Overall, neither the excretion kinetics (Figure 1) nor the total amount of side-chain metabolites formed showed relevant schedule dependency. Even with a 1-h infusion, there was a lag of 3–6 h until dechloroethylation became relevant. The excretion pattern of unmetabolised IFO (not shown) was nearly superimposable. Therefore, toxic peak plasma levels of side-chain metabolites need not be expected even with short-term infusions, and differences in toxicity and efficacy cannot be explained by an influence of the application time on the metabolic profile.

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A Case of Radiation Myelopathy After 2 × 8.5 Gy For Inoperable Non-small Cell Lung Cancer

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A 56-year old male patient presented in August 1992 with haemoptysis, fever, modest effort dyspnoea and no weight loss. A chest computer tomography (CT) scan showed a mass at the right hilum obstructing the main bronchus and extending to the carina, and a few nodules within the right upper lobe. Bronchoscopy confirmed these findings, and showed a large cell anaplastic carcinoma obstructing the termination of the right main bronchus. On physical examination, he was a robust man for his years, with a blood pressure of 130/75. Blood tests were normal. Bone and CT scan of the brain and abdomen showed no evidence of metastatic disease.

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The patient was treated exclusively with radiotherapy (RT) using an 8 MeV linear accelerator, in the supine position, with AP/PA fields 14.5 × 10 cm^2. A 6 × 3 cm^2 lead triangular shielding was also included supralaterally. The spinal cord was not shielded.

Two fractions of 8.5 Gy (midplane dose (MPD) without lung correction) were given 1 week apart. A radiological partial response of the tumour was observed, and substantial palliation in the patient's symptoms was achieved. The patient remained well until 10 months after radiotherapy when he developed a severe, progressive weakness in the legs and neurological examination revealed a complete Brown–Sequard syndrome at the fifth thoracic level. No sphincter function impairment was noticed. MRI scan showed a heightening of signal in the T2 sequence from T4 to T7, a finding consistent with myelitis (Figure 1).

There was no evidence of spinal cord compression. Bone and brain CT scans were normal. Simultaneously, he developed a tonsillar metastasis which was successfully treated by radical RT. On the last follow-up (November 1994), the patient was completely free of symptoms from both the lung and the tonsil. Both tumours were locally controlled and his neurological status remained stable.

The 2 × 8.5 Gy-1 week apart-scheme has been employed in two randomised studies by the Medical Research Council in the U.K. which compared different palliative schemes for inoperable non-small cell lung cancer (NSCLC). In the first study of 374 patients, one case of radiation myelopathy was suspected (no histological evidence of irradiation damage) [1] while in the second, one case with histologically confirmed radiation myelopathy out of 108 patients was reported [2]. The time for clinical expression of the spinal cord injury was 8 and 17 months, respectively.

In a large retrospective study, Marcus and Million [3] have reported the following rates of radiation myelopathy at each dose level: 0/124 at 30–40 Gy, 0/442 at 40–45 Gy, 2/471 at 45–50 Gy and 0/75 at ≥ 50 Gy. McCunniff and Liang [4] also reported one case of radiation myelopathy among 53 patients who received more than 56 Gy to the cervical spinal cord who were followed-up for more than 2 years. Although cases of radiation myelopathy have been reported with doses below 45 Gy, together with a few cases below 40 Gy, it is possible that all of these may be a result of a dosimetric or other technical error or differences in the RBE (relative biologic efficiency) of orthovoltage beams [3].

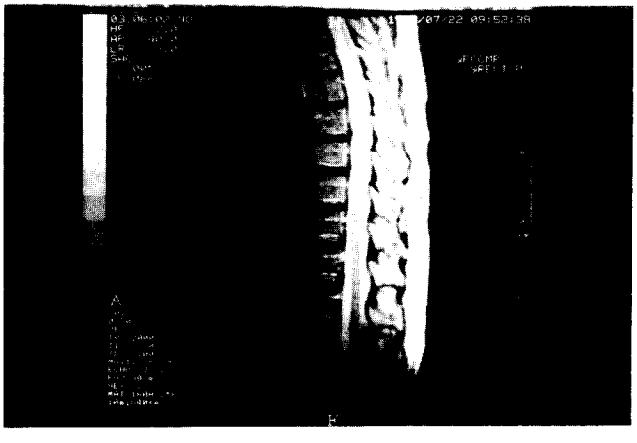

Figure 1. Patient's MRI scan showing a heightening of signal in the T2 sequence.

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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