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Malignant Lymphomas

Low-dose fludarabine and cyclophosphamide in elderly patients with B-cell chronic lymphocytic leukemia refractory to conventional therapy

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ABSTRACT

Background and Objectives. **In recent years fludarabine alone or in combination with other drugs has been reported to be effective in the treatment of B-cell chronic lymphocytic leukemia (B-CLL), both as first line and salvage therapy. Among the different combination regimens, the association of fludarabine and cyclophosphamide has shown a considerable therapeutic efficacy, although a relevant number of infectious complications have been described, particularly in elderly patients. The aim of this work was to evaluate the efficacy, the toxicity, and the incidence of infectious episodes of a regimen combining lower doses of fludarabine and cyclophosphamide in elderly patients with B-CLL refractory to conventional therapy.**

Design and Methods. **Twenty patients with progressive B-CLL with a median age of 75 years (4 in stage B and 16 in stage C) and refractory to conventional therapy were enrolled in this study. The combination regimen was as follows: fludarabine 15 mg/m^2/day i.v. [max 25 mg] and cyclophosphamide 200 mg/m^2/day i.v. for four days.**

Results. **All patients enrolled were evaluable for response. Three out of 20 (15%) patients achieved a complete remission (CR), 14/20 (70%) a partial response (PR) with an overall response rate (CR+PR) of 85%, according to National Cancer Institute-Working Group response criteria. Three patients were considered resistant. In four out of 20 patients (20%), a severe neutropenia (neutrophils < 0.5×10^9/L) occurred and one of them developed an infectious complication which required treatment with systemic antibiotics and granulocyte colony- stimulating factor (G-CSF). Non-hematologic toxicity was negligible in all patients but one, who despite a adequate therapy with allopurinol and hydration, experienced a tumor lysis syndrome with transient but severe renal impairment.**

Interpretation and Conclusions. **The association of low-dose fludarabine and cyclophosphamide appeared to be effective in this subset of B-CLL patients, reproducing a similar overall response rate obtained with other fludarabine-based combination therapies. In addition, in this group of elderly patients, toxic side effects were negligible and infectious complications remarkably low.**

Key words: fludarabine, cyclophosphamide, B-CLL-elderly

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Treatment of patients with B-CLL is generally recommended for patients with advanced or active disease and for patients with progressive disease. Chlorambucil is still an accepted therapy and is particularly indicated in elderly patients. However, when progression occurs in these patients, additional agents should be considered. Despite a certain myelosuppressive and T-cell impairment, fludarabine has been, in this last decade, the most employed and effective drug in both treated and untreated patients with B-CLL. Fludarabine has been used alone and also in combination with mitoxanthrone and cyclophosphamide. This latter combination (fludarabine + cyclophosphamide) has produced an increase in the response rate, particularly in patients resistant to alkylating agents.[1,2] On the basis of these encouraging preliminary reports, we initiated in a group of elderly B-CLL patients with progressive disease and refractory to conventional therapy, a therapeutic approach combining lower doses of fludarabine and cyclophosphamide in order to minimize the therapy-related toxicity.

Design and Methods

Between April 1997 and September 1999, 20 consecutive elderly patients with progressive, advanced B-CLL[3] refractory to conventional chemotherapy, were enrolled in the study after having given written informed consent. The inclusion criteria included normal hepatic, renal, respiratory and cardiac function and a life expectancy > 6 months. The treatment regimen was as follows: fludarabine 15 mg/m^2/day i.v. [max 25 mg] from day 1 to 4 and cyclophosphamide 200 mg/m^2/day i.v. from day 1 to 4. Courses were repeated every 28 days, for a maximum of five cycles.

Patients' characteristics

All 20 patients enrolled in this study were evaluable for response. Eight were females and 12 males; their median age was 75 years (range 61-87 years). Eight patients had received two prior treatments, while the remaining 12 patients had received more than two previous

Table 1. Patients' characteristics and response.

Patient	Age (years)	Sex	Binet stage	N° of previous treatments	Response
1	67	F	C	2	CR
2	61	F	B	3	PR
3	79	M	C	3	PR
4	78	M	C	3	PR
5	76	F	C	3	PR
6	72	M	C	3	PR
7	87	M	C	2	PR
8	82	M	C	3	CR
9	73	F	C	2	PR
10	61	M	C	4	PR
11	77	M	B	3	PD
12	68	M	C	3	PR
13	73	M	C	3	PD
14	68	M	C	3	PR
15	76	M	B	2	CR
16	75	F	C	2	PD
17	72	F	C	2	PR
18	74	F	C	3	PR
19	78	M	C	2	PR
20	86	F	B	2	PR

CR=complete response; PR=partial response; PD=progressive disease.

therapies. First-line therapy had been chlorambucil with or without steroids, second-line CHOP-like regimens, and finally third-line therapy was an association of oral idarubicin and cyclophosphamide. According to the Binet staging system,[4] 4 patients were in stage B, and 16 in stage C (Table 1).

Response criteria

The responses were assessed according to NCI/WG response criteria.[3] In particular, complete remission (CR) was defined by a negative physical examination, absence of systemic symptoms, lymphocyte count $\leq 4\times10^9$/L, polymorphonuclear cell count $\geq 1.5\times10^9$/L, platelet count > 100×10^9/L, hemoglobin value > 11 g/dL and less than 30% bone marrow infiltration. Partial remission (PR) was defined as a reduction > 50% of lymphadenopathies and organomegalies, platelet count > 100×10^9/L, and hemoglobin value > 11 g/dL. Progressive disease (PD) was characterized by an increase in the absolute number of circulating lymphocytes and/or in the size of lymph nodes or organomegalies.

Results

Overall response

Of the 20 patients enrolled in this study, 3 (15%) fulfilled criteria for CR and 14 (70%) for PR with an overall response rate of 85% (Table 1). The remaining three patients were considered resistant. Fifty-eight cycles of chemotherapy were delivered to the 20 patients for a median of about three cycles per patient (range 1-5 cycles). All the cycles were delivered on schedule. Of the 3 patients in CR only one relapsed after 12 months, whereas the other two are still in CR after 18 and 24 months. Overall, seven patients died of causes related to disease (5 in the PR group and 2 in the PD group). In more detail, 1 patient developed Richter's transformation, 4 patients died of hemorrhage, and 2 patients died of progressive uncontrolled disease. The median time to progression of the remaining 9 patients in PR was 10 months (range 2-19).

Toxicity

Four patients (#2, 9, 13 and 17) developed a WHO grade 4 granulocytopenia (neutrophils < 500/μL) associated only in one case (#13) with an infectious complication that required specific treatment. Two patients (#8 and 11) received packed RBCs because of severe anemia (WHO grade 3). None of the patients developed severe thrombocytopenia (WHO grade 4).

Non-hematologic toxicity was negligible in all patients except one (patient #1) who developed, despite allopurinol prophylaxis, WHO grade 4 renal toxicity due to a tumor lysis syndrome. This patient required dialysis for 8 consecutive days before recovering normal renal function.

Discussion

In the last years, purine analogs and particularly fludarabine alone or in combination with other agents, have been reported to be effective in the treatment of low-grade non-Hodgkin's lymphomas and B-CLL, with a higher response rate particularly evident in untreated patients.[2,5-8] However, although fludarabine is the drug that produces the highest remission rate ever reported in B-CLL patients, responses are often complicated, especially in elderly patients, by an increased risk of infection due to neutropenia and, to a lesser extent, to a decrease of CD4 lymphocytes, as well as to the immunosuppressive effect of corticosteroids. On the basis of these data, in a selected group of elderly patients with relapsed/progressed B-CLL after 2 or more chemotherapeutic regimens we combined fludarabine and cyclophosphamide as a very effective therapeutic option. Furthermore, in order to minimize the risk of infectious complications, we avoided the use of corticosteroids and reduced the doses of both fludarabine and cyclophosphamide. This pivotal study conducted in a selected group of patients demonstrated that the combination of low-dose fludarabine and cyclophosphamide was able to produce, in 20 elderly B-CLL patients refractory to conventional therapy, 3 CR and 14 PR with an overall response rate of 85%. Clinical toxicity was mild

or negligible. Major events were a tumor lysis syndrome in a patient who required dialysis treatment before full recovery of renal function, and one single infectious episode which occurred in 1 out of 4 patients who developed a grade IV neutropenia and which resolved with administration of systemic antibiotics and granulocyte colony-stimulating factor (G-CSF). These results suggest that, despite the reduction of fludarabine dosage, the overall response rate is the same as that obtained with other published associations with a very low incidence of therapy-related complications and, in particular, infections.[7,9] Furthermore, it is noteworthy to consider that in 11 patients, CD4 lymphocytes were counted before and after treatment with fludarabine + cyclophosphamide and, despite a reduced number of this T-cell subset in the majority of cases, only 1 patient developed a severe infection (data not shown). On the basis of this finding, with the caution due to the small number of cases analyzed, it appears that the risk of infection is independent of the number of CD4 lymphocytes.

In conclusion, according to this preliminary report, the association of low dose fludarabine and cyclophosphamide seems to be an effective and safe treatment for elderly patients with B-CLL refractory to conventional therapy. This low-dose fludarabine-based regimen appears to be well tolerated and associated with a low rate of infections. It could be an attractive treatment of choice for elderly patients with B-CLL.

Contributions and Acknowledgments

GM was the principal investigator, contributed to the conception of the study, its design, data handling and interpretation and wrote the paper. CB, ML, and MT were involved in the recruitment of and day-to-day contact with patients and contributed to data handling and interpretation. MB contributed to the conception of the study. FL was the principal contributor to the conception of the study and was responsible for direct supervision and critical revision of the final version of the manuscript.

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Disclosures

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Manuscript processing

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Potential implications for clinical practice

- The association of low-dose fludarabine and cyclophosphamide is a safe and effective therapeutic option for elderly patients with B-cell chronic lymphocytic leukemia refractory to conventional therapy.

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