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Retreatment with the Induction Regimen in Small Cell Lung Cancer Relapsing after an Initial Response to Short Term Chemotherapy

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Abstract—*In 37 patients with small cell lung cancer treatment with five cycles of cyclophosphamide, doxorubicin and etoposide (CDE), resulted in 23 complete (CR) and 14 partial responses (PR). Median response duration was 34 weeks. At relapse all patients were retreated with CDE. In 23 (62%) patients this gave a second response (6 CR, 17 PR). Factors influencing the occurrence of a second response were:*

1. *a CR after the first five cycles of CDE; 18 out of 23 CR patients responded again whereas only five of the 14 PR patients responded* ($P < 0.01$).
2. *15 out of 19 patients with a first response duration > 34 weeks reached a second response and in eight of the other 18 patients retreatment was successful* ($P < 0.05$).

Reinduction at relapse, after short term chemotherapy and a treatment-free interval, with the induction regimen is an effective scond line treatment in patients with an initial CR and a first response duration of > 34 weeks.

INTRODUCTION

It is generally assumed that the effect of second-line chemotherapy in small cell lung cancer (SCLC) patients with a relapse is minimal. In this report we describe the results of reinduction with the same regimen used for induction in patients with a relapse after an initial response to short term chemotherapy.

METHODS

All previously untreated patients had histologically proven SCLC, performance score ≤ 3 (ECOG) and gave informed consent.

The treatment consisted of five courses, at 3 week intervals, of cyclophosphamide 1 g/m^2 i.v. day 1, doxorubicin 45 mg/m^2 i.v. day 1 and etoposide 100 mg/m^2 days 1, 3 and 5 (CDE) according to the EORTC 08825 study. The initial staging consisted of physical examination, chest X-ray, standard tomography, or computer tomography (CT) of the chest, bronchoscopy with biopsy, ultra-sound of liver and adrenals or CT of the abdomen, isotope bone scintigraphy, bilateral posterior iliac crest bone marrow biopsy and neurological examination. Laboratory investigations included routine blood cell counts, serum electrolytes and liver and renal function tests.

Limited disease (LD) was defined as tumor limited to one hemithorax, bilateral hilar and supraclavicular nodes. All other patients were staged as extensive disease (ED).

After five courses of CDE restaging was performed by physical examination, chest X-ray, CT or tomography, bronchoscopy to confirm roentgenologically complete remission; all other initially abnormal investigations were repeated. Patients with a complete response received prophylactic cranial irradiation (10 × 3 Gy).

A complete response (CR) was defined as disappearance of all known tumor lesions. A partial response (PR) was defined as a decrease of more than 50% of the product of the largest perpendicular diameters of all measurable lesions. Stable disease (SD) was defined as a less than 50% regression without signs of progression. Progression (Progr.) was defined as an increase of more than 25% of a known tumor lesion or appearance of a new lesion. The duration of a response was measured from the start of chemotherapy.

At relapse all patients were retreated with CDE

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Table 1.

Patients	$n = 37$
Age	38–77 years (mean 59)
Staging	18 LD, 19 ED
Response after 5 CDE	23 CR (15 LD, 8 ED) 14 PR (3 LD, 11 ED)
Response duration (from start of therapy)	20–80 weeks (median 34 weeks)
Staging at relapse	4 LD, 23 ED
Response after re-CDE	6 CR 17 PR
Response duration (from start of re-CDE)	6–53 weeks (median 26 weeks)

at the same dose and schedule as was used during the first five courses of the induction. The maximal number of courses of the retreatment was seven, in order to prevent doxorubicin-related cardiotoxicity. The minimum number of courses was two, unless progression was clearly evident.

The response to the retreatment was evaluated after each course by physical examination and chest X-ray. Chemotherapy was stopped if objective or subjective toxicity was too severe and irradiation of the primary was started in LD patients (10 × 3 Gy). The duration of the response was measured from the start of retreatment.

RESULTS

Patient characteristics, staging and response after the five induction courses and the reinduction courses are given in Table 1. Four of the LD patients had at relapse ED. Of the 23 initially CR patients 18 (78%) had again a response after CDE, whereas five of the 14 PR patients had a second response (36%) ($P < 0.01$). The median duration of the second response was 26 weeks (range 6–53).

In the patients with a first response > 34 weeks ($n = 19$), 15 patients responded again, median response duration 32 weeks (range 22–53). Of the patients with a first response ≤ 34 weeks ($n = 18$), eight responded again ($P < 0.05$), median response duration 17 weeks (range 6–48).

All patients experienced nausea and vomiting during the first 1 or 2 days of CDE, WHO grading 1–2. Hematologic toxicity during the induction period was rather mild; in nine patients dose reduction was necessary during the first five CDE courses due to grade 4 leuco- or thrombocytopenia. Overall 89% of the planned dose was given (range 75–100%).

Other toxic effects were hair loss in the majority of the patients and a few times mild mucositis (WHO grade 1) was seen.

Nausea and vomiting during reinduction were comparable. In contrast the hematologic toxicity was much more expressed. In 10 patients grade 4 leuco- and/or thrombocytopenia were seen during the first course of the reinduction. There were no bleeding episodes or aplasia related infections. Eleven of the patients later on refused further chemotherapy while they were still responding to the reinduction treatment. Ten of these patients received subsequently radiotherapy to the area of the primary tumor.

DISCUSSION

The management of patients with relapsing SCLC is difficult. A variety of drugs, alone or in combination, have been tested in this setting, with generally unsuccessful results. Recently, the combination of etoposide with cisplatinum has been reported to give up to 50% response in second line [1]: however, in heavily pretreated patients the result was disappointing [2]. An influence of the duration of pretreatment on the effect of second line chemotherapy at relapse has also been found by Harper *et al.* [3]. In this latter study second line chemotherapy at progression, after an initial response after four induction courses, resulted in the same median survival as in patients treated with eight induction courses and the same second-line therapy.

In other tumors the efficacy of reinduction therapy after a treatment-free interval has been evaluated. In Hodgkin's disease, breast cancer and myeloma this was an effective approach. In SCLC this has not been sufficiently evaluated. In a group of ED patients, reinduction during a persistent response resulted in a significantly longer survival than in the control group [4]. In a study by Batist *et al.* [5] in a group of only six patients with a response duration of over 27 months, reinduction at relapse resulted in four patients in a second response. Reinduction after a shorter response period, as is more commonly found, has not been reported yet.

In our study a second response was seen in 62% of the patients. Factors favoring a second response included an initially smaller tumor load (LD), a better first response (CR) and a relatively long duration of the first response.

An explanation for this reinducability is not known. It might be the consequence of a too low intensity of the induction treatment, although in this group of patients there was no difference regarding the duration and magnitude of the response between patients who received 100% of the planned dose during the induction and those with a less than 100% dose. In this context the observation of resistance of a SCLC cell line during exposure to doxorubicin disappearing after withdrawal of the drug is of interest [6]. It is uncertain whether a similar phenomenon occurs *in vivo* during chemotherapy for SCLC.

The result of the present study emphasizes the problems of the interpretation of phase-II studies of new drugs in SCLC. The lack of a response in patients with resistant tumors might result in unjustified rejection of useful drugs, as for instance happened with teniposide [7].

This study illustrates clearly that retreatment with the induction regimen is effective in most patients after short term chemotherapy.

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