A tertiary care experience with paclitaxel and cetuximab as palliative chemotherapy in platinum sensitive and nonsensitive in head and neck cancers

Vanita Noronha, Vijay M. Patil, Amit Joshi, Atanu Bhattacharjee[1], Davinder Paul, Sachin Dhumal, Shashikant Juvekar[2], Supreeta Arya[2], Kumar Prabhash

Abstract

Background: The combination of paclitaxel and cetuximab (PaCe) has led to an encouraging response rate in Phase 2 setting with limited toxicity. The aim of our study was to assess the efficacy of this regimen in our setting in platinum sensitive and nonsensitive patients. **Methods:** This was a retrospective analysis of head and neck cancer patients treated with weekly PaCe as palliative chemotherapy between May 2010 and August 2014. The standard schedule of cetuximab along with 80 mg/m^2 of weekly paclitaxel was administered till either disease progression or withdrawal of patient's consent. The toxicity and response were noted in accordance with CTCAE version 4.02 and RECIST version 1.1 criteria, respectively. The response rates between platinum sensitive and nonsensitive patients were compared by Chi-square test. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan–Meier survival method and log-rank test was used for comparison. Cox proportional hazard model was used for identification of factors affecting PFS and OS. **Results:** One Hundred patients with a median age of 52 years (interquartile range: 46–56 years) were included. Forty-five patients (45%) were platinum insensitive, whereas 55 patients (55%) were platinum sensitive. In platinum insensitive patients and sensitive patients, the response rates were 38.5% and 22.2%, respectively (P = 0.104), whereas the symptomatic benefit in pain was seen in 89.5% and 71.7%, respectively (P = 0.044). The median PFS in platinum insensitive and sensitive patients were 150 and 152 days, respectively (P = 0.932), whereas the median OS was 256 days (95% confidence interval [95% CI]: 168.2–343.8 days) and 314 days (95% CI: 227.6–400.4 days), respectively (P = 0.23). Nineteen patients (19%) had grades 3–4 adverse events during chemotherapy. **Conclusion:** Weekly paclitaxel combined with cetuximab has promising efficacy and good tolerability in the palliative setting in advanced head and neck cancer in both platinum sensitive and insensitive patients.

Key words: Head and neck cancer, metastatic, oral cancer, palliative chemotherapy, recurrent, weekly paclitaxel

Introduction

Head and neck cancers comprise a significant portion of the cancer burden in developing countries.[1,2] Most of these patients present in advanced stages.[3,4] In spite of the recent improvements in surgical techniques, radiation techniques, and chemotherapy, which have improved overall outcomes, a significant percentage of these patients still recur.[5-7] The treatment options in such patients are limited. Palliative chemotherapy is the mainstay of management in this situation.[8,9] Addition of cetuximab to the chemotherapy backbone of cisplatin and 5-fluorouracil (5-FU) has led to a survival advantage in these patients.[9] However, the use of this regimen in the EXTREME study was restricted to patients who had failures post 6 months after multimodality treatment or post 1 month postsurgical or radiation treatment.[5] These patients are supposed to have platinum insensitive disease and have dismal prognosis.[9]

At our center, we routinely use a combination of weekly paclitaxel with cetuximab as palliative chemotherapy in head and neck cancers. Both these agents have single agent activity, nonoverlapping side effects, and a biological rationale for combination.[10] Promising results with response rates ranging between 50% and 55% have been reported with this regimen in patients with similar inclusion and exclusion criteria such as EXTREME study.[10]

In this report, we provide the detailed report of our experience with respect to the efficacy and safety of this regimen. The objective of this analysis was to study the efficacy in terms of best response rates, symptomatic benefit at 2 months, progression-free survival (PFS), and overall survival (OS) with this regimen in both platinum sensitive and platinum nonsensitive patients. In addition, we attempted to identify factors affecting PFS and OS.

Methods

Selection of cases and management

Between January 2010 and December 2014, 3720 patients received palliative chemotherapy for advanced head and neck cancer at our institute. All patients were offered cetuximab-based therapy; however, only 111 patients could afford cetuximab [Figure 1]. We have maintained a prospective database in the Department of Medical Oncology for these patients who received cetuximab.

From this database, we identified patients with the following features:

- Recipient of weekly paclitaxel + cetuximab (PaCe) in the palliative setting
- Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2
- Squamous cell carcinoma pathology
- Primary in oral cavity/oropharynx/hypopharynx/larynx.

All of these patients had received weekly paclitaxel (80 mg/m^2) along with cetuximab with standard premedications. The dose of cetuximab was 400 mg/m^2 as a loading dose, followed by 250 mg/m^2 in subsequent weekly cycles. These patients were clinically evaluated weekly for symptom and toxicity assessment; 2 monthly axial imaging was performed for response assessment. The chemotherapy was continued until

Access this article online
Quick Response Code:
Website: www.sajc.org
DOI: 10.4103/2278-330X.202558

Departments of Medical Oncology and [2]Radiodiagnosis, Tata Memorial Hospital, Mumbai, Maharashtra, [1]Division of Clinical Research and Biostatistics, Malabar Cancer Centre, Kannur, Kerala, India
Correspondence to: Dr. Kumar Prabhash, E-mail: kumarprabhashtmh@gmail.com

How to cite this article: Noronha V, Patil VM, Joshi A, Bhattacharjee A, Paul D, Dhumal S, *et al*. A tertiary care experience with paclitaxel and cetuximab as palliative chemotherapy in platinum sensitive and nonsensitive in head and neck cancers. South Asian J Cancer 2017;6:11-4.

disease progression or intolerable side effects or patient's refusal to continue.

Data collection and analysis

The data of these patients were extracted from the database and supplemented by information from the clinical case records and electronic medical records. The details about demographic features, tumor site, subsite, previous treatment, tolerance to PaCe, toxicity of PaCe, best response, symptomatic benefit, and OS were noted. Patients who had failed postmultimodality treatment within 6 months or within a month of single modality treatment either surgery or RT were considered as platinum insensitive. The response was documented in accordance with RECIST version 1.1. Intention to treat analysis was done. The OS was calculated from date of start of PaCe to date of death from any cause, in patients who died; the surviving patients were censored at their last date of follow-up. Survival as measured by the Kaplan–Meier method. The multivariate Cox regression analysis was performed to identify factors affecting PFS and OS. The factors tested were age (continuous variable), gender (male/female), ECOG PS (0, 1–2), site of tumor (oral vs. nonoral), previous RT received (Yes/No, and event-free period post previous treatment (continuous variable).

Results

Baseline details

Out of the 111 patients, 100 patients who received PaCe satisfied the inclusion criteria [Figure 1]. The median age of these patients was 52 years (interquartile range: 46–56 years). About 87 patients were male (87%, n = 100). The ECOG PS was 0–1 in 76 patients (76%) and 2 in 22 patients (22%). The PS of two patients was missing. The tumor and previous treatment details have been shown in Table 1. Ninety-two patients had received some form of previous treatment (either surgery, radiation, chemotherapy, or a combination). Forty-five patients (45%) were platinum insensitive, whereas 55 patients (55%) were platinum sensitive. Of the eight patients who were therapy-naive, five presented with upfront metastases and three had extensive locoregional disease which was not considered suitable for any form of local treatment. The indications for palliative chemotherapy included metastatic disease in 21 patients (21%) and recurrence or progression not amenable to local treatment in 79 patients (79%).

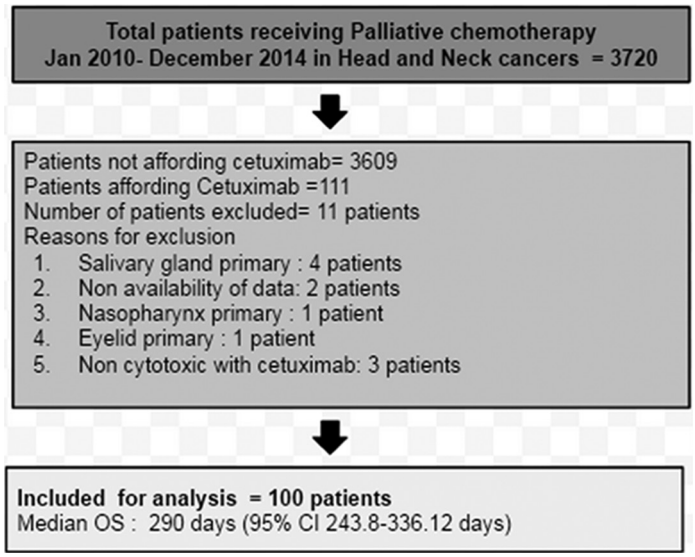

Figure 1: Consort diagram of patient selection for this study

Response and symptomatic benefit

Radiological response was evaluable in 84 patients. The best response seen was complete remission in six patients (7.2%, n = 84), partial remission in 19 patients (22.6%, n = 84), stable disease in 40 patients (47.6%, n = 84), and progressive disease in 19 patients (22.6%, n = 84). Thus, the response rate was 29.8% (95% confidence interval [95% CI]: 20.5–40.9). In platinum insensitive patients and sensitive patients, the response rates were 38.5% (n = 39, responded = 15 patients) and 22.2% (n = 45, responded = 10 patients), respectively (Chi-square test, P = 0.104).

Baseline pain was present in 84 patients. A decrease in pain (by one CTCAE grade at least) at 2 months was seen in 67 patients (79.8%, 95% CI: 69.3–7.4). The pain was scored according to CTCAE grade from 1 to 3. A decrease in the pain score by three grades was reported by seven patients, two grades by 28 patients, and it was of one grade in the remainder of the patients. In platinum insensitive patients and sensitive patients, the symptomatic benefit in pain was seen in 89.5% (n = 38, pain decreased by one grade at least = 34 patients) and 71.7% (n = 46, pain decreased by one grade at least = 33 patients), respectively (Chi-square test, P = 0.044).

Similarly, baseline dysphagia was seen in 44 patients. Relief in dysphagia (decreased by one grade at least) at 2 months was

Table 1: Tumor and previous treatment details

Variable	n=100 (%)
Tumor site	
Oral cavity	58 (58)
Nonoral cavity	42 (42)
Previous treatment received?	
Yes	93 (92)
No	7 (7)
Intent of previous treatment	
Radical	79 (79)
Palliative	14 (14)
Previous treatment administered to radically treated patients	
Surgery only	4 (4)
Radiation alone	2 (2)
Surgery + postoperative RT	23 (23)
Surgery + CRT	18 (18)
CRT	13 (13)
Induction chemotherapy + CRT	8 (8)
Induction chemotherapy + surgery + CRT	8 (8)
Induction chemotherapy alone (had progressive disease after induction chemotherapy)*	3 (3)
Previous treatment in palliatively treated patients	
Platinum-based chemotherapy exposure	12 (12)
Palliative radiotherapy	2 (2)
Overall patients exposed to platinum	62 (62)
Overall patients exposed to radiation	82 (82)
Event-free period following last treatment (months)	Median: 7 (IQR 3-16)
Platinum insensitive patients	45 patients (45)
Platinum sensitive patients	55 patients (55)

*These are patients planned for radical intent treatment but progressed on induction chemotherapy. CRT=Chemoradiotherapy, RT=Radiotherapy, IQR=Interquartile range

recorded in 22 patients (50%). In platinum insensitive patients and sensitive patients, the symptomatic benefit in dysphagia was seen in 55.0% (n = 20, dysphagia decreased by one grade at least = 11 patients), and 45.8% (n = 24, dysphagia decreased by one grade at least = 11 patients), respectively (Chi-square test, P = 0.545).

Overall survival

The median follow-up was 6 months in patients without progression. The median OS and PFS were 290 days (95% CI: 243.8–336.12 days) and 152 days (95% CI: 118.9–185.1 days), respectively [Figure 2]. The median PFS in platinum insensitive and sensitive patients were 150 and 152 days, respectively (P = 0.932). Among factors tested for affecting PFS, the site of tumor had a favorable impact [Table 2]. Oral cancer tumors had a median PFS of 173 days (95% CI: 136.3–20.9.7 days), whereas nonoral primary tumors had a median PFS of 125 days (95% CI: 106.3–143.8 days) (P = 0.03). The median OS in platinum insensitive and sensitive patients were 256 days (95% CI: 168.2–343.8 days) and 314 days (95% CI: 227.6–400.4 days), respectively (P = 0.23). None of the factors we tested significantly affected OS [Table 2].

Toxicity and tolerance

Nineteen patients (19%, 95% CI: 12.5–27.9) had grades 3–4 adverse events during chemotherapy. There was no grade 5 toxicity noted. In general, maculopapular skin rash in 79 patients (79%), mucositis in 63 patients (63%), and myalgia in 50 patients (50%) were among the most common adverse events noted. Toxicity-related stopping of cetuximab and paclitaxel was required in five patients.

Discussion

The median PFS and OS seen in the study conducted by the Spanish Head and Neck Cancer Cooperative Group (TTCC) when they used the combination of weekly paclitxael and cetuximab were 4.2 and 8.4 months, respectively. We found that the median PFS and OS in our study were 5.07 and 9.67 months, respectively.[10] Our findings confirm the efficacy of weekly PaCe. The median PFS and OS seen in the EXTREME study as a result of therapy with cisplatin, 5-FU, and cetuximab were 5.6 months and 10.1 months, respectively.[9,11,12] It seems from our audit and the Spanish study that weekly PaCe combination have a good efficacy and may have a similar in efficacy to the standard combination of cisplatin, 5-FU, and cetuximab. These findings are encouraging as in settings like ours in which the use of infusional 5-FU is fraught with logistic issues. Delivery of continuous infusion of 5-FU is difficult due to the limited bed availability for indoor admissions and the use of infusion pumps on an outpatient basis is demanding considering the low socioeconomic status of the majority of our patients with the attendant challenges they face in the areas of hygiene and sanitation.[8]

Both the EXTREME study and the Spanish study had included patients who had received previous platinum as a part of their previous multimodality treatment. The percentage of patients who had previous exposure to platinum was 94% in the Spanish study, whereas it was 64.3% in the EXTREME study. However, both these studies had excluded patients who had progressed within 6 months of their systemic treatment.[10,12] These patients were excluded from other cetuximab and panitumumab studies too.[13,14] This was not the case in our audit. It was seen in our study that weekly PaCe combination led to similar efficacy in patients who had previous exposure to platinum and also in patients who had progressed within 6 months of receiving platinum-based therapy. The efficacy of weekly PaCe combination in this setting has been described by other authors. In a study by Jiménez *et al*. in a cohort of 20 patients, similar response rates and benefit were seen in both the platinum-sensitive and refractory patients.[15] Similar findings were echoed by Péron *et al*.,[16] Sosa *et al*. have recently reported a study of 33 patients who had progressed on platinum treatment.[17] The combination of weekly PaCe was found to have promising results with a median PFS of 4.0 months and OS of 10.0 months. Thus, it appears that the combination of weekly PaCe is an effective alternative for platinum insensitive patients in whom platinum-based chemotherapy in not being considered.

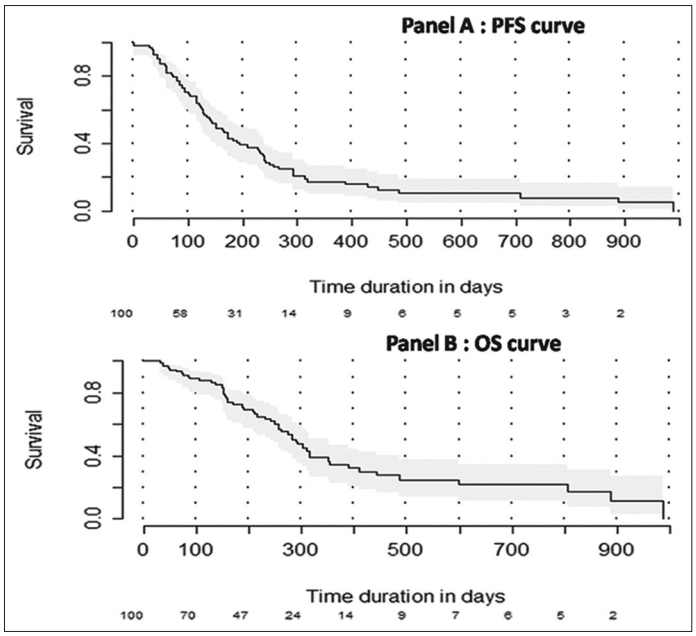

Figure 2: Kaplan–Meier plot showing estimated progression-free survival and overall survival. Numbers at risk are shown at the bottom of the graph

Table 2: Impact of different factors on progression-free survival and overall survival

Variable	Hazard ratio	95% CI of hazard ratio	*P*
PFS			
Age	1.01	0.98-1.04	0.45
Gender	0.85	0.31-2.30	0.75
ECOG PS	0.98	0.55-1.74	0.95
Tumor site	1.74	1.04-2.92	0.03*
Previous RT received	0.92	0.40-2.08	0.84
EFPP	0.99	0.98-1.00	0.38
OS			
Age	1.09	0.97-1.04	0.59
Gender	0.66	0.17-2.46	0.54
ECOG PS	1.66	0.88-3.14	0.11
Tumor site	1.50	0.79-2.84	0.20
Previous RT received	1.08	0.37-3.13	0.88
EFPP	0.98	0.97-1.00	0.25

RT=Radiotherapy, PFS=Progression-free survival, OS=Overall survival, ECOG PS=Eastern Cooperative Oncology Group performance status, EFPP=Event-free period post previous treatment, CI=Confidence interval

Although we found that the PFS, OS, and toxicity of our patients treated with PaCe was similar to that reported in the literature, our response rates were lower.[10,15-17] We had a response rate of 29.8%, which is lower than the 54% response rate reported by Hitt *et al*. and 55% response rate reported by Jiménez *et al*. We are unable to explain the low response rates seen in our study. In spite of the relatively low response rate, symptomatic benefit in pain occurred in 79.7% of patients confirming the efficacy of this regimen.

In the EXTREME study, the cisplatin, 5-FU, and cetuximab arm were associated with grades 3–4 neutropenia in 22% of patients.[12] These findings assume importance as in resource-strained setting like us, indoor admission for supportive care is difficult. PaCe in comparison seem to have a favorable toxicity profile, with no mortality reported across various studies, testifying to its safety.[10,15-17] In addition, it avoids toxicities related to platinum. These findings of similar efficacy and lower toxicity have prompted us to compare paclitaxel, platinum, and cetuximab combination against weekly PaCe combination in a randomized fashion in platinum-sensitive head and neck cancers.

Conclusion

PaCe have promising results and a very tolerable toxicity profile in both platinum sensitive and platinum insensitive head and neck cancer patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Dikshit R, Gupta PC, Ramasundarahettige C, Gajalakshmi V, Aleksandrowicz L, Badwe R, *et al.* Cancer mortality in India: A nationally representative survey. Lancet 2012;379:1807-16.
2. Fact Sheets by Population. Available from: http://www.globocan.iarc.fr/Pages/fact_sheets_population.aspx. [Last accessed on 2015 Mar 23].
3. Joshi P, Nair S, Chaturvedi P, Nair D, Agarwal JP, D'Cruz AK. Delay in seeking specialized care for oral cancers: Experience from a tertiary cancer center. Indian J Cancer 2014;51:95-7.
4. Sankaranarayanan R. Oral cancer in India: An epidemiologic and clinical review. Oral Surg Oral Med Oral Pathol 1990;69:325-30.
5. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, *et al.* Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695-704.
6. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, *et al.* Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705-15.
7. Hitt R, Grau JJ, López-Pousa A, Berrocal A, García-Girón C, Irigoyen A, *et al.* A randomized phase III trial comparing induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as treatment of unresectable head and neck cancer. Ann Oncol 2014;25:216-25.
8. Parikh P, Patil V, Agarwal JP, Chaturvedi P, Vaidya A, Rathod S, *et al.* Guidelines for treatment of recurrent or metastatic head and neck cancer. Indian J Cancer 2014;51:89-94.
9. Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol 2010;21 Suppl 7:vii252-61.
10. Hitt R, Irigoyen A, Cortes-Funes H, Grau JJ, García-Sáenz JA, Cruz-Hernandez JJ; Spanish Head and Neck Cancer Cooperative Group (TTCC). Phase II study of the combination of cetuximab and weekly paclitaxel in the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of head and neck. Ann Oncol 2012;23:1016-22.
11. Rivera F, García-Castaño A, Vega N, Vega-Villegas ME, Gutiérrez-Sanz L. Cetuximab in metastatic or recurrent head and neck cancer: The EXTREME trial. Expert Rev Anticancer Ther 2009;9:1421-8.
12. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, *et al.* Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.
13. Vermorken JB, Licitra L, Stöhlmacher-Williams J, Dietz A, Lopez-Picazo JM, Hamid O, *et al.* Phase II study of pemetrexed in combination with cisplatin and cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck. Eur J Cancer 2013;49:2877-83.
14. Vermorken JB, Stöhlmacher-Williams J, Davidenko I, Licitra L, Winquist E, Villanueva C, *et al.* Cisplatin and fluorouracil with or without panitumumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (SPECTRUM): An open-label phase 3 randomised trial. Lancet Oncol 2013;14:697-710.
15. Jiménez B, Trigo JM, Pajares BI, Sáez MI, Quero C, Navarro V, *et al.* Efficacy and safety of weekly paclitaxel combined with cetuximab in the treatment of pretreated recurrent/metastatic head and neck cancer patients. Oral Oncol 2013;49:182-5.
16. Péron J, Ceruse P, Lavergne E, Buiret G, Pham BN, Chabaud S, *et al.* Paclitaxel and cetuximab combination efficiency after the failure of a platinum-based chemotherapy in recurrent/metastatic head and neck squamous cell carcinoma. Anticancer Drugs 2012;23:996-1001.
17. Sosa AE, Grau JJ, Feliz L, Pereira V, Alcaraz D, Muñoz-García C, *et al.* Outcome of patients treated with palliative weekly paclitaxel plus cetuximab in recurrent head and neck cancer after failure of platinum-based therapy. Eur Arch Otorhinolaryngol 2014;271:373-8.