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ORIGINAL ARTICLE

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Weekly cisplatin paclitaxel and continuous infusion fluorouracil in patients with recurrent and/or metastatic head and neck squamous cell carcinoma: a phase II study

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Abstract *Background*: Cisplatin, paclitaxel and 5-fluorouracil (5-FU) have demonstrated significant activity in patients with advanced squamous head and neck cancer (HNSCC) despite relevant toxicity. A weekly administration of cisplatin and paclitaxel with continuous infusion of 5-FU could offer a better toxicity profile without affecting dose intensity or treatment outcome. We evaluated the toxicity and the activity of weekly cisplatin/paclitaxel with continuous infusion 5-FU in patients with recurrent and/or metastatic HNSCC. *Methods*: A total of 44 patients were studied. Treatment consisted of two 6-week cycles with weekly cisplatin 20 mg/m^2 and paclitaxel 60 mg/m^2 and daily continuous infusion 5-FU 200 mg/m^2 from day 1 to 42. Patients were evaluated for toxicity and response. *Results*: 40 out of 44 patients were evaluable for response. After two cycles we observed seven complete responses (16%) and 12 partial responses (27%), with a 43% (95% CI 28–58%) overall response rate. Stable disease was seen in 13 patients (29%) and progressive disease in 12 patients (27%). Toxicity was mild in treated patients: we observed less than 10% of grade 3/4 hematological and gastroenteric toxicity. *Conclusions*: A weekly schedule of cisplatin and paclitaxel associated with continuous infusion 5-FU showed low toxicity in the treatment of advanced HNSCC while significant activity was conserved.

Keywords Palliative chemotherapy · Head and neck cancer · Toxicity · Weekly chemotherapy · Phase II

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is a common tobacco-related tumor. The estimated incidence is about 500,000 new cases per year world-wide [1]. Most patients have advanced disease at diagnosis at primary and nodal sites (WHO stage III and IV). Surgery and radiotherapy are considered the standard local treatments in these patients; however, the 2-year locoregional recurrence rate is high (50–60%) and 30% of patients develop distant metastasis. Finally, the 5-year survival rate is only 30% [2, 3].

Patients with locoregional recurrence or metastatic disease after definitive treatment are eligible for palliative systemic chemotherapy. The main goal of these treatments is the palliation of pain and other symptoms with the lowest impact on the quality of life even though a survival advantage for palliative chemotherapy versus best supportive care has been reported [4].

There is no true standard palliative therapy in these patients. Methotrexate (MTX) is often considered the control arm in phase III randomized trials, while cisplatin and infusional 5-fluorouracil (5-FU) in combination (PF) is an alternative option for fit patients. Indeed randomized trials (PF vs MTX) have failed to show superiority of PF in terms of survival over MTX (response rate 33% vs 10%, median survival 6.6 months vs 5.6 months) with increased toxicity [5]. New drugs and new combinations and schedules in chemotherapy regimens should be investigated in clinical trials in these patients [6].

Paclitaxel has shown significant activity both as a single agent [7–9] and in combination chemotherapy in HNSCC with the response rate varying from 20% to 40% [10, 11]. A three-drug combination regimen has shown significant toxicity in previous studies [12–14]. Cisplatin, paclitaxel and 5-FU have been evaluated in phase I and phase II studies with response rates ranging between 38% and 60%. Weekly chemotherapy administration has been proposed in order to reduce toxicity

and/or increase the dose intensity of chemotherapy [15, 16]. Finally, 5-FU has shown greater activity and less toxicity when administered as continuous infusion [17]. Phase I studies testing the weekly administration of cisplatin and paclitaxel with infusional 5-FU have been performed in esophageal cancer [18, 19].

The aim of this study was to evaluate a three-drug regimen with weekly administration of cisplatin, and paclitaxel together with a continuous infusion of 5-FU in HNSCC patients with recurrent or metastatic disease. The primary endpoints were tumor response and qualitative and quantitative toxicity assessment; secondary endpoints were time to progression and overall survival.

Methods

Eligibility and exclusion criteria

Patients with histologically proven recurrent or metastatic HNSCC not eligible for further surgical or radiation therapy, 18 years of age or older, with an ECOG performance status less than or equal to 2 and a life expectancy of at least 3 months were eligible for this study.

Patients had bidimensionally measurable disease as determined by physical examination and/or radiographic studies obtained within 28 days of registration. Patients could have received prior radiation or surgical therapy up to 3 weeks before registration but had to have recovered from all acute toxicities related to these therapies. Concurrent hormonal, biological or radiation therapy to measurable lesions were not allowed.

Patients with brain metastasis, with prior chemotherapy treatment, pregnant or lactating, or with baseline serum laboratory tests within 28 days before registration showing leukocyte counts less than 4000/μl, absolute neutrophil count (ANC) less than 1500/μl, platelets less than 100,000/μl, calculated creatinine clearance less than 50 ml/min, serum bilirubin or serum glutamic oxaloacetic transaminase or serum glutamic pyruvic transaminase greater than twice the institutional upper limits of normal or greater than four times the upper limits of normal if liver metastases were present were excluded. Among exclusion criteria were prior malignancies, except for adequately treated basal cell skin carcinoma, in situ cervical carcinoma or other malignancy for which the patient had been disease-free for 5 years.

Written informed consent was obtained from all patients. The study was approved by the local ethics committee.

Treatment plan

Patients were scheduled to receive 20 mg/m^2 of cisplatin and 60 mg/m^2 of paclitaxel by 2-h infusions on days 1, 8, 15, 22, 29 and 36, together with a 200 mg/m^2 per day 5-FU as a continuous infusion from day 1 to day 42. The treatment cycle was repeated after 8 weeks. Clinical evaluation was repeated after every cycle, and radiological evaluation was performed after two courses of 6 weeks or when progression was clinically suspected. Patients with progressive disease (PD) were taken off treatment; patients with a complete response (CR) or partial response (PR) or stable disease (SD) received further cycles (up to four).

All patients received premedication with dexamethasone, diphenhydramine and ranitidine before each paclitaxel administration. Ondansetron was administered as an antiemetic treatment. Saline solution 500 ml and mannitol 18% 125 ml were administered before and after cisplatin infusion. Prophylactic granulocyte colony-stimulating factor (G-CSF) administration was not allowed. Epoietin alpha (EPO) and iron support were given when hemoglobin was <10 g/dl in most patients. All patients were supplied with Groshong or Port-a-Cath type implanted central venous access (CVC) devices. Patients were taken off treatment for unacceptable toxicity, PD during treatment or any other documented reason.

Chemotherapy dose modifications and delays were based on ANC and platelet counts and other toxicities. The standard dose reduction levels (-1) were 16 mg/m^2 for cisplatin, 48 mg/m^2 for paclitaxel and 160 mg/m^2 for 5-FU, respectively. If ANC was less than 1500/μl or platelets were less than 100,000/μl then chemotherapy was delayed on a weekly basis. If ANC was less than 500/μl or platelets were less than 25,000/μl at any time during the treatment, all drugs were reduced to the -1 dose level. In cases of gastrointestinal toxicity or stomatitis of more than grade 1, 5-FU was reduced to the -1 dose level. Chemotherapy was delayed on a weekly basis for grade 2 or higher peripheral neuropathy. After a delay of two consecutive weeks, the patient was excluded from the study.

Response assessment

Patients underwent history and physical examinations before therapy. Toxicity was assessed at weekly intervals during therapy. All patients were clinically reassessed every cycle. Measurable disease was evaluated by radiographic imaging after two and four cycles of therapy, or in all cases of clinically presumed progression.

All patients were followed until death. Responses were determined by the WHO recommendations [20] with amendments according to EORTC procedures [21]. CR was defined as the complete disappearance of all measurable and evaluable disease, without new lesions and disease-related symptoms for at least 4 weeks. PR was defined as a greater or equal to 50% decrease in the sum of the products of the perpendicular dimensions of all measurable lesions, or 30% for unidimensional lesions, and no progression of evaluable disease without new lesions for al least 4 weeks. SD was defined when

CR, PR or progression were absent. PD was defined as a greater than 25% increase in the sum of the products of the perpendicular dimensions of all lesions, the appearance of any new lesion, or a clear worsening of evaluable disease.

Response duration was measured from the date of PR or CR to the date of PD. Time to progression was measured from the date of registration to the date of the first observation of PD, and survival was measured from the date of entry into the study until death or considered to be the date the patient was last observed.

Toxicity was defined according to the WHO criteria [21]. All events occurring during chemotherapy or with a worsening grade in comparison with baseline were considered toxicities.

Statistical analysis

The primary endpoints of this phase II study were to evaluate the overall toxicity and response rate (intent to treat analysis). Patients' characteristics before and after therapy, the safety profile of the treatment and response rate were analyzed using descriptive methods. According to the optimal two-stage phase II study design of Simon [22], the sample size was assessed in order to reject response rates of $< 20\%$ (p0) and to provide a statistical power of 80% in assessing the activity of the regimen as a 40% response rate. The upper limit for the first-stage drug rejection was three responses out of the first consecutive 13 patients, and the upper limit of the second-stage rejection was 12 responders out of 43 consecutively enrolled patients.

Response duration, time to progression and survival were assessed using Kaplan-Meier survival curves. A two-sided significance at the 5% level was applied to all tests. All statistical analyses were performed using the Statistica for Windows software program.

Results

Patients and treatment

Between January 2000 and March 2003, 44 patients (35 males and 9 females) were evaluated (Table 1). Their median age was 59 years (with a range 39–71 years). The ECOG performance status was zero in 17 patients, one in 22 patients and two in 5 patients. Of the 44 patients, 29 (66%) had received surgery followed by postoperative radiation therapy before enrollment in this study. Of the remaining patients, 4 had received exclusive surgical treatment, 7 had received exclusive radiotherapy treatment, and 4 were previously untreated and had metastatic spread at presentation. No patients received prior systemic chemotherapy, either in the adjuvant, neoadjuvant or palliative setting.

Table 1 Patients and disease characteristics

Characteristic ($n = 44$)		No. of patients	%
Age (years)			
Median	59		
Range	39–71		
Sex			
Female/male		9/35	20/80
Performance status			
0		17	39
1		22	50
2		5	11
Site of primary tumor			
Oral cavity		17	39
Oropharynx		9	20
Larynx		17	39
Hypopharynx		1	2
Nasal sinus		1	2
Occult		1	2
Tumor location			
Locoregional		38	86
Distant metastasis		4	9
Both locoregional and distant		2	5
Previous therapy			
Surgery and radiotherapy		29	66
Radiotherapy		7	16
Surgery		4	9
None		4	9

The primary tumor site was oral cavity in 17 patients (39%), oropharynx in 9 patients (20%), larynx in 17 patients (39%), hypopharynx in 1 patient (2%), unknown primary site in 1 patient (2%), and nasal sinus in 1 patient (2%); 2 patients had two sites of disease. At the beginning of the trial 36 patients had inoperable locoregional disease, 4 patients showed evidence of only distant metastasis, and 4 patients had both locoregional and distant metastatic disease (Table 1).

In previously treated patients, the median treatment-free interval was 426 days. All 44 patients enrolled were included in tumor response calculations based on an intent-to-treat analysis. There were four early deaths: three patients suffered an early decline of performance status correlated with clinical tumor progression so chemotherapy was discontinued, and one patient died from the complications after grade 4 diarrhea. All these patients died during first cycle of chemotherapy and never underwent response evaluation, but were considered non-responders based on the intent-to treat analysis.

Patients received 415 of the planned 528 weeks of chemotherapy (79%). The median number of weeks was 12 (range 1–12). The median relative dose intensity for cisplatin and paclitaxel was 91% (range 8–100%). The median relative dose intensity for 5-FU was 85% (range 8–100%). Dose reduction was more common for 5-FU than for cisplatin and paclitaxel. The most frequent reasons for treatment delay were hematological toxicity and gastrointestinal toxicity. The most common reason of 5-FU dose reduction was gastrointestinal toxicity (stomatitis and diarrhea).

Toxicity

Grade 3/4 toxicity was associated with 28 of the 415 weeks of chemotherapy administration (7%). There was one treatment-related death (2%) consequent upon a grade 4 diarrhea. Three patients showed an early progression of disease and died before the first cycle was completed without treatment-related toxicity. They showed worsening of asthenia, performance status and symptoms suggesting PD. Treatment was therefore discontinued but the terminal event preceded any instrumental evaluation of progression.

Four patients (10%) developed grade 3/4 neutropenia after nine chemotherapy administrations (2%). A single case of febrile neutropenia was recorded. Grade 1/2 neutropenia was present after 28 chemotherapy administrations (7%). Grade 1/2 anemia was reported in 9% of patients (37 weeks of administration) and ten patients (23%) required EPO alpha support. Grade 3/4 anemia affected four patients (9%) after 1% weeks of chemotherapy and only one patient required a red blood cell transfusion. Grade 1/2 thrombocytopenia was recorded after 1% of chemotherapy administrations and grade 3/4 in one patient (2%) after a single administration.

Nausea and vomiting grade 1/2 was recorded after 58 chemotherapy administrations (14%) and stomatitis after 43 chemotherapy administrations (10%). Grade 3/4 vomiting and stomatitis were both recorded in two patients (5%) and three patients (7%), respectively, after five (1%) and four (1%) chemotherapy administrations. Grade 1/2 diarrhea was present after 44 administrations (11%) while grade 3/4 diarrhea affected two patients (4%) after three chemotherapy administrations (1%); one of these died from subsequent cardiovascular complications.

Grade 2 nephrotoxicity was observed in a single patient and this patient was withdrawn from treatment.

Neurotoxicity (grade 1/2) appeared in six patients (14%) and one patient (2%), respectively. Two patients (5%) suffered grade 3/4 alopecia. No grade 3/4 myalgias or arthralgias were observed; however, mild asthenia was common. No serious allergic reactions were observed.

Finally, five patients (11%) experienced CVC complications due to an infection in four (9%) and a thrombosis in one (2%). Toxicities is shown in Table 2.

Table 2 WHO toxicity per patient

Adverse event	No. (%) of patients ($n=44$)				
	Total	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	19 (43)	7 (16)	8 (18)	2 (5)	2 (5)
Thrombocytopenia	4 (9)	2 (5)	1 (2)	1 (2)	–
Anemia	17 (39)	12 (27)	1 (2)	3 (7)	1 (2)
Nausea	25 (57)	12 (27)	10 (23)	2 (5)	1 (2)
Vomiting	14 (32)	8 (18)	4 (9)	1 (2)	1 (2)
Stomatitis	18 (41)	7 (16)	8 (18)	3 (7)	–
Diarrhea	13 (30)	7 (16)	4 (9)	1 (2)	1 (2)
Constipation	6 (14)	5 (11)	1 (2)	–	–
Neuropathy	7 (16)	6 (14)	1 (2)	–	–
Nephropathy	1 (2)	–	1 (2)	–	–
Alopecia	8 (18)	4 (9)	2 (5)	1 (2)	1 (2)
Skin toxicity	3 (7)	3 (7)	–	–	–
Asthenia	13 (30)	7 (16)	6 (14)	–	–
CVC infection	3 (7)	–	–	–	–
CVC thrombosis	1 (2)	–	–	–	–

Response

We were able to evaluate the response in 40 out of 44 patients; four patients, who did not complete the first course of therapy were considered non-responders in the intention to treat analysis.

Among evaluable patients, 7 (16%) displayed a CR and 12 (27%) a PR with an overall response rate of 43% (95% CI 28–58%), 13 (30%) exhibited SD as the best response, and 8 (18%) showed PD during or at the end of treatment to give a total treatment failure of 27% (Table 3).

Table 3 Overall response rate (WHO) among 44 patients

Response	No. of patients	%
CR	7	16
PR	12	27
CR + PR	19	43
SD	13	30
PD	8	18
Failure (early death or discontinuation)	4	9
PD + failure	12	27

Among those with CR, five had only locoregional disease and two remained disease-free at the time of data elaboration. Two patients with CR showed only distant metastasis (lung) and one was still disease-free at the time of this report. The median overall survival was 9 months (Fig. 1).

The median duration of response was 5 months (range 1–26 months) with a median overall time to progression of 7 months (Fig. 2). The overall 1-year survival rate was 40%.

Discussion

Patients with recurrent or metastatic HNSCC still have a poor prognosis. Chemotherapy has been extensively used in these patients and many agents have been shown to be active in this disease. Two-drug combination chemotherapy with cisplatin and 5-FU achieves about 30% of objective responses as found in a series of randomized clinical studies [4]. Single-drug chemotherapy [23, 24] and two-drug associations have been studied in phase II trials with response rates ranging between 10% and 40% [25–29]. In a phase III study comparing the cisplatin/5-FU combination with the cisplatin/paclitaxel combination [30], no significant difference in efficacy was shown between the two regimens; however, the cisplatin/

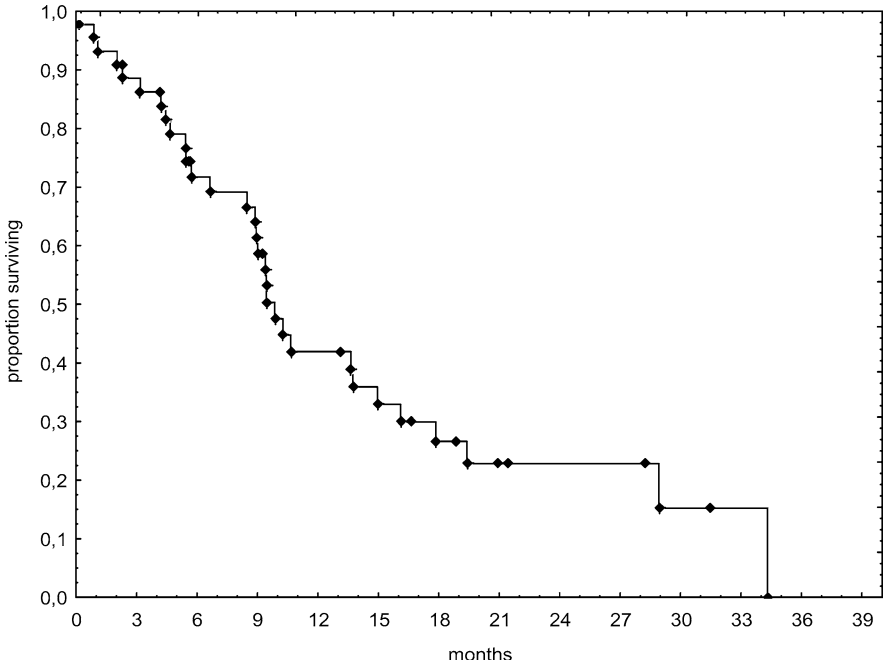

Fig. 1 Kaplan-Meier median overall survival

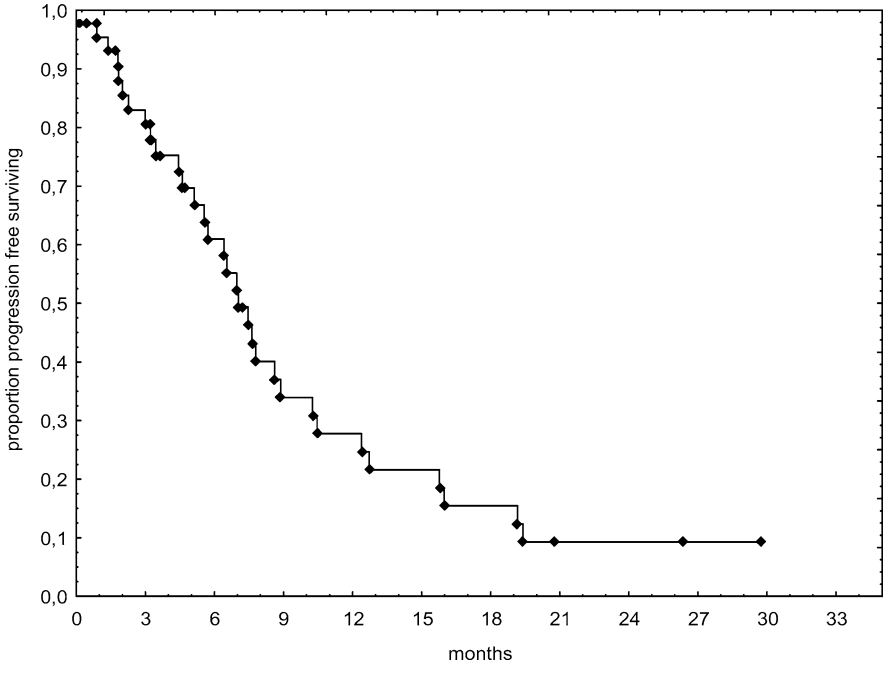

Fig. 2 Median overall time to progression

paclitaxel therapy was associated with decreased toxicity. Three-drug combinations in phase II studies have shown even higher response rates but are associated with a worse toxicity profile, with considerable hematological grade 3/4 toxicity [12–14].

In our study we assessed a three-drug combination comprising a weekly schedule of cisplatin and paclitaxel administered with a continuous infusion of 5-FU. This particular schedule showed a very interesting toxicity profile, with prevalence of grades 1 and 2 hematological and gastrointestinal toxicity. Grades 3 and 4 toxicity were rare, with prevalence of hematological toxicity: only one case of febrile neutropenia was recorded and the period of neutropenia was short. Gastrointestinal grades 2 and 3 toxicity, diarrhea and stomatitis, required 5-FU dose reduction, while nausea and emesis were well controlled with premedication. Five patients (11%) had complications related to the CVC: four showed infection possibly due to management mistakes and involved patients carrying a Groshong type of CVC. This relatively high rate of CVC complications could be a limitation of this infusion regimen; however the use of a reservoir CVC (Port-a-Cath type) and thrombosis prevention could reduce the incidence of CVC complications.

The median relative dose intensities were 91%, 91% and 85% for cisplatin, paclitaxel and 5-FU, respectively,

with more frequent 5-FU dose reductions due to stomatitis or diarrhea. In chemotherapy-naive patients, this combination produced an interesting response rate with 7/44 CR and 12/44 PR. The median duration of response was 5.5 months and median time to progression was 7 months. The median survival was 9 months and 40% of patients survived more than 1 year. These response rate results demonstrate that the predicted dose intensity of the three drugs administered in this weekly schedule is adequate and allows an efficacious dose intensity to be administered.

In conclusion, the three-drug combination studied in this phase II trial administered in the schedule described here showed high tolerability in comparison to the toxicity observed in 3-weekly triple regimens. Moreover, the weekly schedule did not result in any impairment of response rate and survival compared to 3-weekly schedules [12, 13]. Hence, due to the very favorable toxicity profile, this weekly schedule may be better tolerated even in poor-risk patients.

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