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High-dose cyclophosphamide and VP 16 as late dosage intensification therapy for small cell carcinoma of lung

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Summary. This study investigated the use of late dose intensification therapy (LDIT) with cyclophosphamide (180 mg/kg) and VP 16 (1 g/m^2) plus autologous bone marrow rescue in 22 patients with small cell lung cancer (SCLC). These patients were selected from a group of 95 patients who received three courses of a five-drug induction regimen comprising cyclophosphamide (750–1000 mg/m^2), adriamycin (40 mg/m^2), VP 16 (100 mg/m^2) for 3 days, methotrexate (50 mg/m^2) and vincristine (2 mg) (CAVMO). There were 16 patients with limited disease, 8 of whom were in complete remission (CR) and 8 in partial remission (PR) after the induction therapy. The other 6 patients had extensive disease; 3 of these achieved CR and 3 PR after induction therapy. Of the 11 patients in PR, 5 responded to LDIT; 3 had a further PR, and 2 CR. Subsequent to LDIT radiotherapy 4000 cGy was given to the primary site in 10 of the 22 patients. Since the start of the study, 19 of the 22 patients have relapsed and died (median survival 11 months), while 3 remain alive and in remission at 11, 11, and 24 months. Comparison of the survival of patients receiving LDIT with that of an equivalent group (with respect to staging and response to induction chemotherapy) of patients who received induction chemotherapy alone showed no significant difference. In this study, LDIT following conventional induction therapy in patients with chemosensitive tumours did not improve survival.

Introduction

Despite the inherent sensitivity of small cell carcinoma of the lung (SCLC) to cytotoxic drugs, few patients have any prospect of cure [10]. With conventional combination chemotherapy regimens complete response rates of 30% can be expected, but the majority of these patients relapse [8], presumably due to the presence of drug-resistant tumour cells after the apparently successful induction therapy. In animals, there is experimental evidence for the existence of a steep dose-response curve of tumours to cytotoxic drugs [7], which has generated interest in the possible role of dose escalation of chemotherapy for the treatment of patients with SCLC. Indeed, high-dose cyclophosphamide, when used as single-agent induction therapy, has been reported to produce tumour regression in 80% of patients with SCLC, but like that achieved with conventional therapy the associated clinical remission is not durable [16].

We have previously conducted a pilot study of high-dose cyclophosphamide with autologous bone marrow rescue (ABMR) as late dosage intensification therapy (LDIT), following conventional induction therapy in a group of patients with SCLC [2]. Although some antitumour effect of high-dose cyclophosphamide was observed, in patients not responding to induction therapy it was not considered to be a useful salvage treatment, and in those achieving complete or partial response to induction therapy, LDIT did not obviously improve survival. However, as the overall response to induction therapy was poor we concluded that further investigation of LDIT following more effective induction therapy was necessary.

Patients and methods

Patients

Between June 1982 and December 1983 patients were selected to enter this study of LDIT, from among 95 patients with histologically confirmed small cell lung cancer who were receiving induction therapy consisting of cyclophosphamide 750–1000 mg/m^2 on day 1, adriamycin 40 mg/m^2 on day 1, VP 16 100 mg/m^2 on days 1–3, methotrexate 50 mg/m^2 on day 10, and vincristine 2 mg on day 10 (CAVMO), all given IV every 21 days. (Full details of the induction therapy in 95 patients will be published elsewhere.) After three courses of CAVMO patients were restaged by means of bronchoscopy, isotope bone scan, hepatic ultrasound, and trephine bone biopsy. Those who were in complete remission (CR) or partial remission (PR) with a negative marrow, were <70 years of age, and were considered fit for anaesthesia were offered LDIT if they fulfilled the following criteria: white blood count $>4\times10^9$/l, platelets $>100\times10^9$/l, serum creatinine <120 mmol/l, and bilirubin <17 μmol/l. Patients with a history of congestive cardiac failure or recent episodes of angina were excluded. Patients not considered suitable for LDIT and those declining LDIT were not given further chemotherapy, but in two centres 70 patients received radiotherapy (4000 cGy) to the primary site 4–8 weeks later. In all, 22 patients, comprising 17 men and 5 women with a mean age of 52.5 years (range 28–68 years), were selected for and agreed to LDIT. At initial presentation 16 had lim-

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ited disease (LD) and 6, extensive disease (ED). Following CAVMO 8 of the LD group were in CR and 8 in PR, with 3 of the ED group in CR and 3 in PR.

Details of late dosage intensification

Autologous bone marrow rescue (ABMR). Marrow (610–1205 ml) giving an autologous cell count of $1.2–4.3 \times 10^8$/kg was harvested from the iliac crests under general anaesthesia and stored in liquid phase at 4 °C [4]. During the harvest procedure each patient received a transfusion of 1 unit of packed cells. Marrow was reinfused via a peripheral vein 36 h after the beginning of high-dose chemotherapy, which was generally 38–40 h after harvesting. Prior to infusion marrow was left at room temperature for 30 min to allow dissolution of fat globules.

Cytotoxic chemotherapy. Immediately following marrow harvest, a total dose of cyclophosphamide (CTX) 180 mg/kg was given as four 60-min IV infusions in 500 ml 5% dextrose solution at 5-hourly intervals over a period of 20 h. Thirty minutes before the infusion of CTX mesna 36 mg/kg (20% total dose of CTX) was given as an IV bolus and repeated every 3 h to a total of nine doses. VP 16 (1 g/m^2) was given as a 200-mg IV infusion in 500 ml *N*-saline over the 30 min before cyclophosphamide and the remainder given in four divided doses as a 4-h IV infusion in *N*-saline after each infusion of CTX. During chemotherapy the patients' urine output was maintained at 100 ml/h. Routine antiemetic therapy with chlorpromazine 25 mg IV was administered to all patients. After LDIT patient were returned to a general ward. Peripheral blood counts were monitored every 2nd day, and when the neutrophil count became less than 500/m^3 patients were transferred to isolation facilities with laminar air flow. Gut decontamination therapy was given routinely whilst the patients were neutropenic, consisting of Nystatin 1 million units q.i.d., Colistan 1.5 MU q.i.d. and Framycetin 500 mg q.i.d.

Radiotherapy

Radiotherapy at a dose of 4000 cGy was given to the primary tumour site 4–6 weeks after LDIT in two centres (Glasgow Royal Infirmary and Western Infirmary).

Results

Response to LDIT

Twenty-two patients completed LDIT and the results are summarised in Table 1, where survival and remission duration are counted from the beginning of induction therapy. Three patients, two of whom did not receive radiotherapy, remain alive and in complete remission: one of these converted from PR to CR by LDIT (11 months' survival); one patient showed a PR in response to LDIT and had residual bronchoscopic disease which responded to radiotherapy (24 months' survival); and one patient was in CR before LDIT (11 months' survival). Nineteen patients relapsed and are now dead. The initial sites of relapse are shown in Table 2.

Radiotherapy successfully prevented relapse at the primary site in 6 of the 10 patients to whom it was given. There was no difference in median survival for patients who received or did not receive radiotherapy (11 and 12 months, respectively). There was no significant difference between the survival of patients given LDIT and the survival of equivalent prognostic groups of patients given three courses of induction therapy alone (Figs. 1–3). Survival was analysed by the log-rank test as outlined by Peto [14].

Toxicity of LDIT

There were no treatment-related deaths. All patients experienced nausea and vomiting despite antiemetic therapy, but the symptoms resolved within 24 h except in one patient, in whom they persisted for 7 days. Diarrhoea occurred in 12 (54%) patients. It usually began within 12 h of

Table 1. Response amd survival following

	Patients in CR before LDIT	None	Response to LDIT (no. of patients) PR → PR+[a]	PR → CR	Median duration of remission	Median survival	Alive with relapse	Alive in remission
Limited	8	5	2	1	11	12	0	3
Extensive	3	1	1	1	8	10	0	0

[a] Indicates > 50% further reduction in tumour size

Table 2. Site of relapse and survival following LDIT in 19 patients, and the impact of radiotherapy

	Site of relapse						
	Primary alone	Systemic alone	Brain alone	Primary + systemic	Primary + brain	Systemic + brain	Primary + Systemic + brain
Limited	4	2	1	2	3	–	1
Extensive	1	3	1	–	–	–	1
Radiotherapy	–	5	1	1	1	–	1
No radiotherapy	5	–	1	1	2	–	1

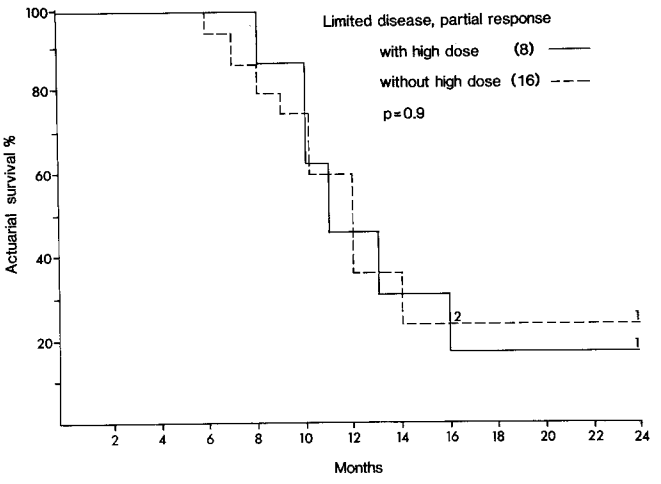

Fig. 1

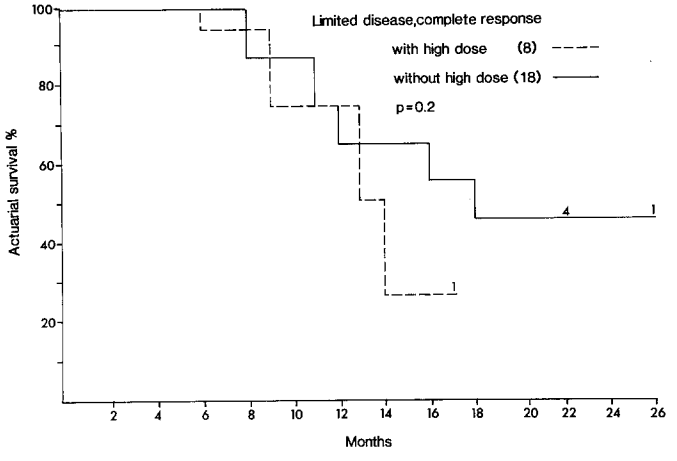

Fig. 2

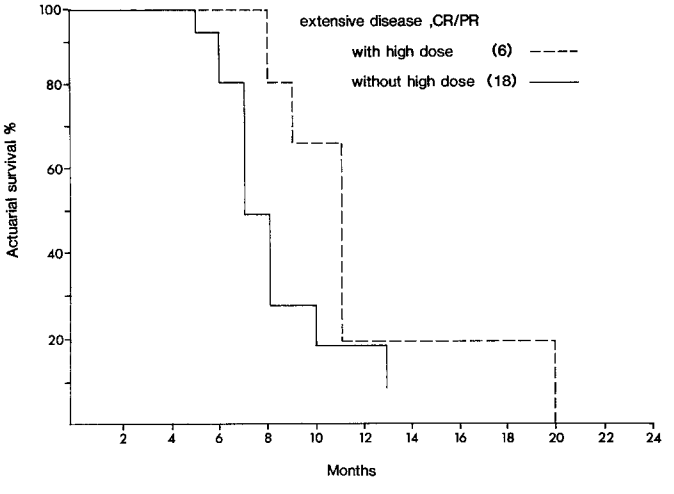

Fig. 3

Figs. 1–3. Survival of patients given high dose chemotherapy as LDIT compared with those patients not given high dose chemotherapy as LDIT

LDIT and was generally mild, resolving spontaneously within 24 h. Two patients had more severe diarrhoea which lasted 7 and 10 days, respectively, and in these cases the diarrhoea was treated with codeine phosphate. Mucositis (WHO grade 2) was observed in 8 (36%) patients. Five patients developed an itchy maculopapular rash, in the trunk and neck regions in four and on the buttocks in one. Three patients became significantly depressed during isolation but were not treated with psychotropic drugs. Two patients had transitory macroscopic haematuria, but there was no associated elevation in serum creatinine. Two patients developed pulmonary oedema within 24 h of LDIT, both of whom responded to diuretics. All patients developed predictable myelosuppression. The mean total white blood cell count nadir was $294 \times 10^6/l$, and the duration of neutrophil count $< 500 \times 10^6/l$ (mean $\pm$SEM) was 13.0 ± 0.8 days. The mean platelet nadir was $11 \times 10^9/l$, and the duration of platelet counts $< 50 \times 10^9/l$ was 13.6 ± 1.4 days. Fourteen (63%) patients became febrile following chemotherapy; 11 of these were neutropenic and thus received antibiotic treatment. Four patients developed a platelet count $< 5 \times 10^9/l$ with associated purpura requiring platelet transfusions.

Discussion

Chemotherapy undoubtedly prolongs survival in patients with SCLC. Indeed, it is now possible to achieve CR in the majority of patients with limited disease, but most of these patients ultimately relapse and die. Maintenance therapy [13] and alternating non-cross-resistant chemotherapy [3, 5, 12] have failed to significantly influence the outlook for patients with SCLC, and therefore there has recently been interest in the role of escalating the dose of chemotherapy either in the induction phase [6, 16] or as LDIT [2] to prevent relapse.

In this study, however, LDIT did not have a significant impact on the survival of a group of patients who were selected ostensibly because they had intrinsically chemosensitive tumours as indicated by the response to induction treatment. The survival of the patients receiving LDIT was compared with that of patients who received three courses of induction therapy alone, matched on the basis of stage of disease at presentation and response to chemotherapy. These comparisons, whilst falling short of a controlled study, are valid because they take into consideration the most important prognostic factors in SCLC, and the conclusions are supported by the literature in which the median survival of patients with limited disease is quoted as 12 months with conventional chemotherapy alone [8, 10].

Although both high-dose cyclophosphamide [16] and high-dose VP 16 [11] have been demonstrated to give response rates higher than expected with conventional doses, it seems doubtful on the basis of our experience that their use will successfully eradicate residual, drug-resistant tumour cells when given as LDIT. However, it could be argued that the flaw in the design of this particular study in its attempts to address the LDIT issue was the use of the same cytotoxic drugs in the late dose intensification phase as in the induction phase. This could conceivably induce a clone of cells resistant to the drugs used for intensification. Nevertheless, Smith et al. [15] have recently reported LDIT using different agents from the induction regimen, with similar results to ours.

Radiotherapy prevented relapse at the primary site in 60% of the patients to whom it was given. Of the patients not given chest radiotherapy all but one relapsed locally. Survival, albeit of groups composed of small numbers of patients, was similar for the patients in both groups, which is consistent with a recent study that demonstrated the ability of radiotherapy to prevent primary relapse but not improve survival [17]. In this study, patients did not receive prophylactic cranial irradiation as there is no clear evidence that it influences survival following conventional chemotherapy [1]. The same may not be true following LDIT, and it is possible that the relapse in the brain as the solitary site which occurred in two patients in this study might have been prevented by cranial irradiation. It has been suggested that escalating the dose of VP 16 may produce sufficiently high levels of the drug in the CSF to prevent CNS relapse in tumours such as SCLC [9]. In our experience this does not seem to be the case, as six patients (27.1%) had cerebral involvement at the time of relapse.

The toxicity of LDIT with the combination of cyclophosphamide and VP 16 was similar to that encountered with cyclophosphamide alone [2]. The only major difference was mucositis, which was more frequent in this study and was presumably due to VP 16, a finding similar to the experience of other workers [11]. In general, the toxicity of LDIT was easily managed and its routine use proved feasible on a moderate scale, but it should be stressed that such therapy should not be instituted outside major centres familiar with the management of problems arising in patients who are profoundly myelosuppressed.

In conclusion, the results of this study are disappointing. Late dosage intensification therapy does not appear to be the answer to the problem of sustaining remission in SCLC. Alternative approaches to the problem of drug resistance in SCLC need to be evaluated.

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