (HCL) is a chronic B-cell malignancy described in 1958 by Bouroncle and colleagues[1] characterized by splenomegaly, pancytopenia, cellular immunodeficiency, "hairy cells" on the peripheral smear, and a characteristic immunophenotype. HCL has a variable clinical course, and some patients may benefit from a watch-and-wait strategy in the absence of symptoms.[2] Indications for treatment include symptomatic splenomegaly, constitutional symptoms, or bone marrow failure.[3] Although chemotherapy is not curative, treatment with a purine nucleoside analog (PNA) results in a complete remission (CR) in the majority of patients. Pentostatin and cladribine are the two agents most commonly used for initial therapy, and show comparable response rates.[4-6] Because classic HCL is a relatively indolent disease, few patients will experience complications from disease progression during treatment, with infections being the major causes of morbidity and mortality early in the treatment course.[7-9] Long-term follow-up studies suggest that patients with HCL will have a near normal life expectancy; therefore, safe administration of initial therapy is critical for optimal outcomes.[4,5] Hematologists at the Ohio State University have employed initial dose reduction of pentostatin for those at high risk of morbidity due to severe myelosuppression. Standard dosing of pentostatin is 4 mg/m^2 every 14 days until CR is achieved, followed by consolidation, although the minimum effective dose has never been truly defined. Two earlier studies of pentostatin in HCL included patients who received initial dosing of 2-3 mg/m^2 for renal dysfunction or poor performance status,[10,11] and showed that immunosuppression and myelosuppression appeared to be dose related. We report the recent outcomes of 7 patients with neutropenia, active infection, or increased bleeding risk who initially received reduced doses of pentostatin during treatment for HCL. The Ohio State University Institutional Review Board approved this study that reviews the medical records of these patients. From 2006-2011, 7 patients with classic HCL who required therapy and were considered to be at high risk of morbidity or mortality due to myelosuppression were treated with reduced initial doses of pentostatin. No patients had previously received therapy with a PNA, though one patient was unsuccessfully treated with rituximab prior to referral to our institution. Three patients received interferon prior to treatment with pentostatin. All patients received at least one dose of pentostatin administered at 2 mg/m^2 at the initiation of therapy, completed a course of 12 doses of therapy with the goal of using standard doses as soon as possible, and were evaluable for response. Every effort was made to increase the dose of subsequent courses of pentostatin to standard therapeutic levels in order to maximize therapeutic potential. In some cases, treatment was delayed because of myelosuppression. Delays were typically of one to two weeks to permit recovery of granulocytes to pre-treatment levels. All patients received PJP and HSV/VZV prophylaxis. Three patients received filgrastim for growth factor support to enhance neutrophil recovery. Responses were based on standard hematologic response criteria for HCL and were classified as either CR or partial remission (PR). Hematologic CR was defined according to National Comprehensive Cancer Center Network (NCCN; www.nccn.org) guidelines as hemoglobin (Hgb) more than 12 g/dL, absolute neutrophil count (ANC) more than 1.5 x 10^9/L, and platelets more than 100 x 10^9/L. Morphological CR required the absence of identifiable hairy cells by morphology on a standard bone marrow preparation. Overall, a CR required both a hematologic CR and absence of identifiable hairy cells by morphology in the bone marrow. Minimal residual disease (MRD) was defined as the presence of cells typical for HCL by flow cytometry or immunohistochemical stains in the absence of identifiable lymphoid aggregates on the hematoxylin and eosin stained sections. Seven patients were treated with an initial dose reduction of pentostatin followed by escalation. Six of the 7 patients presented with neutropenia (Table 1); 2 had an ANC less than 0.5 x 10^9/L at diagnosis, and the other 4 had an ANC less than 1 x 10^9/L. Three had active infections, including appendicitis, pneumonia, and dental abscess with concomitant sinusitis; these patients received intravenous antibiotics until clinical stabilization and all ultimately achieved resolution of infection with antibiotics. Pentostatin was initiated at the discretion of the treating physician following clinical stabilization and infection control. No patient experienced worsening of infection after initiation of treatment. With respect to patients at risk of bleeding, one had a history of deep vein thrombosis (DVT), pulmonary embolism, and positive lupus anticoagulant on long-term warfarin. Another patient had a history of DVT, coronary artery thrombosis, and heterozygous Factor V Leiden mutation on long-term warfarin. Five patients achieved a hematologic CR, with a median time to hematologic CR of 124 days. One patient had a morphological CR documented by bone marrow biopsy; however, due to a platelet count of 97 x 10^9/L, this patient did not achieve a hematologic CR and was then lost to follow up. Finally, one patient achieved a hematologic CR but had MRD on a bone marrow biopsy performed one month after the completion of therapy. CR without evidence of MRD was obtained with as little as 36 mg/m^2 of total pentostatin in one patient over the entire course of therapy. Responses were maintained for a median follow up of 34 months (range 14-83 months). No patient relapsed during this observation period. Of the patients who received filgrastim, all achieved a hematologic CR. For patients on therapeutic anticoagulation, warfarin was held when the platelet count was less than 50 x 10^9/L. No patients experienced hemorrhage or recurrence of thromboembolic disease. Dosing of pentostatin was increased to the standard 4 mg/m^2 as soon as hematologic parameters improved and infections resolved, at the discretion of the treating physician. All patients received 2-6 reduced doses of pentostatin before clinical improvement was observed, and then the dose was escalated to the standard level and administered once every 14 days. Some cycles were delayed one week if worsening neutropenia occurred. Patients were treated until a CR was achieved, followed by two doses of consolidation with pentostatin once every 14 days. The average cumulative dose of pentostatin administered over the entire course of initial therapy plus consolidation was 48 mg/m^2. As shown in this small cohort of patients, infections can be present at the time of diagnosis or early in the course of treatment and are sometimes atypical or severe.[7,8] In several series involving an overall total of 649 patients treated with pentostatin and 1444 patients treated with cladribine, an average of 25%-32% had a documented infection and/or neutropenic fever after the initiation of therapy.[8] The increased risk of infection is likely due to a combination of granulocytopenia, monocytopenia, functional deficiencies in cellular-based immunity, and the tendency of therapy to further compromise blood counts.[7,8,12] In one long-term follow up of 349 patients receiving standard doses of cladribine, 87% developed grade 3-4 neutropenia and 42% suffered a

febrile episode with initiation of therapy.[13] This is consistent with the two most recently reported prospective, randomized controlled trials of PNA therapy in HCL. These two studies were designed to investigate daily versus weekly administration of standard doses of cladribine for initial therapy, and were of similar design.[14,15] Patients were enrolled from 1998-2005, and thus these studies are more likely to reflect modern supportive care practices compared to long-term follow up studies. In the first study, Robak et al. reported a 52%-58% incidence of ANC less than 0.5 x 10^9/L, out of 116 total patients after initiation of therapy. There was an 18%-26% incidence of neutropenic fever/infection. Forty-seven percent of treated patients had progression of neutropenia. Out of the 116 patients, there were 3 early deaths reported related to infections. In the second study, Zenhausern et al. reported an incidence of grade 3 or 4 infection of 18%-22% out of 100 total patients. There was a 34%-38% incidence of hospitalization. Patients were hospitalized for a median of 12 days. There were 2 deaths reported during treatment. Based on current literature, NCCN guidelines now recommend avoidance of cladribine in patients with active infection. For select high-risk patients, an initial dose reduction of pentostatin with titration to standard dosing as hematologic recovery occurs is safe and does not appear to compromise response to therapy. If patients do not show evidence of improvement in hematologic parameters following the initial reduced doses of therapy, subsequent courses of standard dose pentostatin (4 mg/m^2) are utilized in an effort to achieve the desired response. While the ultimate goal of achieving a CR is best served by treating the patient with standard doses of pentostatin, the initial therapy in this disease is often complicated by the severely compromised bone marrow function. Thus, achieving lower infection and hospitalization rates in these patients is of great importance. In patients with severely compromised hematologic parameters or other contraindications to profound or prolonged myelosuppression, initial dose reduction of pentostatin, with subsequent administration of standard doses, may improve the overall safety of treatment. To minimize the risk of infection and morbidity, further investigation into the minimum effective dose of both pentostatin and cladribine in HCL is warranted, as is exploration of new agents that are either less myelosuppressive or immunosuppressive.

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Table 1. Patients' characteristics.

Patient	Gender	Age*	Hemoglobin†	ANC‡ (x10^9/L)	Filgrastim support
1	M	64	14.6 g/dL	0.8	No
2	M	70	10.9 g/dL	0.3	Yes
3	M	55	13.4 g/dL	0.7	No
4	M	48	13.1 g/dL	1.3	No
5	F	49	4.5 g/dL	0.36	No
6	M	58	10.1 g/dL	0.7	Yes
7	F	39	5.5 g/dL	0.61	Yes

	Platelets¶ (x10^9/L)	Spleen Size‖	BM%**	Classic HCL††	Total pentostatin‡‡
1	79		0.8	Y	50 mg/m^2
2	104	17.1 cm	0.5	Y	50 mg/m^2
3	89	14 cm	0.5	Y	45 mg/m^2
4	76	17.8 cm	0.5	Y	47 mg/m^2
5	13	13.7 cm	0.8	Y	46 mg/m^2
6	40	24.4 cm	0.95	Y	36 mg/m^2
7	50	19.7 cm	0.8	Y	60 mg/m^2

	Prior treatment	Comorbidities§§	Hematologic response‖‖	Morphologic response¶¶	Relapse***
1	Rituximab	neutropenia	CR	CR	No
2	Interferon	neutropenia	CR	CR	No
3	No	neutropenia, thrombocytopenia, anticoagulation	CR	CR	No
4	No	thrombocytopenia, anticoagulation	CR	CR	No
5	No	neutropenia, active infection	CR	CR	No
6	Interferon	neutropenia, active infection	PR	CR	No
7	Interferon	neutropenia, active infection	CR	PR	No

**In years. †At diagnosis. ‡At diagnosis. §At diagnosis. ‖At diagnosis. ¶At diagnosis. **Percentage of bone marrow comprised of hairy cells. ††Usual phenotype. ‡‡Total cumulative dose over course of treatment. §§Patient comorbidities present at start of therapy. ‖‖Defined as peripheral Hgb >12 g/dL, ANC > 1.5x10^9/L, platelet >100 x10^9/L. ¶¶Defined as absence of identifiable hairy cells on review of bone marrow sample by pathologist. ***Defined as recurrence of symptoms or peripheral cytopenias.*

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