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Original Paper

A Phase II Study of Combination Paclitaxel and Carboplatin in Advanced Nasopharyngeal Carcinoma

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The aim of this study was to determine the efficacy and toxicity of combination paclitaxel and carboplatin chemotherapy in patients with metastatic and/or locoregionally advanced nasopharyngeal carcinoma (NPC). Patients with metastatic and/or locoregionally advanced NPC were treated with carboplatin calculated according to an AUC of 6 mg ml/min (based on Calvert formula) given as an intravenous (i.v.) bolus, followed by paclitaxel 135 mg/ml^2 given as an i.v. infusion over 3 h with standard premedication. Cycles were given 3 weekly to a maximum of six. From January 1996 to November 1997, 27 patients were entered and assessable for response and toxicity. A total of 122 cycles were given and the median number of cycles given was five. The overall response rate was 59% (16/27). There were 3 (11%) complete responses, 13 (48%) partial responses, 5 (19%) static disease and 6 (22%) progressive disease. Toxicity was mainly haematological including: grade 3/4 neutropenia (39 cycles, 32%), grade 3/4 anaemia (nine cycles, 7%), grade 3/4 thrombocytopenia (eight cycles, 7%). There were three episodes of neutropenic fever (3%). Non-haematological toxicities were mild and infrequent. Paclitaxel and carboplatin combination chemotherapy is active in NPC and has tolerable toxicity. Further study with dose escalation is required to assess its optimal efficacy. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

NASOPHARYNGEAL CARCINOMA (NPC) is an aggressive head and neck cancer, in which systemic spread is common [1]. Metastatic disease usually signifies a poor prognosis [2] with a median survival of 3–12 months [1]. NPC is relatively chemo- and radiosensitive [1]. Chemotherapy has been used in the treatment of advanced NPC in the neoadjuvant, adjuvant and concurrent setting with radiotherapy, and for palliative treatment of metastatic NPC. Single agent therapy has been used, but the response rates have been disappointing at around 20% [3]. In contrast, combination chemotherapy, in particular, platinum-containing regimens, has been shown to have a response rate in the range of 25–80% [3, 4]. Cisplatin has been widely used in metastatic NPC [3, 4], but nephro- and neurotoxicity have limited its use. Although carboplatin may increase myelosuppression, it causes much less renal and neurotoxicity and as a result, has been increasingly adopted.

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We recently reported a prospective study using carboplatin and 5-fluorouracil combination chemotherapy for metastatic NPC with a response rate of 38% [5]. Our relatively low response rate may be attributable to suboptimal dosage of carboplatin which, at the time of the study, had been calculated according to total body surface area of the patients concerned. More recent studies by Calvert and colleagues [6] and Egorin and associates [7] have demonstrated that when the dosage of carboplatin is adjusted according to a targeted area under the concentration versus time curve (AUC), the response rates to carboplatin can be increased without excessive toxicities. In addition, studies in patients with ovarian cancer have shown that an AUC of 5 mg ml/min or above leads to significant improvement in the efficacy of drug [8]. To date, similar data are not available for patients with head and neck cancer, or more specifically, for patients with NPC.

Paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, New Jersey, U.S.A.) is a chemotherapeutic agent which was originally derived from the western yew tree (*Taxus brevifolia*). As early as 1971 [9], paclitaxel demonstrated cytotoxicity

against numerous tumour cell lines, but its scarcity, the difficulty in synthesis and poor solubility delayed its clinical development. However, it has unique antimitotic activity through stabilisation of microtubule formation and is active in patients with ovarian [10] and breast [9] cancers. Furthermore, studies on the use of paclitaxel either as a single agent or in combination with platinum drugs, have shown encouraging results in head and neck cancers [11] and small cell and non-small cell lung cancers [12, 13].

We describe here a prospective study of the use of combination carboplatin (with dose adjustment according to AUC) and paclitaxel in patients with metastatic/locoregionally advanced NPC. The endpoints were objective tumour response, toxicity and survival.

PATIENTS AND METHODS

Between January 1996 and November 1997, 27 patients with metastatic/locoregionally advanced NPC were treated with combination paclitaxel and carboplatin. The criteria for entry into the trial were: informed consent, histologically proven NPC of the undifferentiated or poorly differentiated squamous cell carcinoma type (WHO classification [14]), measurable or evaluable disease (metastatic or locoregionally advanced disease which was not curable with locoregional therapy) on clinical or radiological grounds, age 18 years or above, Karnofsky performance score of 80 or above, adequate haematological (white cell count $\geq 3\times10^9$/l or absolute neutrophil count (ANC) $\geq 2\times10^9$/l, platelet count $\geq 100\times10^9$/l), renal and hepatic functions (total serum bilirubin < 50 μmol/l, albumin ≥ 25 g/l, serum creatinine $\leq 1.5\times$upper limit of the reference range). Patients were required to have received no chemotherapy within 4 weeks of entry.

Pretreatment investigations included a full clinical history, physical examination, flexible nasopharyngoscopy, biochemical profile, 24 h urine for creatinine clearance and a complete blood examination. Computed tomography of the nasopharynx and neck, chest X-ray, bone scintigraphy, abdominal ultrasonography and other tests were performed as indicated by the clinical picture. Patients with isolated bone metastasis without other measurable metastatic disease were excluded. Patients who were pregnant or lactating, had concomitant serious medical illness or a history of significant neurological (sensory or motor deficit of grade 2 or above according to WHO criteria [15]) or psychiatric disorders including dementia that would prohibit the understanding and giving of informed consent or concurrent treatment of other anticancer treatment, were excluded. The protocol was approved by the Ethics Committee of the Faculty of Medicine of the Chinese University of Hong Kong.

The dose of carboplatin was calculated according to an AUC of 6 mg ml/min (according to the Calvert formula [6], with creatinine clearance used to approximate glomerular filtration rate) and given as an intravenous (i.v.) bolus injection. This was followed by paclitaxel at a dose of 135 mg/m^2 over 3 h as an i.v. infusion with standard premedication, which included dexamethasone, diphenhydramine and ranitidine. The treatment was repeated every 3 weeks.

Between each cycle, nadir complete blood examinations with white cell differential count, renal and hepatic function tests, and a 24 h urine collection for creatinine clearance were performed. Toxicity of treatment was scored after each course according to WHO recommendations on acute and subacute toxicity of cancer treatment [15]. Each patient was scheduled to receive all cycles of treatment at the same target dose of paclitaxel and carboplatin. Haematopoietic growth factors were not administered routinely. A dose reduction of 25% was applied for both paclitaxel and carboplatin when post-treatment nadir platelet counts fell to $< 50\times10^9$/l or ANC fell to $< 0.5\times10^9$/l or in the case of severe non-haematological toxicity of WHO grade 3 or above.

Evaluation of response by radiological methods was carried out after three cycles. A maximum of six cycles was to be given for those patients having a favourable response (complete or partial remission) after three cycles. Treatment was stopped in the event of progressive disease or intolerable side-effects.

Classification of response was according to WHO criteria [15]. Complete response (CR) was defined as the complete disappearance of all measurable or evaluable disease and all objective signs and symptoms of the disease with a duration of more than 30 days post-treatment. Partial response (PR) was defined as a decrease of 50% or greater in cross-perpendicular dimensions of all measurable or evaluable lesions for at least 30 days. Static disease (SD) was defined as a response less than PR or an increase in cross-perpendicular dimensions of all measurable or evaluable lesions of less than 25%. Progressive disease (PD) was defined as an objective increase of 25% or more in all measurable or evaluable lesions. Response evaluation was performed after three and six cycles, maximum responses during the treatment were noted and overall response took into account any CR/PR that lasted for 30 days or more. For patients with multiple metastatic sites, the response was recorded for each individual site. In cases where there was a difference in response at the various sites, the worst response grading at any metastatic sites was taken as the overall response of the patient.

The probability of survival or time to progression was calculated by the Kaplan–Meier method. Survival duration was calculated from the first day of the first course of treatment (day 1) to the time of death or last event. Time to progression was calculated from day 1 until the date of progression (or last follow-up evaluation for patients who had not progressed).

RESULTS

From January 1996 to November 1997, 27 patients were entered into this trial. There were 25 males and 2 females, and the median age was 44 years (range: 32–66 years). The median Karnofsky performance score was 90 (range 80–100). The median time interval from initial diagnosis to subsequent development of recurrent/metastatic disease was 22 months (range 0–124 months). The initial staging of the patients ranged between Ho's staging [16, 17] I and V. There were 9 patients who had received previous chemotherapy. 2 patients had previous neoadjuvant chemotherapy at initial presentation (a cisplatin-containing regimen), whilst 7 patients had received one salvage chemotherapy regimen for metastatic disease (2 received a cisplatin-containing regimen and 5 received a non-cisplatin-containing regimen). The details of the patients are shown in Table 1.

Amongst the 27 patients, 25 had measurable disease and 2 had evaluable disease. There were 15 (56%) with intrathoracic metastases (including lung parenchymal nodules, pleural and pericardial effusions and mediastinal lymphadenopathy), 13 (48%) with liver metastases, 3 (11%) with axillary/abdominal paraaortic lymph nodes and 3 (11%) with soft

Table 1. *Patients' characteristics*

Characteristic	No. of patients
No. of patients with measurable disease	25
No. of patients with evaluable disease	2
Male	25
Female	2
Median age (years)	44 (range 32–66)
Prior chemotherapy	9
Disease involvement (%)	
Intrathoracic metastases	15 (56%)
Liver metastases	13 (48%)
Locoregional disease	8 (30%)
Axillary/abdominal lymphadenopathy	3 (11%)
Soft tissue mass	3 (11%)
Bone metastases	11 (41%)
≥ 2 diseased sites	18 (67%)
Stage V disease at presentation	3 (11%)
Median time from initial diagnosis to development of recurrent/metastatic disease (months)	22 (range 0–124)
Median no. of courses of chemotherapy	5 (range 1–6)

tissue metastases. 8 (30%) patients had locoregional disease in the nasopharynx with systemic metastases, including the 3 patients who were treated at the time of initial presentation with stage V disease. There were 11 (41%) patients with bone metastasis together with other site(s) of disease which were assessable. 18 (67%) of the 27 patients had more than one site of disease.

The patients received a median of five cycles of treatment (range: one to six). The overall response rate was 59% (16/27). 3 patients (11%) had CR and 13 (48%) had PR. 5 patients (19%) had SD and 6 (22%) had PD. Of the 7 patients who were previously exposed to chemotherapy for metastatic disease, there were no CRs, 2 (29%) PRs, 1 (14%) SD and 4 (57%) PD. Amongst the 3 patients treated in the study at first presentation with metastatic disease, there was 1 CR, 1 PR, no SD and 1 PD in the local disease; of the 5 patients with recurrent disease who had undergone previous radiotherapy, there was 1 CR, no PRs, 2 SD and 3 PD. The tumour responses according to specific disease sites are illustrated in Table 2.

A total of 122 cycles were given. The dosage was reduced by 25% in 16 cycles (13%) for severe haematological toxicities. Toxicities included: grade 3/4 neutropenia (39 cycles, 32%), grade 3/4 anaemia (nine cycles, 7%), grade 3/4 thrombocytopenia (8 cycles, 7%); there were 3 episodes of neutropenic fever (3%). Non-haematological toxicities were mild and infrequent. There was no grade 3/4 neuro- or nephrotoxicity.

Table 2. *Tumour responses according to specific disease sites*⋆

Specific disease sites	No. of patients	CR (%)	PR (%)	SD (%)	PD (%)
Intrathoracic†	15	0 (0)	11 (73)	3 (20)	1 (7)
Liver	13	3 (23)	4 (31)	3 (23)	3 (23)
Locoregional	8	2 (25)	1 (13)	2 (25)	3 (38)
Soft tissue mass	3	1 (33)	1 (33)	0 (0)	1 (33)
Axillary/abdominal lymphadenopathy	3	0 (0)	1 (33)	0 (0)	2 (67)

⋆For patients with multiple metastatic sites, the worst response grading of all the disease sites was taken as the overall response for the patient. †Includes lung parenchymal nodules, pleural and pericardial effusions and mediastinal lymphadenopathy. CR, complete response; PR, partial response; SD, static disease; PD, progressive disease.

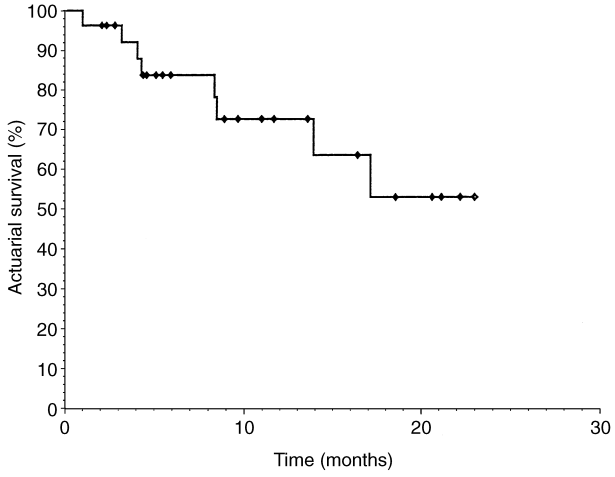

Figure 1. Actuarial survival curve of treated patients.

At the time of analysis, 16 of the 27 patients (59%) had progressed and of these, 8 had died. The mean time to progression was 5.96 months (95% confidence interval (CI)), 4.70–7.22 months). The mean survival time of the whole group of patients was 13.9 months (95% CI 11.14–15.94 months). The actuarial survival curve of the 27 patients is shown in Figure 1.

DISCUSSION

For patients with metastatic/recurrent head and neck cancers who are not candidates for surgery or radiotherapy, chemotherapy is indicated to palliate symptoms. Cisplatin-based regimens have been used to treat metastatic NPC in various combinations with drugs such as 5-fluorouracil, bleomycin and epirubicin [1, 4, 18]. The response rates have ranged from 40 to 80%, depending on the treatment regimen, patient population characteristics and selection criteria. Carboplatin, an analogue of cisplatin, has a more favourable toxicity profile than cisplatin with reduced neurotoxicity and nephrotoxicity, and can be used on an out-patient basis. The reported response rates for carboplatin in recurrent head and neck cancers have been around 25% [19, 20]. In our previous study using combination carboplatin and 5-fluorouracil in metastatic NPC, the response rate was 38% [5]. One of the reasons for the relatively low response rate in these studies was the use of carboplatin at a suboptimal dose; carboplatin was used at approximately 75% (i.e. 300 mg/m^2 instead of 400 mg/m^2) of the pharmacologically equivalent dose to cisplatin [21]. In addition, based on the extensive pharmacological studies of Calvert and colleagues [6] and Egorin and associates [7], it has been shown that the optimal dose of carboplatin can be determined according to a target AUC. While platinum-based chemotherapy has been shown to increase the overall response rate and to palliate patients' symptoms, albeit in the absence of information on quality of life, there has been no conclusive evidence of survival advantage [22].

Paclitaxel has been shown to be effective in ovarian, breast and lung cancer with increased responses when compared

with conventional therapy [9, 10, 12, 13]. Whilst one study showed that paclitaxel at 250 mg/m^2 given as a 24 h infusion with granulocyte colony-stimulating factor support yielded a response rate of 40% in advanced head and neck cancers [23], a similar study in previously treated patients [24] gave a response rate of only 25% with 4 treatment-related deaths. In patients with metastatic NPC, paclitaxel at a dose of 175 mg/m^2 yielded a response rate of 26% [25].

By combining paclitaxel and cisplatin, the overall response rate has been reported to be 24–70% in head and neck cancers, but there has been dose limiting neurotoxicity and myalgia [26, 27]. As the substitution of carboplatin for cisplatin allows out-patient treatment and reduces neurotoxicity and since paclitaxel has an acceptable profile of toxicity, combination paclitaxel/carboplatin has been investigated in head and neck cancers. Fountzilas and colleagues [28] reported the use of carboplatin and paclitaxel in 41 patients with advanced head and neck cancers. In this phase II study, the carboplatin dose was calculated according to a target AUC of 7 mg ml/min, with paclitaxel at 200 mg/m^2 and granulocyte colony stimulating factor support. Prior chemotherapy was only allowed in the setting of concurrent chemoradiation administered at least 1 year before entry. With a total of 160 cycles being administered, and 31 patients eligible for response assessment, the overall response rate was 36%, with NPC patients yielding a higher response than non-NPC patients.

The present study reports the use of combination paclitaxel and carboplatin in a homogeneous group of NPC patients. Despite the absence of haematopoietic growth factor support, the doses used gave an overall response rate of 59% with acceptable toxicity. This is comparable with other platinum-combined regimens. The treatment protocol was initially planned to be of six cycles only as there were no data available on carboplatin and paclitaxel in NPC patients at the time of protocol design. However, with our present knowledge of the efficacy and toxicity of this combination regimen, it would appear that additional maintenance therapy with more courses of the treatment might increase response rates and survival in those patients who responded to the treatment.

A more aggressive approach with dose escalation of both agents may further improve the efficacy of this combination. This is supported by a preliminary report which recorded a response rate of 71% when paclitaxel 175 mg/m^2 was combined with carboplatin at an AUC of 6 mg ml/min [29]. Pharmacological studies have been conducted to determine the maximum tolerated dose of combination paclitaxel and carboplatin in various groups of patients. Creaven and colleagues [30] have reported that, in previously treated head and neck and lung cancer patients, the dose of paclitaxel could be escalated up to 230 mg/m^2 when combined with carboplatin targeted to an AUC of 4.0 mg ml/min with the support of haematopoietic growth factors. In chemotherapy-naive patients, the corresponding figures for paclitaxel and carboplatin were 250 mg/m^2 and an AUC of 4.5 mg ml/min, respectively. Alternatively, without the support of haematopoietic growth factors for previously treated patients, the maximum tolerated dose was only 135 mg/m^2 for paclitaxel and a target AUC of 4 mg ml min for carboplatin–a figure which is consistent with our patient population.

In future studies, we aim to investigate the use of higher doses of paclitaxel and carboplatin with haematopoietic growth factor support in patients with NPC, and to evaluate the quality of life in relation to therapeutic efficacy and treatment-related toxicity.

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