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cis-Platinum and Etoposide Combination Chemotherapy of Advanced Non-Oat Cell Bronchogenic Carcinoma

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Summary. *From December 1981 to November 1982, a consecutive series of 37 patients with advanced non-oat cell bronchogenic carcinoma were treated with cis-platinum and etoposide in doses of 20 mg/m² and 75 mg/m², respectively, for 5 consecutive days every 3 weeks.*

Among the 33 evaluable patients, one complete response, 11 partial responses, five minor responses, seven unchanged states, and nine cases of progression were noted. Median duration of response was 30+ weeks. Toxicity was significant, but no treatment-related deaths were encountered. Combined cis-platinum and etoposide can provide significant palliation in approximately one-third of patients with the doses and schedule used.

Introduction

cis-Platinum (DDP) has been reported by several authors [1, 2, 14] as being active in advanced non-oat cell bronchogenic carcinoma (NOBC). Etoposide (VP-16) has a more limited role as a single agent [3, 7]; however, the therapeutic synergism of DDP and VP-16 in animal tumors [9, 12] and the efficacy of the combination of the two drugs in small cell lung cancer [13] have prompted several studies of combined DDP and VP-16 in NOBC. No study, however, has so far investigated a 5-day schedule of DDP and IV VP-16. The results obtained with this combination in patients with advanced NOBC seen at our institute are the subject of this report.

Patients and Methods

From December 1981 to November 1982, all 37 consecutive eligible patients with advanced NOBC were entered on the study. Conditions of eligibility included: histological or cytological and radiological diagnosis of NOBC, UICC stage III or IV disease (patients with stage III disease were admitted to the study only if they were inelegible for an ongoing study of radio-chemotherapy, either because of previous radiotherapy (RT) or because their disease could not be encompassed in a single radiation port), measurable or evaluable lesions, age less than 70 years, performance status (PS) > 40, adequate liver, renal, and bone marrow function, no previous treatment with chemotherapy. Patients with brain metastases were included only if the neurologic situation was under control after RT. The main patient characteristics are summarized in Table 1.

Treatment consisted in VP-16 75 mg/m²/day IV for 5 consecutive days and DDP 20 mg/m²/day IV on the same days. Treatment was repeated every 3 weeks.

Five-hundred milliliters of 25% mannitol were infused before DDP. No other IV fluids were routinely administered; however, patients were advised to have an oral fluid intake of at least 2,000 ml/day. Patients routinely received metoclopramide 10–20 mg IV before and after chemotherapy; when severe nausea and vomiting were encountered larger doses of metoclopramide were employed.

Pretreatment evaluation included: blood chemistry, chest X-rays and tomogram, bone, liver, and brain scintigrams, audiogram, and any examinations indicated to define tumor extent. Physical examination, complete blood counts, and routine laboratory tests were performed before each cycle of

Table 1. Patient characteristics

Patients entered	37
Median age	59 years (range 22–70)
Sex	
Male	35
Female	2
Median Karnofsky performance status	70 (range 50–100)
Histology	
Squamos cell carcinoma	26
Adenocarcinoma	10
Large cell carcinoma	1
Stage (UICC)	
III	8
IV	29
Sites of disease	
Loco-regional disease	24
Lymph node metastases	11
Bone metastases	12
Lung metastses	4
Brain metastases	3
Pericardial metastases	2
Adrenal metastases	1
Renal metastases	1
Liver metastases	1
Pleural metastases	1
Oral cavity metastases	1

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Table 2. Toxicity (35 patients evaluable)

	Grade				
	0	1	2	3	4
Hematological	12	5	8	8	2
Renal	33	1	1	0	0
Nausea and vomiting	2	4	4	17	8
Diarrhea	34	1	0	0	0
Peripheral neurotoxicity	33	1	1	0	0
Bladder	34	0	1	0	0
Mucositis	31	4	0	0	0
Lethargy	34	1	0	0	0

Weight loss (> 10%) in four patients; symptomatic hearing loss in three patients; severe malaise and anorexia in 10 patients

Table 3. Activity of combined DDP and VP-16 in patients with NOBC without previous chemotherapy

Dosage (mg/m^2)	No. of evaluated patients	No. of responses (%)	Reference
DDP, 90, day 1 VP-16, 50, days 1–5 to be repeated after 4 weeks and thereafter every 6 weeks	8	7 (87.5)	[6]
DDP, 90, day 1 VP-16, 100, days 1, 3, 5 frequency not specified	26[a]	5 (19.2)	[11]
DDP, 100, day 1 VP-16, 80, days 1, 2, 3 every 3 weeks	14	5 (35.7)	[5]
DDP, 100, day 1 VP-16, 120, orally days 3, 4, 5, 6 every 3 weeks	8	3 (37.5)	[5]
DDP, 60, day 1 VP-16, 120, days 4, 6, 8 every 3 weeks	65[b]	30 (46.1)	[8]
DDP, 20, days 1–5 VP-16, 75, days 1–5 every 3 weeks	33	12 (36.3)	Present series

[a] Previous treatment not specified
[b] Not treated with radiotherapy

chemotherapy. Measurements of the index lesions were performed at regular intervals (chest X-rays every two cycles; scintigraphy and computed tomography examinations every 3–4 cycles). Repeat audiograms were performed during treatment. Treatment was continued until progression. If leukothrombocytopenia or transient renal toxicity arose, chemotherapy was delayed until recovery. If severe subjective symptoms or persistent hematologic intolerance were noted, the dosage was attenuated in subsequent courses. In the event of symptomatic hearing loss treatment was discontinued. When maximal response was noted, radiotherapy was considered. Response and toxicity were defined according to reported criteria [10]. In patients with evaluable disease, Eagan's criteria [4] for responses were employed.

Results

Of the 37 patients treated, four were considered unevaluable for response (2 because of refusal due to logistic difficulties, 1 due to early death related to progressive disease, 1 because lost to follow-up). All of these received one cycle of chemotherapy. Survival of the four patients unevaluable for response was 2, 8, 26+, and 35 weeks, respectively.

One-hundred and four cycles of chemotherapy were administered to the 33 evaluable patients (median 3 cycles/patient; range 1–6+). Four patients are still receiving treatment. One complete response (CR), 11 partial responses (PR), five minor responses (MR), seven unchanged disease states (INV), and nine cases of progression (PRO) were encountered, giving a 36.3% response rate. Median duration of response (CR + PR) was 30+ weeks (12–43+). Six patients received consolidation RT to the primary tumor after achieving response in an attempt to improve local control; in three patients a PR was converted into a CR with RT. In these patients response lasted 20, 23, 30, 34+, 36, and 40 weeks, respectively. Loco-regional disease responded in 12 of 22 cases, lymph node metastases in five of 11, bone metastases in one of 10, lung metastases in one of four, pleural metastases in one of one, renal metastases in one of one, pericardial metastases in zero of two, and adrenal, liver, and oral metastases in zero of one patient each. All but two patients are evaluable for toxicity, which was significant and is reported in Table 2.

Three patients refused further therapy due to toxic effects. The dosage was attenuated because of persistent toxicity in five patients. No treatment-related deaths were encountered. Median survival was 21+ weeks (range 5–51+). In responders, median survival was 37+ weeks (range 20–51+); in non-responders, 15 weeks (range 5–42+).

Discussion

Favorable results with the combination of DDP and VP-16 in the chemotherapeutic treatment of NOBC have been reported by several groups. Our experience differs from the studies already published in that a 5-day schedule for both drugs was employed. Moreover, no patients had previously been treated with chemotherapy. In Table 3 the results obtained by various groups using the combination of DDP and VP-16 in untreated patients are reported. With the exception of one multi-center study [8], to our knowledge, this is the largest series that has so far appeared in the literature.

The results obtained by ourselves are comparable in terms of efficacy with those reported by other authors. It is noteworthy that in all studies different drug schedules were used; therefore the dosage of the two drugs does not seem, within certain limits, to be of critical importance in determining the efficacy of the combination. In particular, DDP doses of 60 mg/m^2 [8] and 90–100 mg/m^2, either as a single dose [5, 11] or divided over 5 days (present series), seem to be equivalent in efficacy. It may be noted that when lower doses of DDP were administered a greater total dose of VP-16 was given [8].

The main toxic effect of combined DDP and VP-16 in our hands was myelosuppression, which was particularly notable in patients previously treated with RT less than 2 months before the start of chemotherapy. In such patients we would recommend posponing treatment or attenuating the dosage of VP-16. Two patients in our series had no gastrointestinal symptoms at all and four had only nausea, while nausea and

vomiting were universal in other reports [5, 6, 11]. Within the limits due to the difficulty of quantifying nausea and vomiting, the 5-day schedule of DDP may be better tolerated in this regard than a 1-day schedule when associated with VP-16.

In conclusion, in our hands combined DDP and VP-16 were able to induce responses in approximately one patient of three with NOBC, at the expense of significant, but not prohibitive toxicity. It cannot be established from our data whether the patient population treated benefited from the treatment, even though some patients experienced subjective relief of symptoms. If our experience is added to that of other groups with different schedules, one can conclude that combined DDP and VP-16 offer an alternative to other chemotherapeutic regimens employing conventional drugs, and that randomized studies comparing this with other regimens and with no-treatment arms are warranted.

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