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High-dose cyclophosphamide with autologous bone marrow rescue after conventional chemotherapy in the treatment of small cell lung carcinoma

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Summary. *Whithin an original consecutive series of 94 patients, 36 eligible patients with small cell lung carcinoma were treated with high-dose cyclophosphamide 7 g/m² after conventional chemotherapy with VP16, adriamycin, and vincristine. The first 17 also underwent autologous bone marrow rescue. Treatment was well tolerated apart from one treatment-related death. Measurable tumour was still present in 15 patients before high-dose cyclophosphamide, and although 12 (80%) of these achieved further tumour response, these responses were all short-lived, with a median duration of 9 weeks. In 14 limited-disease patients already in complete remission before high-dose therapy the initial result was better, but 11 (79%) have now relapsed following overall median response duration of 10 months. High-dose cyclophosphamide after conventional chemotherapy is feasible and achieves a high response rate, but it does not appear to be associated with significant survival benefit either overall or in patient subgroup.*

Introduction

Small cell lung cancer is associated with a high initial response rate to chemotherapy, but most patients relapse within a year of treatment and very few achieve long-term survival. High-dose chemotherapy, often with autologous marrow rescue, has recently been investigated in different ways as a possible solution to this problem [4, 5, 6, 7, 9, 10, 15–18]. In one recent study a single very high dose of cyclophosphamide with autologous bone marrow rescue was shown to give a high response rate (84%) and a high complete remission rate (56%) [15], but most patients relapsed in less than a year [16], reflecting experience with conventional chemotherapy.

Based on this experience, we investigated the feasibility of giving high-dose cyclophosphamide *after* conventional chemotherapy in patients with small cell lung cancer. We chose this approach for two main reasons: first, patients with chemosensitive disease and therefore perhaps most likely to benefit from high-dose chemotherapy would be identified in advance by their response to prior conventional treatment; second, initial tumour bulk reduction by conventional chemotherapy might increase the chance of residual tumour eradication by high-dose treatment. Some support for this concept comes from experience in acute leukemia, where very intensive treatment and allogeneic marrow transplantation after remission induction with conventional chemotherapy has allowed a significant improvement in long-term survival [12]. We used an induction regimen which did not contain an alkylating agent, to reduce the risk of cylophosphamide resistance developing before high-dose treatment. During the study, we also investigated the necessity for autologous marrow rescue. Brief preliminary reports on some of these patients [13] and on the need for marrow rescue [14] have already been published.

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Patients and methods

Forty-four patients from an original consecutive series of ninety-four with small cell lung carcinoma referred to the Lung Unit were considered eligible for high-dose cyclophosphamide after conventional chemotherapy. Eligibility was based on a good objective response to conventional chemotherapy (except in 3 otherwise fit patients), age less than 70, general medical fitness after conventional chemotherapy with a Karnofsky performance status of 70 or more, and absence of CNS metastases on CT brain scan. Thirty-six of these patients had this treatment after giving informed consent, while the remaining eight refused after the experimental nature of the treatment had been explained to them. Their median age was 58 years (range 34–69 years). Twenty one (58%) had originally presented with limited disease according to standard staging criteria [8] and the remaining 15 (42%) had extensive disease. Nine (25%) had bone marrow involvement at presentation and six (17%) liver involvement, as defined by abnormal liver function in association with an abnormal isotopic liver scan and/or clinically malignant hepatomegaly.

The overall treatment plan is summarised in Fig. 1 and details are as follows:

Conventional chemotherapy. All patients were treated initially with a combination of VP16 100 mg/m² IV on days 1–3, adriamycin 40 mg/m² IV on day 1, and vincristine 1.4 mg/m² IV on day 1, repeating every 21 days. Thirthy-two patients were given four courses of therapy and towards the end of the study four patients who had already achieved a bronchoscopic complete remission were given only two courses.

High-dose cyclophosphamide. Four weeks after the last course of conventional chemotherapy patients were given a 'priming' dose of cylophosphamide 300 mg/m² by IV bolus injection, followed 7 days later by high-dose cyclophosphamide in a dose of 7 g/m² given in five divided bolus injections over a 12-h period. The rationale for this schedule was based on

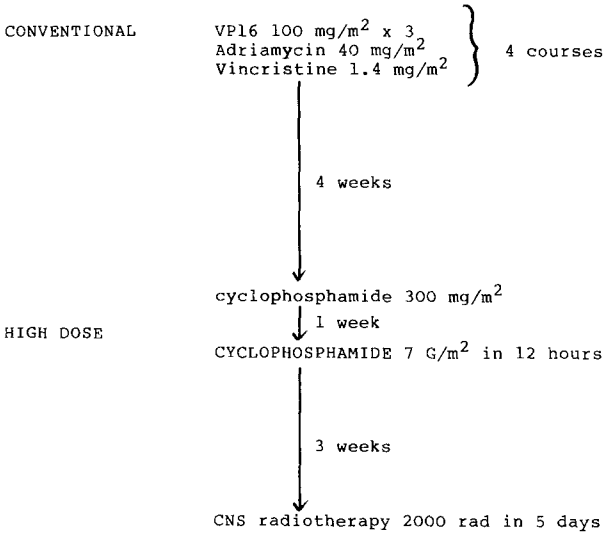

Fig. 1. Summary of the overall treatment plan

experimental data described elsewhere by Evans et al. [5]. For urothelial protection all patients were given Mesna in a dose of 1 g IV 3-hourly for 30 h starting with the first cyclophosphamide injection (total dose 11 g).

Nausea and vomiting after cyclophosphamide were treated with lorazepam 2 mg IV and prochlorperazine 25 mg IV repeated 4- to 6-hourly as required. Diarrhoea during and immediately after cyclophosphamide therapy was treated with codeine phosphate or loperamide. All patients were nursed in a single rooms but without isolation or gut decontaminant antibiotics. Oral antifungal prophylaxis was started immediately with ketoconazole 200 mg daily. Prophylactic parenteral gentamicin and piperacillin were given during the period of neutropenia. Platelet transfusions were given prophylactically if platelet counts fell below 30,000/mm^3.

Autologous bone marrow rescue. The first 17 patients underwent autologous bone marrow harvest under general anaesthetic approximately 2 h before starting cyclophosphamide. Bone marrow was kept at 4° C as previously described [11] and re-infused 12 h after the last dose of cyclophosphamide, i.e., around 26 h after harvesting. No cryopreservation was necessary and no other marrow processing was carried out. The mean harvested nucleated cell count was 2.4×10^8 cells/kg. The next 19 patients did not receive autologous marrow rescue.

Radiotherapy. Prophylactic whole-brain radiotherapy to a dose of 20 Gy mid-plane in 5 days by opposed fields using megavoltage X-rays was given to all but five patients (1 refused; 1 early death; 3 unfit around 4 weeks after high-dose cyclophosphamide. Prophylactic intrathoracic radiotherapy to sites of original local disease was not given, but was reserved for possible future local relapse.

Staging investigations. At initial presentation all patients had a full clinical examination, peripheral full blood count, plasma urea, and electrolytes, serum creatinine and liver function tests, chest X-ray, bone marrow aspirate and trephine biopsy, and isotopic bone scan. Other investigations, including isotopic liver scan and skeletal bone X-ray, were carried out where clinically indicated. Prior to high-dose cyclophosphamide patients were fully restaged. In addition, a CT brain scan was carried out to exclude cryptic CNS metastases and patients with limited disease had a repeat bronchoscopy with biopsy.

Response and toxicity. Tumour response was defined according to standard criteria: complete response was defined as disappearance of all clinical radiological and biochemical evidence of disease for a period of at least 2 months, including a negative biopsy at second-look bronchoscopy if this was carried out: partial response was defined as the reduction in the product of two diameters of measurable disease by at least 50% for at least 1 month. Toxicity was graded according to standard WHO criteria [19].

Results

Response to conventional chemotherapy

Of the 21 patients with limited disease, 14 (67%) achieved complete remission and five (24%) achieved partial response. Two patients (9%) showed no response to conventional chemotherapy but were still given high-dose cyclophosphamide because of their relatively young age and general medical fitness.

Of the 15 patients with extensive disease, seven (47%) achieved complete remission and three (20%) partial response. Four others had shown an original response to treatment but were already relapsing at the time of high-dose cyclophosphamide, and one had never shown evidence of response to conventional treatment.

Of the nine patients initially presenting with marrow involvement, eight achieved complete marrow remission on conventional chemotherapy.

Response to high-dose cyclophosphamide

Of the 15 patients who still had measureable tumour at the time of high-dose cyclophosphamide, 12 (or 80%) achieved a further objective tumour response to this treatment, including five (33%) who achieved a complete remission. However, none of these patients had a sustained response (see below).

Duration of response and survival after cyclophosphamide

The duration of remission after high-dose cyclophosphamide is shown in Fig. 2. The median duration for all patients was 7.5 months from the start of first treatment and only 4 months from high-dose cyclophosphamide. This poor response duration was principally associated with patients who had not achieved a complete remission with conventional chemotherapy or who had presented initially with extensive disease. In this group of 22 patients the median duration of response from initial treatment was only 5.5 months and only 9 weeks from high-dose cyclophosphamide. All these 22 have now relapsed. The 14 limited-disease patients who achieved complete remission after conventional chemotherapy had a median response duration of 10 months from first treatment and 6.5 months from cyclophosphamide. Three of the 14 currently remain in remission.

Survival is shown in Fig. 3. The overall median duration of survival was 11 months from first treatment, and 7.5 months from the time of high-dose cyclophosphamide. The median survival for patients not achieving complete remission or originally presenting with extensive disease was only 9.5 months from the start of treatment and 5.5 months from high-dose cyclophosphamide; only one remains alive. The median survival for patients with limited disease who achieved complete remission with conventional chemotherapy was 20 months from the start of treatment and 16.5 months from high-dose cyclophosphamide; six of the 14 remain alive.

Survival of patients refusing high-dose cyclophosphamide

The median survival of the eight patients who refused high-dose cyclophosphamide was 10 months; one remains alive. These results are similar to those in patients receiving high-dose chemotherapy but the numbers are too small for further comparisons.

Site of first relapse

Of the 14 limited-disease patients who achieved complete remissions after conventional chemotherapy, 11 have so far relapsed: 10 of these have relapsed locally but six have so far also had a systemic relapse within 0–5 months of local relapse.

Toxicity

Severe (WHO grade IV) neutropenia occured in all patients. Peripheral neutrophil counts fell to less than 500/mm^3 on (median) day 7 after treatment (range days 5–8) and rose to greater than 1,000/mm^3 on (median) day 18 (range days 15–23). Neither degree nor duration of neutropenia was influenced by whether or not patients had bone marrow rescue. Severe neutropenic infection developed in four patients (12%), including three with septicaemia apparently related to infected central venous catheters and one with pneumonia, but all recovered fully. Thrombocytopenia of less than 100,000/mm^3 occurred in 35 patients (97%): this included two (6%) with nadir of greater than 75,000/mm^3 (grade 1), two (6%) of greater than 50,000/mm^3 (grade 2), four (11%) of greater than 25,000/mm^3 (grade 3) and the remaining 27 (75%) of less than 25,000/mm^3 (grade 4). In 26 patients prophylactic platelet transfusions were given. Neither degree nor duration of thrombocytopenia was significantly influenced by autologous bone marrow rescue.

Details of nonhaematological toxicity are given in Table 1. Nausea and vomiting occurred in 89% of patients but was of short duration, rarely lasting more than 24 h after treatment and never more than 72 h. Watery diarrhoea occurred in 58% of patients 6–24 h after treatment but was of short duration and readily controlled with codeine phosphate or loperamide. Macroscopic haematuria occurred in six patients (17%) but was never severe and there were never clots; this was usually associated with urethral catheterisation, which was stopped for later patients. Twelve patients (33%) complained of dysuria but this was mild and transient in all but one and again usually associated with catheterisation. Thirteen patients (33%) developed a characteristic transient erythematous maculopapular and sometimes purpuric rash, particularly around the neck area, a few days after treatment. Six patients (17%) developed transient arrhythmias, including atrial fibrillation [2] supraventricular ectopics [1] and ventricular ectopics [1] in the first 24–48 h of treatment, but no episodes of cardiac failure were seen. One patient developed intractable haematemesis, which proved fatal on day 10 after treatment, which a peripheral platelet count of 70,000/mm^3. Post-mortem examination

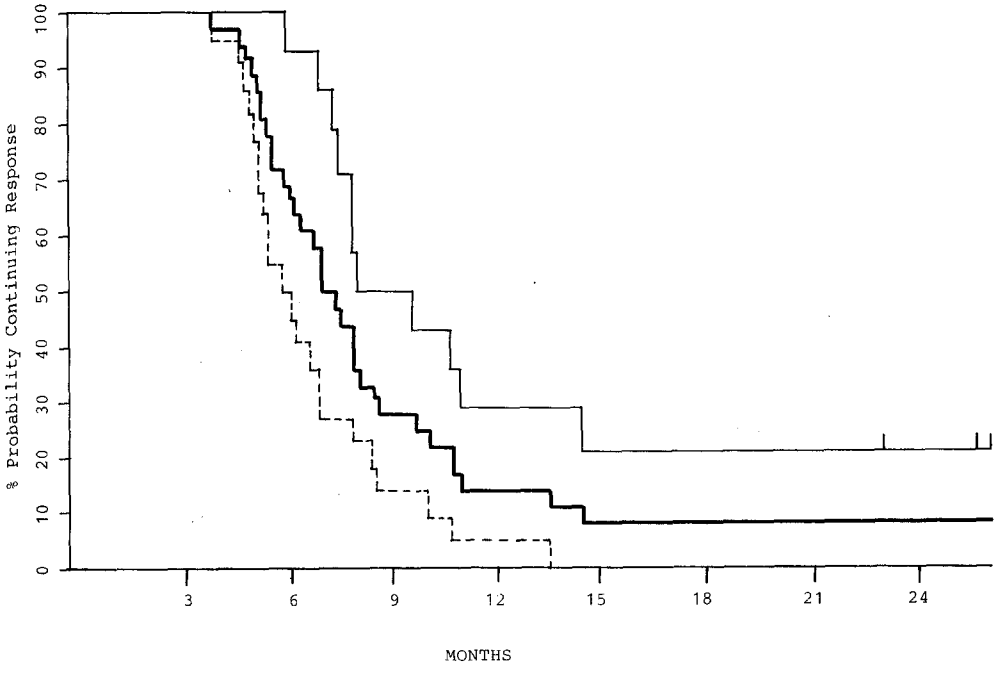

Fig. 2. Response duration from first treatment. (———) all patients; (———), LD in complete remission before cyclophosphamide (14 patients); (— — —), other patients (22 patients)

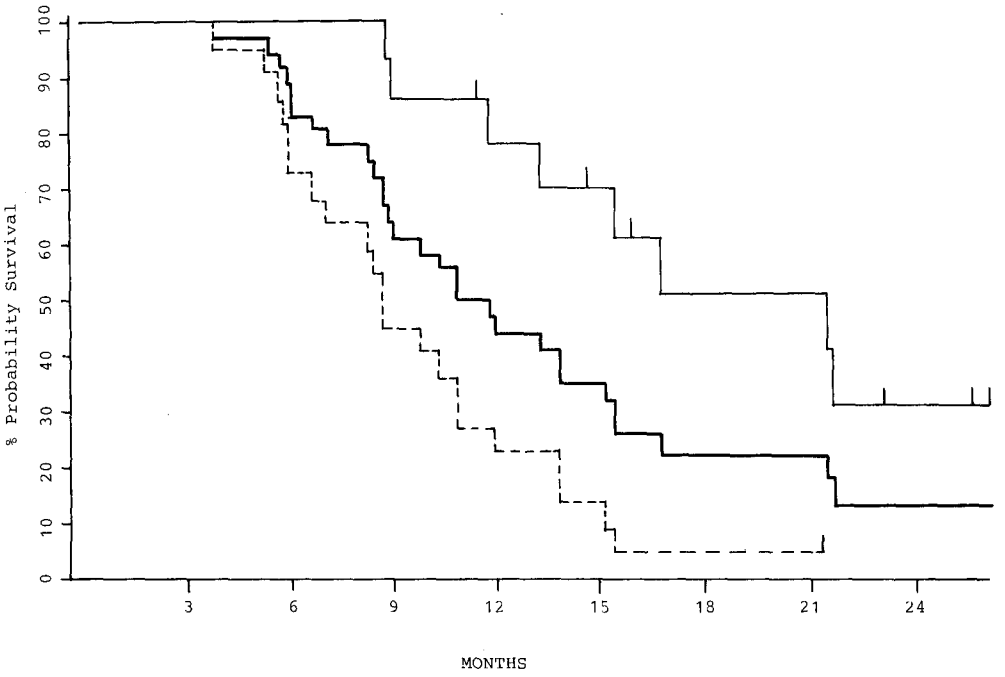

Fig. 3. Survival from first treatment. (———) all patients); (———), LD in complete remission before cyclophosphamide (14 patients); (— — —), other patients (22 patients)

Table 1. Non-haematological toxicity in 36 patients

Toxicity (WHO grade)			
	1–2	3–4	Total
Nausea, vomiting	18	14	32 (89%)
Diarrhoea	14	7	21 (58%)
Haematuria	6	0	6 (17%)
Dysuria	12	0	12 (33%)
Rash	13	0	13 (33%)
Cardiac arrhythmias	6	0	6 (17%)
Cardiac failure	0	0	0

showed multiple small erosions throughout the entire gastric mucosa. Despite these toxicities the majority of patients tolerated treatment well and many complained simply of boredom in hospital as the main problem.

Discussion

This study has demonstrated that it is quite feasible to give very-high-dose cyclophosphamide shortly after conventional chemotherapy to middle-aged patients. The one treatment-related death was of an unusual nature, and overall this treatment was surprisingly well tolerated. Others have made similar observations [7, 15]. It was useful to discover that autologous bone marrow rescue was unnecessary, and we have already cautioned against assuming that this elaborate, time-consuming and expensive procedure is enevitably required with high-dose chemotherapy regimens [14].

The treatment was highly active in terms of response rate, 80% of patients with residual disease after conventional chemotherapy achieving further tumour regression. However, the crucial and disappointing feature of these responses was their consistently short duration. This aspect of response to high-dose chemotherapy after conventional treatment has also been reported elsewhere. In a similarly designed study, 11 patients with residual disease after chemotherapy all achieved a further tumour response to high-dose cyclophosphamide, but all quickly relapsed [7]. A similar pattern emerges in patients treated with high-dose cyclophosphamide combinations at the time of relapse after conventional chemotherapy: further tumour regressions are very common but always of short duration [3, 7]. It therefore appears that an important general statement can be made: patients whose tumours are not in complete remission after conventional chemotherapy have a very good chance of further tumour response to high-dose cyclophosphamide, but this response is of no benefit whatever in terms of prolonged disease control.

In contrast, we initially hoped that limited-disease patients who had already achieved a complete remission after conventional chemotherapy would have a better chance of long-term disease control with subsequent high-dose cyclophosphamide. Again results have proved disappointing. Although six of these 14 patients remain alive with a median survival of 20 months, nevertheless only three of these are still in remission. Furthermore, this highly select group of patients has a relatively good prognosis anyway. In our own recent experience the median survival of 42 limited-disease patients achieving a complete remission after conventional treatment was also 20 months (unpublished data), and others have reported results of around 16 months or more [1, 2]. It is possible that local radiotherapy to the primary tumour site as part of initial management might have benefited a few of these patients, but it should be noted that the majority of those who have relapsed have done so in extrathoracic as well as intrathoracic sites. A randomised trial would be required to determine whether high-dose cyclophosphamide had any

significant survival benefit in this group of patients, but our results suggest that such a trial would hardly be warranted, given the marginal benefit, if any, that could be hoped for, balanced against the toxicity of therapy.

High-dose cyclophosphamide after conventional chemotherapy in the management of small cell lung cancer is feasible and active in terms of tumour response rate, but this pilot study suggests that any significant survival benefit is unlikely overall or in any subgroup of patients.

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