A phase II study of carboplatin and paclitaxel for recurrent or metastatic head and neck cancer

Daris Ferrari[a], Jessica Fiore[a], Carla Codecà[a], Giuseppe Di Maria[a], Samuela Bozzoni[a], Veronica Bordin[a], Sarah Caldiera[a], Andrea Luciani[a], Sabrina Zonato[a], Irene Floriani[b] and Paolo Foa[a]

The aim of this study was to investigate the activity and safety of a regimen containing carboplatin and paclitaxel in patients affected by recurrent or metastatic head and neck cancer. Eligible patients were treated with a 3-week combination of paclitaxel 175 mg/m^2 and carboplatin area under the concentration time curve 5 mg/ml/min for a maximum of four cycles. A total of 27 patients entered the study. One patient (3.7%) had a complete response, whereas six patients (22.2%) obtained a partial response. Stable disease was observed in seven patients (25.9%). The disease control rate was 51.8% (95% confidence interval: 32.0–71.3), whereas overall response rate was 25.9% (95% confidence interval: 11.1–46.3). The median overall survival was 8.0 months (range: 2–27), with a 1-year survival of 30.5%. The median progression-free survival was 1.0 month (range: 0–14). Treatment-related deaths or episodes of neutropenic fever were not registered. Grades 3–4 neutropenia was observed in two patients (7.4%), grades 3–4 anaemia and thrombocytopenia in four (14.8%) and one (3.7%) patients, respectively. Nine patients (33.3%) experienced grades 1–2 and one patient (3.7%) grade 3 peripheral neuropathy. The combination of carboplatin and paclitaxel is safe and moderately effective for the treatment of recurrent or metastatic head and neck cancer. *Anti-Cancer Drugs* 20:185–190 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Division of Medical Oncology, San Paolo Hospital and [b]Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy

Correspondence to Dr Daris Ferrari, MD, San Paolo Hospital, via Di Rudinì 8, Milan, Italy
Tel: +39 02 818 43 159; e-mail: daris.ferrari@ao-sanpaolo.it

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Introduction

Head and neck cancer accounts for roughly 3% of newly diagnosed adult cancer in the United States and globally classifies as the seventh most common cause of cancer. The estimated number of newly diagnosed cases in 2008 in the United States is 35 000, with almost 600 000 cases each year occurring worldwide. [1,2] In Italy, about 75% of head and neck squamous cell carcinoma (HNSCC), the most common type of head and neck cancer, can be attributed to the combination of alcohol abuse and cigarette smoking [3].

At diagnosis, about 70% of patients have locally advanced disease (stages III–IVa/b), with large primary tumours and/or regional lymph node involvement (T3–4; N1–2). Treatment options include a combination of surgery, radiotherapy and chemotherapy, which accounts for a global 5-year survival rate ranging from 30 to 60%, according to the primary site. [1,4] Despite recent improvements in first-line multimodality approach to locoregionally advanced disease, many of these patients develop local relapse and/or distant metastases, which impair further curative treatment options. These patients, along with those presenting with metastatic disease at diagnosis, have dismal prognosis and are candidates only to palliative chemotherapy or, sometimes, to reirradiation.

HNSCC is usually considered chemosensitive, with a 68–72% overall response rate (ORR) achievable with triplets associating a taxane to the standard combination of cisplatin and 5-fluoruracil (PF). [5,6] In contrast, response rates to PF for recurrent and/or metastatic HNSCC (R/M HNSCC) are approximately 30% [7], whereas an ORR of 55% [13% complete responses (CRs)] can be achieved when a third agent, such as vinorelbine is added to PF [8]. Despite higher response rates with combination chemotherapy, several randomized trials have failed to show a statistically significant improvement in overall survival (OS) over monochemotherapy, [9–15] with a treatment-independent 1-year survival rate of 20%. Nonetheless, the potential benefit on the quality-of-life of clinical responses supports combination therapy, either PF or cisplatin/paclitaxel [16], with the former leading to higher toxicities. The choice of the regimen has to be done taking into account the patient's age, performance status, preexisting comorbidities and the tumour burden on vital organs or structures [17].

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The prognosis of patients with R/M HNSCC previously treated with systemic treatment usually is poorer than chemotherapy-naïve patients, because of increased risk of resistance of tumour clonogenic cells. This instance is very frequent as many patients undergo chemotherapy as part of a multimodality treatment (postoperative chemoradiotherapy for high-risk patients, neoadjuvant chemotherapy and exclusive concurrent chemoradiotherapy) [18]. For those patients whose recurrence occurs within short time from primary treatment, resistance to classic first-line treatment drugs (platinum compounds, 5-fluorouracil) limits further systemic treatment options. Taxanes can easily be included in second-line treatment as they have low cross-resistance with alkylating agents and antimetabolites and then higher probabilities of response compared with cisplatin, also with a better tolerability profile [19].

In this phase II study, we investigated the activity and safety of a combination of carboplatin and paclitaxel because a standard second-line chemotherapy for R/M HNSCC is still lacking and the experience with single agents in this background often results in low disease control rate. This study aims to determine whether this could be a valid treatment option for pretreated and clinically fit patients.

Patients and methods

Eligibility criteria

Eligible patients had histologically or cytologically proven recurrent or metastatic head and neck carcinoma not amenable to further surgical or radiation therapy, and were 18 years of age or older, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and a life expectancy of 3 months or longer. Patients had radiologically measurable or clinically evaluable disease and physical exam and radiographic studies had to be obtained within 28 days of registration. Any concurrent local therapy was not allowed, but concurrent palliative radiation therapy to nonmeasurable sites of disease such as painful bone metastasis was permitted. All eligible patients of a childbearing potential had to use effective contraception; that is, double barrier contraceptive methods.

Principal exclusion criteria were brain metastases pregnancy or lactation, and serum analysis within 28 days from registration showing leucocyte counts $\leq 3000/\mu l$, absolute neutrophil count (ANC) ≤ 1500, platelets $\leq 100\,000/\mu l$, calculated creatinine clearance ≤ 50 ml/min, or serum bilirubin or serum alanine transaminase and aspartate transaminase ≥ 2.0 upper limits of normal or ≥ 5.0 upper limits of normal if liver metastases were present. Patients were excluded in the case of prior malignancy except for adequately treated basal cell skin carcinoma, in-situ cervical carcinoma or any other primary solid tumour unless curatively treated more than 3 years before study entry and without active disease. Written informed consent was obtained from all patients.

Treatment plan

The scheduled regimen consisted of paclitaxel 175 mg/m^2 by 3-h infusion, followed by carboplatin at an area under the concentration time curve (AUC) of 5 mg/ml/min in a 30-min infusion. The dose of carboplatin was calculated by using the Calvert formula [20]. The schedule of administration of paclitaxel by 3-h infusion was chosen according to the European Organisation for Research and Treatment of Cancer (EORTC) phase II trial showing better response rate but heavy toxicities with the 24-h infusion of paclitaxel, at the dose of 175 mg/m^2 [21]. The fixed dose of this regimen, which was the same used in the EORTC trial, was confirmed as an ECOG trial showed the absence of a dose–response relationship for a specific dose range of paclitaxel (135–200 mg/m^2) when associated to a fixed dose of cisplatin [22]. All patients received premedication with dexamethasone, diphenhydramine, and H2 blockers. Antiemetics and granulocyte colony-stimulating factor (G-CSF) were used as needed.

Treatment cycles were repeated every 3 weeks, with clinical and radiological evaluation after two cycles; patients discontinued treatment if they had progressive disease, unacceptable toxicity or any other documented reason. Patients with responsive or stable disease (SD) continued treatment with two further cycles of chemotherapy, up to a maximum of four cycles. Criteria for treatment delay were ANC ≤ 1500 or platelets $\leq 100\,000/ml$ on day 1. Chemotherapy was then delayed weekly until complete recovery of blood cell count values. Other reasons for treatment delay were grade 2 neuropathy or higher. Dose reduction was permanent, with a standard dose reduction of 20% whenever ANC fell below 500/µl or platelets were less than 25 000/µl during treatment. Prophylactic use of G-CSF was not allowed.

Response assessment

History, physical examination and evaluation of toxicities were assessed on day 1 of every cycle and radiological assessment of measurable lesions was repeated every two cycles of chemotherapy. Tumour response was assessed according to Response Evaluation Criteria in Solid Tumours [23] and radiological confirmation of response was performed at 4–6 weeks, whereas systemic toxicity from treatment was graded according to World Health Organization criteria [24].

Statistical analysis

The primary endpoint was the disease control rate (DCR), defined as the proportion of patients whose best response rate was either partial response (PR) or CR or

SD, stating as a desirable DCR of at least 50% and an unacceptable DCR of less than 25%. Using the design proposed by A'Hern for binomial distribution, setting the probability of erroneous concluding that the DCR is greater than 25 at 10% (one-sided $\alpha=0.10$) and the probability of correct concluding that DCR is at least 50 at 90% (β error=0.10) it was necessary to have at least 26 eligible patients. The minimum number requested of SD/CR/PR is set at 10 out of 26, as this result is associated with a lower limit of the 80% confidence interval (CI) of 25.4%.

Secondary endpoints included ORR, defined as the proportion of patients whose best response rate was either PR or CR, occurrence of grades 3–4 toxicities, adverse reactions as well as progression-free survival (PFS) and OS. PFS was defined as the time from the date of enrollment up to the date of first progression, second primary malignancy or death from any cause, whichever came first. Patients not progressed or who were dead at the time of the analysis were censored at the last disease assessment date.

OS was defined as the time from the date of enrollment to the date of death from any cause. At the time of analysis, patients who were not reported as having died were censored at the date they were last known to be alive. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. According to a 'per-protocol' approach, all enrolled patients who met the eligibility criteria and did not present major violations while the study was being carried out were included in the analyses. Results are expressed as point estimates and their 95% CIs. To be consistent with sample size calculation only for the primary endpoint an 80% CI is shown, too. Analyses were carried out using SAS Software, version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

A total of 27 patients entered the study, 22 males and five females (Table 1), from November 2004 to March 2008, with a median follow-up of 23 months. None of the patients were excluded from the analysis because of major protocol violations. Their median age was 59.3 years (range: 31–79). All patients had a ECOG performance status of 0–1. Fifteen patients (55.6%) were affected by locoregional recurrence, nine patients (33.3%) had metastatic disease, whereas three patients (11.1%) had both locoregional and distant recurrences.

A total of 24 patients (88.9%) had received prior radiotherapy on primary tumour site, seven patients (25.9%) had received prior surgery and six patients (22.2%) had received both as part of their treatment plan. All patients had received previous chemotherapy, consisting of a platinum analogue and 5-fluoruracil. Thirteen patients (48.1%) received first-line chemotherapy as neoadjuvant treatment for locoregionally advanced disease, whereas 14 patients (51.9%) received chemotherapy in the context of recurrent or metastatic disease. Twenty out of 27 patients (74.1%) had disease progression or relapse within 6 months after chemotherapy completion and were defined as platinum refractory.

Table 1 Patients' characteristics

Number of patients	27
Median age (years)	59.3
Range	31–79
Sex	
Male (%)	22 (81.5)
Organ	
Nasal fossa (%)	1 (3.7)
Salivary gland (%)	1 (3.7)
Larynx (%)	5 (18.5)
Tongue (%)	10 (37.0)
Nasopharynx (%)	9 (33.3)
Hypopharynx (%)	1 (3.7)
Recurrence site	
Distant (%)	15 (55.6)
Locoregional (%)	9 (33.3)
Both (%)	3 (11.1)
Platinum and 5-FU first line	
Neoadjuvant locally advanced (%)	13 (48.1)
Relapsed/metastatic at diagnosis (%)	14 (51.9)

5-FU, 5-fluorouracil.

The most common site of primary tumour was the oral cavity, mainly originating from the tongue (37%), followed by nasopharynx (33.3%) and larynx (18.5%). A total of 78 cycles of chemotherapy was administered (mean 2.9, range 1–4); in seven patients (29.6%) chemotherapy was delayed as a consequence of haematological toxicity, whereas six patients (22.2%) underwent a permanent 25% dose reduction for both carboplatin and paclitaxel. The relative dose intensity was 67.9% of the programmed dose. There were two early deaths because of local disease progression. Both patients died after the first administration of chemotherapy and then were included in the response evaluation as nonresponders. There were no treatment-related deaths.

Response

The ORR was 25.9% (95% CI: 11.1–46.3), with a DCR of 51.8% (80% CI: 38.0–65.5; 95% CI: 32.0–71.3). One patient (3.7%) affected by metastatic nasopharyngeal carcinoma who relapsed 4 years after chemoradiation for T2 N1 disease had a CR, whereas six patients (22.2%) obtained a PR. SD was observed in seven patients (25.9%) (Table 2).

The median OS was 8.0 months (range: 2–27), with an estimated 1-year OS of 30.5%. The median PFS was 1.0 month (range: 0–14) (Fig. 1). A nonsignificant positive trend in OS [hazard ratio (HR): 0.57; 95% CI: 0.20–1.61; $P=0.290$] and PFS (HR: 0.67; 95% CI: 0.28–1.59; $P=0.368$) was observed for patients affected by nasopharyngeal carcinoma; a nonstatistically significant

difference in OS (HR: 1.01; 95% CI: 0.39–2.64; $P=0.977$) and a nonsignificant positive trend in PFS (HR: 0.80; 95% CI: 0.33–1.93; $P=0.617$) were highlighted between patients with locoregional or metastatic recurrence.

Toxicity

A total of 78 cycles of chemotherapy were administered to 27 patients, all considered evaluable for toxicities. The median number of cycles was 2.9 (range: 1–4). We observed neither treatment-related deaths, nor episodes of neutropenic fever.

Grades 3–4 neutropenia was observed in two patients (7.4%), whereas grades 3–4 anaemia and thrombocytopenia were observed in four (14.8%) and one (2.7%), respectively. G-CSF was administered to five patients in nine cycles and darbepoetin 150 μg weekly to three patients in six cycles. Neurotoxicity was the most common treatment-induced toxicity. Nine patients (33.3%) experienced grades 1–2 arm and leg paresthesias, numbness and difficulty in fine movements, whereas one patient (3.7%) who received the total dose of chemotherapy was affected by grade 3 neurotoxicity.

Table 2 Response to treatment ($n=27$)

Response	
Complete response (%)	1 (3.7)
Partial response (%)	6 (22.2)
Stable disease (%)	7 (25.9)
Progressive disease (%)	13 (48.2)
Objective response rate[a] (%)	7 (25.9; 95% CI: 11.1–46.3)
Disease control rate[b] (%)	14 (51.8; 80% CI: 38.0–65.5, 95% CI: 32.0–71.3)

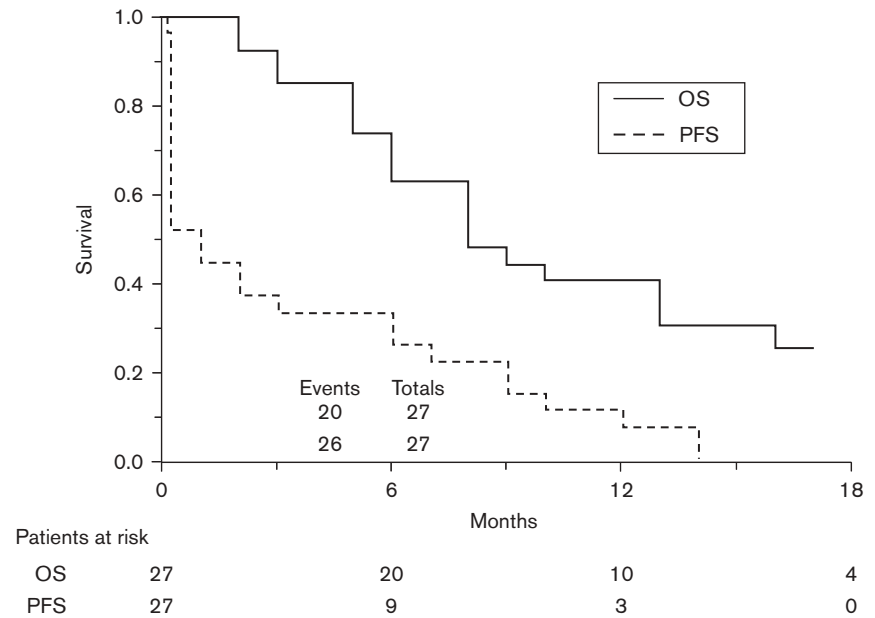
CI, confidence interval.
[a]Objective response rate: complete response and partial response.
[b]Disease control: complete response and partial response and stable disease.

Discussion

Locoregional or distant failures are still a frequent problem in HNSCC, in spite of the several advances that have been made in the past two decades in the management of locoregionally advanced disease at diagnosis. As active chemotherapy agents, including platinum compounds, 5-fluoruracil and taxanes, are frequently included as part of an aggressive and potentially radical primary treatment, only a few treatment options for recurrent disease are available, and the prognosis still remains dismal. Chemotherapy pretreated patients have an even poorer prognosis, as selective pressure on chemoresistant clonogenic cells precludes efficacy of systemic agents.

In this phase II study, we tested the activity and safety of the combination carboplatin-paclitaxel, which is a standard regimen for the treatment of other solid tumours, including non-small cell lung cancer, ovarian cancer and cancer of unknown primary site. As all enrolled patients had undergone prior chemotherapy, DCR was considered the principal end point of the study. We observed an ORR of 25.9%, with a DCR of 51.8%. As no statistically significant difference in OS between patients affected by locoregional failure and those with metastatic

Fig. 1



Kaplan–Meier estimate of progression-free survival (PFS) and overall survival (OS).

disease was recorded, in the latter group a trend towards better PFS was observed.

Median OS and PFS were 8.0 months and 1.0 month, respectively, a result in line with previous studies in the setting of chemotherapy-naïve R/M HNSCC patients; however, it has to be underlined that there was a consistent proportion of patients in the study affected by nasopharyngeal carcinoma, whose higher chemosensitivity can explain such a good result. [25,26] In contrast, 74.1% of patients were considered to be platinum refractory and this could justify the low PFS we reported.

Comparison with similar phase I–II studies (Table 3) is difficult because of differences in patient selection criteria and in treatment schedule. The regimen used in this study was effective at a relative minor cost in terms of toxicity, which should be kept as low as possible in the palliative setting. In particular, Dunphy *et al.* [27], Fountzilas *et al.* [28] and Clark *et al.* [29] reported response rates of 54%, 23% and 27%, respectively, but their series also included chemotherapy-naïve patients and higher doses of carboplatin and paclitaxel. Given these important differences, we reached similar response rates and even superior OS in pretreated patients using lower doses of drugs. Two other studies, by Stathopoulos *et al.* [30] and Moosmann *et al.* [31], applied the same doublet to previously treated patients, obtaining objective responses in 39% and 52% of cases, respectively. It has to be pointed out that in both these studies higher chemotherapy doses had been administered; in particular, Stathopoulos *et al.* [30] observed a higher response rate when compared with this study, but median OS was even inferior (7.0 months). Moosmann *et al.* [31] reported the excellent result of 52% ORR and 12.8 months OS, which can be related to the superior cumulative doses of carboplatin and paclitaxel in the 3-week period (carboplatin AUC 6 mg/ml/min–paclitaxel 240 mg/m^2); clearly this was obtained at the cost of higher toxicity.

The toxicity profile of our regimen was excellent, as we observed grades 3–4 neutropenia only in 7.4% of patients, with no episodes of neutropenic fever, and grades 1–2 neurotoxicity in 33.3%. When compared with the toxicities registered in the studies mentioned above (Table 4), the lower doses of chemotherapeutics we used resulted in a 67.9% relative dose intensity. Myelotoxicity in this study was acceptable while Clark *et al.* [29] registered neutropenic fever in 25% and Stathopoulos *et al.* [30] in 17% of cases. The incidence of chemotherapy-induced neuropathy can be considered similar to other studies.

From the evaluation of our results and the comparison with other studies in a similar background, it can be concluded that the association of carboplatin and paclitaxel is effective in pretreated patients suffering from HNSCC. Although in these patients ORR is lower than in first-line chemotherapy, treatment with a doublet can lead to a significant disease control. To avoid heavy toxicities, we tested a 3-week regimen with slightly lower doses than conventionally used, which resulted in a lower incidence of myelotoxicity and in the absence of febrile neutropenia. Even compared with a weekly schedule regimen, the association of carboplatin AUC

Table 3 ORR and OS in similar studies

Study principal investigator	Treatment schedule	Patient population	Number of patients	OS (months)	ORR (%)
[26]	C: AUC 7.5 mg/ml/min P: 150–265 mg/m^2 Every 21 days	Newly diagnosed phase I	33	–	54
[29]	C: AUC 7 mg/ml/min P: 200 mg/m^2 Every 21 days	Recurrent/ metastatic second line	24	7.0	39
[27]	C: AUC 7 mg/ml/min P: 200 mg/m^2 Every 28 days	Recurrent/ metastatic first line	49	7.3 non-NPC	23 non-NPC 57 NPC
[28]	C: AUC 6 mg/ml/min P: 200 mg/m^2 Every 21 days	Recurrent/ metastatic first line	37	4.9	27
[30]	C: AUC 2 mg/ml/min P: 80 mg/m^2 Weekly	Recurrent/ metastatic second line	31	12.8	52
This study	C: AUC 5 mg/ml/min P: 175 mg/m^2 Every 21 days	Recurrent/ metastatic second line	27	8.0	25.9

AUC, area under the concentration time curve; C, carboplatin; ORR, overall response rate; OS, overall survival; NPC, nasopharyngeal cancer; P, paclitaxel.

Table 4 Reported toxicities in other similar studies

Study principal investigator	Treatment schedule	Grades 3–4 neutropenia (%)	Grades 1–2 neurotoxicity (%)
[26]	C: AUC 7.5 mg/ml/min P: 150–265 mg/m^2 Every 21 days	67	17
[27]	C: AUC 7 mg/ml/min P: 200 mg/m^2 Every 28 days	4[a]	49
[28]	C: AUC 6 mg/ml/min P: 200 mg/m^2 Every 21 days	38	32
[30]	C: AUC 2 mg/ml/min P: 80 mg/m^2 Weekly	22.6	–
This study	C: AUC 5 mg/ml/min P: 175 mg/m^2 Every 21 days	7.4	33.3

AUC, area under the concentration time curve; C, carboplatin; P, paclitaxel.
[a]Prophylactic use of granulocyte colony-stimulating factor.

5 mg/ml/min and paclitaxel 175 mg/m^2 every 3-weeks was better tolerated in terms of haematological complications. Although the prognosis of patients suffering from R/M HNSCC still remains poor, in a subset of fit patients a second-line chemotherapy with an association regimen can still offer a valuable clinical benefit and a reasonable toxicity profile. Further investigations are warranted in a scenario that should also include novel biological agents.

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