According to Schultheiss, even 50 Gy given with 2 Gy daily fractionation, is a safe approach. He has pointed out that the "dogma" that 45 Gy is associated with 5% spinal cord complication rate is incorrect [5].

Using linear quadratic (LQ) isoeffect formulae for a range of α/β values, we can estimate the biologically equivalent total dose (2 Gy/fraction) to be higher than 50 and 55 Gy for $\alpha/\beta<1.5$ and $\alpha/\beta<1$ Gy, respectively, while with the more realistic value of $\alpha/\beta=2$ Gy [6], the equivalent dose is lower than 45 Gy. It is, therefore, obvious that even by the most conservative estimates, the prescribed dose does not exceed the spinal cord tolerance.

In our patient dosimetric error can be excluded. Unusual skin and mucosal reactions were absent. His therapy card and simulator films were carefully reviewed. He did not suffer from hypertension, diabetes mellitus or connective tissue diseases that could possibly contribute to more extensive vascular damage in the spinal cord. His haemoglobin level was also within the normal range during irradiation. All these factors are often related to a more pronounced normal tissue reaction to irradiation.

The only possible explanation is an intrinsic idiosyncratic hypersensitivity of this particular patient to radiation. Ataxia–telangiectasia heterozygotes have an increased radiosensitivity, while a number of genetic syndromes are reported to be associated with hypersensitivity to radiation *in vitro* [7]. The results of recently reported studies on the direction of establishing predictive assays of individual radiosensitivity are very encouraging [8].

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Trofosfamide is Effective in Refractory Non-Hodgkin's Lymphoma

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THE PROGNOSIS of relapsing non-Hodgkin's lymphomas (NHL) is poor, especially among elderly patients [1]. Even palliative treatment of heavily pretreated or elderly patients with recurrent lymphoma is difficult because of their poor tolerance to polychemotherapy due to the decreased cardiac and renal function or diminished bone marrow capacity [2]. The mortality of elderly patients to conventional chemotherapy is much higher than that seen among younger patients. Therefore, the approach of single-agent chemotherapy has been recommended for elderly patients with refractory lymphoma [3].

Trofosfamide is an alkylating agent taken orally as a single agent. It belongs to the group of oxazaphosphorines, together with cyclophosphamide and ifosfamide. Compared to the chemical structure of cyclophosphamide, trofosfamide has a third chlorethyl radical in the position of cyclic nitrogen [4]. Trofosfamide has been shown to be effective both in Hodgkin's disease and NHL [4–7]. In the search for an effective palliative chemotherapy for refractory NHL, we conducted a phase II study with trofosfamide.

17 patients with NHL were treated during 1992 and 1994. Criteria for inclusion of the patient was recurrent disease or reluctance of the patient to aggressive treatment. The median age of the patients was 62 years (range 45–78 years). The performance status on the Zubrod scale was 0–2. There were 11 patients with low, 5 with intermediate and 1 with high grade NHL. Median time from the initiation of chemotherapy to the start of trofosfamide was 31 months (range 0–130 months). The mean number of prior treatment regimens was 1.5 (range 0–6). 6 patients had previously been treated with radiotherapy.

Oral trofosfamide was started with a dose of 50 mg three times daily. The dose was reduced to 100 mg or 50 mg daily when haematological toxicity (grade 2 or 3) was observed. Response and toxicity were evaluated according to the WHO criteria [8]. Pretreatment investigations (clinical status, computed tomography, ultrasonography, thorax X-ray and bone marrow biopsy) were repeated for evaluation of response. Median follow-up time was 11 months until August 1994.

The distribution of patients according to previous treatments and response to trofosfamide is shown in Table 1. Of the 17 patients, 6 (35%) achieved complete remission (CR) and 3 (18%)

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Table 1. Prior treatments and response to trofosfamide and duration of the response

Patient (age)	Primary treatments	Response (duration in months)
1 (78)	RT	NC (22)
2 (65)	COEP, MIME, NOSTE, Chl, RT	PR (7)
3 (58)	—	CR (11+)
4 (61)	COAP	CR (7+)
5 (70)	COAP, Chl+Pre, RT	CR (15)
6 (58)	COAP, ENAP	CR (9)
7 (46)	COP, COAP, CEP	NC (5)
8 (47)	COP, COAP, IM-VP16, OPEC, Chl+Pre, CEP	NC (2)
9 (72)	COP, CPV, CEP, Chl, RT	CR (1)
10 (75)	COP	PR (2)
11 (45)	COAP	CR (5)
12 (56)	Chl+Pre, CEOP, IM-VP16, mitoxantrone+Ara-C, Mini-BEAM	PD
13 (62)	COAP, MIME, mitoxantrone	PD
14 (71)	COAP	NC (2)
15 (68)	COP, CVP, CEP, RT	NC (1)
16 (56)	COAP, COP, ProMACE-CytaBOM	PD
17 (75)	COP, COEP	PD

NC, no change; PR, partial remission; CR, complete remission; PD, progressive disease; RT, radiotherapy; Chl, chlorambucil; Pre, prednisone

partial remission (PR) giving an overall response rate of 53% (95% confidence limit 29–77%). No change (NC) in the disease for at least 8 weeks was observed in 3 patients and progressive disease (PD) in 4. The median time to maximal response was 3 months (range 1–10). The duration of response (CR and PR) was less than 6 months for 4 patients and over 6 months for 5 patients. The median duration of response was 7 months (range 1–15+ months). The response rate was similar in patients with low or intermediate grade malignancy. The number of prior treatments did not influence the response rate. 5 patients were previously treated with chlorambucil, and 4 responded, 2 with CRs and 2 with PRs. The median survival time for all patients was 11 months (range 2–29+).

Haematological toxicity was observed in 16 patients. 10 patients required dose reduction due to leucopenia and 3 patients due to thrombocytopenia. Most of the patients requiring a dose reduction had lymphoma in the bone marrow. One patient required discontinuation of the treatment due to prolonged grade 3 leucopenia. Anaemia was mild and was never the only cause for dose adjustments. A period of infection was observed in 8 patients (5 grade 2 and 3 grade 3), and in these cases a temporary interruption of trofosfamide was required. Grade 1 or 2 neuropathy was observed in 3 patients, 2 of whom were previously treated with vincristine. Some patients experienced grade 1 nausea and fatigue and one patient had grade 2 alopecia. During the treatment period, 4 patients were diagnosed with cardiac dysfunction. The relationship to trofosfamide treatment remained unclear. 3 of the patients had received prior doxorubicin up to the maximal cumulative dose, and one patient suffered from angina pectoris after an acute myocardial infarction, diagnosed before the treatment with trofosfamide was started.

In conclusion, we observed long-lasting responses and disease stabilisation among patients treated with oral trofosfamide for palliation of refractory NHL. An important finding is that 5 of our patients having received earlier chlorambucil responded to the treatment with trofosfamide. This indicates lack of cross-resistance between trofosfamide and chlorambucil, which is in accordance with earlier observations [5]. Toxicity of trofosfamide is dose-dependent [6] and milder than that of cyclophosphamide. Most of our patients were heavily pretreated. For old and frail patients or after several courses of chemotherapy given in hospital, a treatment which can be given as on outpatient basis is preferable. Our study indicates that trofosfamide is feasible and effective in the palliative treatment of refractory NHL.

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