with leukaemia and lymphoma who develop a second tumour being observed. This may reflect improvement in survival following introduction of intensive treatment protocols.

As more children receive intensive chemotherapy and combined modality treatments, the number of long-term survivors should increase and therefore the number of second malignancies can be expected to rise. The occurrence of a small intestinal carcinoma in an 19-year-old male is extremely rare and it seems likely that his previous chemotherapy was a factor in its development. We would urge intensive investigation of iron deficiency anaemia in any patient who received treatment for a childhood malignancy to exclude second malignancy of the GI tract.

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Phase II Study of Trimetrexate and Cyclophosphamide in Previously Untreated Patients with Inoperable Non-small Cell Lung Cancer

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TRIMETREXATE GLUCURONATE is a new dihydrofolate reductase inhibitor, active against solid tumours including lung cancer [1]. In animal experiments (P388 leukaemia), synergy with cyclophosphamide has been reported [2]. In our previously reported phase I study [3], the maximum dose of trimetrexate (TMTX) was 7.5 mg/m^2/day when administered intravenously for 5 days in combination with cyclophosphamide (CTX) (600 mg/m^2 on day 1). On the basis of our phase I study, the dosage chosen for phase II studies was 10.5 mg/m^2 [3]. In the present study, the main objectives were to define the response rate in patients with untreated inoperable NSCLC using the above dosage of TMTX and CTX and to define the associated drug related toxicity.

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The eligibility criteria for the present study were confirmed metastatic or inoperable previously untreated NSCLC, measurable in one or two dimensions; age 18–80 years; life expectancy ≥6 weeks; performance status ≤2 (Zubrod); WBC >1.5 × 10^9/l; serum creatinine <130 μmol/l; bilirubin ≤40 μmol/l and SGOT ≤3× upper limit of the normal range.

Before treatment physical examination, clinical laboratory tests, ECG, chest X-ray and measurement of the reference lesion were carried out. Routine staging procedures included bronchoscopy, computed tomography (CT) of the thorax and upper abdomen and bone and brain scans. Laboratory tests were repeated weekly. Adverse effects were routinely recorded on each assessment day; tumour measurements made at intervals of 6 weeks.

Therapy consisted of a 5 day treatment course of TMTX, 10.5 mg/m^2/day given intravenously (i.v.) as a 10 min infusion, preceded on day 1 by CTX (600 mg/m^2) i.v. at 3 week intervals. A maximum of six courses were administered. Responses were classified according to World Health Organization (WHO) guidelines. The responses of patients who did not receive at least two courses of treatment (except where there was an interruption after the first course because of progressive disease) were not evaluated. Patients were evaluable for toxicity after one dose of TMTX.

Of 39 patients entered into the study, six were men and 33 women. Their median age was 62 years (range 31–80). All 39 were Zubrod 0–1 performance status. Of the total group 17 patients had epidermoid carcinomas, nine adenocarcinomas and 13 large cell anaplastic carcinomas. Thirty-seven patients were previously untreated, two had had surgery. Nine patients were unevaluable; six suffered drug toxicity, two refused and one died early of pneumonia. Five of 30 patients with evaluable responses achieved partial response of duration 36–112 days, median 75; 17/30 had stable disease and 8/30 progressive disease. Four of the five responding patients suffered from epidermoid carcinoma and one from large cell anaplastic carcinoma

All 39 patients were evaluable for toxicity. Haematological adverse effects included grade (gr) 1–4 leukopenia (10 patients) and trombocytopenia (nine patients). One patient had severe gr 4 leukopenia (<1.0 × 10^9/l) and one had gr 4 thrombocytopenia (<10 × 10^9/l), both of which were fully reversible. Mild (gr 1–2) anaemia occured in over 80% of the patients.

Non-haematological toxicities were mild to moderate: nausea (26 patients) and diarrhoea (three patients); skin reactions including rash and urticaria (eight patients). Severe mucositis (gr 3–4) occurred in two patients and mild to moderate mucositis (gr 1–2) in 15 patients.

In conclusion, five short-lasting partial responses were obtained among 30 evaluable patients (17%). In 15% of patients, treatment had to be discontinued because of haematological toxicity or mucositis. The data indicate a low level of activity for combined TMTX and CTX in untreated NSCLC.

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