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Original Paper

Effectiveness of Paclitaxel and Carboplatin Combination in Heavily Pretreated Patients with Head and Neck Cancers

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A phase II study was conducted to evaluate the activity of paclitaxel and carboplatin in advanced head and neck cancer. Twenty-four patients with measurable locoregional squamous cell carcinoma and metastatic disease were entered. All had been heavily pretreated with radiotherapy, surgery and chemotherapy and were at second recurrence or disease progression when they entered the trial. Patients received Paclitaxel 200 mg/m^2 with carboplatin 7 AUC once every 3 weeks with premedication with dexamethasone and diphenyldramine and ranitidine. Twenty-three patients were evaluable for response. Four patients (17%) achieved a complete response and 5 (22%) a partial response for an overall response rate of 39%. Duration of response was 3–9 months. Toxicity was tolerable. Four patients showed Grade III (WHO) and 6 Grade II neutropenia. Nineteen (79%) of patients who received more than two courses of chemotherapy presented neurotoxicity. The combination of paclitaxel and carboplatin was effective in heavily pretreated patients with squamous cell carcinoma of the head and neck. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

HEAD AND neck squamous cell cancers are effectively treated with radiotherapy and/or surgery although failure after these treatments is common. Chemotherapy has little to offer in advanced cases. Induction chemotherapy in head and neck cancers has produced high response rates and, although it has not increased the survival rate, it has produced two benefits: downstaging that results in less surgery, particularly in laryngeal cancer; and cytoreduction which may act as a good prognostic indicator [1–4].

Chemotherapeutic combinations that are considered effective are based on cisplatin, and include 5-fluorouracil as a continuous infusion for 120 h, or bleomycin and methotrexate. Other cytotoxic drugs have rarely been used [5–7]. After failure following the above treatment no other chemotherapy schedule is suggested for second-line or salvage treatment [8].

Paclitaxel, a new antineoplastic agent that augments tubulin polymerisation [9–11], has recently proven to be active in ovarian [12–14] and breast cancer [15] and has shown promising results in other solid tumours such as non-small cell lung cancer [16].

In the present study, we investigated the use of paclitaxel in combination with carboplatin as a second- or third-line treatment in advanced and heavily pretreated squamous cell cancer of the head and neck region. Toxicity of this combination is defined from the treatment of ovarian cancer and is also known for its effectiveness in the same cancer [13].

PATIENTS AND METHODS

Twenty-four patients were entered in the study between June 1995 and August 1996. Eligibility criteria included confirmed histology of squamous cell carcinoma, at first diagnosis and on recurrence; patients with measurable but inoperable disease, previously irradiated and/or with distant metastases; no age restriction, provided that there were no concomitant heart, renal, liver diseases or other serious illnesses; patients could not have failed previous chemotherapy or radiation therapy within the last 6 months. Patients were all in second recurrence or disease progression after first recurrence and non-responsive to previous chemotherapy or radiotherapy. Patients with untreated first recurrence were excluded. Patients required a performance status of 0–2

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(ECOG) to be free of any detectable infection or serious neuropathy (Grade $\leqslant 1$), and to have a life expectancy of at least 3 months. Patients with serum creatinine higher than 1.4 mg/dl or total bilirubin higher than 1.5 mg/dl were excluded. All patients gave written informed consent.

All 24 patients had squamous cell carcinoma, of which 13 were moderately to low, 7 were low and 4 were well differentiated. Patients' characteristics are presented in Table 1. Distant metastases occurred in the lungs.

Nineteen (79%) patients had been heavily pretreated with surgery, 23 (96%) with radiation, the patient not given radiotherapy had distant metastases on recurrence) and 22 (92%) with cisplatin combination chemotherapy. All patients had been treated with at least two of the above treatments.

Half the 22 patients treated with chemotherapy had received more than one type of chemotherapy either as neoadjuvant treatment on first recurrence, or on recurrence after surgery and/or radiotherapy. The 2 patients who had not received previous chemotherapy had been treated previously with radiation therapy and surgery. Previous treatments are presented in Tables 2 and 3.

Pretreatment evaluation

Medical history, physical examination, full blood count, renal and liver profile tests, radiographic and computerised tomography (CT) were performed within 2 weeks before treatment started. Blood tests and chemistry were repeated once a week and CT scan after the second and sixth course of chemotherapy.

Treatment

Paclitaxel was supplied by Bristol-Meyers Squibb vials of 30 mg. The drug was diluted and administered in a solution of 300 ml mixture of dextrose 5% and normal saline for a 3 h infusion. The dose per course per patient was 200 mg/m^2. This was followed by carboplatin 7 AUC for a 2 h infusion in normal saline. Premedication with 8 mg dexamethasone and 50 mg diphenhydramine was given 2–6 h before paclitaxel administration and repeated 8 hourly for 24 h and once a day for 2 days following the treatment. Ranitidine was given before treatment in a normal saline infusion. Chemotherapy courses were repeated every 3 weeks. Dose intensity was retained in all patients throughout the study, apart from in one patient who had Grade III thrombocytopenia where both drug doses were reduced by 25%. Electrocardiogram was performed in every treatment at the end of the paclitaxel infusion.

Table 1. Patients' characteristics

Characteristics	*n*	(%)
No. entered	24	
Evaluable for response	23	
Evaluable for toxicity	24	
Age (years)		
Median	60	
Range	48–82	
Sex		
Male	18	(75)
Female	6	(25)
ECOG performance status		
0	0	(0)
1	17	(71)
2	7	(29)
Primary site of disease		
Larynx	7	(29)
Oral cavity	6	(25)
Mandible	4	(17)
Nasopharynx	3	(13)
Ear	3	(13)
Nasal cavity	1	(4)
Site of recurrence		
Locoregional	21	(88)
Distant*	1	(4)
Both	2	(8)

*Distant metastases were in the lungs.

Table 2. Previous treatments and number of cycles of the present treatment

Previous treatments	No. of patients	(%)
Surgery (once or more)	19	(79)
Radiation	23	(96)
Neoadjuvant chemotherapy (cisplatin combination) on first recurrence or disease progress	22	(92)
No of cycles with paclitaxel + carboplatin		
1	1	(4)
2	4	(17)
3	4	(17)
4	5	(21)
6	10	(42)
Total number of cycles	101	

Response evaluation

Clinical evaluation was done at the end of each cycle of chemotherapy, and after 2 cycles and at the end of each patient's treatment with CT. Response was defined as: a complete response (CR) in the absence of all detectable tumour for at least 8 weeks; partial response (PR), greater than 50% reduction of each and all measurable tumours for at least 8 weeks and with no new lesions; stable disease (SD), less than 25% decrease or increase of the tumour volume during the treatment time or appearance of new lesions; progression of disease (PD), greater than 25% increase of any tumour volume during the treatment period or appearance of new lesions. After the second cycle evaluation, patients with CR, PR and SD continued treatment.

RESULTS

Response

Of 24 patients treated, 23 were evaluable for response. Four out of 23 achieved complete remission (17%, 95% CI 5–39%).

Table 3. Previous chemotherapy

Cytotoxic drugs	Dose	No. of cycles	No. of patients
Cisplatin Bleomycin Methotrexate	90 mg/m^2 30 mg 200 mg	3–10	16
Cisplatin 5-Fluorouracil Continuous infusion 120 h	90 mg/m^2 500 mg/m^2 daily	4–10	6

Table 4. Characteristics of patients who achieved complete and partial response

No. of patients	Primary site	Response	Duration of response (months)	No. of courses	Previous therapy	Duration of follow-up (months)
1	LA	CR	3	6	S,R,Ch	11(A)
2	LA	CR	4	6	R,Ch	7(A)
3	NPC	CR	9	6	R,Ch,Ch	14(A)
4	LA	CR	8	6	S,R,Ch	13(A)
5	NPC	PR	7	6	R,Ch,Ch	16(A)
6	E	PR	5	6	S,R,Ch	6(A)
7	LA	PR	4	4	S,R,Ch	5(D)
8	MA	PR	4	6	S,R,Ch	7(A)
9	LA	PR	3	6	S,R,Ch	5(A)

S, surgery; R, radiotherapy; Ch, chemotherapy; A, alive, D, dead; LA, larynx; NPC, nasopharyngeal; E, ear; MA, mandible.

One patient died of a stroke before the second course of chemotherapy. Five patients achieved partial remission (22%, 95%, CI 7–44%). In total, a major response was achieved in 9 out of 23 patients (39%, 95% CI 20–61%). Stable disease was observed in 11 patients (48%, 95% CI 27–69%) and 3 patients showed disease progression (13%, 95% CI 3–34%).

Three of the 4 complete responders had laryngeal cancer—1 with lung metastases—and 1 patient had a nasopharyngeal cancer. Duration of response was 3–9 months (CR: 3–9 PR: 3–7). Median time to progression was 6 months (range 1.97–10.02). At the end of the study, at a median follow-up of 12 months (range 0.08–19.02), 12 patients (50%) had died and 12 patients (50%) were still alive, 10 with disease and 2 disease free after 6 and 9 months since treatment started. Median survival time was 7.02 months (range 0.98–19.02). The characteristics of the patients that presented complete and partial response are given in Table 4.

Toxicity

Toxicity was assessed in all 24 patients and is shown in Table 5. One patient died of a stroke 20 days after the first course of chemotherapy. This patient was included in the assessment of gastrointestinal, bone marrow or other acute adverse reactions.

Myelotoxicity was observed in the majority of the patients. Four patients (17%) had febrile neutropenia Grade III (WHO) and were treated with G-CSF for 5 days. One also had grade III thrombocytopenia. Six patients (25%) had Grade II neutropenia and 12 (50%) grade I. In one, bacterial infection was detected. Duration of neutropenia without G-CSF was 4–8 days, median 5 days. Nausea and vomiting was seen in 12 patients, 5 had mucositis (grade I). Neurotoxicity (grade I) was observed in all 19 patients (79%) who had more than 2 courses of treatment, 7 patients indicated fatigue (29%). 4 patients had 1 or 2 episodes of hypotension. Tachycardia during or immediately after paclitaxel infusion (up to 120/1') was seen in 6 patients (25%). No serious cardiac adverse reactions were observed. Alopecia occurred in all patients (Table 5).

DISCUSSION

Because paclitaxel has been shown to be effective in some solid tumours that are resistant to established cytotoxic drugs, it may have potential and should be tested in tumours for which no effective chemotherapy currently exists. In ovarian cancer, paclitaxel has proven effective as a second-line treatment [12] and is now used in these tumours together with cisplatin or analogues as a treatment of choice. In breast cancer, paclitaxel has produced responses in anthracycline-resistant tumours [15] and has also produced promising results in lung cancers as a second-line treatment [16].

In head and neck cancers, there is no effective treatment if cisplatin combination chemotherapy fails. In the present study, 39% (9/23) of head and neck cancer patients showed a major response to paclitaxel and carboplatin, with 4 complete and 5 partial responses. Although this is a high response, what is more noticeable is that all the patients had been heavily pretreated with at least one line of chemotherapy after recurrence and some had received second-line or induction chemotherapy. One of the complete responders had had lung metastases and 3 had complete response of disease within the region of previous radiotherapy. Also, the majority of responders had been treated with other cytotoxic drugs and failed to respond within a period of 6 months before the present treatment. Toxicity was tolerable in the majority of the patients and only 17% had febrile neutropenia. No drug-related deaths were seen.

There is very little known about the activity of paclitaxel in head and neck cancers. In a previous study, high-dose paclitaxel (250 mg/m^2) was applied as a 24 h continuous infusion supported by G-CSF. Seven out of 19 evaluable patients showed a major response, including two complete remissions. Four of the responders had been previously irradiated and 3 were untreated [17]. The difference with our patients is that

Table 5. Toxicity

Toxicity	Grade (WHO)	*n*	(%)
Myelotoxicity			
Febrile neutropenia	III	4	(17)
Neutropenia	II	6	(25)
Neutropenia	I	12	(50)
Thrombocytopenia	III	1	(4)
Gastrointestinal			
Nausea and vomiting		12	(50)
Mucositis	I	5	(21)
Neurotoxicity sensory type	I	19	(79)
Fatigue		7	(29)
Hypotension		4	(17)
Tachycardia		6	(25)
Alopecia		24	(100)

they were heavily pretreated and 92% had received one or more chemotherapy regimens, with courses including cisplatin, and 96% had relapsed in previously irradiated regions.

A further study is needed to confirm these observations. It is not clear whether carboplatin is the best drug to combine with paclitaxel. The fact that no response was observed in the same patients who had received cisplatin plus 5-FU or bleomycin and MTX perhaps indicates that there was synergism between paclitaxel and carboplatin. In conclusion, paclitaxel and carboplatin combined treatment is an effective chemotherapy in head and neck cancers, even in heavily pretreated patients and those resistant to previous treatment.

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