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FLU-ID (FLUDARABINE AND IDARUBICIN) REGIMEN AS SALVAGE THERAPY IN PRETREATED LOW-GRADE NON-HODGKIN'S LYMPHOMA

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ABSTRACT

Fludarabine (FLU) is a new antimetabolite chemotherapeutic agent with promising activity in lymphoproliferative disorders and, in particular, in low-grade non-Hodgkin's lymphoma (LG-NHL). Recently, a few reports have described interesting results using FLU in polychemotherapy regimens. In order to evaluate FLU in combination with other antineoplastic agents, we used a combination of FLU and idarubicin, called the FLU-ID regimen, to treat 10 patients with recurrent LG-NHL. The FLU-ID regimen was as follows: FLU 25 mg/sqm i.v. on days 1 to 3 and idarubicin 12 mg/sqm i.v. on day 1. Of the 10 patients, 2 (20%) achieved complete response (CR), 5 (50%) partial response, and the remaining 3 showed no benefit from the treatment. The 2 CR patients are still in remission after 6 and 8 months, respectively. The median duration of overall survival of all patients was 8 months. The major toxic effects observed were neutropenia (40%) and infections and/or febrile episodes (15%); no fatalities due to drug side effects occurred. These results indicate the efficacy of the FLU-ID regimen in inducing a good remission rate with moderate side effects in recurrent LG-NHL.

Key words: combination chemotherapy, fludarabine, idarubicin, recurrent LG-NHL

No aspect of the optimal management of non-Hodgkin's lymphoma patients is more controversial than that of patients with low-grade histologies. Standard regimens including an alkylating agent proved to be palliative treatments with a median survival of 5-8 years; aggressive regimens with anthracyclines have not improved these results. High-dose therapy followed by bone marrow or peripheral blood stem cell support has also failed to prolong survival.

Among conventional drugs, several trials shown that idarubicin is effective, as single agent, in the treatment of relapsed/refractory non-Hodgkin's lymphoma (NHL).[1,2] In the last few years two purine analogs, fludarabine (FLU) and 2-chlorodeoxyadenosine (2-CdA), have been used extensively in previously treated LG-NHL patients,[3-5] producing responses, mostly partial, in 40-50% of patients. In particular, a few investigators have reported data concerning the efficacy and safety of the combination of fludarabine with mitoxantrone[6,7] and fludarabine with cyclophosphamide.[8]

On the basis of these data, we started a pilot trial with FLU and idarubicin (FLU-ID regimen) in previously treated patients with LG-NHL, and in this report we summarize our experience.

Patients and Methods

From June 1994 to December 1994, 10 patients with LG-NHL were entered in this phase II study. The main protocol requirement was that patients initially had advanced (stage III or IV) disease, as outlined by the Ann Arbor Conference,[9] for which first/second-line treat-

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ment had failed to produce complete response or relapse had occurred.

Criteria for entry into the study included: histologic diagnosis of LG-NHL according to the updated Kiel classification;[10] the presence of measurable disease; normal hepatic, renal, cardiac function; radiation and chemotherapy had to be discontinued at least 6 weeks before the start of treatment. Informed consent was obtained from all patients in accordance with the ethical policy of the Institute.

The FLU-ID regimen schedule was as follows: FLU 25 mg/sqm i.v. on days 1 to 3 and idarubicin 12 mg/sqm i.v. on day 1. FLU was supplied by Schering S.p.A. (Milan, Italy). Courses were given at 3-week intervals for a maximum of 6 cycles. All patients received bacterial and *Pneumocystis carinii* prophylaxis with co-trimoxazole (2 days per week) only during the entire course of therapy.

Patients were restaged after completion of 6 cycles. Clinical and pathologic evaluations were made by repeating radiographic investigations and bone marrow biopsy if previous results had been positive.

Patient characteristics

Of the 10 patients with LG-NHL, 6 were males and 4 females and the mean age was 55 years (range 40 to 64 years). Six patients had stage III and 4 stage IV disease; systemic symptoms were present in 3 patients.

The time from the initial diagnosis of LG-NHL to the start of the FLU-ID regimen ranged from 12 to 25 months (median 18 months). All these patients had previously received one (6 patients: 2 patients CHOP regimen, 2 CVP regimen, and 2 patients VNCOP-B protocol), or two (4 patients: 2 patients received CHOP and CVP, and 2 CVP and VNCOP-B) chemotherapy treatments. All the patients had recurrent, relapsed disease and none presented resistant disease; Table 1 depicts the pretreatment characteristics of the 10 patients.

Response criteria

Complete response (CR) was defined as a complete disappearance of signs and symptoms due to lymphoma that was maintained for at least 6 weeks; partial response (PR) was defined as a reduction of at least 50% in the product of two largest perpendicular diameters of all measurable lesions for a duration of at least 6 weeks. Standard Eastern Cooperative Group (ECOG) toxicity criteria were used.[11]

Table 1. Characteristics of 10 LG-NHL patients treated with the FLU-ID regimen.

N. of patients	10
Median age (yr) (range)	55 (40-64)
Sex M/F	6/4
Stage:	
III	6
IV	4
Histology*:	
Cb/CC F	6
Cb/Cc F & D	2
Ic	2
Prior therapy:	
1 treatment	6
2 treatments	4

Cb/Cc F= centroblastic/centrocytic follicular; Cb/c F & D= centroblastic/centrocytic follicular and diffuse; Ic= immunocytoma lymphoplasmacytoid.

Results

Response

Of the 10 patients studied, 2 fulfilled the criteria for CR and 5 for PR (70% overall response rate); the remaining 3 patients did not respond to the therapy. The likelihood of response correlated with the number of previous chemotherapy regimens. In fact, in the 6 patients who had previously received only one regimen, 2 CR and 2 PR were documented. In contrast, among the 4 patients who had received two different previous treatments, 3 PR were documented.

Concerning disease stage, we observed CR in 2 stage III patients; as for histology, the 2 CR patients presented centroblastic/centrocytic follicular lymphomas. Both complete responders had obtained a first CR with the induction treatment, and this remission had lasted for 9 and 11 months, respectively.

They are currently still in remission after 6

and 8 months, respectively. None of the other responses have been maintained. Among the partial responders, one progression was observed and this patient died from the disease. The median duration of overall survival of all patients was 8 months (range 6 to 16 months).

Toxic effects

The FLU-ID regimen was well tolerated in general, and all patients completed the therapy. With regard to hematologic toxicity, neutropenia was observed in 4 (40%) patients, 1 of whom reached grade 3 or 4 (neutrophil count less than 1×10^9/L), whereas thrombocytopenia, which was observed in 3 patients, was much less severe (grades 1 and 2)(platelet count between 50 and 100×10^9/L). Five (8%) of a total of 60 courses were temporarily postponed for one week because of neutropenia and/or thrombocytopenia, but no trend toward cumulative myelosuppression was observed.

Other major toxic effects were represented by infections; 1 episode of pneumonia and one moderately severe febrile episode in a neutropenic patient who showed negative cultures. No direct correlation was noted between the intensity of neutropenia after treatment and the incidence of febrile episodes. Cardiac, liver and renal side effects were not observed, and no fatalities due to drug side effects occurred.

Discussion

In this study, the 10 recurrent LG-NHL patients evaluated for response and toxicity to the FLU-ID regimen registered an overall response rate of 70%, with a CR rate of 20%.

LG-NHL continue to represent a challenge for hematologists. Patients with LG-NHL respond well and often achieve CR with conventional alkylating agent-based chemotherapy, but early relapses are frequent; only approximately 25% of patients are free of disease at 5 years. There is no standard therapy for patients who relapse after or become refractory to alkylating agents. Treatment options range from a *watch and wait* approach for asymptomatic patients to intensive high-dose chemo-radiotherapy with bone marrow or stem cell transplantation.[12]

Recently, FLU and 2-CdA, either alone[3-5] or in combination with other drugs,[6-8,13] have shown promising therapeutic activity of previously treated and untreated patients with LG-NHL.

Our results with the FLU-ID regimen are encouraging and confirm those observed with fludarabine and mitoxantrone;[6,7] in fact, we observed a higher overall response rate as well as a greater percentage of complete responders than that obtained with FLU alone.[3-5] The toxic effects of this regimen were acceptable, with neutropenia and infections being the most prevalent problem.

The above studies on FLU alone indicate that this drug effectively induces remission in patients with LG-NHL, particularly those with follicular histology. However, as with other therapeutic modalities for LG-NHL, remission is rarely maintained beyond two years.[14] On the basis of these data, a fludarabine-idarubicin combination-containing regimen is associated with a significantly higher overall response rate and complete response rate respect to with FLU alone in relapsed and advanced LG-NHL patients. Therefore these data indicate that FLU-ID-based regimens should be incorporated into first-line randomized trials of LG-NHL that compare fludarabine-containing schemes and other LG-NHL treatments, in order to evaluate possible advantages with regard to remission induction and duration of response.

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