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Treatment of hairy cell leukemia

A Saven and LD Piro

REVIEW ARTICLE

Treatment of Hairy Cell Leukemia

By Alan Saven and Lawrence D. Piro

HAIRY CELL LEUKEMIA (HCL), or leukemic reticuloendotheliosis, is a chronic lymphoproliferative disease that was first described as a distinct clinicopathologic entity by Bouroncle et al in 1958.[1] It is characterized by mononuclear cells of B-lymphocyte origin in the peripheral blood that have prominent cytoplasmic projections staining with tartrate-resistant acid phosphatase[2] and by its typical pattern of infiltration in the bone marrow and spleen.[1] Patients, usually middle-aged men, often present with pancytopenia, severe infections, or splenomegaly. Before the introduction of effective systemic therapy, the median survival was only 53 months.[3]

If the morphologic appearance of HCL does not sufficiently establish it as a curious disorder, its treatment history does. First, in contrast to other hematologic malignancies, splenectomy was shown to almost universally result in amelioration of cytopenias, which is often durable. Subsequently, HCL was the malignant disorder for which the first biologic therapy, α-interferon (α-IFN), was successfully used and eventually approved by the Food and Drug Administration (FDA). More recently the nucleosides have been shown to have dramatic activity in HCL; first, deoxycoformycin treatment resulted in frequent durable complete remissions and subsequently 2-chlorodeoxyadenosine has produced high numbers of durable complete remissions with a single infusion of drug. Hence, since the last review of the treatment of HCL here in 1987,[4] dramatic results have been accomplished in the treatment of this rare disorder.[5-8] Treatment advances, management considerations, and a view of the future will be discussed.

INDICATIONS FOR TREATMENT

Although approximately 10% of patients with HCL will never require therapy, most patients ultimately will need treatment. Those patients who do not require therapy are often older with smaller-sized spleens and fewer circulating hairy cells.[3] For those who require treatment, standard hematologic indications for treatment in HCL have included significant anemia, thrombocytopenia, and neutropenia. The exact levels of these hematologic parameters used for the initiation of treatment have varied among institutions. Ranges have generally been as follows: hemoglobin <8 to 10 g/dL or need for transfusion, platelet count <50,000 to 100,000 cells/μL, and an absolute neutrophil count <500 to 1,000 cells/μL. Now that there are multiple systemic agents capable of inducing durable and complete remissions in a high proportion of patients, it may be desirable, given the risks associated with blood product support, to initiate treatment sooner in these patients. If treatment is initiated at a time when disease-induced and treatment-associated cytopenia would not be likely to decline so low as to require blood product support, transfusion-associated risks would be minimized. This may be especially important for the patient who has never previously received blood products. Leukocytosis with high proportion of hairy cells, repeated life-threatening infections, symptomatic splenomegaly, bulky or painful lymphadenopathy, and vasculitis have been other less common indications for treatment.

SPLENECTOMY

Splenectomy was the first treatment modality to be regularly used in the treatment of HCL. The first report of the successful use of splenectomy was in 1958.[1] Splenectomy is able to achieve rapid peripheral hematologic reconstitution even in the presence of severe cytopenias (hematocrit, <25%; absolute neutrophil count, <500 cells/μL; platelets, <50,000 cells/μL) when used as the first therapeutic modality.[9] In the first large series reported of 26 patients, 42% achieved a complete response and 58% a partial response according to the criteria of Catovsky[10] (complete response: hematocrit >36%, neutrophils >1,000 cells/μL, and platelets >100,000 cells/μL; partial response: this degree of improvement in one or two of these parameters or in all three below these levels). These criteria only included peripheral hematologic parameters and did not include bone marrow examination. Although these criteria are not as rigorous as those currently used, a significant proportion of patients achieve hematologic improvement after splenectomy.

There are conflicting results in the literature concerning the relationship between splenic size and response to splenectomy. In one study the salutatory effects of splenectomy appeared independent of splenic size and survival correlated with response status.[9] Another analysis of 65 patients similarly found no correlation between splenic weight and the response to splenectomy.[11] However, contrary to these studies, there is a retrospective multicenter analysis of 391 patients in which splenic weight was correlated with responsiveness to splenectomy such that patients with smaller-sized spleens appeared not to benefit from splenectomy.[12] Splenic red blood cell (RBC) pooling is much greater in HCL than in other lymphoproliferative disorders with comparable splenomegaly.[13] This likely accounts for the lack of consistent correlation between splenic size and response to splenectomy with maximum sequestration occurring even in smaller spleens.

It would appear overall that splenic size alone is not a major determinant in predicting response to splenectomy. Bone marrow cellularity and the platelet count appear to be independent prognostic variables for response to splenec-

tomy.[14] Platelet response has been associated with the bone marrow hairy cell index; expressed as a number from 0 to 1, this index is the ratio obtained by multiplying the percent of marrow cellularity by the percent of hairy cells in the marrow.[11] The lower the hairy cell index, the greater the platelet response to splenectomy. Accordingly, when splenectomy is used it should be reserved for those patients with significant cytopenia and a bone marrow that shows only patchy involvement with HCL regardless of splenic size.

When the results of splenectomy from numerous studies are combined, the following responses, using peripheral blood criteria only, are obtained: the overall response rate is 98%, of which 40% are complete, 58% are partial, and 2% of patients do not respond (Table 1).

Splenectomy is not without risk in these often ill patients where there is a significant risk of subsequent overwhelming infection in the perioperative period.[9] After splenectomy, one half of patients will require systemic therapy at a median of 8.3 months following splenectomy.[4] Thus, splenectomy is assuming an ever-diminishing role in the management of patients with HCL given the multitude of efficacious systemic therapies.

CHEMOTHERAPY, HORMONAL THERAPY, AND RADIOTHERAPY

Chronic low-dose chlorambucil has been the most rigorously studied[15-17] of the systemically administered chemotherapies. Chlorambucil 4 mg orally daily for 6 months in postsplenectomy patients results in hematologic response in a significant number of patients. However, the neutrophil count does not consistently increase above 1,000 cells/μL, leaving patients at risk for serious infections. There are case reports of the aggressive use of chemotherapy resulting in prolonged complete remissions. These have included high-dose cyclophosphamide and cytarabine,[18] and high-dose methotrexate with leucovorin rescue.[19] Treatment with these regimens usually results in prolonged hospitalization because of severe neutropenia. Rubidazone, an anthracycline antibiotic, also has activity.[20]

There are also isolated reports of remissions after the prolonged administration of androgens (oxymetholone)[21] and lithium.[22] A single patient had a prolonged complete remission after syngeneic bone marrow transplantation.[23] Biologic stimulation with allogeneic mononuclear cell-enriched leukocyte transfusions has been shown to improve bone marrow failure in patients with HCL.[24] Serial intensive leukopheresis resulted in hematologic improvement in a

Table 1. Results of Splenectomy in HCL

Investigator (reference)	No. of Patients	Response (%)*		
		Complete	Partial	None
Mintz and Golomb (9)	24	10	14	0
Jansen (12)	205	81	118	6
Golomb and Vardiman (11)	65	27	38	0
Total	294	118 (40)	170 (58)	6 (2)

*Responses according to peripheral blood criteria only.

Table 2. Agents of Historical Interest Active in HCL

Treatment (reference)
Chemotherapy:
High-dose cyclophosphamide and cytarabine (18)
High-dose methotrexate with leucovorin rescue (15)
Rubidazone (anthracycline) (20)
Chlorambucil (15-17)
Other:
Androgens (21)
Lithium (22)
Syngeneic bone marrow transplantation (23)
Biologic stimulation with allogeneic leukocytes (24)
Leukopheresis (25)

single patient[25] and in a separate study failed to demonstrate sustained benefit.[26]

Although massive lymphadenopathy is uncommon in HCL, a single patient was reported to have dramatic regression of bulky painful lymphadenopathy when treated with low-dose radiation therapy.[27] Additionally, lytic bone lesions associated with diffuse bone marrow infiltration may be successfully managed with local low-dose radiation (1,000 to 3,000 cGy[28]).

Given the dramatic responses now seen with present-day therapies, most of these treatments are largely of historical interest, although each may find an occasional application in an individual patient's management (Table 2).

INTERFERONS

The first report of the successful use of IFN in the management of HCL was in 1984.[29] Seven patients, five of whom had previously undergone splenectomy, received 3 million U of partially purified α (leukocyte) human IFN intramuscularly daily. Three of seven patients achieved a complete remission and four a partial remission. The ability of IFN to eradicate hairy cells from the bone marrow as well as to improve peripheral hematologic parameters necessitated the revision of the criteria used to define a response. New criteria defined a complete remission as the presence of <5% hairy cells in the bone marrow as well as bone marrow granulocytes >35%, hemoglobin ≥ 12 g/dL, absolute neutrophil count ≥ 1,500 cells/μL, and platelet count ≥ 100,000 cells/μL.

Because the initial success was with partially purified α-IFN, there was some question as to what was the active component of the preparation. This was later clarified with the successful introduction of purified α2b-IFN synthesized using recombinant technology (Intron A; Schering Corporation, Kenilworth, NJ) demonstrating similar activity to the partially purified preparation.[30,31] In two studies reported, 9 and 22 patients, respectively, received recombinant α2b-IFN 2 million U/m² subcutaneously three times per week. In both studies there were no initial complete responses but partial responses were common. Most patients had transient myelosuppression during the first weeks of therapy.

Following the success with recombinant α2b-IFN, recombinant α2a-IFN (Roferon; Hoffmann-La Roche, Nutley, NJ) was administered to 30 patients with HCL.[32] α2a- and α2b-IFN differ only in the amino acid residue at position 23;

α2a has a cysteine residue and α2b has an arginine residue at this position. Nine of 30 patients achieved a complete remission and 17 patients a partial remission. Seven of the 30 patients had splenomegaly and were previously untreated. These seven patients had complete resolution of their splenomegaly and had a greater likelihood of achieving a complete remission than those in whom splenectomy had been previously performed who largely achieved partial remissions. Thirty-three percent of patients had a clinical relapse at a median of 6 months after discontinuation of therapy. An additional trial reported 15 more patients who received recombinant α2a-IFN with one complete and 12 partial responses.[33]

In 1986 the results of a multicenter study of 64 patients treated with recombinant α2b-IFN at a dose of 2 million U/m^2 for 12 months was reported.[34] Three patients (5%) achieved a complete response, 45 patients (70%) a partial response, and nine patients (14%) a minor response. Three patients (5%) in the study died, two from intracerebral hemorrhage associated with severe thrombocytopenia and one from pseudomonas sepsis.

After these studies showing benefit with 1 year of IFN therapy, a study was initiated to determine whether there was any additional benefit to greater than 1 year of therapy. Ninety patients were randomized after 12 months of IFN to either no further therapy or an additional 6 months of therapy.[35] A total of 18 patients relapsed, 11 (26%) in the no-further therapy group and seven (18%) in the treated group. This difference did not achieve statistical significance and no patient who relapsed was resistant to retreatment with IFN. The investigators concluded that 12 months of IFN therapy is optimal and minimizes the toxicities of therapy. In a study by Berman et al,[36] even after 24 months of continuous α2a-IFN therapy, the rate of disease progression was 50%, again suggesting no advantage for protracted IFN therapy. This same multicenter study was updated in 1987 with 128 patients,[37] in 1988 with 193 patients,[38] and in 1990 with 195 patients accrued.[39] The updated response and relapse rates achieved were comparable with those previously reported,[34] supporting 12 months of therapy as optimal.

The two prognostic variables most predictive of remission duration with IFN therapy are neutrophil alkaline phosphatase score, known to be elevated in HCL, and the degree of residual bone marrow hairy cells at the completion of therapy.[40] Patients with a neutrophil alkaline phosphatase score less than 30 had the best prognosis while patients with residual bone marrow hairy cell ≥ 30% at the end of IFN therapy had the worst prognosis.

The Cancer and Leukemia Group B has reported on 25 patients with previously untreated HCL who received recombinant α2b-IFN.[41] At the time of their interim analysis, 7 of 25 patients (28%) achieved a complete remission, 6 patients (24%) a partial response, and 12 patients (48%) had disease stabilization.

When the results of four independent groups of investigators are combined, the overall response rate is 89%, of which 9% are complete, 71% partial, and 10% minor (Table 3). Obviously, these results should be interpreted

Table 3. Results of α-IFN in HCL

Investigator (reference)	No. of Patients	Response (%)*			
		Complete	Partial	Minor	None
Quesada et al (32)	30	9	17	4	0
Foon et al (33)	14	1	12	0	1
Rai et al (41)	25	7	6	12	0
Golomb et al (39)	195	7	152	10	26
Total	264	24 (9)	187 (71)	26 (9)	27 (10)

*Responses according to peripheral blood and bone marrow criteria.

cautiously given the different types, doses, routes, and schedules of IFN administration in addition to varying response criteria. Additionally, the α2b-IFN results are from multiple institutions, whereas the α2a-IFN responses are from single institutions.

Recombinant β-serine-IFN (Betaseron; Triton Biosciences, Emoryville, CA) at a dose of 90 million U, intravenously or subcutaneously, three times per week has also been studied in the treatment of HCL.[42,43] Sixty-three percent of patients showed improvement of peripheral blood counts but none met the criteria for a complete response. Erythema and induration at the IFN injection site were the major toxicities. Recombinant IFN-γ showed only trivial activity in five patients.[44] There were no complete or partial responses reported.

α-IFN therapy is associated with various toxic effects. The most common occurrence is a flulike syndrome (98%), the symptoms of which include myalgias, fever, and malaise.[37] This often abates after the first several injections. Cutaneous disorders, principally transient macular-papular rashes that often resolve spontaneously, occur in 48% of patients.[34] Application site disorders are reported to occur in 27% of patients. Gastrointestinal disorders including nausea, vomiting, and anorexia occur in 41% of patients. Central and peripheral nervous system complaints occur in 20% of patients. These symptoms include confusion, migraines, depression, and somnolence. Other less common but reported toxicities include asymptomatic hepatitis, abnormal taste, alopecia,[30] and small joint arthritis.[32] Decreased libido with an increased follicle-stimulating hormone was initially thought to occur in one third of male patients.[45] However, subsequent evaluation in a larger group of patients showed no change in sexual function and that IFN did not produce significant gonadal toxicity.[46] Tachyphylaxis to the more common side effects generally occurs with time, and many symptoms can be alleviated by the use of acetaminophen.

In an attempt to minimize toxicity, 22 patients received low-dose α2b-IFN, 0.2 million U/m^2 for 6 to 12 months.[47] Toxicity was trivial but the overall response rate was only 54% and the quality of responses significantly poorer. Additionally, low-dose IFN has been ineffective in the treatment of relapse after previous IFN therapy, making it a largely ineffective regimen.[48]

The mechanisms by which α-IFN exerts its therapeutic effects in HCL are not well understood. α-IFN does have antiproliferative effects on lymphoma cell lines in vitro[49] and induces differentiation of a leukemic cell line.[50] IFN

stimulates natural killer (NK) cells that are known to be deficient in HCL.[33,51,52] Hairy cells express the Tac antigen, a T-lymphocyte marker,[53] and when shed into the circulation can be measured in serum as serum-soluble interleukin-2 receptor levels that correspond to the leukemic cell burden and correlate with the remission status following IFN therapy.[54]

In an attempt to explain the development of resistance to recombinant IFN, samples from 51 patients with HCL were assayed for anti-α2a-IFN antibodies, neutralizing and non-neutralizing to the antiviral effects of α2a-IFN in vitro.[55] There initially appeared to be an association between neutralizing antibodies and the development of clinical resistance to IFN. When these results were recently updated, 3 of 10 patients with previous neutralizing antibodies had become antibody negative, suggesting that these antibodies are synthesized only transiently and do not fully explain the development of IFN resistance.[56,57] Natural α-IFN, which differs from the recombinant product produced in bacteria by the posttranscriptional glycosylation of the natural product,[8] may be able to overcome recombinant IFN resistance mediated through neutralizing antibodies. The utility of natural IFN in the treatment of anti-recombinant α-IFN antibody-positive patients with chronic myeloid leukemia has been reported.[58]

Thus, α-IFN is effective and highly active in the treatment of HCL. As a single agent, it does not produce a level of complete remissions suggestive of having curative potential in HCL. IFN-related toxicity is common but usually not life-threatening. Twelve months of IFN therapy at a dose of 2 million U/m^2 subcutaneously three times per week is recommended.

NUCLEOSIDES

Adenosine deaminase is the enzyme responsible for the irreversible deamination of adenosine to inosine in the purine salvage pathway.[59,60] Hereditary deficiency of adenosine deaminase is responsible for immunodeficiency in about 30% of patients with severe combined immunodeficiency syndrome.[61] These patients are lymphopenic due to elevated plasma deoxyadenosine levels.[62,63] The nucleosides, deoxycoformycin, 2-chlorodeoxyadenosine, and fludarabine, were developed to mimic the metabolic consequences of adenosine deaminase deficiency to produce therapeutic lymphopenia. Nucleosides have been demonstrated to have marked activity in the treatment of malignant lymphoproliferative disorders, especially HCL.

Deoxycoformycin (DCF). 2'-Deoxycoformycin, a natural product isolated from the culture broth of streptomyces antibioticus, is a tight-binding inhibitor of adenosine deaminase. In 1983 it was first shown to have activity in a single patient with HCL.[64] The rapid attainment of complete remissions in two splenectomized patients using a dose of 5 mg/m^2 for 2 to 3 days, then weekly for 15 to 16 doses, was reported in 1984.[65,66]

Although DCF was introduced into clinical trials at about the same time as IFN, the published trials are fewer with less patients accrued. Twenty-eight patients (20 evaluable) received DCF 5 mg/m^2 on 2 consecutive days every 2 weeks.[67] Seven patients were untreated and 13 had previ-

ously undergone splenectomy or received IFN. Thirteen of 20 patients (65%) achieved a complete response and seven patients (35%) a partial response. In a separate report, two nonsplenectomized patients refractory to α2a-IFN received DCF 4 mg/m^2/wk for 8 weeks as an intravenous bolus with one complete response and one minor response.[68]

In an attempt to reduce the toxicity of DCF, 10 patients received low-dose DCF, 4 mg/m^2 every other week by intravenous bolus, for an average of six courses (range, 4 to 13 courses).[69] Nine of 10 patients (90%) achieved a complete response, median duration of 62 months, and one patient (10%) a minor response. These results were later updated with 23 patients accrued and reported similar response rates.[70] In a separate study, eight patients received DCF 4 mg/m^2/wk for 3 weeks repeated every 8 to 10 weeks or a single dose every 3 to 4 weeks, again with comparable response rates.[71]

The Eastern Cooperative Oncology Group treated 37 HCL patients, 27 patients of whom were evaluable, with DCF.[72] The initial dose of DCF was 5 mg/m^2 for 3 consecutive days every 4 weeks. During the study period treatment was changed to 5 mg/m^2 on 2 consecutive days every 2 weeks. Sixteen of 27 patients (59%) achieved a complete remission, 10 patients (37%) a partial response, and one patient did not respond. These responses were durable and independent of previous splenectomy and/or IFN therapy. These results were recently updated and of 50 patients entered, 32 patients (64%) achieved a complete remission and 10 patients (20%) a partial remission.[73] These remissions were again durable with 4 of 32 complete responders and 2 of 10 partial responders having relapsed. The median number of 2-day courses administered was six (3 months of therapy).

DCF has been investigated by the European Organization for Research and Treatment of Cancer (EORTC) as salvage therapy for HCL patients resistant to or failing α-IFN.[74] The dosage of DCF chosen was 4 mg/m^2 weekly × 3, then 4 mg/m^2 every other week × 3. Of 33 evaluable patients, 11 patients (33%) achieved a complete remission and 15 patients a partial remission with an overall median response duration of 11.5 months. Two patients died of fungal pneumonia. Both these patients had previously been treated with protracted α-IFN therapy.

The National Cancer Institute has made DCF available on group C protocol for HCL patients failing α-IFN. The group C experience with DCF administered at 2 to 4 mg/m^2 every 2 weeks was recently updated with 208 patients accrued and 78 patients evaluable.[75] Twenty-nine of 78 patients (37%) achieved a complete response and two patients (26%) a partial response. Responses were more likely in patients who were intolerant of or had progressed after an initial response to α-IFN than in IFN nonresponders.

When the largest of the DCF trials are combined (Table 4) the overall complete response rate is 57%, the partial response rate is 26%, the minor response rate is 10%, and 7% have no response. These studies used different doses and schedules of DCF and various eligibility criteria, but

Table 4. Results of DCF in HCL

		Response (%)*			
Investigator (reference)	No. of Patients	Complete	Partial	Minor	None
Cassileth et al (73)	50	32	10	4	4
Kraut et al (70)	23	20	1	1	1
Ho et al (74)	33	11	15	4	3
Johnston et al (71)	8	2	4	2	0
Total	114	65 (57)	30 (26)	11 (10)	8 (7)

*Responses according to peripheral blood and bone marrow criteria.

combining them cautiously helps in assessing the results of DCF in larger numbers of patients.

DCF administration has been associated with significant toxicity. The early phase I studies in hematologic malignancies encountered life-threatening toxicities at the higher dose levels including neurologic, renal, hepatic, and bone marrow toxicities.[76] In the early studies of DCF in HCL using lower doses, pretreatment hydration and allopurinol, nausea, vomiting, pruritic photosensitive skin rashes, and occasionally keratoconjunctivitis were seen.[66-68] Occasional patients developed fever and reversible impairment of renal function even at the lower doses.[69,70] Serious infections were encountered, including disseminated herpes zoster, *Escherichia coli, Hemophilus* influenza, and pneumococcal infections.[71] Many of these infections were lethal, especially in those patients with a precarious general medical status. Some have recommended that in the presence of an established infection or a poor performance status DCF is perhaps best avoided.[72] At the lower doses of DCF opportunistic infections occur less commonly.[70] DCF-induced neutropenia is usually limited to the first few cycles of therapy, but it is frequent, often being severe and life-threatening.[73,74]

Because DCF is a potent antilymphocyte agent, the nature and severity of DCF-induced immunosuppression has been investigated.[77] In one study before the initiation of DCF most patients had normal numbers of T lymphocytes with normal response to mitogens. During therapy, CD4 and CD8 lymphocytes decreased to levels below 200 cells/μL in all patients and were associated with decreased T-lymphocyte proliferative capacities. This immunosuppression persisted throughout the 14 months of therapy and for at least 6 months after discontinuing therapy, although during this same time period peripheral blood natural killer (NK) activity, a subset of lymphocytes known to be deficient in HCL, increased. However, infections seemed to occur early on after the administration of DCF, and despite the low levels of CD4 and CD8 lymphocytes, there has been no significant incidence of either late infections or secondary malignancies. CD4 and CD8 lymphocytes returned to normal in only 4 of 13 patients. In a separate study, even low doses of DCF resulted in similar significant immunosuppression.[78] DCF at doses of 2 to 4 mg/m^2 intravenously at 2- to 6-week intervals caused significant depression of total lymphocytes, B cells, and T cells (CD4 and CD8 cells), which was long-lasting. The median posttreatment CD4 lymphocyte count was 155 cells/μL.

The exact mechanism of action of DCF is unknown. In

the presence of DCF there is accumulation of deoxyadenosine and adenosine,[79] which are toxic to lymphocytes, partly through inhibition of S-adenosyl-L-homocysteine hydrolase,[80] which is responsible for cellular methylation reactions, and possibly through functional changes of adenosine receptors.[81] Depletion of adenosine triphosphate (ATP) occurs with the associated disruption of DNA integrity.[82,83] The degree of deoxyadenosine elevation after the administration of DCF is erratic and does not strictly correlate either with toxicity or efficacy.

Thus, DCF is a highly active agent in the treatment of HCL with substantial response rates that are often complete and durable. Central nervous system, renal, and hepatic toxicity have been reduced with the use of lower dosages of DCF. The incidence of serious infectious complications and immunosuppression has tempered some of the enthusiasm for this drug, although further experience in larger numbers of patients will clarify these risks. Caution should be exercised in patients with a poor performance status or a history of preceding infections. The recommended dose is 4 mg/m^2 intravenously every other week for 3 to 6 months until maximum response is attained.

2-Chlorodeoxyadenosine (2-CdA). Unlike DCF, 2-CdA is not an adenosine deaminase inhibitor but rather an adenosine deaminase-resistant purine substrate analogue.[84] 2-CdA has been shown to be an active agent in the treatment of chronic lymphocytic leukemia,[85,86] low-grade non-Hodgkin's lymphoma,[87] and cutaneous T-cell lymphoma.[88]

The successful use of 2-CdA in two patients with HCL was first reported in 1987.[89] Both of these patients had progressive pancytopenia after splenectomy. They each received a single 7-day continuous intravenous infusion of 2-CdA at 0.1 mg per kilogram of body weight per day. The responses achieved in both patients were complete and durable and follow-up is now beyond 4 years.

In 1990 the ability of 2-CdA to achieve long-lasting remissions after a single course of therapy without severe toxicity was reported in 12 patients.[90] Patients received 2-CdA at 0.1 mg/kg/d by a 7-day continuous intravenous infusion. All patients had evidence of active disease evidenced by the presence of neutropenia, thrombocytopenia, anemia, symptomatic adenopathy, or repeated infections. Seven of 12 patients had previously undergone splenectomy and five had previously received α-IFN. Eleven of 12 patients achieved a complete remission and the 12th patient a partial remission. The responses were durable with a median duration of 15.5 months. The longest remission reported was 3.8 years and no patients had relapsed. Toxicity was minimal with no nausea, vomiting, alopecia, hepatic dysfunction, renal insufficiency, central nervous system toxicity, or opportunistic infections encountered. Characteristically, there was a rapid decrease in the number of peripheral blood hairy cells that correlated with the development of severe leukopenia and, in some cases, fever. Given the low incidence of documented intercurrent infections, the etiology for the fever is believed due to the release of cytokines from lysed hairy cells. This is currently being investigated. In the ensuing 2 to 6 weeks after therapy

there was peripheral blood hematologic reconstitution, and subsequent bone marrow aspiration and biopsy showed no evidence of HCL in 11 of 12 patients.

Since that report, 185 patients with active HCL have been treated with 2-CdA at Scripps Clinic and Research Foundation. At present, data are available on 86 patients who have been observed for at least 6 months with serial blood counts, and follow-up computerized axial tomographic scans and bone marrow examinations. Interim analysis at this time shows that approximately 80% of these patients have obtained a complete response after a single intravenous infusion of 2-CdA at 0.1 mg/kg/d for 7 days. The majority of the remaining 20% are partial responders with normal peripheral blood counts and minimal residual HCL involvement of the bone marrow. Those patients achieving partial responses have had no progression of disease in their peripheral blood, bone marrow, or spleen size. Responses appear independent of previous splenectomy or IFN therapy. A single patient has had a bone marrow relapse that followed a durable complete response. Other institutions have achieved similar response rates.[91,92] Some patients previously resistant to the action of DCF treatment have responded to 2-CdA, including some complete remissions, possibly suggesting a lack of cross-resistance between 2-CdA and DCF, which will be investigated further.

Toxicity appears largely confined to culture-negative leukopenic fever, which occurs in about 40% of patients associated with the disappearance of peripheral blood hairy cells as previously reported.[90] In these 86 patients only one documented serious infection has occurred, a *Staphylococcus aureus* buttocks abscess without a predisposing risk factor. Only two study patients have died and both were due to causes unrelated to HCL or its treatment. No neurotoxicity, nephrotoxicity, hepatic toxicity, or alopecia occur.

Flow cytometric studies confirm that 2-CdA is also immunosuppressive.[93] Before 2-CdA treatment, the absolute lymphocyte count and T/B-cell ratio were abnormal in most patients, but the ratio of helper/suppressor T cells (CD4/CD8) was normal in the majority. Both T and B lymphocytes were reduced after 2-CdA, and among the T lymphocytes, both CD4 and CD8 lymphocytes were affected. A decrease in the CD4/CD8 ratio was seen due to slower recovery of CD4 cells. Monocytes increased to normal levels within a few months after 2-CdA. Between 6 and 12 months after 2-CdA administration there was a tendency toward restoration of T-cell subsets in the majority of patients with a median posttreatment CD4 lymphocyte count of 540 cells/μL.[93]

2-CdA is a deoxyadenosine analogue resistant to the action of adenosine deaminase. The exact mechanism of action of 2-CdA also remains elusive. The 5'-triphosphate form of 2-CdA accumulates in cells with high deoxycytidine kinase activity, such as lymphocytes. This likely confers tissue specificity and may explain the lack of conventional chemotherapy toxicity. Accumulation of the 5'-triphosphate results in DNA strand breaks and ATP depletion. The cytotoxic action of 2-CdA is independent of cell division.[94] Unlike pentostatin, which elevates plasma levels

of deoxyadenosine and adenosine with consequent inhibition of S-adenosyl-L-homocysteine hydrolase, 2-CdA does not affect this enzyme directly.[95]

In summary, 2-CdA is a simple purine nucleoside that has major activity in HCL achieving complete and durable remissions in the vast majority of patients with a single infusion of therapy. The recommended dosage is 0.1 mg/kg/d as a single 7-day intravenous infusion. Given the indolent nature of HCL and its long natural history, protracted follow-up will be required to ascertain whether these durable and complete remissions result in cures or whether relapse will be the rule. Long-term risks will require longer follow-up to evaluate, but the low doses used and the brief exposure to the drug would seem likely to minimize these risks.

Fludarabine. The third clinically useful nucleoside to have some activity in HCL is fludarabine. Two patients with HCL and one with a variant form of HCL[96] received fludarabine at 30 mg/m² intravenously over 30 minutes daily for 5 days every month.[97,98] Two patients, including the patient with the HCL-variant, achieved a partial response and the third patient had a minor response. Four to 11 courses of fludarabine were administered. Although showing some evidence of activity, fludarabine obviously does not result in the same dramatic responses seen with DCF and 2-CdA.

GRANULOCYTE COLONY-STIMULATING FACTORS (G-CSFs)

In an attempt to abrogate the early myelosuppressive effects of α-IFN, recombinant human G-CSF was given to four HCL patients.[99] G-CSF was administered as a daily subcutaneous injection at an initial dose of 1 μg/kg/d, and later escalated in increments to 6 μg/kg/d. Three of four patients had normalization of their absolute granulocyte counts. A single patient, with a prior history of cutaneous vasculitis, had to discontinue therapy because of the development of acute neutrophilic dermatosis (Sweet syndrome). Six patients were given G-CSF until their absolute neutrophil counts had normalized, after which time α-IFN was administered.[100] The frequency of α-IFN–induced neutropenia was diminished without compromising hematologic responsiveness to the IFN.

Some caution should be exercised in treating HCL patients, especially with a history of vasculitis, with CSFs until further studies are completed demonstrating their safety. The role of G-CSFs in the management of HCL will be principally adjunctive to definitive systemic therapy. The role of CSFs with nucleosides in the treatment of HCL remains to be established.

COMBINATION, RANDOMIZED, AND FUTURE CLINICAL TRIALS

Two phase III trials are currently being performed comparing α-IFN and DCF in different cohorts of patients with HCL. The Cancer and Acute Leukemia Group B is comparing α-IFN with DCF in post-splenectomized patients and the Intergroup study is comparing α-IFN and DCF in previously untreated patients. The results of these trials are as yet unpublished. Randomized comparisons of 2-CdA and DCF will be difficult because they will require

Table 5. Characteristics of α-IFN, DCF, and 2-CdA in the Treatment of HCL

	α-IFN	DCF	2-CdA
FDA status	Approved	Approved	Under review
Synthesis	Recombinant technology	Complex	Simple
Route of administration	Subcutaneous	Intravenous bolus	Intravenous infusion
Recommended dose	2 million U/m^2 3×/wk	4 mg/m^2 every other week	0.1 mg/kg/d for 1 wk
Duration of treatment	12 mo	3-6 mo	1 wk
Responses	80% overall, 9% complete	83% overall, 57% complete	95% overall, 80% complete
Major toxicities	Influenza-like syndrome early infections	Nausea, early infections, immunosuppression	Culture-negative fever, immunosuppression

vast numbers of patients since both drugs achieve high response rates. Such studies would likely be comparisons of toxicity more than response rate.

Alternating cycles of α2a-IFN and DCF have been combined in an attempt to improve response rates and to develop a curative strategy.[101,102] Fifteen patients received DCF 4 mg/m^2 per week × 3 alternating with recombinant α2a-IFN 3 million U subcutaneously daily for 28 days, for 14 months. Nausea, vomiting, neutropenic fever, and localized cutaneous herpes zoster were the major toxicities recorded. Thirteen of 15 patients achieved normal peripheral blood counts. All 14 patients with evaluable bilateral bone marrow biopsies had minimal residual disease and were thus partial responders, indicating that this was not likely to be a curative regimen. An alternative approach was the administration of IFN for 3 months, followed by DCF for 12 months, which resulted in 10 of 15 patients achieving a complete remission, four a partial remission, and one stable disease.[103] Two patients suffered serious infections; one had pneumonia and one had disseminated mycobacterium avium intracellulare.

ON THE CURABILITY OF HCL

The ability of methotrexate in choriocarcinoma, cisplatin in germ cell tumors, and nitrogen mustard in advanced Hodgkin's disease to achieve long-lasting complete remissions as single agents laid the foundation for the development of curative multi-agent regimens for these disorders. Drawing on therapeutic principles from this historical perspective would lead us to believe that HCL should be a curable malignancy. Whether single-agent therapy with DCF or 2-CdA will result in cures or whether combinations of nucleosides, IFNs, and CSFs will yield this result remains to be seen. There is no doubt that the therapeutic opportunities that have evolved for patients with HCL in the last decade represent significant treatment advances and appear destined to alter the survival of patients with this disorder.

TREATMENT CONSIDERATIONS

The management of patients with HCL is presently undergoing evolution. Not only are there questions about which treatment to select, but also the time to initiate therapy can be questioned. In general, guidelines for the degree of cytopenias indicating the need for treatment remain unchanged; however, as discussed earlier, some consideration need be given to initiating therapy earlier in those patients not previously transfused to obviate this need with its attendant risks. The role of splenectomy as primary treatment is rapidly diminishing given the superlative activity of new systemic agents. The three agents (α-IFN, DCF, and 2-CdA) with substantial activity in this disease are compared in Table 5. IFN is an FDA-approved treatment, is generally available and, although treatment is associated with a high response rate, a relatively small number of these responses are complete. Although it appears unlikely to be an agent of curative potential, it is a powerful agent in controlling the disease, and its possible role as adjunctive therapy with the nucleosides remains to be investigated. DCF (Nipent; Parke-Davis, Morris Plains, NJ) has recently been approved and 2-CdA is under review by the FDA. The hierarchical position of these agents in the therapeutic armamentarium of individual patients with HCL is presently undefined but will ultimately be determined by their ability to induce durable responses and potential for toxicity. Although both nucleosides induce high response rates, 2-CdA appears to be an especially favorable agent for the treatment of HCL given the durable complete responses achieved after only a brief exposure to therapy and the desirable toxicity profile. Presently, these drugs are only available through either the National Cancer Institute Group C mechanism or on active clinical research trials. At this time, the best therapeutic approach in the management of a patient with HCL is entry into a study to help determine what is the optimal therapy for this disorder and whether a curative strategy will be possible.

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