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HAIRY CELL LEUKEMIA. A THERAPEUTICAL UPDATE

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This is a review of current treatment for hairy cell leukemia (HCL). Data for this analysis were obtained from the Itaiian HCL Registry, as well as from other published series. We have given space to the impact of interferon and pentostatin on the management of this disease. Other issues are also discussed, such as the relevance of achieving a complete remission with respect to overall and relapse-free survival. We include a final section on recommendations which may prove useful in designing an appropriate therapeutic strategy.

KEY WORDS: Hairy cell leukemia, splenectomy, interferon, deoxycoformycin.

Hairy cell leukemia (HCL) is a chronic lymphoproliferative disease first described and named leukemic reticuloendotheliosis by Bouroncle et al. in 1958 [1]. It received its currently accepted nomenclature when Schrek and Donnelly described the «hairy» cells in the blood of patients with this disease [2]. Typically, this rare disorder (representing approximately 2 per cent of adult leukemias) presents in middle age men as pancytopenia, splenomegaly and infiltration of bone marrow and peripheral blood by morphologically characteristic leukemic cells. These cells are unique because of the presence on their surface of broad-based undulating ruffles, which appear under the light microscope as cytoplasmic projections or «hairs», and the presence of a specific tartrate-resistant acid phosphatase, isoenzyme 5 (TRAP), in the cytoplasm [3]. Evidence to date indicates that in the majority of cases the leukemic cells are of B-lymphocytic lineage, as demonstrated by the presence of surface immunoglobulin, B-cell-specific antigens, and by immunoglobulin gene rearrangements [4-8]; however, several cases of T-cells variance have been identified, four in association with a unique human retrovirus, human T-cell leukemia type II (HTLV-II) [9 10].

The diagnosis can usually be suspected from the clinical manifestations and evaluation of the peripheral blood smear, but a bone marrow biopsy is required for definitive diagnosis.

Some investigators distinguish common HCL [11-15] from HCL variants, which respond differently to treatment [12]: the «HCL variant» a disease with cytological, morphological and clinical features intermediate between HCL and prolymphocytic leukemia (PLL) [12]; «splenic lymphoma with circulating villous lymphocytes (SLVS) [15-17]; and the Japanese variant [13].

In this review we would like to define the modern therapeutical approach to this disease according to the data obtained from the literature and personal experience.

TREATMENT

The treatment approach is related to the consequences of the pancytopenia: recurrent infections secondary to granulocytopenia, and bleeding secondary to thrombocytopenia. Anemia is frequently severe enough to require transfusion. Other serious, complications include pain and significant symptoms related to massive splenomegaly, vasculitis or perivasculitis, bone lesions, a high white cell count secondary to a leukemic evolution, and bulky retroperitoneal disease.

It should be noted that up to 10 per cent of patiens presenting with HCL have an indolent course and fare well clinically for years without any specific therapy. The remaining 90 per cent will usually require some form of treatment within a short period after the diagnosis.

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Splenectomy was generally agreed to be the initial treatment of choice, resulting in a prompt improvement of cytopenia. However this treatment is not curative and has not been shown clearly to influence survival. Other treatment options include single-agent and combination chemotherapy, androgens, corticosteroids, lithium carbonate, leukapheresis, leukocyte infusion, radiation therapy, allogeneic bone marrow transplantation. However most of these treatment modalities induce only a transient improvement or are ineffective, and often they have severe side effects.

Some clinical trials with alpha-interferon and deoxycoformycin have shown a dramatic improvement in therapy outcome, and these agents are now under investigation as potential curative modalities.

Splenectomy

Splenectomy was considered the initial treatment of choice in hairy cell leukemia because of the successful palliation of the effect of hypersplenism on pancytopenia [18]. In addition, since there is no HCL without involvement of the spleen, whereas at least two cases without involvement of bone marrow have been described [19], splenectomy may eliminate a favored site for cellular proliferation. Low surgical mortality (less than 2%) and morbidity continue to favor its application in symptomatic patients with HCL [20-23]. Virtually all patients have a postsplenectomy improvement, with normalization of blood count occurring in 40-60% of patients [18 20-25] and long-lasting non symptomatic stable disease without additional therapy for several years. Of interest, this improvement in the peripheral blood count is not correlated with significant changes in the pattern of bone marrow disease, the hairy cell index (HCI) or the overall bone marrow cellularity. In spite of the relative safety and efficacy of this procedure, there is substantial controversy as to whether response to splenectomy can be predicted in individual cases. Factors predictive of response to splenectomy are not, however, well established, but they may include the HCl [20], initial blood counts and spleen size [21 22 25 26]. In this regard a clinical staging system was proposed by Jansen et al. [21] to select at diagnosis patients for whom splenectomy would be beneficial. In this system, spleen size and hemoglobin level were recognized as the only significant predictive factors. Splenectomy in particular appeared to be the elective therapeutical approach in stage III patients (Hb 8.5-12 g/dl + spleen > 10 cm UCM, or Hb < 8.5 g/dl + spleen ≥ 4 cm UCM), wherease in stage I and II it could be beneficial. Flandrin et al. [22] considering a retrospective series of 211 HCL patients, 85 of whom were splenectomized, reported that the overall survival was better for splenectomized patients and confirmed the beneficial effect on survival of the removal of spleens > 4 cm UCM. In another large series of 235 cases of the Italian Cooperative Group for the study of HCL (ICGHCL), 127 of whom were splenectomized, splenectomy proved to be effective in patients in stage II and III [24]. In a more recent series Golomb et al. [20] failed to demonstrate a clear relationship between spleen size and response to splenectomy, since they could not predict in individual cases whether patients would benefit from this procedure. In fact, even in the absence of splenomegaly, significant cytopenia can occur and this can respond to splenectomy.

Evaluation of the degree of bone marrow infiltration by hairy cells which is associated with bone marrow underproduction may predict the postsplenectomy response. Although Castro Malaspina et al. [271] did not observe any correlation between the apparent degree of bone marrow infiltration by hairy cells and the degree of erythropoietic deficiency, Golomb and Vardiman [20] developed the hairy cell index (HCI) to quantitate the degree of bone marrow infiltration and cell underproduction and, thus, postsplenectomy response. In this system bone marrow replacement with consistent underproduction is the most important factor in predicting the platelet count response to splenectomy and the need for any further therapy.

Whether the hematologic response to splenectomy significantly alters the risk of infectious complications is unclear. In fact infection remains the major cause of mortality in hairy cell leukemia. In this regard Golomb et al. [28] found no clear decrease in the incidence of infection in splenectomized as compared with nonsplenectomized patients, although there was clearly a population of patients who survived for many years without infections after splenectomy.

The impact of splenectomy on survival in HCL has not been demonstrated. Sebahoun et al. [29] reported that patients with splenomegaly who underwent splenectomy experienced longer survival than nonsplenectomized patients with splenomegaly. In a retrospective multicenter analysis studying the effect of splenectomy on survival using the data from the operations, Jansen and Hermans [25] reported that the hemoglobin level and the neutrophil count at 2-3 months after splenectomy proved to be extremely important. On the basis of these findings the authors proposed a postsplenectomy staging system in an attempt to predict the survival time after surgery and to select those patients in need of additional therapy. In fact, patients whith Hb greater than 12 g/dL

and neutrophils greater than $0.5 \times 10^9/l$ (stage A) survived longer than patients with a less complete response to the operation (stage B and C). Using these criteria the actuarial survival curves after splenectomy of Flandrin et al. [22] suggest the same results, although they do not reach significance. However, in a review by van Norman et al. [23] there was no significant improvement in the survival rates of responders as compared with nonresponders to splenectomy. Furthermore the comparison of presplenectomy and postsplenectomy blood counts for 170 previously untreated HCL patients showed that, although all these patients had a postsplenectomy improvement, there was no statistically significant difference in the survival rate of these patients and that of 26 others who were not treated [30]. Although all HCL patients benefit from surgery, splenectomy does not appear to be resolutive of the disease. Disease progression occurs in 30-50% of patients as frank leukemia or increased pancytopenia at intervals from a few months to more than 10 years postsplenectomy, with a median of 8.3 months [30].

Chemotherapy

Different chemotherapeutic approaches had been utilized during progressive disease after splenectomy (Table 1).

Single-agent chemotherapy with chlorambucil [32], rubidazone [33] and methotrexate [34] has been reported as effective in patients with a significant leukemic phase, and variably effective in improving pancytopenia. An update of the efficacy of low-dose chlorambucil therapy in 24 HCL patients was published in 1984 by Golomb et al. [35]. Patients were treated for at least 6 months with 4 mg chlorambucil given daily by mouth. Of 11 leukemic patients all has a considerable drop in their circulating hairy cells, and 7 had increases in their platelet count. Of 13 pancytopenic patients, eight had substantially increased platelet counts and seven had increased hematocrit values, even though six months of treatment were required before response was obtained. Granulocytopenia remained a persistent problem. Half of the patients with pre-treatment and post-treatment bone marrow biopsies had objective improvement, as determined by a decrease in the number of hairy cells (HCs) and an increase in normal marrow elements. However, there were six deaths, all of them associated with infectious complications. In 1985 Joosten et al. [34] reported on six patients who relapsed after splenectomy and were treated with high-dose methotrexate ($2\ g/m^2$) and leucovorin rescue. Five had objective responses, as determined by improved blood cell counts. The response continued for more than 14 months in one case and 44 months in another.

Several combination chemotherpay regimens have been described as active in hairy cell leukemia. In 1984, Annino et al. [36] reported on three patients who were treated using a combination of vinblastine and bleomycin at low doses ($2.5\text{-}5\ mg/m^2$ of each drug every two weeks). A rapid cytoreduction with no evidence of myelosuppression was obtained in all patients. One achieved a complete response and onother a partial response. Neither of them relapsed after follow-up periods of 34 and 17 months, respectively. The third patient, although achieving hematologic improvement, died from a cytomegalovirus pneumonitis after two cycles of chemotherapy. In 1985, Calvo et al. [37] reported on seven patients who were treated with intensive chemotherapy consisting of rubidazone ($450\ mg/m^2$ IV, on day 1), arabinosylcytosine ($200\ mg/m^2$/daily in continuous IV infusion

Table 1. - *Clinical trials of chemotherapy for hairy cell leukemia.*

Study	(Ref.)	Drugs	Patients	Splenectomized	Responses				Survival (mos)
					CR	PR	MR	NR	
Golomb et al.	(35)	Chlorambucil	8	8	0	0	7	1	1– 33+
Annino et al.	(36)	Vinblastine, plus bleomycin	3	1	1	1	1		1– 34+
Calvo et al.	(37)	Rubidazone, cyclophosphamide, cytosine arabinoside	7	6	3	1	0	3	1– 44+
Joosten et al.	(34)	Methotrexate	6	6	0	0	5	1	1– 44+
Cold and Bringker	(38)	Methotrexate, chlorambucil, CHOP	5	4	1	3	0	1	1– 49+

Legend: CR = complete remission; PR = partial remission; MR = minor response; NR = no response.

from day 1 to day 5), cyclophosphamide (2000 mg/m² on day 5). In addition the first two patients received oral 6-mercaptopurine (200 mg/m²/daily from day 1 to day 5). All were hospitalized and received prophylactic oral antibiotics, Fungizone and when needed, granulocyte transfusions. Three patients achieved a complete remission and one had a partial response. However, 3 patients died of infectious complications during aplasia after induction chemotherapy, one of them with a massive diffuse leukemic infiltration, the others with severe bone marrow hypoplasia. In 1987, Cold and Bringker [38] reported on five patients with progressive disease after splenectomy who received multiple course of CHOP (3 patients), cyclophosphamide (1 patient), or cyclophosphamide monotherapy, CHOP and intermediate-dose methotrexate (1 patient). One complete remission and three partial remissions where obtained, while one patient had progressive disease.

As a rule, the reported responses have taken 3-6 months to develop, and treatment has been complicated by a significant risk of serious infection. This may be ascribed to the massive infiltration of hairy cells in the bone marrow and prolonged chemotherapy-induced myelosuppression.

Corticosteroids

Cortiscosteroids have a limited role in the treatment of hairy cell leukemia because the patients treated with them are at significant risk of developing serious infections [39 40]; it is unlikely that these agents have a positive impact on survival. In fact, hairy cells have glucocorticoid receptors but are resistant to the cytolethal effect of glucocorticoids [41-42]. Low-dose glucocorticoids have been effective in the treatment of vasculitis and other autoimmune diseases associated with hairy cell leukemia [43].

Androgens

Androgens have been used in patients with HCL and in some cases an improvement of erythropoiesis could be seen.

Magee et al. [44] treated six patients with postsplenectomy cytopenia with oxymetholone (50 mg three times a day for 3 to 4 mos); three of them had an improvement of anemia and of thrombocytopenia, and in one case in neutropenia. The response occurred 1 to 20 weeks after the initiation of therapy but usually, when discontinued, the peripheral blood cell counts deteriorated drastically. Similar results have been achieved by other authors [31 39 45].

Radiotherapy

Beneficial results, with a decrease in spleen size and an improvement of the hematologic picture, have been reported in 24 patients after splenic irradiation by Bouroncle et al. [19]. Most frequently the response was delayed by weeks after completion of the course of treatment. The total amount of radiation for each course was usually from 400 to 900 Rads. Benefical results have also been reported by other authors [24].

Radiotherapy of single or multiple osteolytic lesions in the proximal portion of the femur or humerus, or aseptic necrosis has also been reported [46].

Furthermore low-dose radiation (from 600 to 750 Rads) in a case of HCL complicated by massive lymphadenopathy after an initial response to splenectomy produced prompt regression of the adenopathy as well as pain relief [47].

The response of patients with these types of local problems suggests that HCL is a radiosensitive disease.

Interferon

The use of interferon in the treatment of HCL was recommended in 1984 by Quesada et al. [50], who first reported their experience in treating seven patients with partially pure alpha leucocyte interferon at a daily dosage of 3×10^6 U by the intramuscular route for at least 6 months. When treatment was initiated all patients had evidence of slowly progressive disease but never developed severe pancytopenia or infection, five of the seven had undergone splenectomy, two had subsequently received chemotherapy, and two had not been treated. After treatment, bone marrow aspirates showed an absence of leukemia cells in three patients and 5% or fewer of then in three others. Anemia, granulocytopenia and thrombocytopenia were reversed in all patients.

Since this first report, several hundred patients have been treated with natural or recombinant alpha interferon, and the approach to patients with HCL has changed significantly. In fact this agent virtually altered the operational definition of remission of HCL, because elimination of hairy cells from the bone marrow could now be achieved with therapy and included as a criterion for evaluation of response (Table 2).

No major differences have been demonstrated between the various types of interferon alpha used, and high total response rates have since been substantiated using either human lymphoblastoid or different types of recombinant alpha interferon [50-69].

Table 2. - *Criteria for evaluation of response to treatment in hairy cell leukemia.*

Complete remission

- Regression to normal of organomegaly.
- Hemoglobin ≥ 12 g/dl.
- Platelets > 100 × 10^9/liter.
- Neutrophils > 1.5 × 10^9/liter.
- No circulating hairy cells (HCs).
- Bone marrow (BM) aspirate (if aspirable) without HCs.
- Bone marrow core biopsy with no discernible HCs

Partial remission

- Reduction of organomegaly by at least 50% of the initial values as assessed by clinical examination. Measurements should be recorded in centimeters below the costal margin for spleen and liver or for the largest diameter of lymph nodes and/or other tumor masses.
- Values for hemoglobin, platelets and granulocytes as for complete remission.
- Reduction of hairy cells in the BM by at least 50%.
- Circulating hairy cells ≤ 5%.

Minor response

- Reduction of hairy cells in the peripheral blood by at least 50%.
- Improvement in one or more of the peripheral blood elements.

No response

- Less than minor response.

Based on the published data (Table 3), the overall response rates after 6 to 12 months of alpha interferon therapy, obtained mainly in patients with progressive disease after splenectomy are in the range of 80 to 90 per cent, including 5-30 per cent complete remissions. Approximately only 5 to 10 per cent of patients do not respond to any of the different types of alpha interferon. The differences in complete remission rates in individual studies may be explained by different induction schedules and dosages, the duration of therapy and, most significantly, the tumor load.

Of interest, recent studies have shown that alpha interferon as initial therapy produces similar response rates in unsplenectomized patients [60 69 70] and data from some investigators suggest that alpha interferon may be more effective in previously untreated patients, probably as a reflection of initiation of therapy at an earlier stage of the disease [56].

Clinical and peripheral hematologic responses to alpha interferon are swift. The initial improvement observed is a rapid decrease of peripheral hairy cells with major changes within the first week of therapy. Splenomegaly, when present, usually regresses in a few weeks [60 69 71]. During the first 1 to 2 months of therapy transient myelosuppression occurs in most patients, occasionally precipitating a transfusion requirement. An increase of platelet count, often as early as two weeks after starting interferon therapy, with the median platelet count reaching a normal value by approximately 1.5 to 2 months, usually precedes the rise of granulocyte count and hemoglobin, which generally do not show a return to normal values until 3 to 5 months. Hemoglobin may continue to increase for as long as 9 months after starting therapy. Monocytopenia usually resolves within 4 or 5 months after the start of therapy. These changes result in a virtual disappearance of transfusion requirements and serious infection, and a striking improvement in the quality of life. In conclusion, IFN therapy in HCL may obtain a partial remission (PR) after a mean time of 16 weeks and a complete remission after a mean time of 35 weeks [72]. The results in the peripheral blood precede those in the bone marrow, where the decrease of hairy cell infiltration occurs later, becoming significant only after 3 or 4 months [58 73-76]. The increase of the percentage and volume of hematopoietic cells (granulocyte and erythroid precursors) parallel that of the peripheral blood. However the median value of the M:E ratio never returns to normal, probably because the suppressive effects of interferon on granulocytic stem cells are greater than those on erythroid progenitors [73 75]. Of interest, a mild marrow hypoplasia is generally observed in patients treated with a daily schedule after 9 to 12 months of therapy [76 77]. Increased amounts of reticulin fibers persist after completion of interferon therapy, with a high incidence of dry taps. After discontinuation of interferon most patients show evidence of a worsening bone marrow status before significant changes occur in the peripheral blood [78].

Several biological markers may be useful for monitoring the effects of therapy in HCL. The sera of patients with HCL contain a factor which corresponds to the soluble form of the interleukin-2 (IL-2) receptor released by hairy cells. The reduction of the serum level of this factor during interferon therapy in HCL patients parelleled clinical recovery and the progressive clearance of hairy cells from the bone marrow [79]. Furthermore the finding during and after interferon therapy that the changes in neutrophil alkaline phosphatase (NAP) scores showed a correlation with the percent of HCs and granulocytes in the bone marrow indicates that the NAP score may be useful in predicting changes in the bone marrow in patients during and after treatment [78 80]. Interferon therapy also changed the tartrate resistant acid phosphatase (TRAP)-positive HCL cells to TRAP-negative, suggesting an inhibition of activity and/or the production of TRAP in HCL cells [74].

Table 3. - *Clinical trials of IFN therapy for HCL.*

Study (Ref.)	IFN type	Dose × 10 and schedule	No. patients (evaluable)	No. splenectomized patients	Induction treat. (mos)	Response			
						CR	PR	MR	NR
Flandrin et al. (58)	alpha-2a alpha-2b leuko	3.0/daily 2/m²×3/wk 3.0/daily	37 (17)	11	4	1	14	1	1
Smalley et al. (62)	ly	2/m²/daily 0.2/m²/daily	138 (138)		>12		80%		
Worman et al. (67)	ly	3.0/daily	50 (43)	39	>12	27	13	3	
Resegotti et al. (68)	ly	3.0/daily	101 (84)	24	3-12	17	50	9	9
Golomb et al. (88)	alpha-2b	2/m²×3/wk	135 (128)	115	>12	5	38	69	16
Thompson and Fefer (103)	alpha-2b	2/m²×3/wk	232 (212)	181	>12	4%	75%	11%	
Mandelli et al. (102)	alpha-2b	2/m²×3/wk	27 (21)	9	12	6	13	2	
		0.5/m²×3wk	7 (0)	2	6	pheriph. hem. improvement			
Quesada et al. (55)	leuko	3.0 daily	22 (22)	22	12	5	13	4	
(56)	alpha-2a	3.0/daily	30 (30)	23	24	9	17	4	
Huber et al. (64)	alpha-2c	5.0/daily	10 (10)			2	5	2	1
			25 (21)	13	>3				
		0.5/daily	11 (11)			1	4	5	1
Liberati et al. (104)	beta	9.0/2.day	14 (14)					12	2
Niederle et al. (66)	r-gamma	4.0/m²/2.day	6 (6)		2-9				6

Legend: CR = complete remission; PR = partial remission; MR = minor response; NR = no response; wk = week.

This observation indicates that TRAP staining is not a reliable method for the evaluation of disease activity in patients with HCL who are undergoing alpha interferon therapy. Morphologic examination by light microscopy may not be sensitive enough to reliably detect residual leukemia after interferon therapy. More sensitive methods may include flow cytometric surface marker analyses in peripheral blood samples or frozen bone marrow sections [81-83], and assessment of the molecular configuration of the immunoglobulin genes by Southern blot analyses [81-84]. Furthermore functional tests such as natural killer cell activity [85], *in vitro* induction of interferon [84], evaluation of delayed hypersensitivity skin testing before and after 12 months of treatment [56], evaluation of the T helper/suppressor *ratio* prior to treatment and 6 to 12 months after beginning treatment with interferon [56 85] may supplement morphologic criteria in confirming complete remission in HCL [86].

The use of alpha interferon in hairy cell leukemia is not without toxicity. Nevertheless, at the low doses of interferon used for HCL the drug has been well tolerated. In addition, tachyphylaxis of the most common systemic symptoms generally occurs, allowing many patients to regain a normal performance status. The most frequent side effects are: flu-like symptoms (95%) including fever, malaise, fatigue myalgias; skin disorders (50%) including dry skin, seborrheic dermatitis, alopecia; gastrointestinal symptoms (30-40%) including anorexia, dry mouth, altered taste, constipation, nausea, vomiting, diarrhea and elevation of transaminase levels; application site disorders with local inflammation (25%); central or peripheral nervous system symptoms (10-20%) including paresthesias, sudden memory loss, confusion and depression [80 86-89]. Other less common toxicities reported in HCL patients treated to date include gynecomastia [90], gonadal failure and impotence [91], decrease in libido [56 57], corneal allograft rejection [92], membrane proliferative glomerulonephritis [93], severe arrhythmias and myocardial infarction with sudden death [68 94], arthritis and/or vasculitis with mild inflammation of small joints of the hands [56].

Many of the adverse effect of therapy with interferon are probably mediated via the action of other cytokines (tumor necrosis factor or interleukin 1) or

through prostaglandin mediated effects. Acute adverse effects can be adequately controlled with paracetamol. Prostaglandin synthetase inhibitors are probably even more effective but because of their potential for interfering with some of the desidered IFN-induced reactions, they must be used with caution. Prednisolone 5-20 mg orally daily may be helpful to control the side effects [95]. Fatigue is by far the most difficult adverse effect to overcome. This can be accomplished either by dose escalation or dose attenuation or periods of therapy discontinuation (3-7 days). The management of adverse effects of alpha interferon therapy is given in Table 4. In addition most patients with HCL develop transient myelosuppression during the first month of interferon therapy. The nadir of neutrophil and platelet counts occurs at a median of one week after starting interferon, usually recovering by the end of the first month [69 56]. Of interest and clinical importance is the observation that, even if granulocytopenia persists, the incidence of serious infections is reduced in interferon treated patients, as compared to the 6-month period prior to therapy [57].

Table 4. - *Management of adverse effects of IFN therapy.*

— Warn the patients well in advance.
— Induce tolerance by dose escalation.
— Keep the interval between injections < 72 hr.
— Give injections in the evening.
— Reduce dose.
— Give acetaminophen (paracetamol) as co-medication.
— Prostaglandin synthetase inhibitors.
— Carefully regulate the dose.
— Consider daily or continuous administration.
— Interrupt therapy for a weekend (or longer).
— Give an enriched diet if weight loss is associated with anorexia.

Rare deaths have been observed early after starting treatment with alpha interferon. Resegotti et al. [68] reported 9 early deaths (6 from sepsis, 1 from pulmonary edema, and 2 from myocardial infarction during the first two months of therapy). Eleven deaths were reported by Pralle et al. [65], 10 from sepsis, and 1 from cerebral hemorrhage due to preexisting thrombocytopenia. Fatal infections were seen in 9 out of 34 splenectomized patients. This high early incidence of deaths in the group of patients with progressive disease after splenectomy was not reported by Glapsy et al. [96] (one from presumed intracranial hemorrhage and one from a prexisting pneumonia), or by Golomb et al. [57] (2 cerebral hemorrhages, 1 sepsis). The observed early deaths reflected mostly the severity and complexity of the underlying disease at entry, especially concomitant infections. Since improvement in blood counts dit not begin until after about one month of therapy and since granulocytopenia was often exacerbated by the interferon, patients with preexisting granulocytopenia were made initially more susceptible to infection. Ideally, patients should begin treatment earlier, before the disease has progressed to that degree of severity.

Despite the increasingly extensive clinical experience concerning the high effectiveness of alpha interferon in inducing remission in HCL, a number of question remains unresolved.

The optimal dosage, schedule and duration of interferon therapy still have to be defined. Most studies have administered low doses of alpha interferon, ranging from 2U/m^2 to 3 MU/m^2 daily or three times weekly. Limited data suggest that merely increasing the dose does not convert nonresponders to responders [57] but may override the antibody response in some patients, who become resistant to interferon because of the development of antibodies [89 97]. On the other hand, very low doses, in the range of 0.2 MU/m^2 to 0.5 MU/m^2, appear to be equally effective as the standard doses in achieving hematologic responses [64 98].

The pratical implications of these observations are twofold: 1) further treatment of HCL patients who develop toxic side effects during therapy with higher doses; 2) primary treatment of HCL patients with advanced age or with severe cytopenia, who are known to develop serious toxicity when treated with conventional doses.

No differences have emerged between the two most commonly used schedules: daily or three-times-a-week injections. There is however a suggestion that the proportion of complete remissions at one year is higher in those starting with a daily dose [67 69 99].

The optimal duration of therapy needed to induce maximal response also remains to be clarified because remissions have been obtained as late as 10, 12 or 24 months after initiation of treatment [67 99 100]. Of interest, preliminary results from two studies [99 100] suggest that continuation of induction treatment up to 18 or 24 months may further delay relapse.

In the multicenter trial reported by Golomb et al. [100], a group of patients completing twelve months of interferon therapy and having minor, partial, or complete remissions was randomized to an additional 6 months of therapy or to observation alone. Of 35 patients randomized to observation alone, 6 relapsed, compared with only two of 29 who received additional therapy.

Quesada et al. [99] reported that discontinuation of recombinant alpha interferon after 12 months was as-

sociated with a larger number of both clinical and bone marrow relapses than in patients whose treatment with natural alpha interferon was extended to 24 months. However the difference was not significant.

The value of maintenance therapy after achieving stable CR or PR has not yet been determined. However there is increasing evidence that a single weekly dose of 3 MU may prevent a clinical and hematological relapse, avoiding the risk of infections [101].

The clinical prognostic significance of a CR versus a PR has also yet to be established with regard to both to durability of the response and the survival benefit. Since survival is determined largely by the degreee of susceptibility to infection and the transfusion requirement, rather than by the existence of hairy cells per se, it is possible that the normalization of the complete blood count observed with a PR may be as effective in prolonging survival as the normalization associated with a CR, especially if it turns out that when HCL progresses after a partial remission, it may respond again to readministration of alpha interferon. In all patients relapsing after discontinuation of interferon, a new satisfactory response was obtained after a reinduction treatment of at least three months' duration [99 102 103].

These data suggest that HCL may be an interferon dependent disease.

Recent studies have shown that alpha interferon is active in unsplenectomized patients [56 60 68 70]. Data from Quesada et al. [56] suggest that interferon may be more effective in previously unsplenectomized patients. However no differences in the overall response rate between splenectomized and previously untreated patients have been shown from other concurrent studies [68 69 100]. The discrepancy between these reports may reflect initiation of treatment at an earlier stage of the disease or other prognostic variables. The question whether interferon should be used as initial therapy instead of splenectomy is being addressed in ongoing prospective randomized cooperative trials.

Limited information is available as to the role of the other various interferons (beta and gamma) in HCL. Preliminary data suggest little activity for gamma interferon [66]. Patients in whom gamma interferon fails may eventually respond to alpha. Preliminary results with intravenous natural beta-IFN [104] or subcutaneous recombinant-beta [96] suggest an efficacy similar to that of alpha interferon. These findings are constitent with the observation that type I (alpha and beta) and II (gamma) interferons are distinct [105] and that *in vitro* growth of hairy cells can be inhibited by alpha but perhaps not by gamma interferon [106].

Deoxycoformycin (DCF)

The evaluation of pentostatin (2'-deoxycoformycin) (DCF) in hairy cell leukemia has proceeded almost simultaneously with the alpha interferon trials, although experience is considerably less extensive (Table 5).

Pentostatin, a product isolated from culture broths of Streptomyces antibioticus [107], is a structural analogue of adenosine that inhibits adenosine deaminase (ADA), an enzyme that catalyzes the deamination of adenosine and deoxyadenosine in the purine salvage pathway. The activity of deoxycoformycin seems to depend on the enzyme profile of the malignant lymphoid cells to be treated. Lower doses of the drug are active in indolent lymphoid neoplasms with low intracellular concentration of ADA, which can be inhibited by small amounts of the drug [108].

Table 5. - *Clinical trials of deoxycoformycin therapy for hairy cell leukemia.*

Study (Ref.)	Dose (IV/m²) schedule	Patients entered (evaluable)	Patients splenectomized	Responses			
				CR	PR	MR	NR
Spiers et al. (110)	5/m² for 2 days every other wk to CR	37 (27)	20	16	10	0	1
Johnston et al. (111)	4/m²/wk for 3 wk repeated every 8-10 wk or sigle dose every 3-4 wk to CR+2 cicles	31 (28)	10	25	3		
Eisenhauer etal. (113)	4/m²/wk for 3 wk every 8 wk to CR+2 cicles	31 (18)	8	15	1	0	2
Kraut et al. (112)	4/m²/every other wk to CR	10 (10)	6	9	0	1	0

Legend; CR = complete remission; PR = partial remission; MR = minor response; NR = no response

In 1984 Spiers et al. [109] first reported of the treatment of two previously untreated, nonsplectomized HCL patients with pentostatin. Hairy cells were cleared promptly from the blood, splenomegaly and lymphadenopathy regressed, and anemia, thrombocytopenia and granulocytopenia were corrected. After approximately four months of treatment, both patient achieved a complete remission, which continued at 9 and 6 months, respectively, after their last treatment. Spiers et al. [110] have recently confirmed their early experience with a report of 37 patients treated with 5 mg/m² IV on two consecutive days every two weeks. Of 27 patients evaluable for response, 16 achieved a complete remission and 10 were classified as having partial responses. Johnston et al. [111] treated using a lower dosage of 4 mg/m² IV weekly for 3 weeks, followed by either a similar schedule every 8 to 10 weeks or a single injection every 3 to 4 weeks. Complete remission occurred in 25 patients, and three had a partial response. Kraut et al. [112] reported complete remissions in 9 of 10 patients with progressive hairy cell leukemia treated with low-dose pentostatin (4 mg/m² IV every other week). Seven patients remained in unmaintained complete remission for a median duration of 6.2 months. Eisenhauer et al. [113] reported 31 patients treated with low-dose pentostatin (4 mg/m² IV weekly for 3 weeks, every 8 weeks). Of 18 patients evaluable for response, there were 15 who had complete remission. The 3 remaining patients included one with a partial response and two with stable disease, all of whom had been evaluated after a single course of therapy.

In each of these reports, responses to deoxycoformycin are extremely rapid, typically occurring within days to weeks, irrespective of previous splenectomy. In the series of Kraut et al. associates [112], the average number of courses required for a complete remission was six (range 4 to 13). In the series of Eisenhauer et al. [113] 5 of 15 complete remissions occurred after a single eight-week course and all complete remissions were seen after 5 courses.

In addition to the rapidity of response, another advantage of pentostatin over interferon may be that complete remission is five to six times more frequent, and unmaintained complete response appears to be very durable. Spiers et al. [110] have not seen any relapse in 16 patients in unmaintained complete remission during a median follow-up of 9 months (range 7 to 24 months). It must be pointed out, however, that no direct comparison of the two agents have yet been reported, nor has it yet been demonstrated that the achievement of complete remission confers a survival advantage upon the patient.
Anecdotal reports suggest that patients who have relapses after deoxycoformycin therapy can be reinduced to complete remissions with additional pentostatin [112]. Previous failure to respond to splenectomy or chemotherapy does not appear to affect the response to pentostatin. Deoxycoformycin has also shown activity in patients for whom interferon treatment failed [114 115].

The optimum dose and frequency of deoxycoformycin administration remains to be established. However, less intensive regimens appear equally effective in inducing complete remission and are associated with less toxicity [112]. The optimal duration of therapy remains to be determined as well. Spiers et al. [110] and Kraut et al. [112] treat until complete remission, whereas Johnston et al. [111] and Eisenhauer et al. [113] consolidate with two additional courses beyond complete remission.

In general, the toxicity with these regimens was mild. Most patients reported mild to moderate nausea and vomiting, usually with onset 24 hr. after drug administration and lasting for less than 24 hr. Lethargy, fever, skin rash, transient reductions in creatinine clearance, altered taste, itching, keratoconjunctivitis and photodermatitis were also reported. All these toxic effects were reversible and well tolerated. Of interest and clinical importance, two patients with creatinine clearance of 50 and 60 ml/min could be treated using very low doses (2-3 mg/m² IV every two weeks), and they obtained complete remissions after 6 and 10 weeks of treatment, respectively [116].

Although pentostatin is not a potent myelosuppressive agent, some worsening of neutropenia is usual at the beginning of treatment. Furthermore pentostatin is a potent immunosuppressive agent and may enhance the liability to infection, already increased in patients with HCL. Opportunistic infections have previously been reported to be uncommon (8 per cent) complications of pentostatin therapy for other lymphoproliferative disorders [117], and the doses currently used to treat HCL are markedly lower. However Spiers et al. [110] reported on one patient who died from multiple opportunistic infections after having a response to pentostatin. Preliminary evidence from the study of Kraut et al. [112] suggests that low-dose pentostatin may be extremely effective treatment for hairy cell leukemia without enhancing the liability to infection.

Comments and recommendations

In recent years major advances, have been made in our understanding of the biology of hairy cell leukemia, in its diagnosis and treatment. The B-lymphocytic character of most cases of HCL has been clearly established by monoclonal antibody phenotyp-