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A NEW EFFECTIVE TREATMENT FOR INDOLENT LYMPHOMA: A PILOT STUDY WITH FLUDARABINE, IDARUBICIN AND PREDNISONE COMBINATION (FLIDA)

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SUMMARY

The management of indolent lymphomas is still controversial. Intensive therapies may improve remission rate but in association with toxicity. Fludarabine and idarubicin are very active drugs in indolent lymphomas. This pilot trial was designed to evaluate the efficacy of a regimen comprising fludarabine, idarubicin and prednisone (FLIDA) in the treatment of low-grade non-Hodgkin's lymphoma at diagnosis. We have assessed the response of 16 adult patients (median age 57 years, range 45–71 years) treated on an outpatient basis: the overall response rate was 93·8 per cent (CR 43·8 per cent, PR $\geq$50 per cent). The toxicity of this regimen was very low, with no relevant hematological and infectious complications. © 1997 John Wiley & Sons, Ltd.

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KEY WORDS NHL; fludarabine; idarubicin

INTRODUCTION

In recent years little progress has been achieved in the treatment of indolent lymphomas. Standard therapies in advanced stage indolent lymphoma are transiently effective, but there is never a plateau in the survival curves. Current treatments are to be considered unsatisfactory, even if life expectancy in these patients is measured in years. Intensive treatments have been shown to induce high complete response (CR) rates, but the median survival duration is similar when compared with patients treated with less aggressive regimens.[1–3]

The new purine analogues, particularly fludarabine, have shown to be very active in indolent lymphoproliferative diseases.[4–7]

Idarubicin has shown to be very active in patients with non-Hodgkin's lymphoma,[8–10] and has been reported to be only partially susceptible to some mechanisms of chemoresistance.[11,12]

Phase I and II trials have demonstrated the efficacy of a combination schedule including fludarabine, mitoxantrone and dexamethasone in patients with relapsed indolent lymphoma.[13]

On the basis of these findings we conducted this pilot study to evaluate the safety and the therapeutic efficacy of the FLIDA regimen (fludarabine, idarubicin and prednisone) in untreated patients with low-grade non-Hodgkin's lymphoma.

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Table 1. Patient and lymphoma characteristics

	n	%
Patients	16	
Median age	57 (range, 45–71)	
Histology (Working Formulation)		
A	7	43·8
B	1	6·2
C	8	50
Stage		
II	1	6·3
III	1	6·3
IV	14	87·4
Sex		
Female	8	50
Male	8	50
Bone Marrow Positive	13	81·3
Leukemic Phase	4	25
LDH median* (range)	404·5 (279–561)	
β2-microglobulin	1·7 (1·0–4·7)	

*Normal values <450 U/l.

PATIENTS AND METHODS

Patients

Between March 1995 and December 1996, 16 adult patients with low-grade lymphomas at diagnosis were sequentially enrolled onto the study. Characteristics of patients are shown in Table 1. Eligibility criteria were histologic diagnosis of low-grade non-Hodgkin's lymphoma (A, B and C of Working Formulation), clinical stage III or IV, performance status 0–3 (ECOG), age <65 years, normal cardiac function (ventricular ejection fraction $\geqslant$ 50 per cent). One patient with clinical stage II was included in the study for the aggressive clinical presentation (B symptoms, node enlargement for only a short time). Exclusions criteria were primitive localization at central nervous system, positive serology for human immunodeficiency virus. Staging included for all patients a full history and physical examination, complete blood counts, blood chemistries, chest X-ray, chest abdominal and pelvic CT scan, bone marrow biopsy, abdominal sonography, rhinopharynx examination, upper digestive endoscopy.

Evaluation of response

Response was carefully evaluated at the end of the treatment and complete remission (CR) was defined as the disappearance of clinical evidence of disease and normalization of all parameters that had been abnormal before therapy. CR was assessed 1 month after the end of the therapy. Partial remission (PR) was defined as a greater than 50 per cent reduction in the dimension of the tumour. Progressive, stable disease or less than 50 per cent regression was defined as a non-response (NR). WHO criteria were used to assess toxicity.[14]

Data analysis

Survival curves were generated using the Kaplan–Meier method.[15]

Table 2. Response to treatment

Patients	CR (%)	PR (%)	NR (%)
Total	43·8	50	6·3
Bone marrow positive	30·8	61·5	7·7
Stage			
II	100		
III	100		
IV	35·7	57·1	7·1
Leukemic phase	25	50	25

Treatment schedule

Chemotherapy was delivered on an outpatient basis. Patients received fludarabine 25 mg/m^2/day intravenously on days 1, 2 and 3, idarubicin 10 mg/m^2/day on day 1 and prednisone 150 mg/day orally on days 1–5. Treatment was repeated every 28 days for three to six courses. All patients were treated with cotrimoxazole and fluconazole or itraconazole prophylactically. Informed consent for the patient's participation was always obtained from the patient.

RESULTS

Response

A summary of response data is presented in Table 2.

The number of courses delivered to the entire group was 87 (the first three patients received three courses of FLIDA). The overall CR plus PR rate was 93·8 per cent (15/16 patients). Seven (43·8 per cent) patients achieved a complete remission, eight (50 per cent) a partial remission and one (6·3 per cent) was considered a non-responder. Among patients with bone marrow involvement at diagnosis 30·8 per cent achieved a complete remission, while all three with no bone marrow involvement achieved CR (100 per cent). In patients with a leukemic picture in the peripheral blood at diagnosis CR was achieved only in one patient, while six patients without the leukemic phase achieved CR. The CR rate was higher for patients in stage II and III (100 per cent) than for those with stage IV (35·7 per cent).

Survival

After a median follow-up of 18 months (range 5–23 months) the 2-year actuarial overall survival (OS) was 85 per cent and the failure-free survival (FFS) was 75 per cent. At the time of this analysis, 14/16 patients are still alive, and 6/7 of CR patients are still in complete remission. One patient who was considered a non-responder developed progressive disease and died of neutropenic sepsis during CHOP therapy 6 months after the FLIDA regimen. One PR patient with early progression of disease died of progressive lymphoma 12 months after discontinuation of FLIDA. One CR patient, who relapsed 11 months after the end of therapy did subsequently respond to chlorambucil treatment.

Toxicity

The toxicity of this regimen was very low (Table 3). No hematological toxicity of grade IV was reported. Only few patients experienced moderate neutropenia, and one patient was

Table 3. Hematological and clinical toxicity

Grade I	Grade II	Grade III	Grade IV	
Anaemia	—	—	—	—
Granulocytopenia	—	43%	21%	—
Thrombocytopenia	—	—	—	—
Infections	2%	2%	—	—

administered granulocytic colony-stimulating growth factor, so therapy was not delayed in the successive course.

No cardiac adverse effect was registered and no relevant infectious episodes were recorded.

DISCUSSION

The optimal care of advanced indolent lymphomas is controversial. Low-grade lymphomas often have an indolent course, but most patients ultimately die of the lymphoma.[16]

'Watch-and-wait' strategies or aggressive treatments may not differ in obtaining long survivals. In this group of lymphomas, particularly in older and asymptomatic patients, a high quality of life is one of the most important objectives of the treatment plan.[2]

It was therefore decided to evaluate the safety and efficacy of a regimen including drugs which are highly effective in the treatment of indolent lymphomas: fludarabine, one very promising purine analogue,[4–7] and idarubicin, an anthracycline which has been reported to be only marginally involved in some mechanisms of chemoresistance.[11,12]

FLIDA is a safe regimen, active in newly-diagnosed patients with low-grade lymphoma. In our previous experience with fludarabine in the treatment of chronic lymphatic leukemia we observed in 15 per cent of cases the onset of autoimmune hemolytic anemia (data not published). So we included in the FLIDA regimen prednisone at moderate doses. No relevant infectious episodes were observed.

The high response rate of this regimen is very encouraging and the results are similar to those reported by McLaughin[13] with the combination fludarabine–mitoxantrone. Fludarabine in 126 patients with previously treated low-grade non-Hodgkin's lymphoma induced a response rate of 64 per cent (18 per cent achieving a CR).[8] On the other hand, the long natural history of this subgroup of lymphomas, with long remissions after a variety of treatments, the relatively high cost of the FLIDA regimen and the relatively small number of patients included in this study, suggest the necessity of confirming these results in a larger randomized study in the future, with the identification of selected subset of patients who may be candidate to this therapeutic approach (histologic subtype, International Prognostic Index), and the possible role of a maintenance therapy.

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