Journal of BUON **9:** 161-165, 2004

ORIGINAL ARTICLE

Paclitaxel and carboplatin in relapsed or metastatic nasopharyngeal carcinoma: a multicenter phase II study

T.E. Ciuleanu[1], G. Fountzilas[2], E. Ciuleanu[1], M. Plataniotis[2], N. Todor[1], N. Ghilezan[1]

[1]Cancer Institute Ion Chiricuta, Cluj, Romania; [2]Hellenic Cooperative Oncology Group, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Summary

Purpose: *This multicenter phase II study was conducted to investigate the activity and toxicity of a combination of paclitaxel and carboplatin delivered on an outpatient basis in relapsed/ metastatic nasopharyngeal carcinoma patients.*

Patients and methods: *Patients aged≥ 18 years with histologically proven recurrent or metastatic nasopharyngeal carcinoma, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and a life expectancy of ≥ 12 weeks were eligible. Measurable disease outside prior radiotherapy ports was required, unless a subsequent progression of the lesion was documented. An interval of ≥ 12 months was required between the previous chemotherapy (neoadjuvant, concurrent chemoradiotherapy or adjuvant) and study entry. Prior radiotherapy or surgery were allowed. All patients had adequate bone marrow (WBC >4000/mL, platelets >100000/mL), hepatic (bilirubin <1,5 mg/dL, SGPT <1.5×N), and renal function (serum creatinine <1.5 mg/dL or creatinine clearance >60 mL/min). Chemotherapy consisted of paclitaxel 175 mg/m², given as a 3-hour infusion, followed by carboplatin dosed to an area under the concentration-time curve (AUC) of 6 mg*min/mL, administered every 21 days.*

Results: *40 patients entered the study. There were 3 complete responders (CR) and 8 partial responders (PR), for an overall response rate (ORR) of 27.5% (95% confidence interval – C.I.: 14.5-44). Median time to progression (TTP) was 3.5 months, and median survival was 11.5 months. Grade 3-4 toxicity included leucopenia (17.5% of the patients), anaemia (17.5%), thrombocytopenia (10%), neutropenia (7.5%), and peripheral neuropathy (2.5%).*

Conclusion: *These data indicate that the combination of paclitaxel and carboplatin can be safely administered on an outpatient basis, but it is only moderately active against relapsed/metastatic nasopharyngeal carcinoma patients.*

Key words: carboplatin, nasopharyngeal carcinoma, paclitaxel, phase II study

Introduction

Long term survival has been noted in some patients with relapsed/ metastatic nasopharyngeal carcinomas treated with chemotherapy. Widespread use of chemotherapy as part of the initial treatment of locally advanced nasopharyngeal carcinomas (cisplatin+5 fluorouracil [1] or bleomycin + epirubicin + cisplatin [2]) creates the need for new efficient second-line chemotherapy regimens for refractory/ relapsed patients. The development of a new generation of agents active in head and neck cancers raises hopes of improving prognosis in relapsed, chemotherapy-pretreated nasopharyngeal carcinoma patients, as well as in patients previously untreated with chemotherapy.

Single-agent paclitaxel has been shown to produce response rates in excess to 38% in advanced head and neck cancers [3]. The combination of paclitaxel with cisplatin or carboplatin exhibits significant antitumor activity in patients with inoperable head

Received 02-12-2003; Accepted 21-12-2003

Author and address for correspondence:

Tudor E. Ciuleanu, MD, PhD
Cancer Institute "Ion Chiricuta"
Department of Radiochemotherapy II
Republicii street 34-36
Cluj Napoca
Romania
Tel: +40 745 64 63 68
Fax: +40 264 19 83 65
E-mail: tudor_ciuleanu@hotmail.com

and neck cancer, with a wide range of overall response rates: 20-70% [4-6]. Among head and neck cancers, the combination of paclitaxel and carboplatin seems especially attractive for relapsed nasopharyngeal carcinoma patients, with reported response rates in the range of 31-50% in single-institution small phase II studies [4,5,7,8].

The Hellenic Cooperative Group, together with the Cancer Institute Ion Chiricuta of Cluj, Romania, conducted a multicenter phase II study of a combination of paclitaxel and carboplatin in relapsed/ metastatic nasopharyngeal carcinoma patients. This protocol allows the treatment to be delivered on an outpatient basis.

Patients and methods

The main objectives of this phase II study were, first, to determine the efficacy of the combination of paclitaxel and carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma and second, to evaluate the qualitative and quantitative toxicity of this combination.

Eligibility criteria

Patients aged ≥18 years with histologically proven recurrent or metastatic nasopharyngeal carcinoma, an ECOG performance status ≤2, and a life expectancy of ≥12 weeks were eligible for the study. Measurable disease outside prior radiotherapy ports was required, unless a subsequent progression of the lesion was documented. An interval of ≥12 months was required between the previous chemotherapy (neoadjuvant, concurrent chemoradiotherapy or adjuvant) and study entry. Prior radiotherapy or surgery were allowed. All patients had to have adequate bone marrow (WBC > 4000/mL, platelets >100000/mL), hepatic (bilirubin <1.5 mg/dL, SGPT <1.5×N), and renal function (serum creatinine <1.5 mg/dL or creatinine clearance >60 mL/min). All females of childbearing potential ought to have negative serum or urine pregnancy test results obtained within 2 days prior to initiation of treatment.

Patients with previous chemotherapy for recurrent and metastatic disease were excluded from the study. Also ineligible were patients with past or current neoplasms other than nasopharyngeal carcinoma, except for curatively treated non-melanoma skin cancer or carcinoma *in situ* of the cervix; a history of atrial or ventricular arrhythmia and/or history of congestive heart failure (even if medically controlled), or myocardial infarction during the previous 6 months; a history of preexisting motor or sensory neurotoxicity grade ≥2, according to World Health Organisation (WHO) criteria (intolerable paresthesia and/ or marked motor loss, or worse); or active infection or other serious underlying medical condition which would impair the ability of the patient to receive the treatment protocol, including prior allergic reactions to drugs containing cremophor, such as teniposide or cyclosporine. Fertile patients without use of contraceptives, pregnant or breast-feeding women were also excluded. Administration of other chemotherapeutic drugs or hormonal therapy was not allowed. The protocol was approved by the ethical committees of all participating centres and by the National Drug Organisation (Athens, Greece).

Treatment plan

The chemotherapy regimen consisted of paclitaxel 175 mg/m^2, given as a 3-hour infusion, followed by carboplatin dosed to an AUC of 6 mg*min/mL in 500 mL normal saline and given as a 30-min infusion immediately following the paclitaxel infusion. Standard premedication was used with cimetidine (300 mg intravenously), dimethidene maleate (phenistyl 4 mg intravenously) and dexamethasone (20 mg intramuscularly) given 12 and 6 hours prior to paclitaxel infusion.

Dosages were reduced if granulocytopenia or thrombocytopenia persisted for ≥7 days or febrile neutropenia developed. The dosing levels used in modifying the paclitaxel dosage were 175 mg/m^2 at level 0, 135 mg/m^2 at level 1, 100 mg/m^2 at level 2, and 80 mg/m^2 at level 3. Any patient who did not tolerate the 80 mg/m^2 level was taken off study. Dose escalation was not allowed in this study. If the nadir absolute neutrophil count of the preceeding cycle was <1000/μl or the platelet count <100000/μl, the dose of paclitaxel was reduced by one dose level. If the absolute neutrophil count was <500/μl or the platelet count <50000/μl, the dose of paclitaxel was reduced by two dose levels. In the presence of febrile neutropenia, regardless of whether it was associated with documented infection, as well as in case of severe bleeding, the paclitaxel dose was reduced by three dose levels. The absolute neutrophil count was required to be ≥1500/μl and the platelet count ≥100000/μl before starting the next treatment cycle. If thrombocytopenia or granulocytopenia reached grade 3 or 4, the carboplatin dose was reduced to an AUC of 5 mg*min/mL for all subsequent cycles. If haematological recovery was not achieved on day 35 of the

cycle, the patient was taken off study. If grade 3 mucositis developed, the dose of paclitaxel was reduced by one dose level, and carboplatin was dosed to an area under concentration-time curve of 5 mg*min/mL. Treatment was discontinued in case of >WHO grade 2 neurotoxicity (intolerable paresthesias and or marked motor loss, or worse), severe hypersensitivity reactions (hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalised urticaria), symptomatic arrhythmia, or atrioventricular block (except first degree), and the patient was withdrawn from study. Toxicity criteria were those adopted by the WHO. Standard ECOG criteria were used for evaluation of tumor response. The statistical analysis was carried out on an "intention to treat" basis. The Kaplan-Meier method was used for estimating time to event curves. Survival was calculated from treatment initiation until death from any cause. TTP was determined by the interval between initiation of treatment and disease progression. Patients who died of causes probably related to chemotherapy or disease, or who discontinued their treatment for any reason other than tumor progression were considered as having disease progression at that time. Patients who were progression-free or alive on the day of the last update (1/7/1999) were censored. Reported 95% C.I. for response to treatment are exact.

Results

Between November 1995 and July 1998, 40 patients entered this study. Their pretreatment characteristics are shown in Table 1.

Compliance with treatment and toxicity

Selected treatment characteristics are depicted in Table 2. As of July 1, 1999, a total of 154 cycles were administered; 149 (97%) have been given at full dose; 30 (19%) were delayed due to late blood count recovery.

Only 11 (27.5%) patients completed all 6 cycles of treatment. Reasons for treatment discontinuation were progressive disease in 13 patients, stable disease without clinical benefit in 4, voluntary withdrawal in 7, toxicity in 2, physician decision to continue with surgery and radiotherapy in 2, and hospitalisation for other disease in 1 patient.

The toxicity profile is depicted in Table 3. Except for alopecia, the most common grade 3-4 toxicities were leucopenia (17.5% of patients), anaemia (17.5%), thrombocytopenia (10%), neutropenia (7.5%), and peripheral neuropathy (2.5%). Febrile neutropenia occurred in 2 patients. G-CSF was administered in 2 (5%) patients at some time of the trial because of neutropenia, antibiotics were used in 3 (7.5%) patients, red blood cell transfusions in 5 (12.5%) and platelet transfusions in 1 (2.5%). Four (10%) patients were hospitalised (median 5 days, range 4 - 16 days) because of febrile neutropenia (2 patients), platelet transfusion (1 patient) and cerebrovascular coma (1 patient) unrelated to cancer or treatment.

Table 1. Patient (n=40) and tumor characteristics

Characteristic	*No. of patients (%)*
Age (years)	
median	53
range	20-73
Gender	
male	29 (72.5)
female	11 (27.5)
ECOG performance status	
0	5 (12.5)
1	17 (42.5)
2	18 (45)
Histology	
squamous cell	7 (17.5)
undifferentiated	32 (80)
mucoepidermoid	1 (2.5)
Primary treatment	
induction chemotherapy followed by RT*	28 (70)
RT alone	9 (22.5)
concurrent chemoradiotherapy	2 (5)
none	1 (2.5)
Sites of disease	
locoregional only	29 (72.5)
distant only	6 (15)
locoregional and distant	5 (12.5)
Description of locoregional involvement	
primary	25 (62.5)
cervical nodes	21 (52.5)
Number of locoregional locations	
0	6 (15)
1	22 (55)
2	12 (30)
Description of metastatic involvement	
nodes	4 (10)
bones	5 (12.5)
liver	3 (7.5)
lung	3 (7.5)
Number of metastatic locations	
0	29 (72.5)
1	7 (17.5)
2	4 (10)
Bidimensionally measurable disease	25 (62.5)
Evaluable disease	15 (37.5)

*radiotherapy

Table 2. Treatment characteristics

	C*	N§
Number of cycles per patient	1	2
	2	8
	3	8
	4	9
	5	2
	6	11
Total number of cycles		154
Number of cycles with full dose		149
Number of cycles with a delay		30
Duration of treatment (weeks)		
median		12.5
range		3-29
DI† of paclitaxel		
planned		58.33
delivered		
median		53.8
range		31-63
Relative DI† of paclitaxel		
median		0.92
range		0.53-1.1
Cumulative dose of carboplatin (mg)		
median		2175
range		450-4570

*number of cycles; §number of patients; †dose intensity

Table 4. Response to chemotherapy

Response	*No. of patients (%)*	*95% CI*
CR	3 (7.5)	1.5-20.5
PR	8 (20)	9-35.5
SD	22 (55)	38.5-70.5
PD	6 (15)	5.5-30
Not assessed*	1 (2.5)	
Total	40 (100)	

ORR= 27.5% (95% CI: 14.5-44)

*Only 2 cycles; hospitalized unconscious, treated with antiepileptic medication

Table 5. Response by site

	Locoregional		*Distant*			
	Primary	*Nodes*	*Nodes*	*Bones*	*Liver*	*Lung*
CR	2	3	–	–	–	–
PR	7	4	1	–	1	1
SD	12	13	1	3	1	1
PD	3	1	2	2	1	1

Note: The not assessed patient (Table 4) had locoregional disease

Response and survival

In one (2.5%) patient response could not be assessed because he was hospitalised unconscious after 2 cycles, necessitating antiepileptic medication and died after 5 days. Three patients (7.5%, 95% CI: 1.5-20.5), all of them with locoregional relapse (primary in 2 and nodes in 3 patients), achieved CR, and 8 (20%, 95% CI: 9-35.5) PR, for an ORR of 27.5% (95% CI: 14.5-44) (Tables 4 and 5). The CRs lasted 1.5, 12.5+ and 17 months respectively. Furthermore, 22 patients (55%, 95% CI: 38.5-70.5) demonstrated disease stabilization. Median response duration was 10.5 (CI 95% 3.5-17 months), and range 1.5-21+ months. As of July 1, 1999, after a median follow-up of 20 months (range 3-31+), 34 (85% patients) had developed disease progression and 26 (65%) had died. Median TTP was 3.5 months (95% CI: 1.5-5.5), and range 0-23.5+ months (Figure 1). Median survival was 11.5 months (95% CI: 9.5-13.5), and range 3-31+ months (Figure 1). Six patients were treated with additional chemotherapy after they

Table 3. Incidence (%) of various toxicities

Toxicity	*Grade*			
	1	*2*	*3*	*4*
Nausea/vomiting	62.5	20	7.5	
Leucopenia	30	22.5	10	7.5
Neutropenia	2.5			7.5
Thrombocytopenia	7.5	5	7.5	2.5
Anaemia	40	12.5	12.5	5
Myalgias/arthralgias	5			
Peripheral neuropathy	2.5	2.5	2.5	
Infection		7.5		
Alopecia	2.5	10	85	
Fatigue	5	12.5		
Fever		2.5		

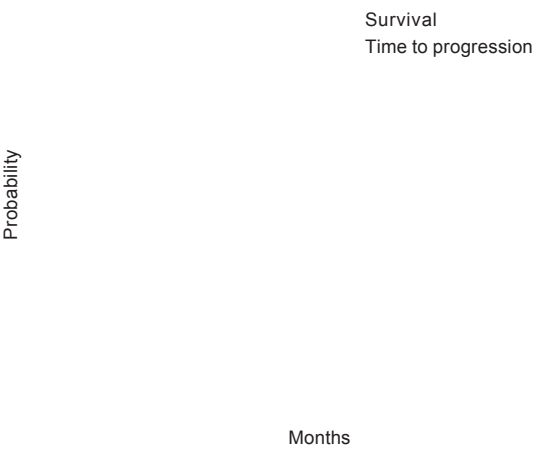

Figure 1. Time to progression and survival.

had progressed. Among 28 patients who received induction chemotherapy there were 3 CRs and 5 PRs (ORR 28.5%). Nine (37.5%) were seen in the primary tumor, 7 (33.3%) in the regional nodes and 3 (20%) in the metastatic sites (Table 5). It is worth noting that all 3 CRs were observed within locoregional preirradiated areas.

Discussion

This phase II study reports results on the activity and toxicity profile of the combination of paclitaxel and carboplatin in patients with recurrent or metastatic nasopharyngeal carcinoma. Our data suggest that this combination, at the drug doses used, appears to be moderately active in this patient population. The response rate observed is somewhat lower than that reported in our previous studies with this regimen, which included lesser patients [4,7-9], but the confidence intervals have common domains. It is worth noting that CRs were seen in previously irradiated areas, a rare finding in the head and neck salvage chemotherapy where the relatively high doses of radiotherapy delivered usually impair the access of cytotoxic drugs to the target tumor. No toxic deaths were reported and toxicity (mainly leucopenia and anemia) was moderate. In comparing our results with other studies we should note that in our series 20% of patients had epidermoid (type I) carcinomas and 75% had received chemotherapy as part of their primary treatment. Yeo et al. [10] reported a higher response rate (59%) in a series of 27 patients with undifferentiated (type III) or poorly differentiated (type II) nasopharyngeal carcinoma patients, but only 9 (33%) of them had prior chemotherapy. Tan et al. [11] reported an even higher 75% response rate in 32 metastatic (type III) nasopharyngeal carcinoma patients, all of them being chemonaïve. Median TTP with paclitaxel and carboplatin combination chemotherapy was 3.5 months in our series and 6-7 months in the asian studies. There were no striking differences in median survival between our series (11.5 months) and the two asian studies (12-13.9 months).

Other paclitaxel-based protocols are under evaluation in nasopharyngeal carcinoma patients in our institutions (paclitaxel+liposomal doxorubicin in Greece, paclitaxel+5 fluorouracil+folinic acid in Romania). The combination of paclitaxel with 5 fluorouracil and folinic acid proved only marginally active with a dissapointing 12.5% response rate and 7.3 months median survival in a series of 24 patients with refractory/ relapsed nasopharyngeal carcinoma treated at the Cancer Institute in Cluj [12].

We conclude that the combination of paclitaxel and carboplatin, administered in an outpatient setting, could represent a well tolerated, but only moderately active treatment option in relapsed or metastatic nasopharyngeal carcinoma patients.

References

1. Al Saraf M, Le Blanc M, Giri PG. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized Intergroup study 0099. J Clin Oncol 1998; 16: 1310-1317.
2. International Nasopharyngeal Cancer Study Group Vumca I Trial: Preliminary results of randomized trial comparing neoadjuvant chemotherapy (cisplatin, epirubicin, bleomycin) plus radiotherapy vs radiotherapy alone in stage IV (>N2, M0) undifferentiated nasopharyngeal carcinoma: A positive effect on progression-free survival. Int J Radiat Oncol Biol Phys 1996; 35: 569-577.
3. Forastiere AA, Shank D, Neuberg D et al. Final report of a phase II evaluation of paclitaxel in patients with advanced squamous cell carcinoma of the head and neck: An Eastern Cooperative Oncology Group trial (PA 390). Cancer 1998; 82: 2270-2274.
4. Fountzilas G, Athanassiades A, Samantas E et al. Paclitaxel and carboplatin in recurrent or metastatic head and neck cancer: A phase II study. Semin Oncol 1997; 24 (Suppl 2): S2-65, S2-67.
5. Fountzilas G, Athanassiades A, Kalogera-Fountzila A et al. Paclitaxel in combination with carboplatin or gemcitabine for the treatment of advanced head and neck cancer. Semin Oncol 1997; 24 (Suppl 19): S19-S32.
6. Hitt R, Hornedo J, Colomer R et al. Phase I-II study of escalating doses of paclitaxel + cisplatin with G-CSF (filgrastim) as first line therapy for head and neck carcinomas: Preliminary results. Proc Am Soc Clin Oncol 1995; 14: 300, A 868 (abstr).
7. Ciuleanu E, Todor N, Ghilezan N, Ciuleanu TE. A salvage regimen for relapsed nasopharyngeal carcinoma: paclitaxel and carboplatin. J BUON 1998; 3 (Suppl 1): 88, A 208 (abstr).
8. Ciuleanu TE, Ciuleanu E, Todor N, Ghilezan N. Paclitaxel and carboplatin salvage chemotherapy in relapsed nasopharyngeal carcinoma. Ann Oncol 1998; 9 (Suppl 4): 76, P365 (abstr).
9. Fountzilas G, Skarlos D, Athanassiades A et al. Paclitaxel by three hour infusion and carboplatin in advanced carcinoma of nasopharynx and other sites of head and neck. Ann Oncol 1997; 8: 451-455.
10. Yeo W, Leung TWT, Chan ATC et al. A phase II study of combination paclitaxel and carboplatin in advanced nasopharyngeal carcinoma. Eur J Cancer 1998; 34, 13: 2027-2031.
11. Tan EH, Khoo KS, Wee J et al. Phase II trial of a paclitaxel and carboplatin combination in Asian patients with metastatic nasopharyngeal carcinoma. Ann Oncol 1999; 10: 235-237.
12. Ciuleanu E, Ciuleanu TE, Todor N et al. Efficacy of paclitaxel in second line combination chemotherapy for relapsed nasopharyngeal carcinoma patients. Radioter Oncol Medic, 2001; 2: 192-196 (in Romanian).