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Phase II study of the combination of carboplatin and 5-fluorouracil in metastatic nasopharyngeal carcinoma

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Abstract A carboplatin and 5-fluorouracil (CF) chemotherapy protocol was designed to evaluate tumor response and toxicity in patients with metastatic nasopharyngeal carcinoma (NPC). Patients with metastatic NPC were treated with a maximum of eight courses of CF. Carboplatin was given at 300 mg/m^2 by intravenous bolus on day 1 and 5-fluorouracil at 1 g/m^2 per day by continuous infusion on days 1–3; cycles were repeated once every 3 weeks. A total of 42 patients were evaluable for response and toxicity. They received a median of 6 courses (range 2–8) of chemotherapy. The overall response rate was 38% (16/42), comprising 7 complete responses (CR, 17%) and 9 partial responses (PR, 21%). The median survival was 12.1 months (range 6–54.2 months). The treatment was well tolerated. Toxicity was mainly bone marrow suppression. There were four episodes of neutropenic fever, but no renal toxicity or treatment-related death was documented. The combination of carboplatin given at a fixed dose of 300 mg/m^2 for 1 day and 5-fluorouracil given at 1 g/m^2 per day for 3 days produced an objective response rate of 38% and tolerable side effects.

Key words Carboplatin · 5-Fluorouracil · Metastatic nasopharyngeal carcinoma

Introduction

Nasopharyngeal carcinoma (NPC) is a prevalent diseases in Hong Kong. The 5-year survival rate of patients with NPC ranges from 15% to 70% depending on the stage [1, 8, 20]. In Hong Kong, the proportion of NPC patients presenting with distant metastases is lower than those reported in other countries [8]. Nonetheless, after radical radiotherapy a significant number of patients will develop distant metastases, whether or not the primary tumor is controlled, and systemic failure has been the predominant failure site for our NPC patients. Metastatic disease usually signifies a poor prognosis, and the median survival ranges from 3 to 12 months in metastatic liver and lung diseases, respectively [8, 14, 15].

NPC is radiosensitive, and radiotherapy alone provides excellent local control in about 80% of cases [8]. NPC is also chemosensitive, and as a result, chemotherapy has been used in the treatment of advanced NPC in neoadjuvant and adjuvant protocols as well as in palliative treatment of metastatic NPC. Common sites for metastasis in NPC are bone, lungs, and liver [14, 15]. Single-agent therapy such as mitozantrone [10], 5-fluorouracil (5-FU) [15], and 4′-epidoxorubicin [18] has been used but the response rates have been disappointing at around 20% [7, 11, 12]. On the other hand, combination chemotherapy, in particular, cisplatin-containing regimens, has been shown to yield higher response rates ranging from 25% to 80% [4, 6, 9, 19].

However, cisplatin produces renal and neurotoxicity, which has limited its use. Carboplatin, on the other hand, has considerable advantages in that it causes much less renal and neurotoxicity. It can also be used on an outpatient basis because it does not require hydration. Carboplatin has been used as a single agent or in combination therapy for other head and neck cancers [11, 16]. In this phase II study, carboplatin was used in combination with 5-FU in the treatment of patients with metastatic NPC.

Patients and methods

Between 1987 and 1993, 42 patients with metastatic NPC gave consent and were treated with a carboplatin and 5-FU (CF) regimen. The criteria for entry into the trial were as follows: histologically proven NPC of the undifferentiated or poorly differentiated squamous-cell carcinoma type (WHO classification) [21], measurable metastatic disease on radiological grounds, an age of between 16 and 70 years, adequate hematological function (white cell count $>3\times10^9$/l, platelet count $>100\times10^9$/l) and renal function (plasma urea <10 mmol/l, creatinine <120 μmol/l), and a Karnofsky performance score of 80 or

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above. Other pretreatment workups in the protocol included a full clinical history and physical examination, flexible nasopharyngoscopy, a biochemical profile, a complete blood picture, computer tomography of the nasopharynx and neck, a chest X-ray, bone scintigraphy, abdominal ultrasonography, and other tests as indicated by the clinical picture. The initial staging of NPC was carried out according to Ho's staging classification [13] and to the American Joint Committee (AJC) for Cancer Staging [3, 20]. Patients should have had no serious concomitant medical illness and no previous chemotherapy within 4 weeks prior to entry. Patients who had been exposed to cisplatin-containing regimens during neoadjuvant or adjuvant chemotherapy at initial presentation were nonetheless eligible for this study. Isolated bone metastasis without other measurable metastatic disease was excluded.

Treatment was given as follows: carboplatin at 300 mg/m^2 by intravenous bolus on day 1 and 5-fluorouracil at 1 g/m^2 per day by 24-h continuous intravenous infusion on days 1–3, with cycles being repeated once every 3 weeks. Evaluation of response by radiological methods was carried out after three cycles. A maximum of eight courses were to be given to patients having a favorable response (complete or partial remission) after three cycles. Treatment was stopped for progressive disease or intolerable side effects.

Classification of the response was carried out according to WHO criteria [21]. A complete response (CR) was defined as the complete disappearance of all measurable or assessable disease and all objective signs and symptoms of the disease for more than 30 days posttreatment. A partial response (PR) was defined as a decrease of 50% or more in the cross-perpendicular dimensions of all measurable or assessable lesions for at least 30 days. Static disease (SD) was defined as a response amounting to less than a PR or an increase of less than 25% in the cross-perpendicular dimensions of all measurable or assessable lesions. Progressive disease (PD) was defined as an objective increase of 25% or more in the dimensions of all measurable or assessable lesions. Response evaluation was performed after three, six, and eight cycles, maximal responses during the treatment were noted, and the overall response took into account any CR/PR that lasted for 30 days or more. For patients who had multiple metastatic sites the response was noted in each individual site, with the worst response grading of all the metastatic sites being taken as the overall response of the patient. Survival duration was calculated from the 1st day of the first course of treatment to the time of death or last event. The probability of survival was plotted by the Kaplan-Meier method.

Blood biochemistry and blood counts were taken before each cycle to assess renal and hematological toxicity. The toxicity of treatment was scored after each course at day 21 according to the WHO recommendations on acute and subacute toxicity of cancer treatment [21]. The worst event was taken as the overall toxicity grade.

Results

From 1987 to 1993, 42 patients were entered into this trial. There were 35 men and 7 women, and the median age was 44 (range 25–61) years. The median Karnofsky performance score was 90%. The median interval from the initial diagnosis to the subsequent development of metastatic disease was 17 months. There were nine patients who had concurrent locoregional disease, of whom three had newly diagnosed NPC. The initial staging of the patients ranged between Ho's stages I–V and AJC stages III–V. There were five patients who had received previous chemotherapy. Four patients had previous neoadjuvant chemotherapy at initial presentation (all involving cisplatin-containing regimens), whereas the remaining patient had received other chemotherapy regimens for his metastatic disease prior to entry (a carboplatin-containing regimen 2 years previously and a cisplatin-containing regimen 1 year prior to our CF regimen in another hospital). The characteristics of the patients are shown in Table 1.

Table 1 Patients' characteristics

Characteristic	Number of patients
Median Karnofsky performance score	90 (range 80–100)
Sex:	
M	35
F	7
Median age (years)	44 (range 25–61)
Prior chemotherapy	5
Disease involvement (%):	
Liver metastases	25 (59%)
Lung metastases	27 (64%)
Bone metastases	19 (45%)
Mediastinal/abdominal lymphadenopathy	5 (12%)
Submental mass	1 (2%)
Concurrent locoregional disease	9 (21%)
Median number of courses of chemotherapy	6 (range 2–8)

Table 2 Responses to chemotherapy based on individual metastatic sites

Metastatic sites	Number of patients with the involved site	Responses in individual metastatic sites			
		CR	PR	SD	PD
Lungs	27	5	8	11	3
Liver	25	5	4	5	11
Mediastinal/abdominal lymphadenopathy	5	3	1	1	–
Submental mass	1	1	–	–	–
Locoregional disease	9	2	3	3	1

Of these 42 evaluable patients, there were 25 (59%) with liver metastases (9 with liver metastasis only, 16 with other sites of disease), and 27 (64%) with lung metastases (11 with lung metastasis only, 16 with other sites of disease). There were 19 (45%) patients who had bone metastasis together with other site(s) of disease that was evaluable. Nine patients had concurrent locoregional disease in the nasopharynx. Three patients were newly diagnosed as having NPC with systemic metastasis on presentation. All the patients received a median of 6 cycles (range 2–8) of CF. The overall response rate was 38% (16/42), including 7 CRs (17%) and 9 PRs (21%). There were 13 patients (31%) with SD and 13 (31%) with PD. The response rates are shown in Table 2.

Of the 42 patients, 15 (36%) had more than 1 site of disease involvement; there was a differential response to chemotherapy over the various sites of involvement in 6 of them. As described above, the worst response grading of all the involved metastatic sites within one patient was taken as the overall response of the patient.

Five patients are alive at the time of this writing. Five patients were lost to follow-up; they had survived for a minimum of 5.6 months when last seen. The median duration of survival of the whole group is 12.1 (range

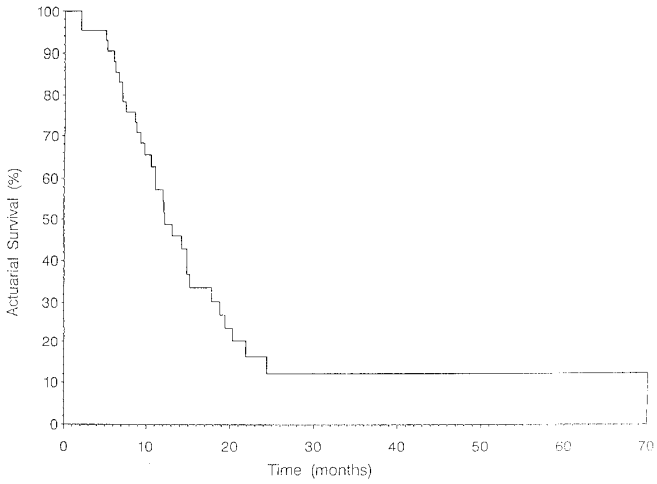

Fig. 1 Actuarial survival curve generated for 42 patients with metastatic NPC undergoing treatment with the CF regimen

Table 3 Toxicity encountered according to grade

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Nausea & vomiting	28	8	4	1	1
Leukopenia	12	13	14	2	1
Thrombocytopenia	33	4	4	1	0
Renal toxicity	42	0	0	0	0

6–54.2) months. One patient who had lung metastases achieved a PR after CF treatment, underwent pulmonary metastectomy, and is now disease-free at 52 months. Of the three newly diagnosed NPC patients with metastatic disease, only one patient received radiotherapy to the primary tumor in addition to chemotherapy, and this patient was reported to have achieved a CR in the nasopharyngeal region but had PD in the liver metastases. The other two patients had PD in their liver metastases and died at 2 and 6.6 months, respectively, after the initiation of chemotherapy. The actuarial survival curve of all patients is shown in Fig. 1.

The treatment was generally well tolerated. Most patients had mild symptoms of nausea and vomiting. There were four episodes of neutropenic fever. In all, 17 patients had leukopenia of grade 2 or worse and 5 patients had thrombocytopenia of grade 2 or more. No renal toxicity or treatment-related death was documented. The toxicity grading is shown in Table 3.

Discussion

The present series is the first phase II study of a CF regimen in the treatment of metastatic NPC. NPC is known to be one of the most chemosensitive and radiosensitive head and neck cancers. Single-agent chemotherapy has been used with minimal effect [7, 10, 15, 18]. Combination chemotherapy has been reported to produce an overall response rate ranging from 25% to 80% [4, 6–9, 12, 19]. Cisplatin-based regimens have commonly been used for recurrent and metastatic NPC patients. A retrospective study by Choo et al. [17] revealed that cisplatin-containing combination chemotherapy was superior to single-agent therapy, with the overall response rate being 70% for metastatic and/or locoregional recurrent disease. The overall median survival from the initiation of chemotherapy was 9 months, but no difference in survival was found between combination and single-agent therapy.

With two cisplatin-based regimens, Decker et al. [9] treated 17 NPC patients and obtained an overall response rate of 25%. On the other hand, in the series of Chi et al. [6], 15 patients with metastatic NPC achieved a response rate of 80% with a cisplatin/5-FU/leucovorin combination, with the overall median survival being 20 months. A larger-scale study by Cvitkovic et al. [8] used two comparable regimens, cisplatin/bleomycin/5-FU and cisplatin/bleomycin/epirubicin, and obtained an overall response rate of 80% and a CR rate of 18% in the 100 patients treated.

The response rate obtained in the present study appears to be lower than those of other trials using cisplatin-based regimens. This may be due to our higher proportion of patients with multiple metastatic site (36%) involvement

Table 4 Previous studies of metastatic and/or recurrent NPC patients, with indication of the individual metastatic site involved

Reference	Number of patients	% of liver metastases	% of lung/pleural metastases	% of bone metastases	% with multiple metastatic sites	% of locoregional recurrent alone	% of overall response (CR)	Regimens
Cvitkovic et al. 1991 [8]	100	27	23	65	27	–	80 (18)	Cisplatin/bleomycin/5-FU Cisplatin/bleomycin/epirubicin
Boussen et al. 1991 [4]	48	23	52	77	Figures not available	17	79 (19)	Cisplatin/bleomycin/5-FU
Gebbia et al. 1993 [12]	40	15	12.5	12.5	Figures not available	72.5	64 (20.5)	Cisplatin-based
Su et al. 1993 [19]	25	40	44	72	56	8	40 (4)	Cisplatin/bleomycin/5-FU
Present study	42	59	64	45	36	–	38 (17)	Carboplatin/5-FU

and of patients with liver metastasis (59%) as compared with other studies, as is illustrated in Table 4. Boussen et al. [4] used a cisplatin/bleomycin/5-FU combination and showed that lung metastases had the highest CR of 25% (3 of 12 patients), followed by bone secondaries with a CR of 19% (7 of 37 patients). From Boussen's series, 11 patients had hepatic metastases and none of them showed any response to the treatment, and the overall median duration of response was only 4 months. In the series of Su et al. [19], 40% of the patients had liver metastases and 44% had lung metastases, and the overall rate of response to chemotherapy was 40%. The distribution of sites of metastases in Su et al.'s series is closest to that of our study. Also, in the present study the response rate of liver and lung metastases was 36% (9 of 25 patients) and 48% (13 of 27 patients, Table 2), respectively, which are similar to the rates reported by Su et al. [19].

Another factor may be the dose regimen of 5-FU used. In most regimens given for head and neck cancers the dose of 5-FU has been 1 g/m^2 per day for 5 days. Our earlier study, using such a dose in a neoadjuvant setting, had resulted in intolerable toxicities. A 3-day regimen was therefore used in this study.

Furthermore, a lower response rate may be due to a suboptimal dose of carboplatin. Although at the time of our study a carboplatin dose of 300 mg/m^2 every 3 weeks was considered to be adequate, more recent studies by Reyno et al. [17] and Calvert et al. [5] have shown that the dose of carboplatin should be adjusted to a target AUC (area under the plasma carboplatin concentration versus time curve). Our present dose regimen, therefore, appears to have insufficient data for a direct comparison of efficacy between carboplatin and cisplatin.

It may appear that the median of six cycles delivered was somewhat higher than expected, considering the low response rate observed. This was mainly due to six patients who had multiple sites of disease and a differential response. The worst response grading was taken as the overall response. The phenomenon of differential response, as noted in these patients, has not been previously reported. It may be due to the presence of multiple clones of differing chemosensitivity within an individual patient. Furthermore, as seven patients experienced a subjective improvement in their symptoms in terms of general well-being and quality of life, further chemotherapy was given despite their response being less than a PR.

It is generally believed that chemotherapy-naive patients may have a better response to chemotherapy [5, 19]. However, the contrary has also been reported [6, 8, 10]. Our series appears to support the latter; 5 of the 42 assessable patients had previously undergone chemotherapy, of whom 3 responded to the present regimen. It is noteworthy that one patient in the present study, who had previously been exposed to carboplatin and cisplatin, responded to the present CF regimen.

There has thus far been no study that compares the efficacy of cisplatin and carboplatin in NPC. Carboplatin is used in other head and neck cancers [2]. In a three-arm study by Forastierre et al. [11], carboplatin/5-FU has been compared with cisplatin/5-FU and single-agent methotrexate for the treatment of metastatic head and neck cancers. The responses rates observed were 32%, 21%, and 10%, respectively, in the three arms. However, there was no statistically significant difference in the median duration of response and the median survival determined for the three arms.

The overall response rate obtained with the present CF regimen cannot be compared directly with other cisplatin-based regimens and cannot be recommended at the present stated dose schedule for routine use in metastatic NPC. However, with the advantage of reduced nephrotoxicity and the convenience of delivery of carboplatin and with the availability of colony-stimulating factor support, further studies of carboplatin given at a dose adjusted to a target AUC are warranted to evaluate fully its efficacy in metastatic NPC.

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