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Vincristine and Etoposide: An Effective Chemotherapy Regimen with Reduced Toxicity in Extensive Small-Cell Lung Cancer

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Abstract—*Chemotherapy prolongs survival of patients with small-cell lung cancer, but very few are cured, and the treatment is unpleasant. Thirty patients, 28 with advanced disease, were treated with etoposide 250 mg/m² orally, daily for 5 days, plus vincristine 2 mg intravenously on the first day, the cycle being repeated 3-weekly, to a maximum of 6. There was a response rate of 70%, a median survival of 249 days, and an 11% 2-year survival. Symptomatic side-effects were less pronounced than with most other regimens of comparable efficacy.*

INTRODUCTION

ALTHOUGH chemotherapy has been shown to prolong median survival of patients with small-cell lung cancer (SCLC), it is usually associated with unpleasant side-effects, and there are still very few patients who achieve long-term remissions, especially among those with extensive disease (ED). Retardation of the progress of the disease in these patients has thus only been achieved at significant cost. Until better cure rates can be achieved (an apparently remote goal at present), regimens of currently available drugs are needed that will be less unpleasant to patients without compromising efficacy.

Etoposide and vincristine are established as 2 of the most active single agents against SCLC [1], and are both relatively well-tolerated. Their major toxicities, with the exception of alopecia, do not overlap, the former being myelotoxic, with moderate gastro-intestinal side-effects; the latter is mainly neurotoxic. Their anti-tumour effects are also probably dissimilar. A combination of the 2 drugs was therefore investigated in the treatment of patients with extensive-stage SCLC, assessing response rates, duration of survival, and incidence of subjective side-effects.

Other severe impositions on incurable patients are prolonged treatments and frequent hospital visits. Previous studies in this Department have shown that short courses of chemotherapy for SCLC give results comparable to those of prolonged courses [2, 3], so a maximum of 6 cycles of treatment was adopted for this study. To minimise hospital attendances, the vincristine was administered on the day of each visit, and a supply of oral etoposide was provided to take home.

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PATIENTS AND METHODS

Between May, 1983, and August, 1984, 28 consecutive patients who met the following criteria were treated. All had histologically-confirmed SCLC, were less than 70 years old, had a pre-treatment performance status (WHO scale) [4] of less than 4, and had ED, as assessed by physical examination, biochemical profile, bone marrow aspirate and trephine, and liver scan. Patients with supraclavicular lymphadenopathy, large pleural effusions, or presumptive biochemical evidence of hepatic involvement (significant abnormality of liver function tests—elevation of 2 or more serum enzyme levels—in the absence of other demonstrable hepatic pathology) were assessed as having ED. Not all patients underwent the full range of staging investigations—once ED was established, further tests were omitted. Two patients with limited disease, but who were considered unsuitable for aggressive chemotherapy, were also treated, giving a total study group of 30.

The drugs were administered on an out-patient basis, in 3-weekly cycles, subject to marrow recovery. Each cycle consisted of an intravenous injection of vincristine 2 mg on Day 1, and oral etoposide 250 mg/m² daily on Days 1–5. Treatment was

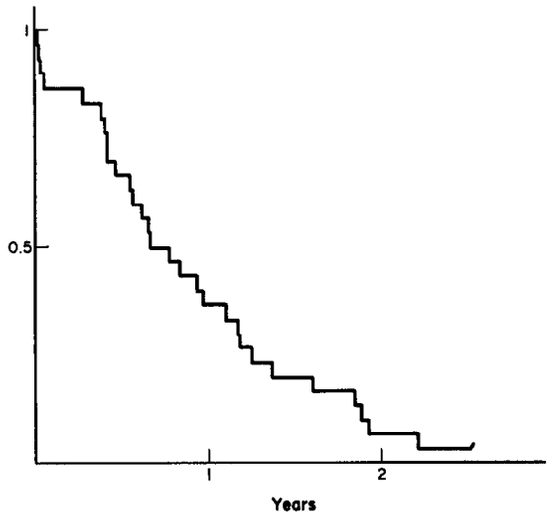

Fig. 1. Survival curve.

discontinued if there were signs of progression; responding patients received a maximum of 6 cycles. Response was assessed clinically and radiologically using WHO criteria [4]. Routine repeat bronchoscopies were deemed inappropriate in this group of patients.

Two patients presented with brain metastases, and received cranial irradiation at the start of treatment. Palliative radiotherapy was the usual treatment, if any, at the time of relapse or progression, except for 1 patient who had achieved a radiologically-complete remission, and was given second-line chemotherapy on relapse, with no response. No other chemotherapy was used at all.

Survival times were measured from the day of starting treatment; performance status, response, and side-effects were assessed using WHO criteria [4].

RESULTS

Measurable responses were seen in 21 of the 30 patients (70%), 7 of these being apparently complete responses, and 14 partial.

The survival curve of the 30 patients is shown in Fig. 1. The median length of survival was 249 days (290 days if the 2 limited-stage patients are excluded!). The survival rate at 1 year was 37%, and at 2 years 11%. At the time of writing, 1 patient remains alive, and clinically disease-free, nearly 3 years from start of treatment.

Symptomatic side-effects are tabulated in Table 1; as 4 patients died before receiving a second cycle, only 26 patients could be assessed symptomatically.

Of the 4 deaths that occurred between the first and second cycles of chemotherapy, one was attributed to septicaemia in a neutropaenic patient, but the other 3 occurred outside hospital, in uncertain circumstances. Three of these 4 patients (including the one who died of infection) had documented bone marrow metastases, and at least 1 other site of extensive disease; the fourth had brain metastases and marrow examination had not been performed, ED having been established. Twelve other patients underwent marrow examination, and all were negative; none of these patients died of infection. Other evidence of bone marrow toxicity was not great, and is tabulated in Table 2.

Table 1. Frequency and severity of symptomatic side-effects (numbers of patients affected)

	Severity (WHO scale)				
Side-effect	0	1	2	3	4
Gastrointestinal symptoms (modal score)	15	7	3	1	0
Peripheral neurotoxicity (maximum score)	13	9	4	0	0
Oral mucositis	25	0	0	1	0
Alopecia	0	0	5	21	0
Infection	0	0	0	0	1

Eight patients died before completing 6 cycles of treatment: 4 are discussed above; the other 4 had no common distinguishing features in terms of extent of disease nor pre-treatment performance status. Of the 22 who did receive 6 cycles, post-treatment performance status was better than pre-treatment in 11, unchanged in 9, and worse in 2 (one of whom had been asymptomatic on presentation, and was so again within 2 months of finishing treatment).

DISCUSSION

For patients with extensive disease, the 70% response rate compares well with that reported for other regimens, as does the 8 month median survival time.

The acceptability of a treatment to patients undergoing it is a subjective assessment, and cannot readily be recorded objectively, but the reported rate of significant gastro-intestinal side-effects in this study is as low as for any other regimen of comparable efficacy, and it is such symptoms that are usually the most distressing aspect of chemotherapy to those receiving it. Of course, alopecia and peripheral neuropathy are unpleasant, and, although transient, particularly unfortunate occurrences in patients with only a very limited life expectancy, but the overall impression was formed that patients tolerated the side-effects of this regimen much better than those of most others of proven efficacy in this disease. The other usually adopted parameter of quality of life—performance status—showed a marked tendency to improvement in those patients responding to treatment.

Table 2. Haematological toxicity, based on blood counts taken at attendance for subsequent cycles

	WHO grade of toxicity				
	0	1	2	3	4
Haemoglobin—maximum toxicity (no. of patients affected)	14	7	5	0	0
Leucocytes—per assessable treatment cycle	104	15	21	0	1
Platelets—maximum toxicity	26	0	0	0	0

(4 patients who died after 1 cycle unassessable for haemoglobin and platelets.)

Our results indicate that this treatment provides worthwhile prolongation of survival for patients with extensive SCLC, at the expense of an 'acceptable' degree of toxicity, apart from 1 slightly-disturbing feature—the number of early deaths. Although these were all in patients with very advanced disease, in the absence of more information about 3 of them it is not possible to exclude myelosuppression as a major factor, and the data on marrow infiltration add to this concern. For this reason, we are currently assessing a regimen in which the dose of etoposide has been reduced, but which is otherwise identical.

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