Outcomes of Chemotherapy plus Cetuximab as First-line Treatment in Patients with Metastatic, Recurrent, Unresectable Head and Neck Cancers: Real-life Data

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ABSTRACT

Objective: To examine the treatment outcomes of the EXTREME regimen as the first-line therapy for recurrent/metastatic squamous cell carcinoma of the head and neck.

Study Design: Observational study.

Place and Duration of the Study: Department of Medical Oncology, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Turkiye, between January 2014 and December 2021.

Methodology: A total of 60 patients with recurrent/metastatic head and neck cancers were treated with EXTREME regimen. Survival curves were estimated using the Kaplan-Meier method. Cox proportional hazards regression models were used to determine the factors associated with progression-free survival (PFS) and overall survival (OS).

Results: Patients receiving cetuximab in combination with chemotherapy for metastatic or unresectable disease were obtained from patient files and electronic medical records. Majority of patients were male (78.3%). The median PFS of patients was 7 months. The median survival of the patients was 9.06 months. During follow-up, 55 patients (91.7%) relapsed, and 51 patients (85%) died. The median survival of patients with eastern cooperative oncology group (ECOG) performance status 0, 1, and 2 was 16, 9, and 4 months, respectively. And the survival of patients was found significantly lower with lower ECOG performance scores.

Conclusion: OS was determined as 9.06 months. ECOG performance score had an important effect on the survival.

Key Words: *Cetuximab, Head and neck cancer, Chemotherapy.*

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INTRODUCTION

Head and neck squamous cell (HNSC) cancers constitute approximately 4% of all cancers across the world according to GLOBOCAN data.[1] It is estimated that there will be 66,740 new cases of head and neck cancer in the United States in 2022, and approximately one in four will die due to the disease.[2,3] There is a chance of a cure *via* surgery or radiotherapy in early head and neck cancer, but the risk of recurrence is high.

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In metastatic disease, there is no chance of cure *via* chemotherapy, but survival is increased. To date, the best results have been achieved through cisplatin-based combination chemotherapy. Survival rates were increased by combining paclitaxel or docetaxel with cisplatin.[4,5]

Epidermal growth factor receptor (EGFR) is also intensely expressed in head and neck cancers.[6] Cetuximab is an anti-EGFR monoclonal antibody. Prior to the introduction of cetuximab, survival for HNSC cancers was around 8 months. Survival was found as 10.1 months in EXTREME study comparing cisplatin plus 5-fluorouracil (CF) in combination with cetuximab with CF alone, due to the numerically better results of Cetuximab plus cisplatin.[7,8] It took its place in the treatment of metastatic HNSC cancer by showing a survival advantage. Survival was increased to 14 months *via* Docetaxel/Paclitaxel plus cisplatin in combination with cetuximab, known as TPEX (taxane platinum EXTREME).[9,10]

Combination of CF and Cetuximab was recommended as standard first-line treatment in the guidelines, until pembrolizumab showed a survival advantage in head and neck cancers.[11] Survival increased to 14 months through the use of pembrolizumab as a first-line treatment. Many targeted-therapy agents and immunotherapies are being investigated to improve these results.

In this study, the aim was to evaluate the outcomes of CF-cetuximab treatment as the first-line treatment in metastatic head and neck cancers.

METHODOLOGY

In this retrospective study, 60 patients diagnosed with recurrent/metastatic head and neck cancer were selected from those treated between January 2014 and December 2021. Data were obtained from patient files and electronic medical records. Inclusion criteria were patients aged 18 years and older, with histologically or cytologically confirmed recurrent or metastatic HNSC carcinoma, who were not considered suitable for local treatment. Non-squamous cell cancers, patients with performance statuses 3, 4, and patients who received chemotherapy in the first-line were excluded from the study.

Patients were given cisplatin (75mg per square meter of body surface area as an intravenous infusion on day 1) or carboplatin [AUC 5 (area under curve) 1-hour intravenous infusion on day 1] and fluorouracil infusion every 3 weeks (750mg/m2 per day for 5 days). Cetuximab was administered at an initial dose of 400 mg/m^2 and given as a 2-hour intravenous infusion, followed by weekly doses of 250 mg per square meter.

Tumour responses were assessed by computed tomography (CT) or magnetic resonance imaging (MRI) at 2-3-month intervals at baseline and after treatment initiation until disease progression.

Mean and median values of quantitative data were expressed according to whether following normal distribution or not. The normal distribution of data was assessed using the Kolmogorov-Smirnov/Shapiro-Wilk test. Descriptive statistics were presented as frequency and percentages, for normally distributed data as mean±standard deviation, and non-normally distributed as median (minimum-maximum). Progression-free survival (PFS) was calculated as the time duration from the date of first recurrence or metastasis to the date of progression or death. Overall survival (OS) was calculated as the time duration from the date of first recurrence or metastasis to the date of death in decedents, and to the date of last control for survivors. Survival curves were estimated using the Kaplan-Meier method. Cox proportional hazards regression models were used to determine factors associated with PFS and OS. The value of $p < 0.05$ was considered statistically significant. Statistical Package for the social sciences (SPPS) 20.0 (Chicago, IL, USA) was used for data analysis.

RESULTS

Medical records of 237 patients, who underwent treatment for head and neck cancer in the clinic between June 2014 and November 2021, were screened retrospectively, and the data of patients receiving cetuximab in combination with chemotherapy for metastatic or unresectable disease were obtained from the patient files and electronic medical records. A total of 60 patients were eligible for the study. Clinicopathological characteristics of the patients are shown in Table I.

The median age of patients was 58 (26-82) years. Majority of patients were males 47 (78.3%) and 13 (21.7%) were females. Forty-three patients (71.7%) were under 65 years of age. Of the patients, 30 (50%) had been treated for laryngeal tumour, 16 (26.7%) for oral cavity tumour, 8 (13.3%) for hypopharyngeal tumour, and 6 (10%) for tumour of unknown primary. Three patients had grade 1 (5%) tumour, 24 (40%) patients had grade 2 and 21 (35%) patients had grade 3 tumour, while the tumour grade of 12 (20%) patients was unknown. The median number of treatment cycles in patients receiving cetuximab was 6 (1-30).

The median PFS of patients was 7 months (95% confidence interval (CI) 5.868-8.132, Figure 1). The median survival of the patients was 9 months (95% CI 4.031-13.966) (Figure 2). During follow-up, 55 patients (91.7%) relapsed, and 51 patients (85%) died.

Age ($p=0.658$), gender ($p=0.742$), performance status ($p=0.126$), cancer localisation ($p=0.054$), histological grade ($p=0.095$), chemotherapy receiving status ($p=0.577$), and status of cisplatin resistance ($p=0.645$) were found to have no significant effects on PFS (Table II).

The median survival of patients with eastern cooperative oncology group (ECOG) performance statuses 0, 1, and 2 were 16, 9, and 4 months, respectively. Survival of patients with lower ECOG performance scores was found significantly lower. The survival of male patients was 9 months while it was found 18 months in female patients. Despite this quantitative difference, no statistically significant difference was found between male and female patients in terms of survival ($p=0.557$). The median survival was found 7 months for patients with laryngeal tumour, 13 months with oral cavity carcinoma, 13 months with hypopharyngeal cancer, and 16 months with carcinoma of unknown primary. There was no significant difference in terms of survival between tumour localisations ($p=0.897$). Median survival was found as 9 months in patients aged 65 years and over while it was 13 months in patients under 65 years of age. There was no significant difference in terms of survival between age groups ($p=0.071$).

The median survival of patients with grade 1 and 2 tumour was 18 months, while it was 7 months for patients with grade 3 tumour. The survival of patients with high grade tumours was found to be significantly lower ($p=0.044$). Although the median survival of patients receiving chemotherapy previously was 13 months, and of patients not receiving chemotherapy was 8 months, the difference was not statistically significant ($p=0.686$). While the median survival of patients with cisplatin resistance was 7 months, and 13 months in non-resistant patients, the difference was not statistically significant ($p=0.238$, Table II).

Table I: Clinicopathological characteristics of patients.

Characteristic	N (%)
Median age 58 years (range 26-82 years)	
Gender	
Male	47 (78.3)
Female	13 (21.7)
Localisation of tumour	
Larynx	30 (50)
Oral cavity	16 (26.7)
Hypopharynx	8 (13.3)
Unknown	6 (10)
Performance status	
0	26 (43.3)
1	25 (41.7)
2	5 (8.3)
Histologic grade	
1	3 (5)
2	24(40)
3	21 (35)
Unknown	12 (20)
Disease status	
Local recurrence	34 (56.7)
Distant metastasis	26 (43.3)
Platinum resistance	
Yes	9 (15)
No	51 (85)
Surgery	
Yes	37 (61.7)
No	20 (33.3)
Unknown	3 (5)
Median cycle of cetuximab	6 (range 1-30)

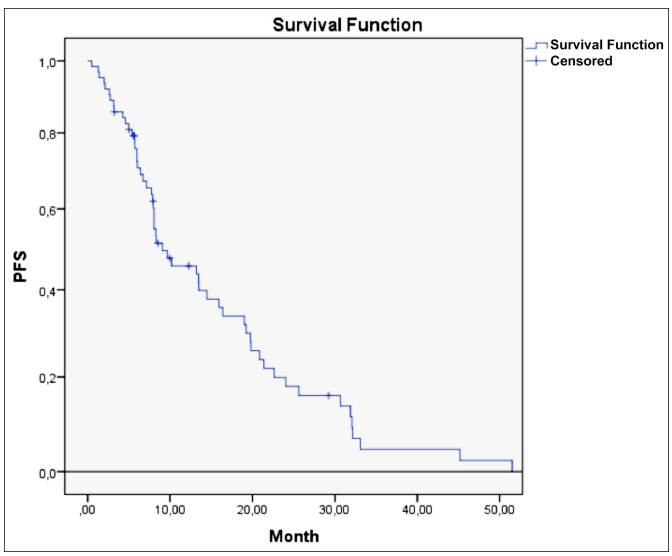

Figure 1: Kaplan-Meier curve of median progression-free-survival (PFS).

DISCUSSION

Metastatic or recurrent unresectable HNSC cancer is difficult to treat. Both the sense organs of sight, taste, hearing, and smell, and digestion starting regions such as mouth, tongue, teeth, pharynx, and esophagus are affected as well as the respiratory tract. Therefore, it requires not only chemotherapy, but also a multidisciplinary approach as required, such as percutaneous endoscopic gastrostomy (PEG) for nutritional support, tracheostomy for respiratory support, and psychological support. Prior to cetuximab, chemotherapy protocols including cisplatin, carboplatin, and fluorouracil were used for treatment, while CF was standard treatment before these protocols. In a study comparing the combination of cisplatin and paclitaxel with the combination of cisplatin and fluorouracil, the OS was found to be 8.7 and 8.1 months, respectively, and no statistical difference was found.[5] Then taxanes were added to the treatment protocol. Successful results were obtained *via* induction treatments with DCF (docetaxel, cisplatin, and fluorouracil). However, no phase 3 study was conducted for the treatment of metastatic or recurrent, unresectable HNSC cancer.

In a retrospective analysis performed by Demirci *et al*., OS was found 11 months in patients receiving a modified DCF protocol.[12] No similar result was found in the literature. Docetaxel, cisplatin, and fluorouracil combination, which was mostly used as induction therapy, has been shown to be beneficial in tumour shrinkage.

In the EXTREME trial, a phase 3 study, conducted with 477 patients by Vermorken et al., comparing CF plus cetuximab combination with CF, OS was found as 10.1 and 7.4 months, respectively.[8]

In this study, the authors retrospectively analysed the outcomes of patients receiving platinum + fluorouracil + cetuximab for metastatic or recurrent, unresectable HNSC cancer. The findings of this study relating to survival were similar to the literature. In this study, OS was determined as 9.06 months. In the EXTREME study, PFS was found to be 5.6 months in patients receiving CF plus cetuximab, and 3.3 months in patients receiving CF, while it was found 7 months in the current study. This difference in PFS is thought to result from the hight-quality supportive care provided to these patients.

Later, survival increased to 14 months in the GORTEC trial, a phase 2 study using docetaxel, cisplatin, and cetuximab. Similarly, in another phase 2 study using paclitaxel, cisplatin, and cetuximab, OS was found as 14 months.[9] In a phase 2 study conducted by Tahara *et al*. with 47 patients, in which paclitaxel, carboplatin, and cetuximab were used together, OS was found 14.7 months and PFS was 5.2 months.[10]

The KEYNOTE-048 study, a phase 3 trial in which effectiveness of pembrolizumab was evaluated in metastatic or recurrent head and neck cancers, conducted with 882 patients divided into 3 groups for comparison of pembrolizumab alone, pembrolizumab plus chemotherapy, and EXTREME protocol. The OS was found 13 months in pembrolizumab plus chemotherapy group, 11.5 months in pembrolizumab alone, and 10.7 months in CF plus cetuximab group. Although it was not statistically significant, there was a quantitative difference between OS of the groups. If the programmed death ligand-1 (PDL1) and combined positive score (CPS) is 20 and above, OS reaches 14.9 months with pembrolizumab alone and a statistically significant survival difference is obtained.[11] In this study, pembrolizumab alone provided OS advantage in the patients with a PDL1 CPS score of 20 and above.

Table II: The effects of clinicopathological features of patients on OS and DFS.

	PFS p-value	HR(95% CI)	Os p-value	HR (95% CI)
Gender				
Female *vs.* Male	0.742	0.870 (0.381-1.989)	0.557	0.760 (0.303-1.901)
Age				
<65 *vs.* >65	0.658	1.172 (0.581-2.364)	0.071	0.478 (0.215-1.064)
Cancer localisation				
Larynx	0.054	0.706 (0.495-1.006)	0.897	0.978 (0.696-1.374)
Oral cavity				
Hypopharynx				
Lips				
Unknown				
Histological grade				
Grade1-2 *vs.* grade3	0.095	1.376 (0.946-2.002)	0.044	1.539 (1.012-2.341**)**
Prior chemotherapy status				
Applied *vs.* not applied	0.577	0.824 (0.418-1.625)	0.686	0.862 (0.419-1.772)
Cisplatin resistance				
yes *vs.* no	0.645	1.244 (0.491-3.149)	0.238	1.763 (0.688-4.519)
Performance status				
0 *vs.* 1 *vs.* 2	0.126	1.553 (0.884-2.726)	0.013	2.274 (1.193-4.333)

CI: Confidence interval; HR: Hazard ratio.

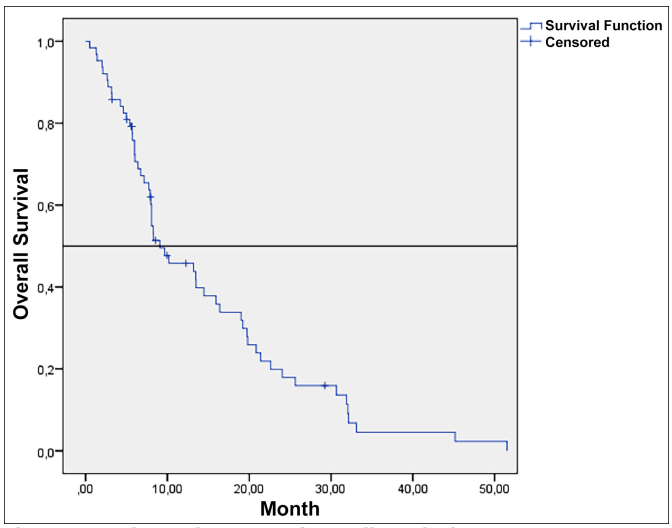

Figure 2: Kaplan-Meier curve of overall survival.

In the phase 2 study of Chung *et al*., nivolumab plus cetuximab combination was used in 88 patients. The OS was found as 11 months in patients receiving this combination as second-line treatment while it reached to 20 months in 43 patients receiving as first-line.[13]

The limitations of the present study, are having a retrospective design and relatively small sample size. Many trials are being conducted to improve survival in metastatic HNSC cancers, both with molecular targets and immunotherapy agents. Cetuximab protocols are still among the standard therapies. This study was found similar to other cetuximab studies.[14,15] Although an increase in survival has been achieved with immunotherapies, it is not sufficient. A better OS may be obtained by further studies involving molecular and genetic mutation analyses, and targeted therapies with immunotherapy agents, or immunotherapy plus immunotherapy agents, or immunotherapy and other targeted agents.

CONCLUSION

OS was determined as 9.06 months. ECOG performance score had an important effect on the survival.

ETHICAL APPROVAL:

The study protocol was approved by the Ankara Diskapi Yildirim Beyazit Training and Research Hospital at the University of Health Sciences Ethics Committee.

PATIENTS' CONSENT:

Consent was not received because the study is retrospective and most of the patients die when the study is planned.

COMPETING INTEREST:

The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

DY: Study conception and design.
DY, HS, GS, GII, MHK, OB, YS: Acquisition of data: contribution of all authors.
YS: Analysis and interpretation of data.
DY, HS: Drafting of manuscript.
DY, HS, GS, GII, MHK, OB: Critical revision, Contribution of all authors.
All the authors have approved the final version of the manuscript to be published.

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