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Short Communication

Trofosfamide as a Salvage Treatment with Low Toxicity in Malignant Lymphoma. A Phase II Study

M.D. Helsing

Department of Oncology, Örebro Medical Center Hospital, S-701 85 Örebro, Sweden

37 patients with disease progression after prior treatment for malignant lymphoma (27 low grade, 7 high grade and 3 Hodgkin's) were treated with oral trofosfamide daily. Most of these patients were heavily pretreated, with a median number of two regimens. Their median performance status was 1 (22 patients with 0–1 and 14 with 2–3). The overall response rate was 49% (18/37; 3/37 CRs and 15/37 (41%) PRs). Median time to progression (TTP) from start of therapy was 4 months for patients with low-grade lymphoma and 2 months for high-grade lymphoma. For responding patients (CR + PR), TTP was approximately 10 and 7 months, respectively, for the two groups of lymphomas. Median survival from the start of treatment was 11 months (range 1.3–46.6) for low-grade lymphoma and 3.8 months (range 2.2–17.6) for high-grade lymphoma. Haematological and other toxicities were low and did not cause any major treatment interruptions. Trofosfamide is an interesting and a non-toxic palliative treatment for relapsing malignant lymphomas especially in elderly patients. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: trofosfamide, non-Hodgkin's lymphoma

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INTRODUCTION

RECURRENT HIGH-GRADE non-Hodgkin's lymphoma (NHL) and Hodgkin's disease in elderly patients are usually incurable. In low-grade NHL the treatment in stage II–IV is palliative from the beginning and probably does not prolong life. Hence, this lymphoma has a high response rate to different chemotherapies with low toxicity. When first and often second (or more) lines of treatment for these patients have failed, the options for further treatment with chemotherapy are few. Any further treatment with chemotherapy would be questionable unless it is non-toxic and easy to administer to the patient. The aim of the treatment would be to postpone symptoms in patients and give the patient improved quality of life.

Trofosfamide (Ixoten®, Asta-Werke) is an alkylating drug with a resemblance to both cyclophosphamide and ifosfamide. It is administered orally and is transformed mostly to ifosfamide in the liver [1]. It has been reported [2–4] to be a relatively non-toxic treatment, with a response rate [4] of 61% and a median response duration of 4 months in NHL stage III or IV with low-grade malignancy or relapsing NHL with high-grade, even in elderly or pretreated patients. These results merit further evaluation, and, therefore, a phase II study using trofosfamide was performed.

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PATIENTS AND METHODS

The aim of the study was to investigate the number of responses, time to progression and toxicity when treating patients with continuous oral trofosfamide.

Inclusion criteria were: confirmed progression of Hodgkin's disease or high grade non-Hodgkin's lymphoma; where patients under 65 years of age had relapsed or had progressive disease after a minimum second-line treatment and patients older than 65 years after first-line treatment; and low-grade non-Hodgkin's lymphoma after a second progression or if deemed unsuitable for our standard treatment with prednimustine or chlorambucil + cortisone; measurable disease; performance status WHO ≤ 3; informed consent. Exclusion criteria were performance status WHO > 3, leucocyte count < 2.0; platelets < 50; creatinine > 200 μmol/l.

37 patients were included and their characteristics are shown in Table 1. Mean age was 70.9 years (range 33–89). Four patients are still alive (at 8, 20, 43 and 46 months follow-up) and two patients under treatment (4 and 12

Table 1. Characteristics in 37 patients treated with trofosfamide

	No.
Male	27
Female	10
Grade	
Low	27
High	7
Hodgkin's	3
Stage	
II	2
III	9
IV	26
Performance status WHO	
0	13
1	9
2	9
3	5
Number of prior regimens	
0	2
1	12
2	12
3	7
4	2
5	2
Age (median)	
Male	72
Female	77.5
All	73

months). All other patients were followed to death. Median time from diagnosis to start of trofosfamide treatment was 25.7 months (range 0.7–96). Median performance status was WHO 1. The median number of prior chemotherapy regimens was two. Histopathological diagnosis according to the Kiel classification is shown in Table 2.

Trofosfamide was given orally at a dose of 50 mg three times daily until the occurrence of disease progression, haematological toxicity or any other toxicity. If the medication was discontinued due to toxicity, it was restarted at a lower dose (50 mg twice daily) after one week of rest. No dose escalation was performed.

Tests for haemoglobin, leucocyte and platelet counts were made every second week for the first 2 months and then every third week. Tests for serum albumin, LDH (lactate dehydrogenase) and creatinine were performed every fourth to sixth week, and an X-ray or a CT scan was performed when indicated.

Table 2. Histopathological diagnosis according to Kiel classification

Diagnosis	No.
Low-grade lymphoma	
Centroblastic/centrocytic follicular	10
Centrocytic	2
Chronic lymphatic leukaemia	8
Immunocytoma	2
Lennert's lymphoma	1
NUD	4
High-grade lymphoma	
Centroblastic	5
Immunoblastic	1
Undifferentiated	1
Hodgkin's	
Mixed cellularity	1
Nodular sclerosis	2

All patients included in the study have been included in the statistical analysis. Response and time to progression were calculated from the patient's first day on trofosfamide.

RESULTS

Response was evaluated according to the WHO criteria. (CR defined as no evidence of residual disease; PR was defined as greater than 50% reduction of measurable disease; CR and PR were measured if there was a duration of at least 4 weeks, i.e. two medical examinations.)

Complete remission was achieved in 2 (7%) out of 27 patients with low-grade non-Hodgkin's lymphoma and in 1 of 3 patients with Hodgkin's disease resulting in a CR of 8% (3/37). Of the 37 patients, 15/37 (41%) achieved a partial remission (10 low-grade, 4 high-grade, 1 Hodgkin's), thereby giving an objective response rate of 49% (18/37) (95% confidence limit 33–65%). 15 patients (41%) had a stable disease (13 low-grade, 1 high-grade, 1 Hodgkin's). 4 patients had progressive disease (2 low-grade, 2 high-grade).

The time to progression after initiation of trofosfamide for patients with CR ranged from 6 to 12 months, for PR, 2–46 months and for SD 1–19 months. The median time to progression for low-grade NHL was 4 months (9.5 for CR, 10 for PR), for high-grade NHL, 2 months (7.8 for PR) and for Hodgkin's, 5.3 months (6 for CR, 8 for PR). There was no notable difference between males and females regarding the number of responses or time to progression (median females 5 months and males 4 months). Patients aged 73 years and older showed a longer time to progression than that seen in younger patients, 5 versus 2.5 months. Older patients were also slightly more responsive with 55% objective response in those $\geqslant$73 years of age ($n = 20$) versus 41% ($n = 17$) for patients aged less than 73 years. The three CRs were patients $\geqslant$73 years of age.

The median time on the scheduled dose for patients with high-grade lymphomas was 1.5 months (range 0.5–9). 3 patients continued on a lower dose, 100 mg/day, over a median of 3 months (range 0.5–7). 2 patients were treated continuously for more than 1 year. For patients with low-grade lymphomas, the median time on the scheduled dose was 3 months (range 0.5–22.5). 10 patients (37%) continued with a dose of 100 mg/day over a median period of 4 months (range 0.5–12). Of the 3 patients with Hodgkin's disease, one was treated for 2 months with the scheduled dose and the other 2 were treated from the start with 100 mg/day over an 8-month period.

Haematological toxicities were seen in 7 patients, where the Hb decreased to less than 80% of the original pretreatment level. This was observed after 2, 2.5, 3, 6, 11, 15 and 17 months of treatment. 2 of these patients continued treatment with a lower dose for 6.5 and 8 months.

4 patients had grade 3 leucopenia after 1, 2, 2.5, 4 and 8 months after treatment, 2 of which continued with trofosfamide on a lower dosage for a further 2.5 and 4 months. One patient had grade 3 thrombocytopenia after two months of treatment and was also shown to be anaemic and leucopenic. 3 patients had grade 2 thrombocytopenia after 1, 6.5 and 15 months of treatment. The patients with this toxicity continued treatment for a further 2 months on a

lower dose without worsening of the thrombocytopenia. Other toxicities seen were tiredness (2), eye problems (1), herpes infections (1) and recurrent sinusitis (1).

Some patients changed the intended dose of 50 mg three times daily to 150 mg once a day and thus had fewer problems with gastric discomfort and abdominal ache. This was not intended in the protocol, and thus is not recorded (from my own experience and the medical record of the patients, it can be estimated to be of the magnitude of 20%). No patient discontinued treatment because of gastric problems.

The median survival for patients with high-grade NHL was, from diagnosis, 28.1 months and from the start of trofosfamide treatment 3.8 months (range 2.2–17.6). One patient is still alive after 12 months of treatment. The median survival for responders (PR) was 7.9 months.

For patients with low-grade NHL, the median survival from diagnosis was 40.4 months and from the start of trofosfamide treatment 11 months (range 1.3–46.6). 5 patients are still alive after 4, 8, 20, 43.3 and 46.6 months. The median survival for responders was 17 months and for SD and PD, 10.4 and 1.3 months, respectively.

The 3 patients with Hodgkin's disease had a survival of 48.9, 59.5 and 59.8 months, from diagnosis, and 6.6, 19.7 and 11.9 months from the start of the trofosfamide treatment.

DISCUSSION

Heavily treated patients with progressive lymphoma seem to benefit from treatment with trofosfamide. This result is of the same magnitude as that reported previously [2–6]. Wist and Risberg [4] observed 22% CR and 39% of PR in 23 patients with lymphoma. These patients were less heavily treated with a mean number of prior regimens of 1.5, otherwise the patient populations was similar to ours with respect to age, performance status and stage. Their median duration of response was 4 months. Salminen and associates [5] observed, in their study, a CR rate of 35% and an overall response rate of 53% in 17 patients. These patients were also similar, although they had fewer prior treatments (median 1.5), were somewhat younger (median 62) and there were no patients with a performance status of 3. Their median duration of response was 7 months. Martinsson and associates [6] observed 32% responders (9 out of 28) and 5 more still under treatment. Comparison with other reports is more difficult since they did not describe prior treatments, but Potzi and associates [2] treated 29 malignant lymphomas with trofosfamide and achieved 13 CRs and 11 PRs. Falkson and Falkson [3] treated patients with chronic lymphocytic leukaemia and 21 out of 24 patients showed an objective response.

All the malignant lymphomas, with the exception of the 2 patients with centrocytic lymphoma, responded to our treatment with at least stable disease being achieved. The toxicities were easy to manage and no serious adverse events occurred. Only 1 patient showed severe bone marrow toxicity, but this patient had simultaneous disease progression. Patients with leucopenia recovered quickly when the dose was reduced, or in some patients after 1–2 weeks rest from treatment. Some patients experienced gastric discomfort with slight abdominal ache. These patients were advised to take the drug after supper or prior to bedtime, resulting in most of the problems disappearing. The haematological toxicity seen in our study is in the same range as that described by Wist and Risberg [4]. Martinsson and associates [6] had, among their 36 patients, 14 patients with grade 3–4 leucopenia and 7 patients with the same degree of thrombocytopenia. This cannot be explained by differences in inclusion criteria. It might be due to differences in the patient population, performance status and type of lymphoma. An additional factor might be that an estimated 20% of our patients were taking trofosfamide 150 mg once daily.

Many of the responses in our study were of short duration, although responders were free from disease progression for a median of 10 months and non-responders (SD) for 2.5 months in low-grade malignant lymphoma.

The slight difference in magnitude of response between younger and older patients is probably due to the differences in prior treatment, especially with respect to the number of regimens.

These results make trofosfamide an interesting drug in the palliative treatment of malignant lymphoma. The responses are achieved with very little side-effects and the drug is easy to administer. The drug should be considered as an alternative for palliation after first-line treatment failure, especially in elderly patients. Further studies as a first-line treatment or as part of such treatment should be undertaken in elderly patients.

1. Boos J, Küpker F, Blaschke G, Jürgens H. Trofosfamide metabolism in different species—ifosfamide is the predominant metabolite. *Cancer Chemother Pharmacol* 1993, **33**, 71–76.
2. Potzi P, Kühböck J, Aiginger P. Ixoten maintenance therapy in solid tumours and malignant lymphomas. *Proceedings of the 13th International Congress of Chemotherapy 1983*, Vienna, August 28–September 2, 1993, 210, 21–26.
3. Falkson G, Falkson HC. Trofosfamide in the treatment of patients with cancer. *S Afr Med J* 1978, **53**, 886–888.
4. Wist E, Risberg T. Trofosfamide in non-Hodgkin's lymphoma. *Acta Oncol* 1991, 7, 819–821.
5. Salminen E, Nikkanen V, Lindholm L. Trofosfamide is effective in refractory non-Hodgkin's lymphoma. *Eur J Cancer* 1995, **31A**, 2419–2420.
6. Martinsson U, Carlsson S, Christiansen I, Glimelius B, Hagberg H. Ixoten® in non-Hodgkin lymphomas. *Abstract P692, 19th Congress of the European Society for Medical Oncology*, Lisbon, 1994.