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Hairy Cell Leukemia: An Elusive but Treatable Disease

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Key Words. Hairy cell leukemia • Chronic leukemia • Aplastic anemia • Cladribine • Pentostatin

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe what is known about the biology and pathogenesis of HCL.
2. Discuss the clinical presentation and differential diagnosis of HCL.
3. Identify important diagnostic markers for HCL.
4. Discuss treatment options and response and adverse effects to therapy for HCL.

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ABSTRACT

Hairy cell leukemia (HCL) is a unique chronic lymphoproliferative disorder that can mimic or coexist with other clonal hematologic disorders and has been associated with autoimmune disorders. It should be entertained as an alternative diagnosis in patients with cytopenias being assigned the diagnosis of aplastic anemia, hypoplastic myelodysplastic syndrome, atypical chronic lymphocytic leukemia, B-prolymphocytic leukemia, or idiopathic myelofibrosis. Causative etiology or molecular defects remain unclear, although nonspecific chromosomal and molecular changes have been described. The typical presentation is that of a middle-aged man with an incidental finding of pancytopenia, splenomegaly, and inaspirable bone marrow. Treatment with a purine analogue, cladribine or pentostatin, results in extremely high, durable, overall, and complete response rates, although resistance and relapses do occur. A variant subtype exists and is frequently associated with a poor response. Because of its simplified dosing schedule, cladribine is commonly used as the initial therapy. Treatment of relapsed HCL is dictated by the duration of the preceding remission. Relapsed disease after a prolonged remission can often be successfully retreated with the same initial agent. Resistance in typical HCL is treated with the alternate purine analogue. New agents, such as rituximab and BL22, are actively being evaluated and show promising results in both HCL subtypes. This article uses two patients diagnosed with aplastic anemia and recently seen in consultation at our institution as a springboard to discuss the biology, pathogenesis, clinical presentation, diagnostic evaluation, and treatment options of HCL. *The Oncologist* 2006;11:780–789

INTRODUCTION

Hairy cell leukemia (HCL) is a unique chronic lymphoproliferative disorder characterized by cytoplasmic villous (hairy) projections and diffuse infiltration of the bone marrow and spleen [1], leading to peripheral cytopenia and splenomegaly. Circulating hairy cells may be present.

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Historically, HCL was first described in 1920 and called by various names, including leukemic reticuloendotheliosis, histiocytic leukemia, malignant reticulosis, and lymphoid myelofibrosis. It was further characterized in 1958 by Bouroncle and colleagues [2] as a unique entity with distinct histopathologic and clinical characteristics. Based on the microscopic observation of their hair-like cytoplasmic projections, Schrek and Donnelly [3] coined the term hairy cell in 1966. HCL makes up 2% of all leukemias, with 600 new cases in the U.S. per year [4]. The median age at diagnosis is 55 years, and there is 5:1 male preponderance [5, 6]. A variant form (HCL-V), which differs both morphologically and in clinical behavior, makes up 10%–20% of cases [4, 7 ,8]. Among the chronic leukemias, HCL is frequently misdiagnosed but interestingly represents one of the most successfully treated leukemias when the appropriate diagnosis is made. Thus, recognizing its features and considering it in the differential diagnosis under the right clinical setting is crucial. This review introduces two recent consultation cases seen at our institution and uses them as a springboard to discuss the biology, pathogenesis, clinical presentation, diagnostic evaluation, and treatment options of HCL.

Case Presentation

Patient A is a 46-year-old female attorney with a history of stable psoriasis who was incidentally found to have pancytopenia during an annual physical examination 4 years earlier, with a WBC of 1,700/µl, hemoglobin level of 11.0 g/dl, and platelet count of 109,000/µl. She had mild easy fatigability and an incident of opportunistic pox infection of her left finger several months prior to discovering her pancytopenia. Her social history is important for owning and operating a farm, where she also lives. As a result, she had exposure to insecticides, fuel, kerosene, and other farm chemicals. Initial physical examination was unremarkable. During the intervening 4 years, she sought care in both a private and an academic medical center, where extensive laboratory evaluation was apparently normal. Her initial bone marrow biopsy and aspirate demonstrated 30%–40% cellularity and a decreased myeloid to erythroid (M:E) ratio but appropriate maturation without a clonal population. A second bone marrow biopsy and aspirate 2 years later was difficult to aspirate and had 30% cellularity and a decreased M:E ratio but appropriate maturation and no detectable clonal population. There were lymphocyte aggregates in the marrow that were not further defined. Flow cytometry and cytogenetics were not available at the time of our consult. Paroxysmal nocturnal hemoglobinuria (PNH) tests were negative on the two bone marrow evaluations. A diagnosis of aplastic anemia was rendered, with a plan to start immunosuppressive therapy when she progressed to severe aplastic anemia. Over time, her peripheral count decreased but without infectious complications or transfusion requirement.

Two months prior to consulting us, she had been diagnosed and surgically treated for stage III right invasive breast cancer. The consult question was how to manage her aplastic anemia in order to safely provide the needed adjuvant chemotherapy and radiation. On examination, she had splenomegaly, which was confirmed on computed tomography (CT) scan, but no lymphadenopathy. Peripheral blood flow cytometry showed 5% abnormal lymphocytes consistent with HCL, based on immunophenotypic findings of positive CD19, CD20, CD22, CD25, CD103, and κ surface immunoglobulin (SIg) and negative CD10 and CD5. Repeat bone marrow biopsy and aspirate showed 50% cellularity with 40% hairy cell involvement.

Patient B was 65 years old in 2003 when he also was incidentally found to have a WBC of 2,000/µl, mild anemia with a hemoglobin level of 12.7 g/dl (normal range, 13.7–17.3), and a normal platelet count during an annual primary care evaluation. He had no antecedent infections and no other significant past medical history. He is an army veteran who had served in Vietnam with an apparent exposure to Agent Orange. His physical examination was normal. He was referred to hematology, where a bone marrow aspirate and biopsy showed 5%–10% cellularity with no spicules on the aspirate. Flow cytometry and morphology were unremarkable, and fibrosis was absent. Cytogenetics showed a normal karyotype. An abdominal CT scan was negative for splenomegaly or lymphadenopathy. PNH, B_{12}, and other laboratory data were negative. He was subsequently diagnosed with aplastic anemia and, as his counts declined, he began treatment with combined antithymocyte globulin (ATG), cyclosporine, and steroids without response. We saw him in consultation for a second opinion. His physical examination and other laboratory evaluation were unremarkable. His bone marrow biopsy and aspirate showed 30% cellularity with 70% HCL involvement. There was mild dyserythropoiesis noted. Flow cytometric analysis of the marrow sample was positive for pan B-cell antigens and HCL-specific immunophenotype—CD 103, CD11c, and CD25.

Biology and Pathogenesis

An in-depth review of the biology and pathogenesis of HCL is beyond the scope of this article. Nonetheless, hairy cells are distinct, activated, clonal proliferating B cells that are arrested at a late stage of maturation [9–11]. HCL shows features of activated cells, with strong expression of light-chain-restricted SIg, expression of multiple

clonally related heavy-chain isotypes, *VH* gene mutation, and expression of mature B-cell CD markers [12, 13]. In contrast to the suggestion by some investigators that hairy cells originate from the germinal center or naïve B cells, gene-expression profile data by Basso et al. [9] strongly suggest that hairy cells arise or are related to memory B cells. In addition, that group identified a set of 89 genes that are specifically overexpressed or downregulated in patients with HCL and might account for HCL propagation as well as its distinct functional features such as the hairy morphology, bone marrow fibrosis, and its response to cytokine treatment [10].

Despite these advances, the actual oncogenic events driving its development remain unclear. Numerous but inconsistent chromosomal and genetic abnormalities have been reported in HCL and include trisomy 5, trisomy 12, and deletion or mutation of *p53* [12–14]. In their series, Vallianatou and colleagues [8] reported loss or deletion of *p53* in 75% and 100% of patients with typical and variant HCL, respectively, while trisomy 12 was found in about 8% of each hairy cell subtype. *bcl-6* mutations occur in 25% of HCL cases, while overexpression of cyclin D1 (BCL-1 or PRAD-1) has been reported [15]. Interestingly, cyclin D1 expression in HCL is not associated with 11:14 translocation, as is usually seen in mantle cell lymphoma [13]. Furthermore, angiogenesis and strong expression of cytokines, adhesion molecules, and growth factors such as tumor necrosis factor alpha or interleukin-2 (IL-2), IL-4, IL-13, G-CSF, or GM-CSF have been described, all of which may contribute to the pathogenesis of HCL through promotion of cell proliferation or inhibition of apoptosis [6, 13, 16–19]. In addition, there is suggestion that activating viruses such as human T lymphotropic virus (HTLV)-2 may play a role, especially in the case of HCL-V [20].

Clinical Manifestation

The typical presentation of HCL is that of a middle-aged man with pancytopenia, splenomegaly, and inaspirable bone marrow resulting from myelofibrosis (Table 1). However, there are salient clinical distinctions between classic HCL and HCL-V (Table 2). Monocytopenia is a frequent feature, and few patients, especially those with HCL-V, have circulating hairy cells. It is thought that the 5:1 male predominance seen with HCL may be related to the higher occupational exposure of men to ionizing radiation and benzene and other solvents [5]. Pancytopenia is seen in about 50%–70% of patients, while 30%–50% show varying degrees and combinations of cytopenias [13]. Cytopenias are often an incidental finding and are usually seen in asymptomatic patients. Splenomegaly is present in about 80% of patients [21] but apparently is much less common in HCL-V (Table 2). When symptoms are present, they are often the result of cytopenic complications such as infection, fatigue, or bleeding. Splenomegaly may cause abdominal pain and early satiety.

Table 1. Clinical diagnostic features of hairy cell leukemia

Pancytopenia
Monocytopenia
Splenomegaly
Circulating hairy cells
Bone marrow reticulin-fibrosis/myelofibrosis
Inaspirable bone marrow

There are numerous case reports of atypical manifestations of HCL and coexistence with other B-lymphoid malignancies. For example, HCL may atypically present with cutaneous, visceral, bone, pleural, and meningeal involvement [22–29]. Polyclonal and monoclonal gammopathy have been reported in 3%–20% of patients and may be related to an associated plasma cell dyscrasia, lymphoma, or autoimmune disorder [30–32]. For reasons not yet elucidated, HCL may be associated with a variety of autoimmune disorders, most commonly vasculitis [25, 33–39]. The convergent factors of rare disease, variant type, unusual manifestations, and coexistence with other malignancies often result in delayed or wrong diagnosis. When HCL is misdiagnosed, aplastic anemia is a commonly assigned diagnosis. Thus it is crucial to consider the differential diagnosis carefully (Table 3). Fortunately, recent diagnostic advances, such as immunohistochemical (IHC) staining and immunophenotypic analysis, have now made such clinical discrimination easier than was the case in the past. It is particularly important to differentiate among HCL, HCL-V, splenic lymphoma with villous lymphocytes (SLVL), and B-prolymphocytic leukemia (B-PLL).

Diagnostic Evaluation

Traditionally, diagnosis was based on a morphologic evaluation of the bone marrow and peripheral blood, with confirmatory evidence provided by cytochemical staining of hairy cells for tartrate-resistant acid phosphatase (TRAP). TRAP testing has, for the most part, been relegated to history. Current diagnostic laboratory methods rely less on TRAP, which is laborious and cannot be performed effectively on paraffin-embedded tissues sections. Instead, IHC staining and the immunophenotypic pattern on flow cytometry, combined with the constellation of cytopenias, splenomegaly, and morphology, are used with great diagnostic accuracy. Because the bone marrow, the spleen, and, less often, the peripheral blood are the major sites involved

Table 2. Clinical distinction between hairy cell leukemia (HCL) and HCL variant (HCL-V)

Classic HCL	HCL-V
Patients are younger	Patients are older
Cytopenia with monocytopenia	Leukocytosis without monocytopenia
Splenomegaly often present	Splenomegaly less common
Myelofibrosis often present, leading to inaspirable bone marrow	Bone marrow usually hypercellular with mild myelofibrosis
Resembles small B-lymphoid cells with oval nuclei and abundant cytoplasm with hairy projections	Resembles prolymphocytes
Associated with autoimmune diseases	Associated with autoimmune diseases
Responds well to standard therapy	Responds poorly to standard therapy

Table 3. Important differential diagnosis for hairy cell leukemia (HCL)

HCL variant
Aplastic anemia
Splenic lymphoma with villous lymphocytes
Large granulocytic leukemia
B-prolymphocytic leukemia
Hypoplastic myelodysplastic syndrome
Paroxysmal nocturnal hemoglobinuria
Atypical chronic lymphocytic leukemia
Hypersplenism
Idiopathic myelofibrosis

in HCL, diagnostic evaluation requires bone marrow aspirate/biopsy, imaging studies to assess for splenomegaly if it is not palpable on physical examination, and the review of a peripheral blood count and smear. Among these, the bone marrow biopsy and aspirate represents the best test for an accurate diagnosis [40].

Morphology

Classic HCL consists of small to medium-sized lymphocytes with an oval or indented nucleus, loose chromatin, and inconspicuous nucleoli [40]. There is abundant cytoplasm with hairy projections. HCL-V resembles a prolymphocyte with round or oval nucleus, which is occasionally bilobed and has moderately basophilic villous cytoplasm [40].

Immunophenotype

No single marker is diagnostic when differentiating HCL from other B-cell leukemias. Instead, laboratory diagnosis is best made by integrating morphologic features and the strong expression of pan B-cell markers and HCL-specific markers (Table 4) [6, 40, 42–44]. Recently, a scoring system of immunophenotypic markers has been proposed as a way to further improve phenotypic diagnostic accuracy [41]. Yet, despite this effort, a proportion of HCL cases may remain undiagnosed by immunophenotype alone [10].

IHC Staining

Unlike the tedious enzymatic analysis for TRAP, which is poorly reproducible and could not be performed on paraffin-embedded tissues, growing lists of simplified IHC stains have been introduced. Two commonly used IHC stains are HC2 and 9C5. IHC has the advantage of being easy to perform on both peripheral blood and paraffin-embedded tissues, making it useful in monitoring minimal residual disease (MRD) [45,46]. The sensitivity and specificity vary among tissue type and for 9C5 appear to be better when done on paraffinized tissues [46]. Ongoing advances such as gene profiling are identifying new targets for immunostaining. One such marker is annexin A1 (ANXA1), which is one of the genes upregulated in HCL. In an immunostaining study of 500 varied B-cells tumors, ANXA1 clearly discriminated among typical HCL, HCL-V, and SLVL with 100% sensitivity and specificity [10].

Treatment

Despite its indolent course, most patients require treatment at some point. There is no specific guideline for initiating therapy. Generally, worsening cytopenias, recurrent cytopenic complications, progressive visceral involvement, prominent unusual manifestations such as bulky adenopathy, and significant autoimmune disease constitute reasons to start treatment. Historically, therapy for HCL has evolved. Prior to the advent of nucleoside analogues, which are currently the standard initial treatment, interferon and splenectomy were the most effective therapies. While complete remission was very rare with splenectomy alone, it improved cytopenias and provided relief for symptomatic splenomegaly, but long-term survival was not demonstrated in any randomized trial [47]. Today, splenectomy is rarely used and only in patients who are not candidates for or are resistant to current standard therapies.

Interferon-α was used in HCL with great effectiveness in the early 1980s. It was typically advocated for patients who had failed splenectomy [48]. The usual dose is 3×10^6 IU s.c. daily until remission. Responders were subsequently

Table 4. Phenotypic differential diagnosis of hairy cell leukemia

	HCL	HCL-V	B-PLL	SLVL	Typical CLL
SIg	S+	+	S+	S+	W+
B-cell antigens					
CD19	+	+	+		W+
CD20	+	+	+	+	W+
CD22	+	+	+	+	W+
CD79a	+	?	+	+	+
CD79b	–	–/+	+	+	–
CD5	–	–	+/–	–	+
CD10	–/+	–	?	–	–
CD23	–	–	–	–/+	+
CD11c	S+	+	+/–	+	W+
CD25	S+	–	–	+/–	–
CD103	S+	–/+	–	–	–
FMC7	+	+	+	+	–/+
HC2	S+	–/+	–	+/–	–
TRAP	+	–/+	–	+/–	–

Abbreviations: +, positive; +/–, usually positive but can be negative; –, negative; –/+, usually negative but can be positive; B-PLL, B-prolymphocytic leukemia; HCL, hairy cell leukemia; HCL-V, hairy cell leukemia variant; S+, strong positive; SIg, surface immunoglobulin; SLVL, splenic lymphoma with villous lymphocytes; TRAP, tartrate-resistant acid phosphatase; W+, weak positive.

treated with a long maintenance of 18–24 months, given three times per week. One of the first publications was on seven patients reported by Quesada et al. [49]. The overall response rate was 100%, with a complete response (CR) rate only 43.6%, which was maintained for a short duration of 6–10 months. This finding has been corroborated by other investigators. A large, multicenter, prospective trial of 104 HCL patients lead by the Italian Cooperative Group of Hairy Cell Leukemia (ICGHCL) showed an overall response rate of 93%, with a CR rate of 13% [50]. Several mechanisms have been postulated for the rapid activity of interferon in HCL. Lepe-Zuniga et al. [51] presented in vitro data that showed a direct relationship between disease activity and constitutional ability to produce interferon-α, implying that deficiency of endogenous production of interferon-α may be implicated in the induction and sustenance of remission in patients with HCL. Similarly, relapses may be partly associated with failure to fully restore endogenous interferon-α production after treatment. Despite its salutary effect, clinical use of interferon-α was limited by the small number of complete responses and the side effects associated with prolonged maintenance in responders [52, 53].

The purine analogues cladribine (2-chlorodeoxyadenosine) and pentostatin (2′-deoxycoformycin) came into clinical use in the mid-1980s and are currently the cornerstones in the initial treatment of HCL [53, 54]. Cladribine is given at a dose of 0.1 mg/kg per day as a continuous i.v. infusion for 7 days, or more recently, the same total dose at 0.14 mg/kg is given as a 2-hour infusion over 5 consecutive days, while pentostatin is administered at 4 mg/m^2 every 2 weeks until maximum response [4]. With the 7-day cladribine continuous infusion, the overall response rate is in the range 95%–100%, with a CR rate of 82%–91% [55, 56]. The 5-day cladribine infusion obviates the need for a portable pump required with the 7-day infusion, which has been associated with underdosing errors and poor clinical response [57]. In a prospective, randomized trial of 118 patients, Robak et al. [58] compared two methods of cladribine administration. One group was treated with cladribine at a dose of 0.12 mg/kg per day in a 2-hour i.v. infusion for five consecutive days while the second group received the same dose once a week for 6 weeks. That study found comparable overall and complete response rates in the two groups. Toxicities were similar, though thrombocytopenia was worse with the 7-day continuous infusion.

Further simplification of the cladribine administration schedule to a single weekly dose for 5 weeks has been proposed. Zinzani and colleagues [59] compared this schedule with the 5-consecutive-days schedule in a series of 37 patients followed over 122 months (range, 54–156) and reported similar response rates and CR rates of 100% and 79%, respectively. Relapse rates were not statistically different, but fewer cases of grade 3–4 neutropenia were reported with the weekly dosing schedule, suggesting that this may be

a safer option for HCL patients presenting with neutropenia. Although both cladribine and pentostatin are efficacious, the simplicity in dosing of cladribine coupled with its favorable toxicity profile, high percentage of complete remissions, and low incidence of relapse has earned it the first choice of treatment for HCL. Cladribine, like pentostatin, induces apoptosis by disrupting cellular metabolism through inhibition of DNA synthesis in both resting and dividing cells [54, 55, 60].

In general, cladribine is well tolerated, but further hematological deterioration in the early stage of treatment as well as prolonged lymphopenia of the CD4 subset may occur following treatment and lead to infectious complications [61, 62]. Cladribine is commonly chosen as the initial treatment. Pentostatin is an alternative choice, although it is more frequently used after relapse following cladribine or in cladribine-resistant disease. Long-term follow-up studies demonstrate that, while both agents result in a high complete remission rate and overall survival rate, cure is not achieved with either agent. This was illustrated in a recent publication by Else et al. [63] in which 219 patients with HCL were followed for 12.5 years (range, 1.0–34.6 years) from their initial diagnosis. One hundred eighty-five patients received pentostatin and 34 patients were given cladribine. The overall and complete response rates for cladribine were 100% and 82%, respectively, versus 96% and 81%, respectively, with pentostatin. The median disease-free survival (DFS) times for cladribine and pentostatin were 11 years and 15 years, respectively. The 5-year and 10-year relapse rates were 33% and 48%, respectively, in the cladribine-treated group, versus 24% and 42%, respectively, with pentostatin. The overall 10-year survival rates for cladribine and pentostatin were 100% and 96%, respectively, but neither agent achieved a plateau in DFS.

Drug Resistance, Disease Relapse, and Monitoring MRD

Despite revolutionizing the treatment of HCL, resistance and relapses occur with purine analogues. Resistance is a major problem with HCL-V in particular [44]. A pooled analysis of four clinical trials [64–67] with more than 152 patients that included 14 HCL-V patients treated with either cladribine or pentostatin demonstrated a lack of response in 78.6% and partial response in 22.4% of patients. There were no CRs. Fortunately, despite this resistance, most patients with HCL-V appear to have a benign chronic course of more than 4 years before disease progression [44]. Relapses in HCL are in the range of 20%–30% at 5 years and up to 48% at 10 years [59, 63, 68, 69]. This level of relapse raises several questions, including the feasibility of detecting MRD, whether MRD detection can predict relapse, and, finally, whether treating detected cases will improve survival.

While MRD can be detected by flow cytometry and IHC methods, the ability to predict relapse has been mixed [47, 61, 70–72]. For patients who achieve a CR after therapy, the rate of MRD does not appear to differ between those treated with cladribine and pentostatin [72]. Moreover, the rates of MRD detection by these methods are only modest. Bengio et al. [70] reported detection rates of 64% and 46% with flow cytometry and IHC detection methods, respectively, and neither method predicted hematological relapse. To our knowledge, there is no randomized study showing that treating patients with MRD offers any survival advantage when compared with watchful waiting for clinical disease recurrence before retreatment.

When clinical relapse occurs in typical HCL, the therapeutic options include retreatment with the same purine analogue as the initial treatment or employing alternate agents. Although the purine analogues, including the newer fludarabine, share similar chemical structures and mechanisms of action, there is surprisingly little or no crossresistance among them [60, 73, 74]. In a study of 144 treated patients, Piro and coworkers [74] identified five patients who were either resistant to or intolerant of pentostatin. Retreatment of these patients with cladribine resulted in a 100% overall response rate with an 80% complete remission rate. Similarly, in a large review of 210 patients previously treated with either pentostatin or cladribine, Dearden et al. [73] identified 21 patients with relapsed or resistant disease. Retreatment of these patients with the other agent resulted in markedly high second remissions. O'Brien and Keating have suggested retreatment with the same first-line agent if the patient has had more than 3 years of remission before relapse and choosing an alternative agent if remission has been <3 years. To improve on the remarkable therapeutic successes in HCL over the past 20 years, new agents are actively being evaluated (Table 5). These include the purine analogues fludarabine, clofarabine, and nelarabine as well as monoclonal antibodies and immunoconjugates. Rituximab has been shown to achieve a CR rate of 13%–53% in relapsed or refractory HCL and appears to be active with HCL-V, as well [75, 76]. In a recent study by Ravandi et al. [77], 11 newly diagnosed and two refractory HCL patients were treated with daily cladribine at 5.6 mg/m^2 i.v. over 2 hours for 5 days, followed by eight doses of weekly rituximab at 375 mg/m^2. While all 13 patients achieved a CR and 92% had eradication of MRD, it is not known, given the small size of the study and short follow-up, if this strategy offers an additional therapeutic advantage over cladribine alone in these cohorts of patients. In a phase I clinical trial of BL22 that included HCL-V patients, the overall response rate was 79%, with a CR rate of 61% [78]. The search for

Table 5. New and experimental agents for the treatment of hairy cell leukemia

Agent	Class
Fludarabine, clofarabine, nelarabine, immucillin-H	Purine analogues
Rituximab	CD20 monoclonal antibody
Thalidomide	Antiangiogenesis/immunomodulatory
BL22	Anti-CD22 *Pseudomonas* exotoxin A immunoconjugate

newer agents is especially needed for the 10%–20% of HCL patients with the variant phenotype, who currently have limited therapeutic options.

Adverse Effects of Therapy

Hematologic, neurologic, and immunologic dysfunction are the major toxicities seen with the purine analogues [60]. However, concerns about the development of second malignancies, usually occurring many years after initial treatment with interferon and nucleoside analogues, have been raised [47, 48, 79–82]. Yet it remains unclear whether this phenomenon is a result of an inherent tendency of HCL patients to develop second malignancies or is a result of treatment. The incidence of second malignancies is in the range of 8%–21.3% [81, 83]. In a retrospective review of 1,022 patients treated initially with either best supportive care, single-agent chemotherapy, splenectomy, interferon, or purine analogues, the ICGHCL found a 5.3% incidence of second malignancies, excluding skin cancer [84]. Of the 54 patients with second malignancies, only six patients had previously been treated with a purine analogue. The cumulative risks for the development of a second cancer were 5%, 10%, and 14% at 5, 10, and 15 years, respectively, but the overall incidence of second malignancies was not significantly higher than the expected standardized incidence ratio of 1.01 (95% confidence interval [CI], 0.74–1.33). Nonetheless, the standardized incidence ratio of non-Hodgkin's lymphoma in the entire cohort was higher at 5.3 (95% CI, 1.9–11.5). This and other published data seem to support the notion that these second malignancies are not related to genetic predisposition of HCL or to treatment effect [83]. Despite this observation, close cancer monitoring and prevention for these patients is strongly advised.

Follow-Up on Presented Patient Cases

The two patients introduced in this review have classic HCL and clinically represent the usual diagnostic problems that clinicians face with HCL and which often result in unnecessary treatments. Both cases were initially misdiagnosed as aplastic anemia, with patient B going on to receive prolonged immunosuppressive therapy but, as expected, without response. When HCL was finally diagnosed many years after their initial presentation, both patients were treated with cladribine at 0.14 mg/kg i.v. for 5 days. Both tolerated the treatment fairly well except for an episode of neutropenic fever in patient A and moderate malaise in patient B. Patient A achieved a CR and is currently completing adjuvant chemotherapy for her stage III breast cancer. Patient B did not respond but remained fairly asymptomatic despite persistent cytopenias. His lack of hematological response may be a result of his previous extensive treatment or because of cladribine resistance. For now, he will be watched carefully for a few more months before retreatment, although there is the concern of further hematological deterioration if his counts are not fully recovered before additional therapy.

Summary and Conclusions

HCL is a unique chronic lymphoproliferative disorder that can mimic or coexist with other clonal hematologic disorders. It can present with pancytopenia or variable cytopenias, associated with splenomegaly and inaspirable bone marrow resulting from fibrosis. Unusual manifestations can be seen. HCL should be entertained as an alternative diagnosis in patients being considered for the diagnosis of aplastic anemia, hypoplastic myelodysplastic syndrome, atypical chronic lymphocytic leukemia, B-PLL, and idiopathic myelofibrosis. HCL-V makes up about 10% of cases. Despite advances in cell biology and molecular genetics, the etiology and molecular defects underlying HCL have not been fully elucidated. Nonetheless, a high treatment response rate and durable remission are frequently achieved for classic HCL, in contrast to the poor response seen with the variant type. Diagnosis of HCL is based on careful consideration of the differential diagnosis and combining presenting findings with laboratory data. Flow cytometry and IHC now play prominent roles in HCL diagnosis. The purine analogues cladribine and pentostatin are the cornerstone of treatment, with cladribine frequently used because of its simple dosing schedule. Resistance to these agents occurs in a small number of cases, but relapse, albeit after long duration, is much more common. Thus, cure does not currently exist for this disorder. Therapy for relapsed disease relies on retreatment with the same agent if previous remission has been durable or treatment with a previously unused purine analogue in patients with shorter

remissions. New agents are being explored that should hopefully improve on current treatment responses and bring HCL closer to cure.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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