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Short Report

Vincristine, Adriamycin, Cyclophosphamide, and Etoposide (VP16-213) in Small-cell Anaplastic Carcinoma of the Lung

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Summary. *Twelve patients with small-cell anaplastic carcinoma of the lung were treated with vincristine 1 mg/m² i.v. day 1, adriamycin 50 mg/m² i.v. day 1, cyclophosphamide 1,000 mg/m² i.v. day 1, and etoposide 80 mg/m² i.v. day 2, 4, 6 given on an outpatient basis and repeated at 3-week intervals. As consolidation therapy seven patients received two courses of BCNU median 29 mg/m² (range 24–73 mg/m²) short term intraarterial infusion in the bronchial artery with 2 to 3-weeks intervals.*

One patient with limited disease had no evidence of disease for 13+ months and one patient complete remission for 3+ months. Four of ten patients with extensive disease had complete remission for median 5 months (range 2+ to 5+ months) and four patients had partial remission for median 5 months (range 4 to 5+ months). Despite side effects the chemotherapy was well tolerated by the patients.

The results correspond to those obtained with other effective regimens in small-cell anaplastic carcinoma of the lung.

Introduction

At our institution three patients are alive without evidence of disease more than 2 years from onset of therapy out of 30 patients with small-cell anaplastic carcinoma of the lung treated with adriamycin, vincristine, cyclophosphamide, and methotrexate with loco-regional irradiation or without [1]. Etoposide (4′-demethyl-epipodophyllotoxin 9-(4,6-0-ethylidene-β-D-glucopyranoside), VP16-213) was effective as single drug treatment both as induction chemotherapy and as maintenance after the above regimen [13]. In the present study we therefore combined vincristine, adriamycin, and cyclophosphamide with etoposide as induction chemotherapy. The dosage of cyclophosphamide was high as this dosage was superior to a lower dosage [4]. The schedule of etoposide was based on a experimental study of the timing of vincristine and etoposide [3] and a clinical study of the schedule dependency of etoposide [2]. Short term intraarterial BCNU infusions to the area of the primary tumor was used as a consolidation treatment as local recurrence was the dominant tumor lesion in autopsies of treatment failure patients in our previous series [1, 13]. This paper presents our preliminary results.

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Patients and Methods

Twelve patients (11 men, one woman) with histologically or cytologically proven small-cell anaplastic carcinoma of the lung were treated at the Department of Oncology and Radiotherapy, Malmö General Hospital, from July 1980 to March 1981. Median age was 54 years (range 42–71). Two patients had previously undergone lobectomy for the primary tumor. No patient had received irradiation. One patient had had two courses of mitomycin C in the bronchial artery as initial therapy [6]. One patient had more than 5 years earlier been treated for breast carcinoma and one for bladder carcinoma without evidence of relapse. No subclassification of the small-cell anaplastic carcinoma was performed [11]. One patient had a normal performance status (PS 0), three normal activity with effort (PS 1), six some waking hours in bed (PS 2), and two more than 50% of waking hours in bed (PS 3). At the initiation of the treatment all patients had a physical examination, and a complete blood count, serum electrolytes, serum bilirubin, serum lactate dehydrogenase, serum aspartate aminotransferase, serum alanine aminotransferase, serum glutamyl transferase, serum CEA, and serum calcitonin determination. Posterioranterior and lateral chest roentgenograms and bone, liver and brain scintigrams were obtained. Specimens of bone marrow aspiration were obtained from the sternum. Fiberbronchoscopy was performed in eight patients and computed tomography in five. None of the patients underwent peritoneoscopy or had a percutaneous liver specimen taken for biopsy. These examinations showed that two patients had limited disease, i.e., carcinoma confined to one hemithorax with involvement of supraclavicular lymph nodes or without, and ten patients had

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extensive disease, i.e., spread beyond the hemithorax and adjacent nodes.

The patients had a physical examination before each course of treatment. Chemical blood analyses were performed regularly. Scintigrams were obtained as indicated. All patients were followed by chest roentgenograms at 1 to 2-months intervals. Computed tomograms of the chest or liver or both were used for the follow-up in four patients.

The induction regimen consisted of vincristine 1 mg/m^2 i.v. bolus injection on day 1, cyclophosphamide 1,000 mg/m^2 i.v. 1-h infusion on day 1, adriamycin 50 mg/m^2 i.v. bolus injection on day 1, and etoposide 80 mg/m^2 i.v. 2-h infusion on day 2, 4, and 6. The courses were repeated at 3-weeks intervals for four times given on outpatient basis. A dose reduction scheme was used (Table 1). Metoclopramide in the dosage of about 10 mg/m^2 i.v. or p.o. was given to eliminate vomiting.

As consolidation therapy seven patients received two courses of BCNU in the dosage of median 29 mg/m^2 (range 24–73 mg/m^2) short term infusion in the bronchial artery with 2 to 3-weeks interval. One patient received loco-regional irradiation (48 Gy, 2 Gy per treatment, 5 days/week) and three prophylactic brain irradiation. (30–35 Gy, 2.5 Gy per treatment, 5 days/week). Patients with complete remission after the consolidation received further zero to six courses of the induction regimen.

Complete remission (CR) was defined as complete disappearance of all lesions, normalization of pathological biochemistry, and of performance status for at least 1 months. Partial remission (PR) was defined as at least a 50% regression of measurable lesions for at least 1 months. No change (NC) was defined as changes of the initial lesions less than 50%. Progression (PD) was defined as increase in lesions of 50% or more or occurrence of new lesions. The duration of remission was calculated from the first date of objective remission to the first date of PD. The duration of survival was calculated from the start of treatment.

Table 1. Dose reduction scheme

Leukocytes ($\times 10^9$ cells/l)	Thrombocytes ($\times 10^9$/l)	Vincristine	Adriamycin	Cyclophosphamide	Etoposide
≥ 4.0	≥ 125	100%	100%	100%	100%
2.0–3.9	75–124	100%	50%	50%	50%
≤ 1.9	≤ 74	0%	0%	0%	0%

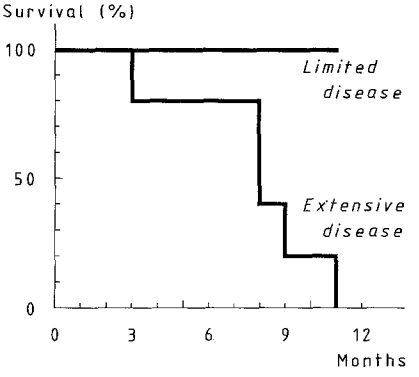

Fig. 1. The survival of two patients with limited disease was superior to that of ten patients with extensive disease, but the difference was not statistically significant ($0.1 < p < 0.25$, log-rank test)

Results

One patient with limited disease had no evidence of disease for 13+ months and another patient had CR for 3+ months. Four of ten patients with extensive disease had CR for median 5 months (range 2+ to 5+ months) and four patients had PR for median 5 months (range 4 to 5+ months). Figure 1 shows the survival of the two groups of patients according to life-table analyses. The median interval from the start of treatment to objective remission was 1 month (range 0.3–2 months). The response related to the performance status at the start of treatment (PS 0: 1 CR, PS 1: 1 CR, 1 PR, and 1 no evidence of disease, PS 2: 3 CR, 1 PR, 1 NC, and 1 PD, PS 3: 2 PR).

The patient with no evidence of disease is alive at 13+ months. The patients with CR have been followed for 5+, 6+, 7+, 9, and 9+ months, and the patients with PR for 5+, 8, 8, and 10+ months. The patients with NC and PD died after 11 and 3 months.

The nadir leukocyte count after the induction regimen was above 3.5×10^9 cell/l in one patient, between $2.0–3.4 \times 10^9$ in three patients, between $1.0–1.9 \times 10^9$ in five patients, and below 1.0×10^9 cells/l in three patients. The nadir thrombocyte count was above 100×10^9/l in five patients, between $50–99 \times 10^9$/l in one patient and between $30–49 \times 10^9$/l in six patients. None of the patients were admitted to hospital for fever during leukopenia. Thrombocytopenic bleeding did not occur.

All patients had total alopecia. Seven had vomiting, three fatigue, one epigastric pain, one obstipation, one paresthesias, one depression, one tonsillitis, and one inflammation in perineal fistulas. Nevertheless the treatment was well tolerated by the patients. Three patients experienced thoracic pain by the intraarterial BCNU infusions. One of these had hypotension necessitating observation at an intensive care unit for 4 days. No drug-related deaths occurred.

Discussion

A high remission rate with the induction regimen was found in our patients with small-cell anaplastic carcinoma of the lung (eight out of 12 patients, five CR, and one no evidence of disease). The same results have been reported elsewhere [5, 9, 12].

Alleviation of tumor symptoms with the induction regimen was observed faster than with our previous regimens [1, 13]. The toxic side effects were well accepted. The use of a higher dosage of metoclopramide (about 30 mg/m^2 i.v. repeated at 3-h intervals) has recently reduced the nausea and vomiting in connection with the first day of the course [7]. Two patients with limited disease continously have no evidence of disease after the treatment was stopped. This finding corresponds with the results by a similar approach in a larger series of patients [10]. While widespread metastases have been claimed to be the main problem in treatment failure, patients with small-cell anaplastic carcinoma of the lung, local recurrences were found the leading site at progression in our previous and other series [8, 10]. Intraarterial BCNU courses to the primary tumor and prophylactic brain irradiation was used in some of the patients to increase disease control. The BCNU treatment was intensely painful in half of the patients. This side effect has not been observed in short term intraarterial BCNU in the carotid arteries or with mitomycin C [6] or with adriamycin in the bronchial artery in our experience. No CR has been obtained so far by the consolidation or reinduction treatments or by the irradiation.

The induction regimen appears to be the most effective phase in our ongoing study. The combination regimen of vincristine, adriamycin, cyclophosphamide, and etoposide was well tolerated and can be used in outpatients. About 80% of the patients may achieve objective remission and improvement in quality of life. Patients with limited disease may remain in CR after the treatment is stopped.

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