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Treatment of refractory and relapsed non-Hodgkin's lymphoma with ifosfamide, methotrexate and etoposide

Graeme Sangster[1], W. Nigel Patton[2], Richard I. Harris[2], Robert J. Grieve[3], and Michael J. Leyland[1]

[1] Department of Clinical Haematology, East Birmingham Hospital, Bordesley Green East, Birmingham, England
[2] Department of Haematology, Walsgrave Hospital, Coventry, England
[3] Department of Radiotherapy, Coventry and Warwickshire Hospital, Coventry, England

Summary. The combination of ifosfamide, etoposide and methotrexate was evaluated in 22 patients with non-Hodgkin's lymphoma (NHL) whose disease had relapsed or was resistant to first-line adriamycin-containing treatment. Only 4 of the 22 patients underwent remissions, 3 of which were complete and 1, partial. Two of the complete remissions occurred in patients with "high-grade" histology who received IMVP-16 after first-line treatment had induced only a partial remission. Bone marrow suppression was the limiting toxicity of this regime, which may be of value in the salvage therapy of selected patients with NHL.

Introduction

With current combination chemotherapy regimes, 30%–40% of patients with non-Hodgkin's lymphoma (NHL) of 'high-grade' histological type are curable [8]. Patients who relapse after or fail to obtain a complete remission (CR) on initial treatment such as CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone) have a poor prognosis. Those patients with NHL of 'low-grade' histological type may have a more prolonged clinical course but are rarely cured of their disease. The need for effective salvage therapy, especially for high-grade tumours, is clear, but the results of most second-line treatment have been poor. However, Cabanillas et al. [2] have reported encouraging results for the combination of ifosfamide (I), methotrexate (M) and etoposide (VP-16), and in this study we describe our experience with the IMVP-16 regime.

Materials and Methods

Patients with relapsed or refractory non-Hodgkin's lymphoma were eligible for treatment with the IMVP-16 regime described below if they were aged <75 years, had a creatinine clearance of >25 ml/min and had not previously received ifosfamide or VP-16. In all, 22 consecutive patients, 16 male and 6 female, with a mean age of 51 years (range, 24–68 years) were eligible for inclusion in the study. The lymphoma histology was typed according to the Kiel Classification.

Offprint requests to: G. Sangster, University Department of Geriatric Medicine, Royal Liverpool Hospital, Prescot Street, Liverpool, L69 3BX, U. K.

A total of 12 patients had high-grade NHL, including 2 centroblastic, 4 immunoblastic, 3 lymphoblastic, 2 high-grade unclassifiable and 1 true histiocytic lymphoma; each of these patients had received either CHOP (9 cases) or a similar adriamycin-containing induction therapy. Ten patients were given IMVP-16 immediately following initial treatment when either a partial response (PR) (seven patients) or no response (NR) (three patients) was seen, and two were treated at first relapse after being in CR (duration, 6 and 48 months). Ten patients had low-grade NHL, including five centrocytic, three centroblastic-centrocytic, one lymphoplasmacytoid and one lymphocytic lymphoma; prior treatment in this group included chlorambucil alone or cyclophosphamide, vincristine and prednisolone (COP) in two patients, chlorambucil or COP followed by CHOP in three patients and CHOP alone in five. Of the eight patients who had received CHOP, four had achieved CR (duration, 2, 4, 18 and 30 months) and received IMVP-16 on first relapse. Bone marrow involvement was observed in eight patients, four with low-grade and four with high-grade NHL. CNS involvement by low-grade NHL became evident during treatment in two patients with low-grade lymphoma whose repeat lymph node biopsies showed no evidence of transformation to high-grade lymphoma.

The IMVP-16 regime consisted of 1 g/m^2 ifosfamide infused in 1 l dextrose saline over 2 h daily for 5 days (3 patients) or 4 g/m^2 ifosfamide infused in 3–4 l dextrose saline over 24 h (19 patients), followed by 100 mg/m^2 etoposide in 1 l saline over 2 h daily for 3 days and 30 mg/m^2 methotrexate i.v. on days 3 and 10. A diuresis was initiated prior to the ifosfamide infusion because of the possible anti-diuretic hormone-like activity of this drug, and mesna was given to prevent urothelial toxicity.

Patients who had received fractionated ifosfamide were given three i.v. bolus injections of 400 mg/m^2 mesna 4 h apart, commencing with the ifosfamide infusion, whereas those receiving a 24-h ifosfamide infusion were given an i.v. bolus of 0.8 g/m^2 mesna, then a 24-h infusion of 4 g/m^2 mesna with ifosfamide, followed by a 12-h infusion of 2.4 g/m^2 mesna. Initially, a fractionated schedule of ifosfamide administration was chosen to minimise urothelial toxicity, but this constraint was lifted when Klein et al. [5] showed that urothelial toxicity could be prevented even with prolonged, high-dose infusions of ifosfamide by the concurrent infusion of mesna at the appropriate dose. The urinary output was carefully monitored during treat-

ment and diuretics were given if it fell to <100 ml/h. All urine specimens were examined for microscopic or macroscopic haematuria.

Toxicity was assessed in each of the 70 treatment courses given, and treatment responses were defined according to standard WHO criteria [7]. Patients were assessed for response after two and four treatment courses; the courses were repeated every 21–28 days and continued either until progressive disease developed or for at least two cycles after achieving CR. Patients with bone marrow involvement were given initial treatment at full doses. The protocol permitted either a reduction of 25% in the previous dose of ifosfamide or VP-16 or a delay in treatment of up to 1 week if the neutrophil count was $<1.0\times10^9$/l or platelet count, $<50\times10^9$/l on day 28.

Results

All 22 patients were evaluated for response, including 3 who received less than two courses of treatment. Two of the latter died of sepsis associated with neutropenia during the first treatment cycle without showing any tumour response, and one died of progressive NHL. The remaining 19 patients received a mean of 3.8 courses of IMVP-16 (range, 2–6).

Four patients (18%) achieved an objective response. Of these, only three (14%) patients were in CR after four courses of IMVP and one (4%) achieved a PR. Two of the patients who obtained a CR had high-grade histology and had achieved only a PR during initial induction treatment; they remain in complete clinical remission 9 and 12 months after treatment, respectively. The third CR was seen in a patient with low-grade NHL in first relapse after 30 months who had only minimal residual disease in the mesenteric lymph nodes after surgical resection of a lymphoma recurrence in the small bowel. His relapse-free survival is now >24 months. A PR lasting more than 5 months was achieved in a heavily pre-treated patient with low-grade NHL in whom IMVP-16 was stopped after three cycles due to marked deterioration of a pre-existing vincristine-induced peripheral neuropathy. The responses to IMVP-16 according to previous treatment responses and histological grade are shown in Table 1.

Among the remaining 15 patients, 6 (4 with low-grade and 2 with high-grade NHL) had progressive disease after two treatment courses. Nine patients (six with high-grade and three with low-grade NHL) showed only minor or no responses after two treatment courses; after four courses, three of this group had progressive disease and no objective response was recorded in the other six patients. A median survival of only 5 months was found in the whole study group.

Table 1. Results of IMVP-16 salvage treatment in NHL according to response to previous therapy and histological grade

Previous treatment response	Patients	CR	PR	NR/PD
PR on first-line treatment	7 (7)	2 (2)	0	5 (5)
Relapse after CR on first-line treatment	6 (2)	1 (0)	0	5 (2)
NR/PD on first-	4 (3)	0	0	4 (3)
or second-line treatment	5 (0)	0	1 (0)	4 (0)
Totals	22 (12)	3 (2)	1 (0)	18 (10)

Numbers in brackets indicate the numbers of patients with 'high-grade' NHL
CR, complete remission; PR, partial remission; NR, no response; PD, progressive disease

Toxicity

The main toxicity of this regime was marrow suppression, the degree and duration of which was greater amongst the 8 patients with marrow involvement, who received 19 of the 70 treatment courses given. However, 61 treatments were given within a 28-day cycle, and persisting neutropenia or infection resulted in less than 1 week's delay in the remaining 9 courses; a subsequent 25% dose reduction was made in only 3 courses. Nadir blood counts showed grade 4 neutropenia ($<0.5\times10^9$/l) in 25 courses (12 in patients with marrow involvement) and grade 4 thrombocytopenia ($<25\times10^9$/l) in 7 courses (4 in patients with marrow involvement). No haemorrhagic complications were encountered, but nine episodes of infection associated with neutropenia occurred in seven patients (six episodes in four patients with marrow involvement). In three patients, death due to sepsis occurred in association with persistent lymphoma. The study numbers were too small to compare marrow toxicity between patients who received a 24-h infusion of ifosfamide and those given fractionated ifosfamide. No urothelial or CNS toxicity was observed. Prophylactic anti-emetics were usually given during the infusion of ifosfamide, and nausea and vomiting were generally mild (mean grade, 1.2; range, 0–3). Oral mucositis of grade 2 was seen in only one patient in association with neutropenia. Alopecia occurred in all patients.

Discussion

In this group of patients with relapsed or refractory NHL, a low overall response rate of 18% and a CR rate of 14% was seen. This contrasts with the results of Cabanillas et al. [2], who reported a 37% CR rate and 62% overall response rate amongst 52 patients treated with an IMVP-16 regime including 1 g/m^2 ifosfamide on days 1–5. However, Segal et al. [10] reported on 19 patients with NHL who were treated with 750 mg/m^2 ifosfamide and 40 mg/m^2 etoposide on days 1–5; these authors found a lower overall response rate of 21% and a CR rate of 10%. Hagberg et al. [3] have recently reported similar results, namely, an overall response rate of 19% and a CR rate of 9%, in a study of 57 patients using the same IMVP-16 regime as Cabanillas et al. [2], although some of the patients did not receive methotrexate. However, the response rates were no greater amongst patients who received methotrexate.

Cabanillas [1] has identified several factors important in predicting a favourable response to second-line treatment in NHL including, in order of decreasing significance, the achievement of CR or PR on first-line treatment, intermediate and high-grade tumour histology and the absence of CNS involvement. With respect at least to previous treatment response and the histological grade of lymphoma, the patients studied by Cabanillas et al. and Hagberg et al. appear comparable and the differences in response rates recorded between those studies cannot readily be explained. In our series, 6 of 22 patients with NHL were treated in first relapse and 7 of 22 were treated

after a PR to first-line chemotherapy, compared with 15 of 52 and 6 of 52 in the corresponding groups in Cabanillas et al.'s study [2] and 17 of 57 and 4 of 57 in Hagberg et al.'s study [3].

Although most of the responses seen in our study (three of four) occurred in those groups in keeping with the experience of these authors, our response rates were low. This may reflect the lower proportion of high-grade lymphomas in our first-relapse group than in those of Hagberg et al. and Cabanillas et al. All patients treated after partially successful induction therapy in our study had high-grade histology, as in the studies of Hagberg et al. [3] and Cabanillas et al. [2], but their patients may have achieved a higher degree of initial response, which would account for the improved response rates. Treatment delays and dose modifications were infrequent in our patients, including those with bone marrow infiltration. Although Cabanillas et al. and Hagberg et al. have not reported the details of these factors, it seems unlikely that our patients were under-treated in comparison with those groups.

Until recently, fractionated ifosfamide administration was advocated to reduce urothelial toxicity, but with the development of mesna, this constraint is no longer required [5]. There is also pharmacokinetic evidence that the continuous infusion of ifosfamide increases the maximum tolerated dose of ifosfamide compared with single (2-h), daily, short-term (3- to 5-day) infusion, during which significant enzymatic induction of liver metabolism can occur [9]. In soft tissue sarcomas, similar response rates have been seen when ifosfamide has been given as a 24-h [4] or 5-day continuous infusion [6]. For these reasons and as a means of shortening the hospital stay, a 24-h infusion of ifosfamide was used; however, further studies are required to test the dose and duration of administration in lymphomas.

The infectious morbidity associated with IMVP-16 must be interpreted in light of the fact that many of the patients had been heavily pre-treated and had bone marrow involvement. Adequate facilities for the supportive care of such patients are required. With careful attention to hydration and the use of mesna by infusion, urothelial toxicity was prevented. Gastrointestinal toxicity was not marked, even with the 24-h infusion of ifosfamide, and the patients' tolerance of treatment was high.

A further adaptation of the IMVP-16 regime with 1.5 g/m^2 ifosfamide on days 1–3 has recently been adopted by the British National Lymphoma Investigation (BNLI) for patients with high-grade lymphoma histology and bone-marrow involvement who have not achieved CR after three courses of CHOP. The results of this large study will better establish the role of IMVP-16 in the management of patients with NHL.

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