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Favorable impact of low-dose fludarabine plus epirubicin and cyclophosphamide regimen (FLEC) as treatment for low-grade non-Hodgkin's lymphomas

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ABSTRACT

Background and Objective. **In recent years, conventional dose of fludarabine (FLU) alone or in combination with other drugs has been reported to be effective in the treatment of low-grade non-Hodgkin's lymphomas (LG-NHL). In particular, FLU and cyclophosphamide (CY) or FLU and mitoxantrone or idarubicin combined regimens have shown considerable therapeutic activity both as first line and salvage therapies, producing overall response rates ranging from 40-50% in previously treated patients and up to 70-90% in untreated ones. However severe neutropenia and infective complications have been reported in a significant number of patients. Based on these premises we evaluated the efficacy and toxicity of a new regimen combining low-doses of FLU with epirubicin (EPI) and CY (FLEC) in a group of advanced treatment-requiring LG-NHL patients. The aim of this study was to evaluate a strategy aimed at lowering therapy-related toxic effects without affecting the reported good response rate.**

Design and Methods. **Thirty patients with *de novo*, relapsed or refractory LG-NHL entered the study. FLEC regimen was as follows: EPI 60 mg/m² i.v. on day one, plus FLU 15 mg/m²/day i.v. (max 25 mg) and CY 250 mg/m²/day i.v. for four days.**

Results. **All 30 patients were evaluable for response, 13 (43%) fulfilled the criteria for CR and 11 (36%) for PR with an overall response rate of 79%. None of the 13 patients who achieved CR had relapsed after a follow-up of 2 to 23 months (median duration 13 months). With regard to age, 13/14 older patients (≥70 years) responded to the treatment and 9 of them maintained their response after a median of 13 months (range 2-22); six of the 14 (43%) obtained a CR. Therapy-related toxicity was mild regardless of age, neutropenia (43%) and fever of undetermined origin (26%) being the major side effects. Remarkably, a documented infection was recorded only in 2/30 (6%) patients.**

Interpretation and Conclusions. **A low-dose FLU-based FLEC regimen appeared to be effective for advanced treatment-requiring LG-NHL, reproducing a similar overall response rate (79%) reported to have been achieved with other FLU based combination therapies. Toxic side effects were negligible and in particular documented infections were remarkably uncommon even in the group of elderly patients.**

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In recent years, fludarabine (FLU) alone or in combination with other drugs has been reported to be effective in the treatment of LG-NHL. Objective response rates, ranging from 30 to 70%, have been reported in non-comparative studies evaluating FLU monotherapy at dosage regimens of 20 to 30 mg/m²/day administered for 5 consecutive days and repeated every 3-4 weeks.[1-4] In general, previously treated patients showed lower response rates than untreated ones. Major toxic effects included neutropenia (41-70%) and infections (0-20%).[4-6]

More recently, experimental evidence that FLU is a potent inhibitor of repair of DNA damage has led to this purine analog being combined with other agents such as mitoxantrone or idarubicin in order to improve therapeutic results. Overall, higher response rates (40-94%) and especially more complete responses (CRs) were observed, but a higher incidence of documented infections and particularly opportunistic ones was also reported.[7,8] The combination of FLU plus cyclophosphamide (CY) also seems to be promising despite the not negligible treatment-related toxicity observed.[9]

Based on these findings, we wanted to evaluate the efficacy and toxicity of a new regimen combining low doses of FLU, epirubicin (EPI) and CY (FLEC regimen) in groups of untreated and previously treated LG-NHL patients. The study had three objectives: i) to confirm the high response rate reported for other combined regimens, ii) to decrease therapy-related myelosuppression and infectious complications and iii) to evaluate feasibility and toxicity of this treatment in the elderly.

Design and Methods

Between September 1996 and June 1998, 30 consecutive patients with *de novo*, relapsed or refractory LG-NHL entered the study after having given informed consent, according to institutional guide-

lines. The criteria for entry included the presence of measurable disease, normal hepatic, renal and cardiac function and histology reassessment for relapsed patients. Staging evaluation was based on hematologic and chemical profiles including lactate dehydrogenase (LDH), bone marrow biopsy, immunophenotypic analysis of peripheral blood and bone marrow, and CT scan of the chest and abdomen.

The FLEC regimen was as follows: EPI 60 mg/m^2 i.v. on day one, FLU 15 mg/m^2/day (max 25 mg) i.v. from day 1-4 and CY 250 mg/m^2/day i.v. from day 1-4. Only in the first cycle prednisone (P), at the dose of 40 mg/m^2/day i.v. from day 1-4, was added. Courses were repeated at 21-28 days for a maximum of five cycles. Patients aged between 70 and 75 years old received 70% of the scheduled dose of EPI, while all patients ≥75 years old received a fixed dose of 50 mg. No infection prophylaxis with ciprofloxacin and/or cotrimoxazole was given, but treatment with ciprofloxacin (1 g per day for at least 5 days) was started in any patient whose neutrophil count was found to be below 1×10^9/L.

Patients' characteristics

All 30 patients enrolled in the study were evaluable for response. Eighteen were male and 12 were female; their median age was 68 years (range 32-82 years). Fourteen patients were ≥70 years old. Twenty patients were at the onset of their disease and 10 had received one or more prior treatment regimens (mean 2 regimens, range 1-4) frequently including doxorubicin and/or mitoxantrone. The majority of patients (28/30) had stage III-IV disease and 23 of them had bone marrow involvement. Eight out of the 30 patients had extranodal disease (2 skin, 3 tonsil, 1 lung and 1 pleural involvement). By histology subtypes, 11 patients had a B small lymphocytic lymphoma, 11 a follicular center, grade II lymphoma, 6 a mantle cell lymphoma, 1 a marginal zone lymphoma and 1 a mucosa-associated lymphoid tissue (MALT) lymphoma. Nineteen out of the 30 patients had a grade 0-1 and 11/30 a grade 2-3 performance status.

Response criteria

Complete remission (CR) was defined as the disappearance of all evidence of disease for at least 6 weeks. Partial remission (PR) was defined as reduction of the disease by at least 50% for at least 6 weeks. No response (NR) was defined as an increase or decrease of disease by less than 25%. Progressive disease (PD) was defined as an increase in the size of disease by at least 25% or the appearance of new lesions. Disease or progression-free intervals were calculated from the date of response until the time of disease progression or recurrence. Patients were evaluable for response if they received at least 3 cycles of FLEC.

Statistics

The survival curve was measured from entry into the protocol until death; the progression-free interval was calculated from the date of response until relapse or progression. Survival and progression-free survival curves were calculated according to the method of Kaplan and Meier.[10]

Results

Overall response

Of the 30 patients evaluable for response, 13 (43%) fulfilled the criteria for CR and 11 (36%) for PR with an overall response rate of 79%. The remaining 6 patients were considered poor responders or resistant to the treatment (21%). None of the 13 patients who achieved CR had relapsed after 2 to 23 months (median duration of 13 months). Among partial responders only 4 out of 11 (2 of whom had been pretreated) have so far progressed after 4, 4, 5 and 8 months. One patient died in CR of causes not related to either disease or therapy, while 2 among PRs and all 6 non responders died of disease progression. The overall survival rate at 27 months was 70% with a median duration of 13 months, while progression-free survival rate at 24 months was 79% with a median duration of 10 months (Figure 1).

Results were also correlated with age, stage, histology subtype, previous treatment, LDH level and bone marrow involvement (Table 1).

With regard to histology subtypes, a better response

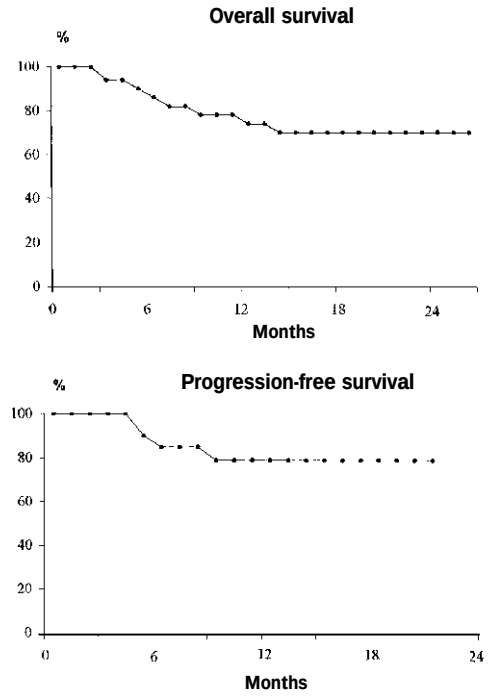

Figure 1. The overall survival curve of all 30 patients entered into the study and the progression-free survival curve of partial and complete responders.

rate was obtained for follicular center and B lymphocytic lymphomas (91% and 81% overall response rate, respectively) than for mantle cell subtype (67%). Moreover, in this last subgroup, only 2/4 responsive patients mantained their response.

Surprisingly, we observed a better overall response rate in ≥70 years old versus younger patients (92% vs 69% respectively). In particular, 13/14 older patients responded to the treatment with 6/14 (43%) fulfilling the criteria for CR and 9 of them still maintaining their response after a median of 13 months (range 2-22). In contrast, only 11/16 under 70 year olds showed a response (7/16 achieved CR and 4/16 PR) while the remaining 5 were resistant to the treatment. However, none of the younger responder patients showed any progression of the disease after a median follow-up of 12 months (range 2-23). As expected, both patients with limited disease (stage II) easily achieved a persistent CR. It is noteworthy that among the 23 patients with bone marrow involvement 19 showed a response [9/23 (39%) a CR and 10/23 (43%) a PR]. No clearcut relationship between response and histology subtype and LDH level was observed.

Although the overall response rate was always higher in untreated patients (85%) regardless of stage, age, histology or LDH level, previously treated patients still showed encouraging results with 3/10 patients achieving CR and 4/10 a PR accounting for an overall response rate of 70%.

Table 1. Patients' characteristics and response rate.

	No. of patients	*CR(%)*	*PR(%)*	*CR+PR(%)*
All patients	30	13 (43)	11 (36)	24 (79)
Male/female	18/12			
Median age (range)	68 (32-82)			
Age				
< 70	16	7 (43)	4 (25)	11 (69)
≥ 70	14	6 (43)	7 (50)	13 (92)
Histology				
B lymphocytic	11	4 (36)	5 (45)	9 (81)
Follicular center	11	7 (64)	3 (27)	10 (91)
Mantle cell	6	1 (17)	3 (50)	4 (67)
Marginal zone	1	–	–	0
MALT	1	1	–	1 (100)
Stage				
I-II	2	2 (100)	–	2 (100)
III-IV	28	11 (39)	11 (39)	22 (78)
Previous therapy				
none	20	10 (50)	7 (35)	17 (85)
>1 regimen	10	3 (30)	4 (40)	7 (70)
LDH				
Normal	17	8 (47)	7 (41)	15 (88)
Elevated	13	5 (42)	4 (30)	9 (69)
BM involvement	23	9 (39)	10 (43)	19 (82)

Toxicity

The FLEC regimen was very well tolerated and was given in an outpatient setting to the majority of patients. Thirty patients received a total of 127 cycles (mean 4.2, range 2-5) and all were evaluated for toxicity. Neutropenia and fever of undetermined origin (FUO) were the major side effects. In particular, grade IV neutropenia was observed in 13/30 patients (43%) and in 19/127 FLEC cycles (15%) while thrombocytopenia (grade II-III) was observed in only 3/30 (10%) patients, 2 of whom were already severely thrombocytopenic at diagnosis. Both granulocytopenia and thrombocytopenia were usually of short duration and only 5/127 (4%) courses were temporarily postponed by one week. No dose reduction was applied and only one patient required administration of granulocyte colony-stimulating factor. Eight out of 30 patients (26%) experienced a transient FUO but only in 2 (6%) was the fever associated with a documented infection (1 lung infection, 1 urinary infection). *Pneumocystis carinii* pneumonia was never recorded and no patient required hospitalization because of fever or infection.

Treatment toxicity was also acceptable in the 14 older patients. Transient grade IV neutropenia was observed in 6/14 patients (43%) and in 10/54 FLEC cycles (18%). FUO was recorded in 4/14 patients (28%) but none of them had documented infections. Dermatomal herpes zoster occurred three months after the end of therapy in one patient.

Discussion

This study demonstrates that a new treatment schedule based on low-dose FLU combined with EPI and CY produces an encouraging overall response rate of 79% with a 43% CR rate in low-grade NHL, regardless of the patient's age, histology subtype and disease status. In previously untreated patients, the overall response rate was 85%. The treatment was very effective in older patients in which the overall response rate reached 92% and the CR rate 43% with mild toxicity mainly characterized by neutropenic episodes rarely associated with documented infections.

LG-NHL continues to challenge physicians' therapy decision-making. Despite the wide range of treatment options, ranging from observation only,[11] conventional alkylating agents-based therapies[12] up to high-dose chemotherapy with bone marrow or peripheral stem cell rescue,[13] LG-NHL patients often follow a fluctuating clinical course of regression and progression regardless of the chosen therapy. Thus, how to treat and when to treat patients with these diseases are still open questions, particularly in elderly patients with advanced stage disease.[14-16]

In recent years, purine analogs appeared to offer an effective treatment for LG-NHL patients. In particular FLU has been shown to induce sustained remission either given alone or in combination with other drugs

such as mitoxantrone, idarubicin and/or CY.[1-9] With regards to the FLU and mitoxantrone combination, McLauglin *et al*. obtained an overall response rate of 84% and a CR rate of 47% in 51 patients with recurrent or refractory indolent lymphomas.[7] Even more encouraging data were reported by Hochster *et al.* on the combination of FLU and CY; 27 patients treated at three different dose levels of CY obtained an overall response rate of 100% and a CR rate of 89%.[9] Nevertheless, in both these reported studies as well as in several others employing FLU at conventional doses (25-30 mg/m^2/day for 3 to 5 days) therapeutic success was often followed by frequent early infections associated with neutropenia and prolonged immunosuppression.[7-9,17] Thus, our rationale of using a low-dose based FLU regimen was twofold. On the one hand, we wanted to preserve the high response rate, reported in the literature, to other FLU-based associations and on the other hand, we wanted to reduce the fairly high rate of therapy-related myelosuppression and infections particularly in elderly patients.[18]

The results of our study show that the combination EPI-FLU-CY is very effective and even reducing the dose of FLU by about 35% with respect to standard protocols, the overall response rate is in the range given for other published associations.[7-9] In the light of a CR rate apparently lower than other FLU-including schemes even in untreated patients, two aspects should be emphasized. First, 23/30 patients had bone marrow involvement with 15 of them showing leukemic disease and second, our criteria for CR was disappearance of all evidence of disease also confirmed by immunophenotypic methods. In support of the good quality of our CRs it is noteworthy that no patient who obtained a CR has so far relapsed. The results obtained in the older patients are particularly promising: in fact, elderly, previously untreated patients with follicular center histology appeared to be the best responders to this treatment (100% overall response rate). The fact that in this subgroup of patients the dose of EPI was lowered by about 30 to 50% reinforces the crucial role of the association of low-dose FLU and CY in producing this encouraging response.

It is noteworthy that this comparable good response rate was followed by a significant reduction of therapy-related complications and particularly documented infections. In fact, toxicity of FLEC was, as expected, mild and consisted mainly of transient neutropenia and some very short FUO episodes. In fact, though the number of neutropenic episodes we observed was comparable with that reported in other studies employing conventional doses of FLU, the number of documented infections was notably lower: only 2/30 (6%) patients manifested an infectious episode, neither requiring hospitalization or parenteral antibiotics. The frequent but brief neutropenic episodes despite the low dose of FLU, could be mainly attributed to the concomitant administration of EPI and CY.

In conclusion, the FLEC regimen seems to be an effective and safe treatment for advanced treatment-requiring low-grade NHL. This new low-dose FLU-based regimen appears to be well tolerated, mildly toxic and scarcely complicated by infections. Moreover, the high and persistent response rate together with the reduced therapy-related toxicity observed in the elderly group, demonstrates that the FLEC regimen is an attractive treatment choice for elderly patients with low-grade NHL.

Contribution and Acknowledgments

MB was the principal investigator, contributed to the conception of the study, its design, data handling and interpretation and wrote the paper. CB, SM and FF were involved in the recruitment of and day-to day contact with patients and contributed to data handling and interpretation. GM contributed to the conception of the study and its design. 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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