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Low-grade non Hodgkin's lymphomas in the elderly: impact of a low-dose fludarabine-based combination regimen (mini-FLEC)

Regimens combining fludarabine with cyclophosphamide and mitoxantrone or doxorubicin have shown to be an effective therapy for elderly patients with advanced-stage low-grade non-Hodgkin's lymphomas (LG-NHL) although complicated by frequent treatment-related neutropenia and infections. We evaluated the efficacy and toxicity of a low-dose fludarabine-based combination regimen (mini-FLEC) in 20 elderly patients with advanced LG-NHL.

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Despite the wide range of treatment options, how to treat and when to treat elderly LG-NHL patients are still open questions; the effectiveness of the treatment and the quality of life should both be taken into consideration.[1-3] The efficacy of several fludarabine-based regimens (more often in association with mitoxantrone and/or cyclophosphamide) in LG-NHL patients has been widely demonstrated,[4-6] although the relevant incidence of therapy-related toxicity, including severe neutropenia and documented infections, still adversely affects the clinical outcome especially in elderly patients.[7]

We have previously shown the effectiveness and low toxicity of a low-dose fludarabine-based regimen (FLEC) including epirubicin and cyclophosphamide, in 30 patients with LG-NHL.[8] In that study we recorded a satisfactory overall response rate of 79% with 43% complete remissions (CR) and 36% partial remissions (PR). Therapy-related toxicity was mild regardless of age and consisted mainly of transient neutropenia and fever of undetermined origin while only 2/30 patients experienced a documented infection. Thus, we decided to extend the study to elderly patients with advanced stage LG-NHL by further reducing the doses of epirubicin and cyclophosphamide. Our intent was to offer an effective and fairly well tolerated treatment to a population of patients often showing a less responsive disease.[9]

Between September 1996 and March 2000, 20 consecutive elderly patients with *de novo*, relapsed or refractory LG-NHL received 5 monthly cycles of the mini-FLEC regimen (epirubicin 30 mg/m^2 i.v. on day one, fludarabine 15 mg/m^2/day (max 25 mg) i.v. from day 1-4 and cyclophosphamide 200 mg/m^2/day i.v. from day 1-4) after having given informed consent, according to institutional guide-lines. Prednisone was administered at a dose of 40 mg/m^2/day i.v. from day 1-4 only in the first cycle. No infection prophylaxis was given. All 20 patients enrolled were evaluable for response as they received at least 3 cycles of mini-FLEC and their pertinent data are listed in detail in Table 1. It should be noted that we also included in the study 8 patients with mantle cell lymphoma, formerly defined as a LG-NHL, which often behaves clinically as an aggressive lymphoma.

Six CR (30%) and 11 PR (55%) with an overall response rate of 85% were recorded. Only 3 patients did not respond. As expected, better results were achieved in the untreated group of patients in whom the response rate was 100% (4 CR and 6 PR) (Table 1). The median time to achieve CR was after 4 courses (range, 3 to 5) and the median duration of CR was 40 months (range, 6-61). Three of 6 patients who achieved CR relapsed after 6, 12 and 30 months, while the remaining 3 are still in CR after 50, 51 and 61 months. Eight of 11 patients, who had a PR, developed progressive disease after 3-15 months. Ten patients died of disease progression: all 3 patients who had no response, 6 of the partial responders whose disease progressed and 1 patient who obtained a CR but then relapsed and died after 6 months. One patient died of causes not related to the lymphoma, after 56 months of stable PR. The histologic subtype did not influence the response rate, although all 6 patients with follicular center (grade I) lymphoma subtype achieved a response (4 CR and 2 PR). Appreciable results were also recorded among the 8 patients with mantle cell lymphoma (2 CR and 5 PR) confirming the efficacy of a fludarabine-based regimen in this subtype of lymphoma with an unfavorable prognosis.[10] The overall survival and progression-free survival at 4 years were 48% and 45% with a median duration of 40 months (range 4-61) and 33 months (range 6-58), respectively. Overall and progression-free survival curves are shown in Figure 1.

The mini-FLEC regimen was very well tolerated and was given in an outpatient setting to most of the patients. No differences in therapy-related adverse effects were recorded between treated and untreated patients. All 82 cycles (mean 4, range 2-5) were evaluated for toxicity. Hematologic toxicity consisted mainly of transient grade III-IV neutropenia documented in 10/20 (50%) patients and in 20/82 (25%) cycles. Nevertheless, no dose reduction was applied and only 3/82 cycles were postponed by one week. Three of 20 patients received granulocyte colony-stimulating factor. One patient developed grade II thrombocytopenia. Extra-hematologic toxicity consisted of grade I nausea and vomiting observed in 7/82 cycles. A short-lasting fever of unknown origin (mean 3 days) was observed in 7/20 patients and in 10/82 cycles, most

Table 1. Clinical and histologic characteristics, results and outcome of 20 elderly LG-NHL patients treated with mini-FLEC.

Pt.	Age/Sex	Stage	Histol.	BM INV	PB INV	Symptoms	LDH	Previous therapy	Response	Duration remission (months)	Current status	Survival (months)
1	70/F	IV	FL	No	No	No	Normal	No	CR	58	CCR	61
2	76/M	IV	MCL	Yes	No	No	Normal	No	CR	46	CCR	50
3	70/F	IV	FL	Yes	Yes	No	Normal	No	CR	12	A*	49
4	82/M	IV	FL	Yes	Yes	Yes	Normal	No	CR	30	D	40
5	79/M	IV	MCL	Yes	Yes	Yes	Normal	No	PR	51	D°	56
6	68/F	IV	MCL	Yes	Yes	Yes	High	No	PR	13	D	24
7	75/F	IV	LL	Yes	Yes	Yes	High	No	PR	41	CPR	45
8	72/F	IV	MZL	Yes	No	No	Normal	No	PR	15	A*	29
9	68/M	IV	LL	Yes	Yes	No	Normal	No	PR	33	CPR	36
10	70/M	IV	MCL	Yes	Yes	Yes	Normal	No	PR	27	CPR	30
11	68/M	IV	FL	Yes	No	No	Normal	Yes	CR	43	CCR	51
12	73/M	IV	MCL	Yes	No	No	High	Yes	CR	6	A*	52
13	72/F	IV	FL	Yes	No	Yes	High	Yes	PR	6	A*	51
14	68/M	IV	MZL	No	No	No	Normal	Yes	PR	14	D	29
15	69/F	IV	MCL	Yes	No	No	Normal	Yes	PR	7	D	16
16	66/M	IV	FL	No	No	Yes	High	Yes	PR	6	D	14
17	77/F	IV	MCL	Yes	No	Yes	Normal	Yes	PR	8	D	12
18	68/M	IV	LL	Yes	Yes	No	High	Yes	NR	–	D	7
19	69/M	IV	MCL	Yes	Yes	Yes	High	Yes	NR	–	D	19
20	74/F	IV	MZL	Yes	No	No	Normal	Yes	NR	–	D	4

FL: follicular lymphoma; MCL: mantle cell lymphoma; LL: lymphocytic lymphoma; MZL: marginal zone lymphoma; BM INV: bone marrow involvement; PB INV: peripheral blood involvement; CR: complete remission; PR: partial remission; NR: no response. A: alive with lymphoma; D: death with lymphoma; D°: death in CPR; CCR: continuous CR; CPR: continuous PR. Histol.: histology; Sympt.: symptoms; Resp.: response; Surv.: survival.*

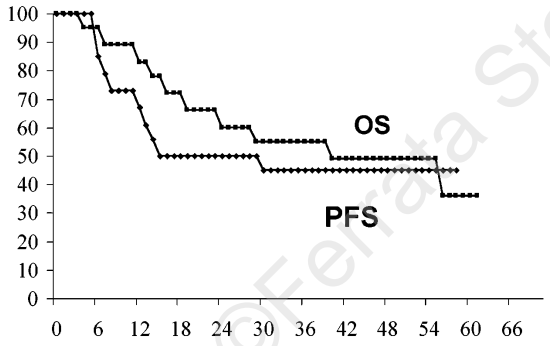

Figure 1. Overall and progression-free survival curves in 20 elderly LG-NHL patients treated with mini-FLEC.

frequently after the first cycle of mini-FLEC cycle (5/7 patients). Those patients who developed fever received antibiotic treatment, although an infectious complication (*Staphylococcus epidermidis pneumonia*) was documented in only one case. No infection-related deaths were recorded.

In conclusion, we showed the feasibility of mini-FLEC treatment which, with the caution due to the relatively small number of patients, seems to be effective and safe for elderly patients with advanced LG-NHL requiring treatment. In addition, when an oral formulation of fludarabine becomes available, the administration of both cyclophosphamide and fludarabine *per os* should further facilitate compliance with the mini-FLEC treatment protocol.

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