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Short communication

Etoposide combination therapy for small cell carcinoma of the lung

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Summary. Sixty-three consecutive patients with small cell carcinoma of the lung were treated by six cycles at 3-week intervals of etoposide 120 mg/m^2 i.v. on day 1 and orally on days 2–5, adriamycin 40 mg/m^2 i.v. on day 1 and vincristine 1.4 mg/m^2 i.v. on day 1. Tumour bed irradiation was administered to patients with limited disease after chemotherapy. In limited-disease and extensive-disease patients the median survival was 12 and 6 months respectively. The 2-year survival rate (life table) in limited-disease patients was 26%. Treatment morbidity was low.

A prospective randomised trial is being undertaken to further evaluate the role of oral etoposide in combination chemotherapy.

Introduction

This study was undertaken to evaluate the use of oral and intravenous etoposide in a low-toxicity combination-chemotherapy regimen with supplemental irradiation.

Methods

Sixty-three consecutive patients with previously untreated small cell carcinoma of the lung (SCCL), excluding patients who presented with cerebral metastases, were entered into this study between January 1983 and December 1984. Patients were staged as having limited disease (LD), i.e. disease limited to the mediastinum and supraclavicular glands, or extensive disease (ED) by serum liver function tests, liver scans and bone scans.

Patients received six cycles of chemotherapy at 3-week intervals. The drug dosage for each chemotherapy cycle was etoposide 120 mg/m^2 i.v. on day 1 and orally in capsule form on days 2–5, adriamycin 40 mg/m^2 i.v. on day 1 and vincristine 1.4 mg/m^2 i.v. on day 1. In patients with LD, tumour bed irradiation was administered 2 weeks after the completion of chemotherapy to a dose of 2880 cGy eight fractions of 360 cGy – three fractions per week (unconventional fractionation used because of limited therapy unit availability at the time of the study).

Response to chemotherapy was assessed prior to irradiation in LD patients. Patients with no evidence of disease clinically or on chest roentgenograms were considered as having had a complete response (CR). Patients with a 50% reduction in surface areas of the most clearly visible lesion on serial chest roentgenograms and with no evidence of disease progression elsewhere were considered as having a partial response. The WHO grading system of toxicity was used [5]. Patient survival was determined by the life table method.

Results

The patient characteristics and results of therapy are presented in Table 1. The median survival for LD and ED disease patients was 12 and 6 months respectively. The 2-year survival rate in the 35 patients with LD was 26%, with one patient dying of intercurrent disease, one patient lost to follow-up, and eight patients alive at 2 years. Five of the eight patients were continuously disease free and three had undergone repeat chemotherapy for relapsed disease.

The initial site of failure in the 28 relapsed patients with LD (25 of whom have died of disease and three of whom are alive) were the primary site in 13 (48% of relapses), the lung outside of the primary site in two, the brain in ten (38%), the bones in two, and the adrenal gland

Table 1. Patient characteristics and the results of therapy for small cell carcinoma of the lung

	LD	ED	TOTAL
Patients	35	28	63
Age – mean (range)	59 (43–76)	58 (41–72)	59
Male – female ratio	1.5:1	1.8:1	1.6:1
Performance status (SWOG)			
0 and 1	20	10	30
2 and 3	15	18	33
Response – no. (rate as %)			
CR	22 (63)	6 (21)	28 (44)
PR	9 (26)	10 (36)	19 (30)
CR + PR	31 (89)	16 (57)	47 (74)
Failed	4 (11)	12 (43)	16 (25)
Survival			
Median (months)	12	6	9
Mean (months)	14+	7	11+
1-yr (%)	51	10	32
2-yr (%)	26	0	13

SWOG, South West Oncology Group; *CR*, complete response; *PR*, partial response

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in one. An increase in performance status was noted during follow-up in 26 (78%) of the patients with LD and in 15 (54%) of the patients with ED.

There were nine patients who had grade-2 myelosuppression, with WBC between 2000 and 2900/mm^3 or platelet counts between 50000 and 74000 at the time of the subsequent cycle of chemotherapy. There were no episodes of severe haematological suppression. Thirteen of the patients developed grade-I vincristine-related paraesthesiae, after which their vincristine was stopped. None of the patients had protracted symptoms from their paraesthesiae. All patients developed alopecia and grade-I nausea, which was controlled with standard anti-emetics. There were no radiation-related complications apart from transient radiation oesophagitis.

Discussion

Etoposide has the highest tumour response rate (45%) of all the single agents for SCCL [3] and is the only single agent reported to cure a patient with SCCL [1].

Etoposide has been reported as requiring administration over 3–5 days for optimal effect [2]. This data has been criticized, as the patients treated in divided doses had increased myelotoxicity [7]. The bio-availability of etoposide following oral administration is approximately 50% of that from the i.v. route, but it is variable [6]. The bio-availability is dose dependent and is relatively the greatest in the low oral-dose range of 200 mg when compared with higher doses [4].

There will be a bias towards a higher proportion of patients with LD relative to ED in this series compared with those in which bone marrow trephines were done for staging purposes. The median survivals of patients with LD and ED of 12 and 6 months respectively, however, compares favourably with others reported in the literature. In a similarly staged series in which the patients were treated with etoposide by single infusion (300 mg/m^2) and with the same dosages of adriamycin and vincristine, the median survivals were 7 and 4 months for LD and ED patients respectively [7]. Direct comparisons between series cannot be made because of factors such as patient population and selection.

In a prior series of patients treated with etoposide alone at our institution [8], the response rate for LD and ED together was 51% and the mean survival in LD patients 9 months. These results improved with the combination regimen to 74% ($P=0.011$) and more than 14 months respectively.

The morbidity of therapy was relatively low, despite the development of vincristine-related grade-I paraesthesiae in 22% of the patients. An improvement in performance status in 78% of the patients with LD and 54% of those with ED indicates that palliation was achieved in the majority of patients. The incidence of tumour recurrence in the original radiation port is relatively high (48%). It is possible that this may be reduced by using a higher dose of radiation with conventional fractionation.

We are undertaking a prospective randomised trial to evaluate the role of oral etoposide in combination chemotherapy and will be comparing the chemotherapy regimen using oral and intravenous etoposide, as above, with the regimen containing single-infusion etoposide.

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