Paclitaxel is effective in relapsed head and neck squamous cell carcinoma: a retrospective study of 66 patients at a single institution

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The standard first-line treatment of recurrent/metastatic head and neck squamous cell carcinoma is cisplatin-based chemotherapy, but taxanes can also be beneficial after progression or in patients not eligible for cisplatin. The objective of this retrospective study was to evaluate paclitaxel in this population. We reviewed 66 patients who were treated with paclitaxel at a single institution (Lyon, France) between January 2003 and November 2008. Paclitaxel was administered as first, second or more line of treatment; alone or in combination with carboplatin or cetuximab; every 3 weeks (175 mg/m^2) or weekly (80 mg/m^2). Forty-six (70%) patients received paclitaxel as first-line therapy after relapse and 26 (39%) patients as monotherapy. The objective response rate was 30% [95% confidence interval (CI): 20–43%]; 37% (95% CI: 23–52%) in the first line after relapse, and 20% (95% CI: 4–48%) in the second line. Rates were 19% (95% CI: 7–39%) after monotherapy and 36% (95% CI: 20–55%) after combination with carboplatin. Two of the six patients receiving cetuximab had a partial response. The overall survival of all patients was 7.2 months (95% CI: 5.2–8.8). Paclitaxel can be used in symptomatic patients. Although no improvement of overall survival can be expected, paclitaxel treatment is safe and achieves interesting response rates. ***Anti-Cancer Drugs*** **21:553–558 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2010, **21**:553–558

Keywords: cisplatin failure, paclitaxel, recurrent head and neck cancer

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Received 10 November 2009 **Revised form accepted** 10 February 2010

Introduction

Head and neck squamous cell carcinoma (HNSCC) accounts for 5% of newly diagnosed cancers in adults in the United States and 8% of cancers worldwide [1]. Most patients present with locally advanced disease and, despite aggressive and optimal plurimodality treatment with surgery, radiotherapy and chemotherapy, about one third to 50% of patients in Western countries relapse. Although HNSCC is initially chemosensitive [induction chemotherapy with a combination of cisplatin, fluorouracil (5-FU), and docetaxel leads to 70% response] [2,3], results are poor after relapse. Monotherapy with methotrexate achieves 10–16% response rate with an overall survival of approximately 6 months [4,5]. Although higher response rates are obtained with combination chemotherapy (around 25%), numerous randomized trials have failed to show a statistically significant improvement of overall survival [4,6,7]. Cisplatin achieves better response rates than carboplatin and there is also a trend for better survival, although no definitive evidence has been reported in published randomized clinical trials [4]. Relapsing patients often have a local recurrence and symptoms such as trouble in swallowing, eating and speaking. Despite no increase in overall survival, cisplatin-based chemotherapy, whenever it is possible, is associated with higher objective response and could therefore be beneficial for the patient and improve quality of life. Recently, a new standard of treatment has been proposed for patients in relapse. A clinical study with the combination of cisplatin, 5-FU, and cetuximab has shown a significant increase in overall survival at 10.1 months [8]. The response rate is also enhanced. However, only few patients are candidates for this combination because many have poor performance status (2 or 3) at relapse, and many have received initial treatment with cisplatin and are not eligible for reintroduction because of neuropathy, renal deficiency or rapid progression after platinum-based treatment. After failure of a platinum-based chemotherapy, taxanes may offer some clinical benefit for the patients. Several studies have shown the efficacy of taxanes used as monotherapy or in combination with cisplatin or carboplatin. The objective of this retrospective study was to assess the efficacy of paclitaxel used alone or in combination with carboplatin or cetuximab in patients with recurrent/metastatic HNSCC treated at a single institution.

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Patients and methods

Retrieval procedure and file selection

We retrospectively reviewed the data of all patients with histologically confirmed HNSCC treated by paclitaxel at our institution between January 2003 and November 2008. Most patients had received at least one earlier chemotherapy regimen including cisplatin (possibly given in induction or in combination with radiotherapy), and were progressive at the time of starting paclitaxel.

Treatment

Different treatment regimens were used: either paclitaxel alone, or a combination of paclitaxel with cetuximab or carboplatin. When used alone or in combination with cetuximab (400 mg/m^2 then 250 mg/m^2 weekly), paclitaxel was given weekly at a dose of 80 or 60 mg/m^2 administered as a 1-h intravenous infusion. When combined with carboplatin (area under the curve = 5, every 3 weeks), paclitaxel was given at a dose of 175 mg/m^2 administered as a 3-h intravenous infusion every 3 weeks.

The type of chemotherapy was determined as follows. In first line, patients sensitive to platinum but ineligible for cisplatin (for combination with 5-FU ± cetuximab) received the combination of carboplatin and paclitaxel (weekly administration with demonstrated superiority [9,10]). Other first-line patients or patients treated in second line after developing resistance to platinum received weekly paclitaxel monotherapy. Since the American Society of Clinical Oncology 2007 meeting, patients not treated with cetuximab in first line have received a weekly combination of paclitaxel and cetuximab [11].

For each course of paclitaxel (q1w or q3w), premedication with 20 mg of dexamethasone, 50 mg of ranitidine, 5 mg of dexchlorphreniramine, and 8 mg of ondansetron or 20 mg of metoclopramide was administered. All patients were required to have adequate hematological and hepatic functions before treatment.

Response was evaluated every 6–8 weeks by repeated clinical and CT scan assessments based on the extent of disease at presentation. Antitumor activity was evaluated according to the Response Evaluation Criteria In Solid Tumors criteria (version 1.1 [12]).

Statistical design

The response rate was estimated as the proportion of patients who achieved a complete or partial response in the total number of patients who had received at least one cycle of paclitaxel. Overall survival (OS) was defined as the time from the date of first paclitaxel administration to the date of death. Progression-free survival (PFS) was calculated from the date of first paclitaxel administration to the date of disease progression or death or to the date of last follow-up for patients alive without progression at last contact. Survival distributions were estimated by the Kaplan–Meier method.

Results

Patient characteristics

Between January 2003 and November 2008, 66 patients with histologically confirmed HNSCC were treated at the Centre Léon Bérard (Lyon, France) with a paclitaxel-based chemotherapy (60 patients since January 2005). Patients' characteristics are summarized in Table 1. Patients were mainly men (59 patients, 89%) with a median age of 60.7 years at onset of paclitaxel.

The two most common sites of primary tumor were the hypopharynx (20 patients, 30%) and the oropharynx (20 patients, 30%). Tumors were advanced at the time of initial diagnosis, with seven (11%) patients with metastases, 37 (56%) patients with stage IVa or IVb tumors and 13 (20%) with stage III.

Initial treatment consisted of neoadjuvant platinum-based chemotherapy (without paclitaxel) for 18 (27%) patients; 40 (61%) patients received surgery and 52

Table 1 Patient characteristics at onset of palliative treatment with paclitaxel (unless otherwise indicated)

	N	%
Median age, years (range)	60.7 (36.4–88.2)	
Sex		
Female	7	11
Male	59	89
Localization at initial diagnosis		
Oral cavity	12	18
Oropharynx	20	30
Hypopharynx	20	30
Larynx	8	12
Nasopharynx	2	3
Neck nodes of unknown origin	4	6
Tumor stage at initial diagnosis		
I	1	1
II	7	11
III	13	20
IVa	35	53
IVb	2	3
IVc	7	11
Unknown	1	1
Initial treatment		
Neoadjuvant chemotherapy (without paclitaxel)	18	27
With docetaxel	2	3
Surgery	40	61
Radiotherapy	52	79
Alone	13	20
With chemotherapy or cetuximab	35	53
Unknown	4	6
No previous treatment	11	17
Pattern of disease		
Primary metastatic	7	11
Primary locally advanced (palliative treatment)	4	6
Relapse	55	83
Local only	38	58
Metastatic only	10	15
Local and metastatic	7	11
Performance status at onset of paclitaxel		
0	4	6
1	34	51
2	20	30
3	7	11
4	1	1

(79%) received radiotherapy, mostly in combination with chemotherapy (35 patients, 53%).

Recurrence was localized, metastatic or both for, respectively, 38, 10, and seven of the 55 relapsing patients. Of the 38 patients with localized relapse, 13 received surgery and 10 were irradiated before second failure.

On account of the pattern of relapse, many patients experienced serious symptoms at the beginning of paclitaxel therapy, with 28 (42%) patients with performance status ≥ 2.

Paclitaxel delivery and safety

Data about paclitaxel delivery are summarized in Table 2. All patients received paclitaxel for palliation. Most ($N=46$, 70%) received paclitaxel as the first line of palliative chemotherapy; of these, nine were naive of any treatment for head and neck cancer. The other 20 (31%) patients received paclitaxel for second-line or subsequent chemotherapy.

Paclitaxel was used as monotherapy in 26 (39%) patients whereas 40 (61%) received a combination chemotherapy with carboplatin (33 patients, 50%) or cetuximab (six patients, 9%). Paclitaxel-based chemotherapy was safe. Patients were treated for a median of 8 weeks (0–67). Only 16 (24%) needed a dose reduction and eight (13%) had to stop treatment (three were taken off treatment after dose reduction, and three because of an infection not related to paclitaxel) (Table 3).

Efficacy

As shown in Table 4, the overall response rate according to the Response Evaluation Criteria In Solid Tumors criteria was 30% (95% CI: 20–43%). Paclitaxel-based chemotherapy produced a clinical benefit in 67% of the cases, with the best response being stable disease in 24 (36%) patients. Twenty (30%) patients progressed and two (3%) were not evaluable for response. In the first line, the overall response rate was 37% (95% CI: 23–52%). Results for other lines are not reliable because of the small number of patients and the too large confidence interval [in second line, 20% (95% CI: 4–48%)]. Monotherapy with paclitaxel, which was often performed after failure of cisplatin-based chemotherapy, achieved a response rate of 19% (95% CI: 7–39%). First-line combination treatment with carboplatin achieved a response rate of 36% (95% CI: 20–55%).

The PFS and OS of the 66 patients who were followed are presented in Fig. 1. The median PFS was 3.9 months (95% CI: 2.6–4.8 months) and the median OS was 7.2 months (95% CI: 5.2–8.8 months).

Table 2 Delivery of paclitaxel as palliative treatment

	N	%
Previous lines of chemotherapy		
0	46	70
First treatment of an advanced disease	9	
Relapse of a previously treated disease	37	
1	15	23
2 or more	5	8
Regimen		
Monotherapy	26	39
Combination	40	61
Carboplatin	32	48
Cetuximab	6	9
Carboplatin and cetuximab	1	2
Other (erlotinib)	1	2
Dose (mg/m^2)		
60 (q1w)	17	26
80 (q1w)	40	61
175 (q3w)	8	12
225 (q3w)	1	2

Table 3 Toxicity of paclitaxel-based chemotherapy (detailed toxicities with common terminology criteria for adverse events grading were not available for this retrospective study and only dose reduction or cessation of treatment are indicated)

	N	%
Median duration of administration, weeks (range)	8 (0–67)	
Any grade toxicity leading to modification of treatment	21	32
Dose reduction	16	24
Stop of treatment	8	13
After dose reduction	3	
Not related to paclitaxel	3	
Type of toxicity ($N=21$)		
Neutropenia	7	11
Febrile neutropenia	1	
Infection without neutropenia	3	5
Neuropathy	7	11
Asthenia	3	5
Elevation of transaminases	1	1

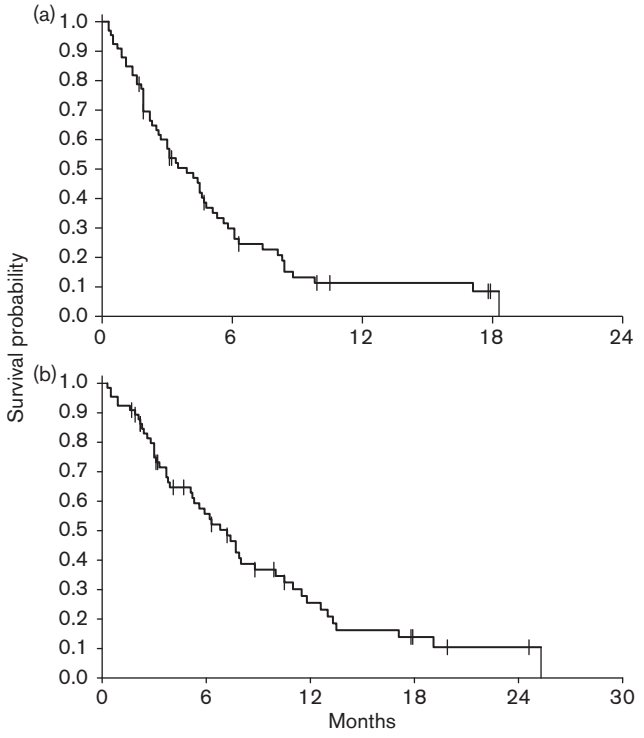
Table 4 Best response to paclitaxel-based chemotherapy

	N	%
Best response		
Overall response rate	20	30
Complete response	3	5
Partial response	17	26
Stable disease	24	36
Progressive disease	20	30
Not evaluable	2	3
Overall response rate according to the scheme of treatment	%	95% CI
Monotherapy	19	7–39
Combination with carboplatin	36	20–55

Discussion

This study confirms the effectiveness of taxane-based chemotherapy in HNSCC. Indeed, while the interest of neoadjuvant chemotherapy with cisplatin, 5-FU was debatable because of an absolute benefit at 5 years of only $2.4 \pm 1.4\%$, versus $6.5 \pm 1.0\%$ for concomitant chemoradiation [13,14], the addition of docetaxel (cisplatin, docetaxel, 5-FU regimen) clearly restored the validity of this therapeutic approach for organ preservation but also for use in inoperable patients [2,3]. Indeed, induction with cisplatin, docetaxel, 5-FU significantly increased overall survival and organ preservation compared with treatment with cisplatin, 5-FU.

Fig. 1



Progression-free survival (a) and overall survival (b) in our patient population.

Taxanes have also shown a significant clinical benefit in relapsed or metastatic patients. A first phase II study testing docetaxel monotherapy administered weekly × 3 every 4 weeks has reported a response rate of 27% (95% CI: 21.7–32.3%) and a median overall survival of 3.7 months [15]. Another phase II study of docetaxel administered weekly × 4 every 5 weeks has achieved a response rate of 42% (95% CI: 26–58%) and a median OS of 11.3 months [16]. Combination phase II studies of first-line docetaxel and cisplatin in relapsed or metastatic patients have shown response rates between 33 and 53% and median OS durations between 9.6 and 11 months [17–22]. With a response rate of 30% (95% CI: 20–43%) and a median OS of 7.2 months (95% CI: 5.2–8.8 months) for paclitaxel-based chemotherapy, our study shows similar results. Our data are also consistent with other studies, which have reported response rates between 20 and 52% and median OS durations between 5.4 and 10 months for recurrent or metastatic patients treated with paclitaxel alone or in combination with platinum agents [9,23–27]. The triplet paclitaxel, cisplatin and 5-FU have shown similar results in this situation [28,29]. Taxanes are thus an essential part of the therapeutic arsenal for relapsed or metastatic HNSCC patients. In terms of efficacy, paclitaxel, and docetaxel seem equally efficient in recurrent HNSCC but their tolerability profiles are different, with more neuropathy for paclitaxel and more hematologic or mucous toxicity for docetaxel (as shown by a randomized study in breast cancer) [10]. Consequently, tolerability results are more in favor of weekly paclitaxel.

On the whole, in terms of OS, no monotherapy or chemotherapy doublet has shown any superiority over weekly methotrexate, which thus remains a standard of treatment. However, although in oncology OS and PFS data tend to become a crucial yardstick for measuring response to treatment, in HNSCC, information on survival remains important because the majority of the patients are symptomatic at the time of relapse. These symptoms mainly include eating or speech disorders. Therefore, when equivalent results can be achieved in terms of OS, a chemotherapy regimen ensuring a strong response rate should be chosen. Paclitaxel (either alone or in combination with carboplatin) can achieve this objective while assuring good tolerability. Paclitaxel-based chemotherapy therefore constitutes an alternative to regimens such as cisplatin, 5-FU, cisplatin-docetaxel or docetaxel monotherapy.

Recently, the EXTREME study showed that the triplet cisplatin, 5-FU, cetuximab led to increased response rates (36%) and longer OS (10.1 months) compared with the association cisplatin and 5-FU (20% and 7.4 months, respectively) [8], suggesting that this triplet could become a new standard of treatment. However, in routine practice, few relapsed patients are really eligible for this association. Furthermore, toxicity is increased by the addition of cetuximab, even if the quality-of-life studies do not seem to indicate any deterioration [30]. The therapeutic sequence must also be discussed given that cetuximab monotherapy is effective in cisplatin-refractory patients with a response rate of 10% and a median OS of 6 months [31,32]. At a time when medico-economic evaluation and health cost management are becoming crucial issues, combination treatment may appear less cost-effective than sequential treatment. A major argument in favor of a better possible sequence of cetuximab is the demonstration of an important synergy between EGFR inhibitors and taxanes. Indeed, in first line treatment of recurrence, a phase II study has shown a high response rate of 71% using this combination [11]. After failure of platinum-based chemotherapy, the combination of weekly docetaxel and cetuximab achieved 12% response and a median survival of 7 months [33]. In our study, six patients received the weekly paclitaxel–cetuximab combination: two experienced a partial response and four had stable disease, without progression. Results of a phase III study presented at the American Society of Clinical Oncology 2009 meeting were disappointing because the combination of docetaxel and gefitinib (an oral EGFR inhibitor) did not show any superiority over docetaxel alone [34]. However, gefitinib might well not be the most effective treatment for

patients with HNSCC and certain antibodies (such as cetuximab, which is an IgG1) might prove superior in particular because they mediate antibody-dependent cell death [35]. Studies in lung cancer have shown that oral inhibitors of EGFR are effective in the presence of EGFR mutations. A similar mechanism could be involved in HNSCC, but such mutations are rare in this disease. Further studies are necessary to conclude on this point, in particular a phase III study testing the paclitaxel–cetuximab combination.

In conclusion, our study shows the efficacy of paclitaxel-based chemotherapy, which induces high response rates in symptomatic patients, with good tolerability and with a median overall survival similar to that obtained with the standards. Paclitaxel thus appears an interesting option for treating relapsed HNSCC routinely.

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