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Perspectives and Commentaries

Perspectives in the Treatment of Hairy Cell Leukemia

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HAIRY cell leukemia (HCL), although rare, has become a well-defined clinicopathological entity. The disease, affecting mainly men aged between 35 and 55 years, is characterized by splenomegaly, pancytopenia and morphologically typical cells in blood, spleen and bone marrow. Hairy cells (HC) are leucocytes with prominent cytoplasmic villi, tartrate-resistant acid phosphatase activity and inducible phagocytic properties. Their B-cell nature has now been definitely assessed. The bone marrow is difficult to aspirate and myelofibrosis is often present.

Symptoms are most often related to a reduction in circulating blood counts, the main problem being an increased susceptibility to infections due to neutropenia and monocytopenia.

The median survival of patients with HCL is 4–5 years but some 10% of cases have a very indolent course.

The different therapeutic options investigated in HCL will be briefly reviewed with some more emphasis on the very promising new results obtained with interferon (IF) and deoxycoformycin (dCF).

SPLENECTOMY

Splenectomy has for long been considered the treatment of choice in HCL. The aim is primarily to remove splenic sequestration of normal blood cells and thus alleviate pancytopenia. Pancytopenia can, however, also be caused by bone marrow insufficiency due to infiltration.

After splenectomy, the hematological recovery is usually rapid (less than 2 months). The platelet count is the factor that shows an increase most often while the neutrophil count increases the least frequently.

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A beneficial effect of splenectomy on the blood parameters and even on survival has been shown in several studies. The precise indications for splenectomy are however still debated. From a large retrospective multicenter analysis, Jansen *et al.* concluded that the splenectomized group (255 patients) survived significantly longer than the non-splenectomized (166 patients). The survival advantage was, however, restricted to patients with large spleens and cytopenia. Indeed, the patients with low hemoglobin or neutrophil levels whose spleen was not enlarged did not do better than their non-splenectomized counterparts [1].

After variable delays ranging from a few months to more than 10 years, the post-splenectomy improved blood parameters will deteriorate again in a large number of patients who will then require other treatment modalities.

CHEMOTHERAPY

For post-splenectomy patients 2 main chemotherapeutic approaches have been tried. Low-dose continuous chlorambucil (CBL) is usually effective but not without hazard and the impact of this treatment on survival has not been settled. Although the circulating HC can be reduced and the platelet and hemoglobin levels can be increased, the granulocyte count frequently remains low leaving the patients susceptible to life-threatening infections [2]. Moreover a patient has been described to have died from a dysmyelopoietic syndrome developed 3 years after the initiation of CLB therapy. Alternatively, high-dose chemotherapy, mostly a combination of several cytotoxic drugs used in patients with an advanced stage of HCL, can result in complete remissions but at the price of prolonged aplasia and toxic deaths. The published data on high-dose chemotherapy in HCL, which are all favorable, probably do not

represent a random sample of this form of therapy [3].

BIOLOGIC THERAPY OF HCL

First attempts

Multiple abnormalities of the immune system have been described in patients with HCL and it has been hypothesized that some of them, such as monocytopenia, could play a role in the defective hematopoiesis afflicting these patients.

Theoretically stimulating are the results obtained with costly experimental approaches such as leukapheresis or transfusions of mononuclear-enriched fractions from siblings. These transfusions resulted in long-lasting hematological improvements in 4 out of 11 HCL patients [4]. To explain these effects, favorable cellular interactions resulting in production of colony-stimulating activity or transfer of other molecular information have been suggested. On the other hand, the beneficial effects of leukapheresis reported in 7 out of 14 evaluable cases reviewed by Yam [5] have been ascribed to the removal of a large number of malignant cells or putative cellular or humoral inhibitory factors.

Improvement of cytopenia has been reported occasionally with androgens or corticosteroids but it is admitted that this latter treatment is most often ineffective and probably even harmful by promoting opportunistic infections.

We have been impressed by the responses in 2 of 3 HCL patients who were given lithium carbonate for severe hematopoietic failure. As previously described [6], we could observe not only a striking improvement in normal blood counts but also a dramatic decrease of circulating HC. Considering the low cost and toxicity of this treatment, we estimate that it is worthy of further evaluation.

New developments

Interferons. The encouraging preliminary results reported in 1984 by Quesada [7] on the use in HCL of a partially purified preparation of leukocyte interferon (IF-α) have been confirmed by several other investigators using purified recombinant IF-α or lymphoblastoid IF. For Quesada, complete remission (CR) is defined as complete clearance of HC from blood and bone marrow and disappearance of organomegaly or lymphadenopathy. For partial remission, a decrease of 50% of HC in blood and marrow is required and a decrease of organomegaly by at least 50%. All the remitters had hemoglobin $\geq$ 12 g/dl, neutrophils $\geq 1.5 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l. In some studies, a third category, improvement or minor response, implies some decrease of HC infiltration and return of at least 1 of the blood parameters to the levels defined above.

Applying the stringent response criteria and administering rather low IF doses (ranging from 2 mega-units 3 times a week to 5 mega-units daily) to patients with progressive HCL, the authors report 75% remissions and about 15% minor responses. CR however are rare except in a few previously untreated patients [8].

At least 4-6 months of therapy are needed to attain significant responses and further improvement, such as the disappearance of marrow fibrosis, can be observed even later: between the 6th and 9th month of treatment as reported by Berneman. The first signs of response are generally the disappearance of organomegaly and HC from the blood, occurring during the first month while neutrophils are decreasing. Mean platelet levels increase within the first 2 months, followed by a significant increase in neutrophils and hemoglobin only after the end of the second month. Transient monocytosis is common during the third month [9].

Systemic toxicity is mostly minor but the myelosuppression during the first month of IF therapy can be severe enough to induce infectious complications.

The optimal duration of IF treatment in HCL remains an open question that will be settled hopefully by several ongoing randomized trials. During therapy, the responses are usually sustained. After discontinuing IF treatment which lasted 12 or 18 months, preliminary data of Ratain *et al.* [10] indicate unmaintained remissions up to 9 months.

Another unsettled point is the mechanism of action of IF. Is it only a direct antitumor effect or also an antiviral effect directed against a possible viral infection implicated in the etiology of HCL? Does the increase of natural killer activity observed during IF treatment play a role [11] or is HCL an IF-deficiency syndrome because monocytes which are the major source of IF-α are severely depressed in this disease? [12]

Deoxycoformycin. 2′-Deoxycoformycin (dCF), a potent inhibitor of adenosine deaminase (ADA), seems particularly active in HCL. Four studies totaling 39 evaluable patients report on a response rate higher than 90% with 50% complete remissions after a short course of dCF given intravenously at 4–5 mg/m^2/week [13–15]. The responses started early, were oberved even in patients with a huge tumor load or refractory to IF and persisted up to 24 months after the end of therapy.

Weekly dCF administration can cause lethargy, reversible renal impairment, gastrointestinal disturbances and a slight neutropenia in some patients. Untoward effects, especially skin rashes, seem to be potentiated by concomitant allopurinol intake.

The antitumor activity of dCF has not been elucidated. Before treatment, the blood mononuclear cell ADA activity in the patients was below

normal or in the normal range and was suppressed by 4 mg/m^2 dCF. The plasma levels of IF did not change during treatment making it unlikely that dCF exerts its activity by inducing endogenous IF synthesis [16].

CONCLUSION

The availability of IF and dCF opens a completely new era in the treatment of HCL. Until very recently our therapeutic problem was limited to the choice of the best moment to perform splenectomy and the best way to improve the blood counts in patients without splenomegaly or in those relapsing after splenectomy.

The promising new data are raising questions related to the mechanisms of action of these agents but also to the therapeutic strategy in HCL. To what extent can these results improve survival in HCL? When should the treatment of HCL patients with minimal cytopenia and no clinical manifestation be started? Do the prolonged complete remissions observed with IF and with dCF permit some hope of curability in this disease? Is splenectomy still the first line treatment? Is dCF superior to IF? Is there any place for combination or sequential therapy, i.e. dCF followed by a well-tolerated IF maintenance regimen or by chemotherapy whose hematoxicity will perhaps be less severe if applied in remission? Regarding the rarity of the disease, only well conducted multicenter randomized trials will answer these questions in the forthcoming years.

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