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Treatment of Small Cell Lung Cancer with a Combination of VP16-213 and Cyclophosphamide with Cisplatin or Radiotherapy

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Summary. *Fifty five patients with small cell lung cancer were treated with a VP16-213 combination chemotherapy regimen in two consecutive series. The first series included 24 patients; 10 with limited and 14 with extensive disease were treated with VP16-213, 120 mg/m² p.o. daily for 5 consecutive days, Cyclophosphamide 600 mg/m² i.v. and Cisplatin 80 mg/m² i.v. with hydratation and manitol induced diuresis. The cycle was repeated every 3 weeks. The second series included 31 similar patients, 16 limited, and 15 extensive disease, treated with VP16-213 at the same dose and Cyclophosphamide at 1,200 mg/m² i.v. also repeated every 3 weeks; after three cycles the patients were treated with radiotherapy to the primary tumor and regional lymph nodes with 4,000 rads in a split course of three weeks interval, followed by the same combination chemotherapy. Response rate was 75% for the first series with 6 of 24 (25%) of complete responses in four limited and two extensive disease and a median survival time of 24 weeks. In the second series of patients there were 26 of 31 (83.8%) responses with 10 of 31 (32%) complete responses in nine limited and one extensive disease and a median survival time of 33 weeks for responders. Duration of response for complete responders was 36.8 weeks for the first series and 51 weeks for the second. Toxicity was mild and includes nausea and vomiting, myelosupression, alopecia in both series, with one toxic death in the second series.*

Both regimens are active with a low complete response rate, which was increased in the second series by the addition of radiotherapy, which did not increase overall survival.

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Introduction

Small Cell Lung Cancer (SCLC) accounts for about 20% of all lung cancer [3, 25]. This tumor is often widely disseminated at the time of diagnosis and for that reason the use of local treatment alone is ineffective [3, 13].

Staging based on the clinical extent of the disease at the time of diagnosis has some prognostic value. Without treatment, except supportive care patients with limited disease, clinically localized to the hemi-thorax and its draining lymph nodes, have the same median survival time as those in whom it had already disseminated [28].

Radiotherapy, alone to the primary tumor and lymph nodes increases median survival to 30 weeks in patients with limited disease, but has no effect on survival in extensive disease [12, 20, 21].

The addition of chemotherapy to radiotherapy has been established as beneficial, with improved response and survival in several controlled studies [1, 9, 17, 21]. Although combined modality treatment produces tumor regressions in the majority of patients, the impact on long term survival has been small and the 2 year survival is still at less than 10%.

Cyclophosphamide is one of the most active agents against SCLC and is included in the majority of combination chemotherapy regimens [2, 4, 15]. VP16-213 is a new synthetic podophyllotoxin derivative which has shown remarkably high activity in SCLC with an overall response rate as a single agent of 45% [5, 6, 8]. At the present this compound has to be considered the most active agent against this tumor [16]. Cisplatin a new inorganic compound recently introduced into the clinic, has shown activity in different solid tumors and its synergism with other drugs is well known in animal models [26]. The activity of the combination of Cisplatin and VP16-213

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in SCLC was reported by Sierocki for induction therapy in a five drugs chemotherapy regimen with a good response rate either in limited or extensive disease [27].

Based in this data we developed two sequential studies for the treatment of SCLC patients with a combination of Cyclophosphamide and VP16-213 with the addition of a third treatment. In the first series we added the new drug Cisplatin to the above mentioned combination and in the second series of patients we combined Cyclophosphamide and VP16-213 with radiotherapy.

This article describes the results of the treatment of 55 patients included in this study.

Material and Methods

Fifty five patients with biopsy proof of SCLC were elegible for entry into this study. Patients were stratified before treatment by performance status according to the Karnofsky scale and by extent of disease. Those with clinical evidence of tumor confined to the hemithorax and supraclavicular nodes were considered to have limited disease and all others were considered to have extensive disease.

Pretreatment studies included complete history, physical examination, complete blood count with differential and platelets, chest-X-ray, liver an renal function tests, liver plus bone scans and bone marrow biopsy.

During therapy and subsequently, patients were seen at 3 or 4 week intervals. At each visit routine hematology and chest-X-ray-studies were done and every 3 months all positive studies for tumor localization were repeated.

Patients were treated with different regimens in two consecutive series. In the first series of 24 patients treatment was Cyclophosphamide 600 mg/m^2 by i.v. injection on the first day; Cisplatin 60 mg/m^2 in 1 h infusion with hydratation and manitol induced diuresis on the second day with VP16-213 100 mg/m^2 p.o. during 5 consecutive days from day 3 to day 8 Cycles were repeated every 3–4 weeks until response or relapse. Treatment of the second series of patient was Cyclophosphamide 1,200 mg/m^2 i.v. on the first day and VP16-213 at the same dose and schedule as in the first series. The regimen was repeated three times at 3–4 weeks interval. After the thrid cycle responding patients received radiotherapy with supervoltage to primary tumor, hiliar, mediastinal and supraclavicular lymph nodes at a dose of 2,000 rads in 5 days. After 3 weeks of rest another 2,000 rads with the same regimen were given, and patients with response were continued with the same induction chemotherapy regimen until relapse.

Responses were evaluated in the first series every three cycles of treatment and before and after radiotherapy in the second series. Repeated bronchoscopy was not performed systematically, and more elaborate radiological or scintigraphic studies were done only if new symptoms developed. Survival was analyzed by the actuarial method with the use of the Kaplan and Meier method [19]. Response rate and survival were compared using the paired analysis Student's *t*-test.

Complete response was defined as disappearance of all known neoplastic disease. Partial response was defined as a decrease equal to, or greater than 50% of the product of the two greatest perpendicular diameters of well outlined lessions, for at least 3 weeks in the absence of progressive disease elsewhere or the development of any new lesions.

Survival was measured from the time of first treatment until death.

Results

The analysis of results was done separately for the two series. Of 55 patients evaluated for response, 26 had limited disease and 29 had extensive disease. Most patients were male, with a median age of 54 years. The majoritiy were ambulatory falling into Karnofsky categories 50 through 100 (Table 1). Two patients of the second series received on course of Cyclophosphamide for a SVC sydrome before their inclusion into the study and were considered elegible because the regimen was completed by adding VP16-213 afterwards.

Responses were observed in 9 of 10 patients (90%) with limited disease and in 9 of 14 (64.2%) of those with extensive disease in the first series, and in 14 of 16 (87.5%) patients with limited disease and in 11 of 15 (73.3%) with extensive disease in the second series. Overall response rate was 75% and 83.8% for each series respectively (Table 2).

Six patients (25%), four limited and two extensive of the first series and ten (32.2%) nine limited and one extensive of the second series, achieved complete remission during the induction period of treatment. The analysis of responses after radio therapy in patients with limited disease of the second series, showed that five partial responders achieved complete remission at the end of this therapy bringing the complete remission rate of this group from 25% to 56.2%.

Response rate was examined in both groups of patients as a function of age, sex, and performance status. There were no difference for age and sex although the response rate was significantly higher for those patients who were fully ambulatory, defined as equivalent to a Karnofsky performance status of 70% and above. There were no complete responses in patients with a performance status below 70%.

Table 1. Patient characteristics

	Total	Limited	Extensive
Number	55	26	29
Male/female	48/7	19/5	27/2
Age yr. (range)	54 (26–71)	54 (26/71)	59 (38/70)
Previous therapy	2	–	2
P.S. > 70%	28	19	9
< 70%	27	16	11

Table 2. Response and Survival

	All	CTX – VP16-DDP		CTX – VP16-R/T	
		Limited	Extended	Limited	Extended
No	55	10	14	16	15
CR	16	4 (25%)	2	9 (32,1%)	1
PR	23	5	7	5	10
GR (%)	70.9	90	64.2	87.5	73.3
Survival (weeks)	–	31.2	18	51	27

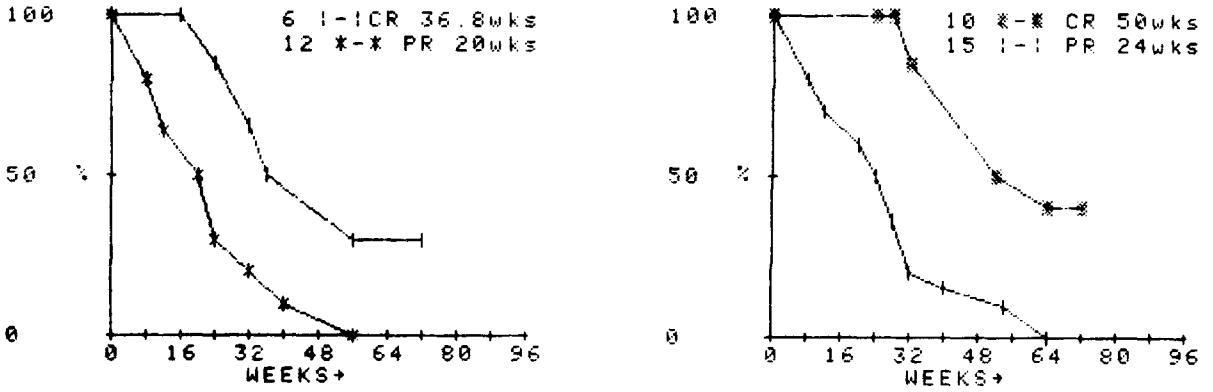

Fig. 1. Duration of complete and partial responses: *left*: first series of patients *right*: second series

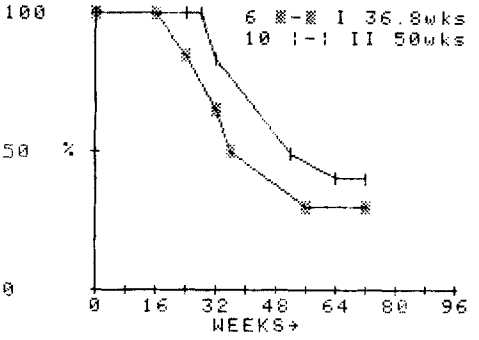

Fig. 2. Complete response duration: series 1: 36.8 weeks. series 2: 50 weeks

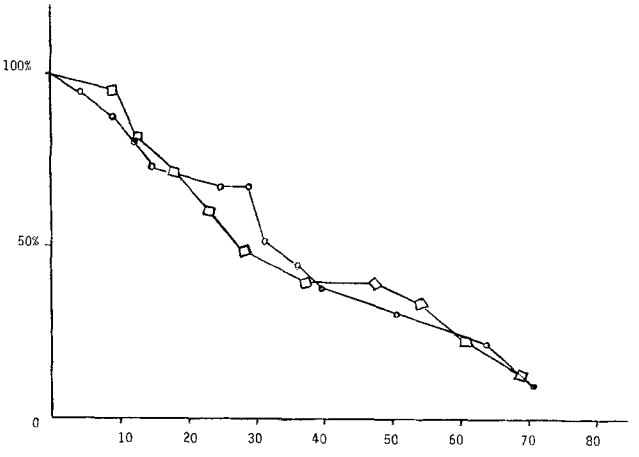

Fig. 3. Overall survival: Series 1 (◇———◇) 24 weeks, series 2: (○———○) 33 weeks

The duration of complete and partial response for patients in each series is plotted in Fig. 1. Complete responses in the first series lasted a median duration of 36.8 weeks and 20 weeks for partial responders. Median duration of response for patients in the second series was 50 weeks for complete responders and 24 weeks for partial responders. Complete response duration was significantly longer (P: 0.029) in the second series that the first one (Fig. 2). Response for this analysis refers to the response seen after 8 courses of induction chemotherapy for the first series of patients and response seen after radiotherapy for patients of the second series.

The median survival time of all 55 patients in this study was 41.2 weeks. A comparison of the survival for both series is shown in Fig. 3. There was only a

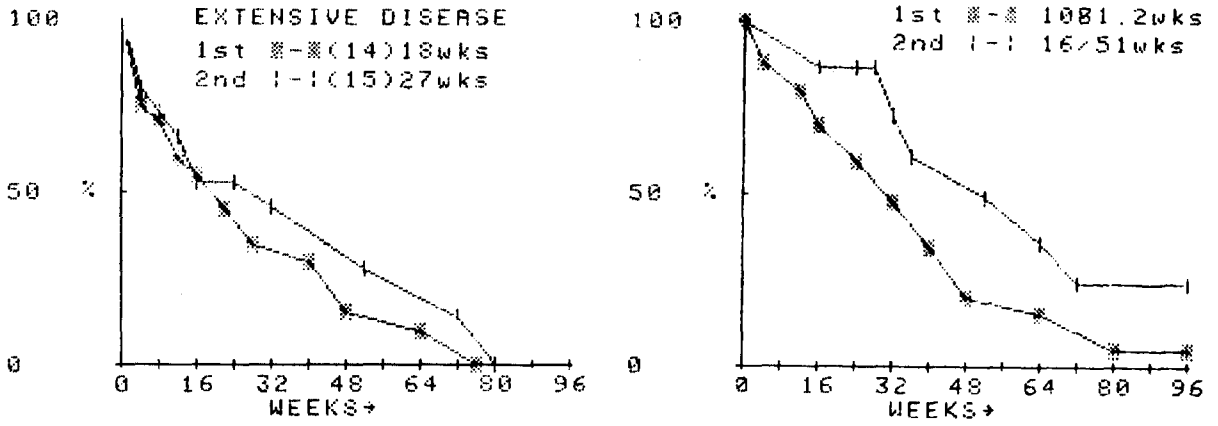

Fig. 4. *Right*: limited disease; *left*: extensive disease

Table 3. Toxicity

	CTX-VP16-DDP	CTX-VP16-R/T
Nausea/vomiting	100%	83%
Leukopenia (< 2,000)	25%	58%
Thrombocytopenia (< 100,000)	14%	13%
Alopecia	75%	71%
Granulopenic fever	33%	35%
Infections	8%	9.6%
Creatinine clearance < 50 ml/min	12%	–
Peripheral neuropathy	3/4	–
Radiation neumonitis	–	1
Toxic dead	–	1

slight difference between the overall survival periods in both series of patients, 24 vs 33 weeks. The survival of patients with limited disease was significantly longer (*P*: 0.068) in the second series of patients with a median of 51 weeks compared with 31.2 weeks for similar patients of the first series (Fig. 4, right). This difference was not observed in extensive disease patients from second series, 27 vs 18 weeks, in comparison with survival of extensive disease patients from the first series (Fig. 4, left).

Toxicity

In Table 3 we describe the different toxicities observed. The most common side effects were nausea and vomiting in all patients from the first series and in 83% of the second one. Alopecia occured in 75% and 71% respectively. Leukopenia (< 2,000 WBC/cumm.) occurred in 25% of patients of the first series and in 58% of patients of the second series mainly after radiation therapy.

Thrombocytopenia (< 100,000 platelets/cumm.) was seen in 14% and 13% respectively, with two platelet nadirs below 40,000/cumm. in the second series.

A total of five proven episodes of infection occurred during treatment but 19 patients developed fever above 38° C during the granulocytopenia phase which required hospitalization and parenteral antibiotic therapy.

Three of four of the first series of patients, had electromyographic evidence of peripheral neuropathy due to Cisplatin with minor clinical symptoms. Cisplatin also produced reduction of creatinine clearance in 3 of 24 patients in the same series.

Radiation pneumonitis occurred in one patient of the second series with radiological and functional signs. There was one toxic death from sepsis which did not respond to antibiotic and support therapy.

Discussion

The results of 55 patients treated with a similar combination chemotherapy with and without radiotherapy, described herein are very similar to results reported recently by other investigators [10, 18, 24]. Of particular importance is the improved outlook for patients with limited disease at clinical presentation in both groups and the increase in response rate and survival when radiation therapy is given. Combination chemotherapy of VP16-213 and Cyclophosphamide as active, giving a good response rate in excess of 75% in patients with limited disease with some lower response rates in patients with extensive disease.

Cisplatin, which was shown to be effective when used as a single agent or in combination in SCLC, at a

dosage administered in the first series, does not appear to have contributed to the increase in the response rate in comparison with that obtained in the second series with VP16-213 and Cyclophosphamide alone, plus radiotherapy.

The place of radiation therapy in the treatment of SCLC remains controversial. As we have shown in our second series radiotherapy helps to complete the response obtained by chemotherapy alone in limited disease. Radiotherapy may further prevent local chest recurrence. This is why most recent studies support the use of radiotherapy after a period of chemotherapy induction [7, 11, 24].

In a non-randomized trial, Natala [24] reports a high complete remission rate in limited disease. However, despite the use of radiotherapy, most patients relapsed within the chest after complete unmaintained remission. A lessening of chest recurrence incidence in patients randomized to receive radiotherapy after treatment with chemotherapy as been shown by the group of Hansen [7] and the Australian group of Tattersall [11] but in both groups overall survival has not been modified by combined treatment.

The different results observed between some of these studies may be due to the time at which the radiotherapy was administered and the dosage fractions used.

The difference in responses may also be different if radiotherapy interrupts the chemotherapy instead of continuing this throughout the radiotherapy.

When both treatments are given simultaneously the toxicity is increased along with response and overall complete remissions rate as was observed in Greco's original study [14].

On the other hand when radiotherapy and chemotherapy are not administered simultaneously the degree of toxicity particularly myelosupression is much lower, but patients could relapse outside radiotherapy field during the period when chemotherapy is interrupted.

In our second series of patients we found that interrupting chemotherapy with radiotherapy not only did not give us the reduced toxicity as expected, but was also associated with a complete remission rate less than half that obtained by other investigators [14, 19, 23]. For this reason we believe that the best therapeutic approach in patients with limited disease is combination chemotherapy at full dosage to achieve maximum response rate. For those with good response the addition of radiotherapy without interupting chemotherapy could improve considerably the complete response rate.

The addition of (Adriamicin) to the combination of VP16-213 and Cyclophosphamide may offer us a more effective combination in obtaining better and longer responses. The addition and timing of radiotherapy still requires further studies particularly in limited disease patients.

New approaches are also required for patients with extensive disease and current investigations with half body irradiation and the use of radiosensitizers and radioprotective drugs are ongoing. Also it is necessary to investigate the use of high linear energy transfer radiation, such as neutrons in patients with both limited and extensive disease, in association with chemotherapy.

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