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NEW TARGET OF CHRONIC LYMPHOCYTIC LEUKEMIA TREATMENT

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Chronic lymphocytic leukemia (CLL) is a hematologic neoplasm characterized by proliferation and accumulation of small, relatively mature appearing, immunologically incompetent lymphocytes, usually of B-lineage. CLL is the most frequent form of leukemia in Western countries, with an incidence of 3 to 5 new cases per 100,000 people per year. Characteristically, CLL is a disease of advancing age, the peak incidence being between 60 and 80 years.[1] However, the disease is increasingly being diagnosed more frequently among younger age groups and is no longer considered unusual even in patients 30-35 years of age. In fact, their number is rising as routine hematochemical screening is being undertaken more and more often in our health-conscious society.

CLL belongs to the category of low-grade malignant lymphomas and is, in many cases, of an indolent nature: the annual mortality rate is about 8%, median survival is nearly 6 years, and 20% of patients survive more than 10 years.[2,3] Although chlorambucil and cyclophosphamide have been the mainstays of chemotherapy[4-6] in CLL for over 20 to 30 years and both these drugs are known to have significant clinical effects, usually assessed as partial remissions, it is also recognized that no treatment available to date has been able to improve the natural history of the disease. In addition, there are no convincing data demonstrating that combination chemotherapy with COP is superior to chlorambucil with or without prednisone;[7,8] preliminary data suggest a possible benefit from CHOP in advanced disease.[9] So far treatment has not been aimed, with good reason, at curing the disease but rather at prolonging survival and improving the quality of life.

In the last 5 years clinical trials have demonstrated that three purine analogs may be clinically useful in CLL: fludarabine, 2-chlorodeoxyadenosine (2-CdA) and 2-deoxycoformycin (DCF). These drugs, in particular fludarabine, are already the treatment of choice for patients failing to respond to conventional therapies.[10-19] In this context preliminary results, which show a very high response rate with these new drugs, seem to offer some hope of progress in the foreseeable future. The role of these agents as frontline treatment in CLL is more uncertain. In the present issue of *Haematologica* a paper by Spriano et al.[20] reports on the high efficacy of fludarabine in untreated CLL patients. Although it is likely that in the near future the purine analogs will substitute chlorambucil for treating CLL, the superiority of these drugs over chlorambucil and CHOP in terms of survival has not yet been proved in randomized trials.

On the other hand, initial pilot trials with allogeneic[21-23] and autologous[24-26] transplantation in refractory young CLL patients with advanced disease demonstrate that this therapy is feasible and perhaps beneficial. As in other settings, results are better when the patient is transplanted with minimal disease that is still responding to conventional therapy. In some patients, immunoglobulin gene rearrangement studies showed no residual disease,[21,22] raising the possibility that allogeneic bone marrow transplantation might represent a potentially curative therapy for younger patients with CLL.

So, if CLL is curable, the next step would be to explore the feasibility and practicality of a therapeutic approach aimed at these goals: inducing complete response and curing the patient. These goals would pertain to a specific

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subgroup of patients, the youngest subset, because for the majority of elderly CLL patients needing treatment the most reasonable aim would be to obtain the greatest response with acceptable toxicity. In contrast, young patients with poor risk factors warranted new approaches in an attempt to achieve cure. The poor prognostic features in younger patients that justify trying to eradicate the disease include advanced clinical stage, diffuse bone marrow histopathology, and high and/or rapidly increasing blood lymphocyte count. Age alone should not be considered a criterion for initiating therapy. In fact, patients with these characteristics, if treated with conventional drugs, have a median survival of less than 5 years.

With the aim of eradicating the disease, frontline therapy with fludarabine or 2-CdA is more likely to induce a complete response than chlorambucil.[20] Next, the possibility of performing an allogeneic bone marrow transplant should be considered in these poor-risk young patients with minimal disease or in complete remission for whom an HLA-matched donor is available. However, the potential benefits of a transplant should be balanced against its well-defined risks, i.e. the high mortality rate related to the procedure. In some circumstances, e.g. the unavailability of an HLA histocompatible donor, and provided a complete clonal remission has been obtained with standard therapy, an autologous procedure could be an alternative to allogeneic transplantation. Thus, the use of purine analogs and transplant in sequential combination represents the new target and, probably, the gold standard approach in the next decade for younger CLL patients with poor risk factors.

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