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Ifosfamide, Carboplatin and Etoposide for Good Prognosis Small Cell Lung Cancer: Are Four Courses Inadequate?

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THATCHER AND associates [1] reported promising results using six courses of ifosfamide, carboplatin, etoposide, midcycle vincristine and thoracic radiotherapy for good prognosis small cell lung cancer (SCLC). Treatment produced significant toxicity, but the actual 2-year survival rate was 33%.

The optimum duration of therapy has not been established [2, 3]. Attempting to decrease toxicity, we gave four courses of chemotherapy (omitting midcycle vincristine) to patients with favourable prognosis SCLC [4]. The doses and schedule of all other agents were identical.

Patients with histologically proven SCLC, with a maximum of two adverse features described by Cerny [4], were eligible for this study. Those aged over 75 years of previously treated for SCLC were excluded. Ifosfamide 5 g/m^2 and mesna 5 g/m^2 were given as a 24-h infusion, with mesna 3 g/m^2 infused over the next 12 h. Carboplatin 300 mg/m^2 was infused on day 1. Etoposide 120 mg/m^2 was given intravenously on days 1 and 2, then orally (240 mg/m^2) on day 3. All patients had intravenous hydration and routine antiemetic prophylaxis. Treatment was repeated every 4 weeks and toxicity recorded according to WHO criteria [5]. Dose reductions were made for patients who experienced life-threatening complications of myelosuppression.

The complete responders received external beam radiotherapy treatment to the primary site and mediastinum, using megavoltage or cobalt machines (a midplane dose of 40 Gy given in 15 fractions). These patients were considered for prophylactic cranial radiation. Those who progressed on chemotherapy were withdrawn, and the partial responders and patients with stable disease were observed after completing treatment. All patients were offered further palliative treatment when indicated.

Non-haematological toxicity was mild, but one death occurred secondary to neutropenic sepsis, 7 patients were withdrawn early and 4 required dose reduction because of haematological toxicity. After two cycles, we saw an 89% response rate, but unfortunately, efficacy was not maintained and the median response duration and survival were disappointing (Table 1). 2 patients died of other malignancies (confirmed at autopsy) with the SCLC in remission.

Table 1. Patients characteristics, treatment response, relapse and survival rates

Number of patients	36
Male/female	18/18
Mean age, years (range)	58.7 (37–74)
Good prognostic group (*n*)	28
Intermediate prognostic group (*n*)	8
Median time symptomatic, months (range)	3 (1–7)
Complete remission, *n* (%)	17 (47)
Bronchoscopically confirmed, *n* (%)	11 (31)
Partial remission, *n* (%)	15 (42)
Stable disease, *n* (%)	1 (3)
Progressive disease, *n* (%)	3 (8)
Median relapse time, months (interquartile range)	8 (6–11)
Site of first relapse	
Local (%)	20 (56)
CNS (%)	10 (28)
Liver	1
Bone	1
Median survival time, months (interquartile range)	10 (7–15)
2-year survivors, *n* (%)*	4 (11)

*1 patient alive and disease free at 44 months.

The results of treatment with six courses of ifosfamide, carboplatin and etoposide are among the best reported for SCLC [2]. We attempted to reduce toxicity by decreasing it to four courses but response duration and survival were disappointing.

Comparing our group with those treated in Manchester shows small differences in prognostic indicators but these are unlikely to account for the differences in survival.

Vincristine was introduced after radiological evidence of regrowth was observed between cycles of carboplatin [6]. We found no evidence of progression between chemotherapy courses, and do not feel the omission of midcycle vincristine accounts for the better results from Manchester.

A contributory factor to our inferior results could be the lower proportion receiving radiotherapy (53% compared with 86%). We recorded a higher local relapse rate (56%), but feel the main factor leading to our poorer survival figures was the use of four cycles of chemotherapy as opposed to six by Thatcher and colleagues [2]. Taken in conjunction with other trials [7], it suggests a limit to the degree that chemotherapy can be reduced without affecting survival.

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1. Thatcher N, Lind M, Stout R, *et al.* Carboplatin, ifosfamide and etoposide with mid cycle vincristine and thoracic radiotherapy for 'limited' stage small cell carcinoma of the bronchus. *Br J Cancer* 1989, **60**, 98–101.
2. Giaccone G, Dalesio O, McVie GJ, *et al.* Maintainance chemotherapy in small cell lung cancer; long-term results of a randomised trial. *J Clin Oncol* 1993, **11**, 1230–1240.
3. Medical Research Council Lung Cancer Working Party. A randomised trial of three or six courses of etoposide cyclophosphamide methotrexate and vincristine or six courses of etoposide and ifosfamide in small cell lung cancer. I: survival and prognosis. *Br J Cancer* 1993, **68**, 1150–1156.
4. Cerny T, Blair V, Anderson H, *et al.* Pre-treatment prognostic factors

and scoring system in 407 small cell lung cancer patients. *Int J Cancer* 1987, **39**, 146–149.
5. Miller AB, Hoogstraten B, Staquet M. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
6. Smith IE, Evans BD, Gore ME, *et al.* Carboplatin (paraplatin; JM8) and etoposide (VP 16) as first line combination therapy for small cell lung cancer. *J Clin Oncol* 1987, 5, 85–89.
7. Spiro SG, Souhami RL, Geddes DM, *et al.* Duration of chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. *Br J Cancer* 1989, **59**, 578–583.

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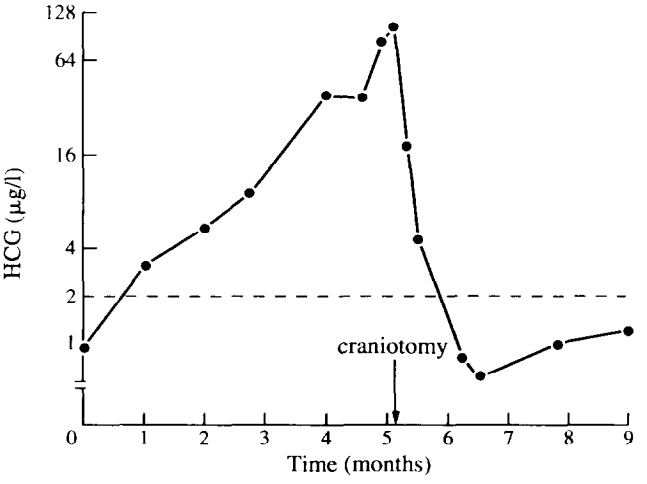

Figure 1. Serum human chorionic gonadotrophin level of the patient (below ------ indicates normal level).

Elevation of Serum Human Chorionic Gonadotrophin as the Only Indication for Isolated Cerebral Relapse of a Germ Cell Tumour of the Testis

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HIGH-DOSE CHEMOTHERAPY with peripheral stem cell or autologous bone marrow support has become more commonly used in patients with refractory or relapsed testicular cancer [1]. However, before starting such intensive treatment, it is important to be sure that no other curable option is available. Germ cell tumours can easily be detected by measurement of serum tumour markers α-fetoprotein (AFP) and human chorionic gonadotrophin (hCG). A persistent elevation or rise in these tumour markers is very suggestive of the presence of a tumour, even when no tumour can be found radiographically.

We report a case of a 28-year-old male with a misleading rise in serum hCG. Two years earlier, this patient presented with retroperitoneal lymph node metastases and a rise in serum AFP and hCG from a germ cell tumour. He underwent orchidectomy and received consecutive chemotherapy (bleomycin, etoposide and cisplatin). After an initial complete response, a rise in serum hCG was observed 3 months later. Histological examination of a retroperitoneal mass revealed chorioncarcinoma. Second-line chemotherapy consisted of vincristine, high-dose methotrexate and cisplatin. Despite normalisation of the tumour marker, repeat laparotomy showed vital tumour, which was completely resected.

Three months later, the serum hCG rose again. Lung metastases were observed and third-line chemotherapy with etoposide, ifosfamide and cisplatin was initiated. Again, a complete remission was induced but, in the follow-up, a rise in serum hCG was found. This time, no localisation of metastases could be detected and preparations for high-dose chemotherapy with autologous bone marrow and stem cell rescue were made. In the final stage of preparation, the patient suddenly complained of severe headache. A lumbar puncture was performed. The hCG in the CSF was nine times the value of the serum hCG, 700 and 81 μg/l, respectively, making the diagnosis of brain metastasis very likely [2]. Computed tomography confirmed this diagnosis. The patient underwent craniotomy with complete resection of the metastasis, followed by radiotherapy. As is shown in Figure 1, after craniotomy the serum hCG completely normalised. Six months later, the serum hCG rose again, based on lung metastases alone, for which he was treated with high-dose chemotherapy, consisting of carboplatin and etoposide, with autologous bone marrow and stem cell support. Despite a complete biochemical remission, three months later he relapsed again with pulmonary and cerebral metastases and died.

Isolated central nervous system relapse of non-seminomatous germ cell tumour is very rare [3, 4]. However, before starting intensive chemotherapy for a rise in tumour marker alone, the possibility of this localisation should be considered. Although this patient finally expired, with appropriate therapy even long-term remissions of cerebral relapses have been described [3, 4].

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1. Mulder POM, de Vries EGE, Schraffordt Koops H, *et al.* Chemotherapy with maximally tolerable doses of VP16-213 and cyclophosphamide followed by autologous bone marrow transplantation for the treatment of relapsed or refractory germ cell tumours. *Eur J Cancer Clin Oncol* 1988, **24**, 675–679.
2. Rushworth AGJ, Orr AH, Bagshawe KD. The concentration of HCG in the plasma and spinal fluid of patients with trophoblastic tumours in the central nervous system. *Br J Cancer* 1968, **22**, 253–257.
3. Raina V, Singh SP, Kamble N, *et al.* Brain metastasis as the site of relapse in germ cell tumour of testis. *Cancer* 1993, **72**, 2182–2185.
4. Perry JJ, Jelinek JS. Isolated central nervous system relapse of testicular cancer. *Med Pediatr Oncol* 1992, **20**, 68–70.