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High activity of mitoxantrone in previously untreated low-grade lymphomas

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Summary. A consecutive series of 21 previously untreated patients with low-grade non-Hodgkin lymphomas were treated with mitoxantrone 5 mg/m^2 daily for 3 days every 3 weeks. The cumulative dose did not exceed 165 mg/m^2 in any patient. In this group, 7 patients had small lymphocytic lymphomas, 10 patients had follicular small cleaved cell lymphomas, and 4 patients had follicular mixed small- and large-cell lymphomas. Of the 21 patients, 20 obtained remission (complete in 6, partial in 14), and 15 of these are still in remission. Relapse-free survival is 68% at 2 years. None of the patients has died. Nonhematologic toxicity was modest. No severe alopecia was seen, and only 6 patients had nausea and vomiting (WHO grade 1–3). No cardiac toxicity was seen. In conclusion, mitoxantrone is a highly active and well-tolerated drug in this subset of patients. Hematologic toxicity, especially leukopenia, was dose limiting, and a reduction of the dose was necessary in 15 out of the 21 patients.

Introduction

The treatment of low-grade non-Hodgkin lymphomas is still under debate. While it is recognized that in some patients the treatment can be deferred for years, other patients with symptoms or a heavier tumor load need initial treatment. The response rate to single-agent chemotherapy, combination chemotherapy, or radiotherapy is usually relatively high, but in most studies the subsequent relapse rate is constant at 20%–30% per year and median survival is only around 7–9 years in large patient series [3, 6].

More recently, prospective randomized series have shown no superiority of such combinations as CHOP-Bleo, COPP, or BCVP over single-agent cyclophosphamide [7] or cyclophosphamide plus prednisone [2] with respect to frequency and duration of remission. At this time there seems to be no difference in survival, but longer observation times are needed for the analyses. Since the ultimately fatal outcome of low-grade stage III and IV lymphomas has not been changed by current therapy, there is a need to identify new agents with more selective activity in this group of patients.

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Mitoxantrone (Novantrone) is a new synthetic anthracenedione, which in phase I–II studies was shown to be well tolerated [9, 10, 11] and which has demonstrated significant antineoplastic activity in previously treated lymphoma patients [1, 4, 5].

Since the true activity of a new agent is difficult to evaluate in heavily pretreated patients we performed and report here a phase II study of mitoxantrone in previously untreated patients with stage III–IV low-grade lymphomas.

Methods

Patients. Consecutive patients with the following histological diagnosis based on the International Working Formulation (IWF) were considered for the trial: diffuse small cell (DSL), follicular small cleaved (FSC), and follicular mixed small and large cell (FM) lymphomas.

Standard staging procedures (including liver and bone-marrow biopsy, chest X-ray, lymphangiography, in selected cases CT scan of the abdomen) were applied to select eligible patients, who had stage III or IV disease, had received no prior therapy, and showed no evidence of cardiac disease or other severe complicating diseases that might interfere with therapy. Glucocorticosteroids could not be given as antiemetic therapy. During and after the treatment, the patients were followed up by means of physical, radiologic, and blood tests. Electrocardiograms were performed in each cycle, and cardiac function was evaluated in addition by multiple gated acquisition (MUGA) scintigrams after the 8th cycle and when therapy was discontinued. Following 8–11 cycles of therapy, the patients were observed without therapy until relapse occurred. At the time of this report (November 1987) all patients are alive and under observation in our department.

Treatment. Mitoxantrone, 5 mg/m^2 body surface area, was administered by i.v. 5-min infusion daily for 3 days, repeated every 3 weeks. A minimum of 8 cycles was planned in responding or stable patients. If a reduction in tumor size occurred in a patient in PR (partial remission), a further 3 cycles were admissible, provided no cardiac side-effects had occurred and MUGA scintigrams showed a satisfactory ejection fraction. A sliding scale of downward dose adjustment was used for leukopenia and thrombocytopenia. No other toxicities were so severe as to demand dose adjustment.

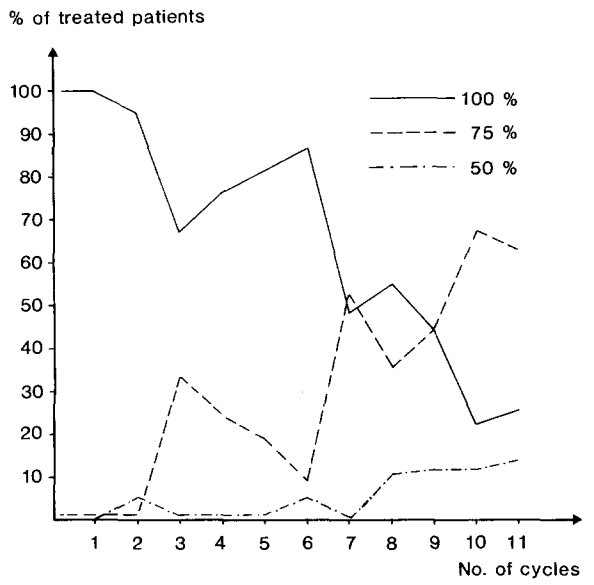

Fig. 1. Percentage of planned dose given during each cycle of therapy

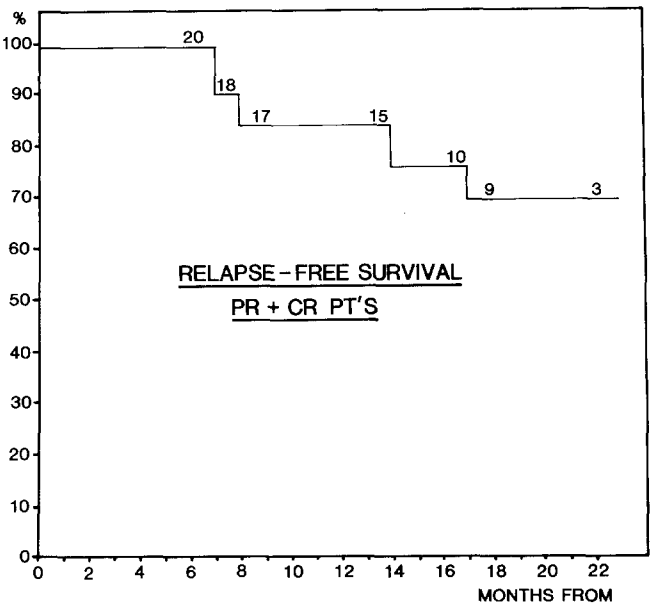

Fig. 2. Relapse-free survival

Table 1. Patient characteristics

Total		21
Male/female		11/10
Age:	Median	53
	Range	32–74
Stage	III A	8
	IV A	9
	IV B	4
Bone marrow involvement		12
Liver involvement		8
Histology[a]	DSL	7
	FSC	10
	FM	4

[a] DSL, diffuse small cell lymphoma; FSC, follicular small cleaved cell lymphoma; FM, follicular mixed small and large cell lymphoma

Table 2. Response to mitoxantrone according to histology

Histology (IWF)	*n*	CR	PR	CR + PR
DSL	7	1	5	6
FSC	10	3	7	10
FM	4	2	2	4
	21	6 (29%)	14 (67%)	20 (95%)

Table 3. Hematologic toxicity in 21 patients

	Number of patients with toxicity WHO grade[a]				
	0	1	2	3	4
Hemoglobin	12	8	1	0	4
WBC	0	0	11	9	1
Platelets	15	3	0	3	0

[a] [12]

The dose administered to each of the 21 evaluable patients was calculated and expressed as a percentage of the planned protocol dose (Fig. 1).

Response was assessed at restaging after 8 cycles and – in those patients who received the additional 3 cycles – after 11 cycles. Initial liver and bone-marrow involvement necessitated repeat biopsy.

WHO criteria were used for CR (complete remission) and PR (>50% regression) and toxicity [11]. Duration of remission was calculated from the onset of PR to the date of the last follow-up examination or date of relapse.

Results

Characteristics of the 21 consecutive, eligible patients are shown in Table 1. All received treatment as per protocol. Reduction in volume of the lymphomas was usually apparent within the first 2 cycles. In 6 patients, CR was obtained, while 14 patients obtained PR (Table 2). While a median of 2 cycles (range 2–8) led to PR, CR was seen after a median of 8 cycles (range 7–9). The histological subtypes in CR patients were: DSL, 1 patient; FSC, 3 patients; and FM, 2 patients. One relapse has been observed in the CR patients (DSL). Among the 14 patients with PR, 4 relapsed at 7, 7, 8½, and 14 months after achieving PR, and these patients are now receiving other therapy (Fig. 2). The other 10 patients continue in PR, but the follow-up period is still short (median 15 months, range 9–24).

Toxicity during treatment was mild, and all patients could be treated on an outpatient basis. The dose-limiting toxicity was hematologic (Table 3), mainly taking the form of leukopenia and necessitating dose reduction in 15 patients (as demonstrated in Fig. 1). In 5 of these patients, it was also necessary to extend the interval between treatments in a total of 9 cycles because of prolonged leukopenia. The 15 patients demonstrating hematologic toxicity included 9 who had bone-marrow involvement by lymphoma before therapy.

Non-hematologic toxicity was very mild. Partial alopecia was noted in 1 patient, and only 6 patients had nausea

and vomiting (WHO grade 1–3). An unusual side-effect was partial and reversible loss of fingernails, which was observed in 2 patients. Cardiac toxicity was not seen in any patient. MUCA scintigraphic examination was performed in 9 patients who received more than 8 cycles of therapy: in all 9, the ejection fraction was unaltered after 11 cycles of mitoxantrone.

Discussion

The response rate of 95% observed in this study is much higher than those previously reported with mitoxantrone in low-grade lymphomas [1, 4, 5]. The explanation for the difference is that only untreated patients were included in our study and the problem of cross resistance was thus avoided. Complete remission was obtained in 29% of the patients. This frequency was reached after a treatment duration of 24–33 weeks. Single-agent cyclophosphamide led to 66% CR in a CALGB study of patients with nodular lymphomas, but the median time to CR was 9 months [7]. It is not possible to predict whether a more prolonged treatment with mitoxantrone would reach the same level of activity as cyclophosphamide in this type of lymphoma.

An important issue in the introduction of new drugs in the treatment of low-grade lymphomas is toxicity. Most of these patients have no disease symptoms and have a good quality of life. The side-effects seen in this study, in which mitoxantrone was given in a 3-day schedule, were minimal. Although hematologic toxicity, and especially leukopenia, was dose-limiting, all patients were treated as outpatients and no septicemia was seen. Cumulative toxicity was noted, but therapy could usually be given with only a moderate reduction of the initial dose. It is possible that cumulative toxicity might be a problem if treatment had to be given over longer periods of time. Cardiac toxicity has been described in patients receiving mitoxantrone [8], but this was not observed in our study, in which the cumulative dose did not exceed 165 mg/m^2.

We conclude that mitoxantrone is a promising new drug for the treatment of low-grade malignant lymphoma. A further evaluation in combination chemotherapy regimens is necessary, not only in low-grade but also in more aggressive lymphomas.

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