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Short Report

Chemotherapy Combination with Cyclophosphamide (CTX) Adriamycin (ADM), Vincristine (VCR), and VP16-213 in Small Cell Carcinoma of the Lung (SCCL)

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Summary. *Twenty-four evaluable patients with small cell carcinoma of the lung were treated with an escalating chemotherapy regimen including Cyclophosphamide, Adriamycin, Vincristine and VP16-213. The initial doses were: CTX 800 mg/m² i.v. day 1; ADR 50 mg/m² i.v. day 1; VCR 1.4 mg/m² day 1 weekly; and VP16-213 100 mg/m² i.v. days 14–18 every 4 weeks. CTX and ADR were escalated by 100 and 10 mg/m² respectively in each subsequent cycle according to blood count. Hematologic toxicity was minimal and the treatment was well tolerated. Partial responses and complete responses were 9 of 19 and 5 of 19 respectively for patients with limited disease, and 4 of 5 and 1 of 5 respectively for patients with extensive disease. The overall response rate for the whole group was 79%. These results must be considered preliminary.*

Introduction

Small cell carcinoma of the lung (SCCL) is a tumor very sensitive to radiotherapy and chemotherapy, and the results of treatment have considerably improved during the last years [1, 2]. The role of radiotherapy in the management of this tumor is not defined, and further studies are required to determine its value in the control of the primary tumor [5]. Prophylactic cranial irradiation has been shown to decrease the incidence of CNS relapses without increasing the survival time [6].

Combination chemotherapy with Cyclophosphamide (CTX), Adriamycin (ADR) and Vincristine (VCR) is probably the most effective regimen [2]. VP16-213, has shown a 43% response rate in patients with SCCL, indicating a high degree of activity for a single agent in this disease [4].

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This paper reports the preliminary results of treatment of SCCL with a combination of CTX, ADR, VCR, and VP16-213.

Patients and Methods

Previously untreated patients with SCCL diagnosed by bronchoscopic biopsy were selected for this study. Liver biopsy and both marrow aspiration and biopsy were performed on every patient as part of the initial work-up studies. Patients were classified as having Limited Disease (LD, i.e., disease confined to one hemithorax including ipsilateral scalene lymph nodes) or Extensive Disease (ED, i.e., disease beyond those limits).

Treatment Schedule. CTX 800 mg/m² i.v. day 1; ADR 50 mg/m² i.v. day 1; VCR 1.4 mg/m² i.v. day 1 (maximum dose 2 mg); and VP16-213 100 mg/m² i.v. days 14–18, were repeated every 4 weeks. Vincristine was administered weekly for 6 weeks and thereafter every 2–4 weeks according to neurologic toxicity. CTX and ADR doses were escalated by 100 and 10 mg/m² respectively if WBC > 3,000/mm³ and platelets > 175,000/mm³ on day 14 of the cycle. VP16-213 was initially given for 3 days, and 4 months after the start of the study was increased to 5 consecutive days. This drug was administered if WBC > 2,000/mm³ and platelets > 75,000/mm³ on day 28 of the cycle.

Patients were considered evaluable at the completion of two cycles of treatment. Criteria for measurable or evaluable disease, and criteria for the evaluation of response were those recommended by the WHO [3]. Thirty-three patients were entered and 24 were fully evaluable. Reasons for non evaluability were: early death, two patients; too early, five patients; and death because of progressive disease before the completion of two cycles, two patients. The median age was 59 years (range 32–71). The median Karnofsky index was 70 (range 60–90) and the male/female ratio was 22/2. Twenty-two patients had SCCL lymphocyte-like subtype and two patients had intermediate-cell subtype. Five patients had ED and 19 LD. Patients received 103 cycles of therapy, with a median of four cycles per patient (range 2–8).

Results

The response rate to therapy is shown in Table 1. The overall response rate was 79% (19 of 24), ten patients

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Table 1. Results of the treatment

	CR	PR	SD	P	CR + PR
Limited disease	9 (47)[a]	5 (26)	4	1	14/19 (73)
Extensive disease	1	4	–	–	5/ 5
					19/24 (79)

[a] Percentage between brackets
CR = complete remission; PR = partial remission; SD = stable disease; P = progression

Table 2. Hematologic toxicity

CTX (mg/m^2)	ADR (mg/m^2)	No. of cycles	WBC at day 14		
			< 2,000	2,000–3,000	> 3,000
800	50	44	3	8	33
1,000	60	40	3	16	21
1,100	70	17	3	4	10
1,200	80	2	1	1	–
VP16	100 mg/m^2		WBC at day 28		
× 3 days		21	–	–	21
× 5 days		61	3	5	53

had a complete response (CR) and nine patients had a partial response (PR). Those patients with LD had a response rate of 73% (14 of 19) with 9 CR and 5 PR.

Toxicity. Table 2 collects the hematologic toxicity related to drug increments. Maximum doses reached were CTX 1,200 mg/m^2 and ADR 80 mg/m^2. When VP16-213 was administered for 3 days, no hematologic toxicity appeared on day 28, and when this drug was increased to 5 days this toxicity was minimal. There were no toxic deaths.

All patients developed alopecia. Nausea and vomiting were common. Other side effects encountered were: paresthesiae, 13 patients; weakness, five patients; and there were 20 episodes of stomatitis. One patient had an anaphylactic-like reaction to VP16-213.

Discussion

The different therapeutic approaches to the management of SCCL yield a high response rate. One of the most important problems in this disease is the maintenance of the remission in those patients achieving a CR, so that the increase in disease-free interval can eventually lead to cures.

The purpose of our study was to evaluate the influence that an escalating chemotherapeutic regimen could have on the number and duration of objective responses.

The percentage of responses obtained (Table 1) was comparable to that of other reported series [1–2]. The hematologic toxicity encountered (Table 2) was tolerable and was not significantly increased by the administration of VP16-213 for 5 days, starting on day 14 of each cycle.

At the time of this preliminary report, the median follow-up time is too short (4 months) to draw any valid conclusion related to the duration of response. Up-dated results of this study will be published in the future.

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