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## Cetuximab and methotrexate in recurrent or metastatic head and neck squamous cell carcinoma—A single institution analysis of 54 patients

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### 1 | INTRODUCTION

Platinum-based chemotherapy is the standard of care treatment for patients with non-resectable, recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC).

<sup>1</sup> However, the toxicities of platinum must not be ignored. In reality, many patients with non-resectable R/M HNSCC cannot tolerate platinum-based chemotherapy due to their performance status (PS) and/or comorbidities.

Methotrexate (MTX), a folate antimetabolite that inhibits DNA synthesis, repair and cellular replication, has shown a modest response rate (RR) of 10% while RR was 32% for cisplatin/5-FU in R/M HNSCC, although this was in exchange with significantly increased toxicities with cisplatin/5-FU compared to MTX ( $P = 0.001$ ).<sup>2</sup>

Cetuximab (CTX) is a chimeric monoclonal antibody directed against the extracellular portion of the epidermal growth factor receptor (EGFR). CTX monotherapy has shown RR of 13% in R/M HNSCC post-platinum-failure.<sup>3</sup>

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**CONFLICT OF INTEREST**

None to declare.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Both CTX and MTX have shown single-agent activity in non-resectable R/M HNSCC with favourable toxicity profiles. However, data on combination CTX/MTX are limited. The purpose of this study is to provide outcomes data on combination CTX/MTX in non-resectable R/M HNSCC patients.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethical considerations

Approval for data collection and analysis was obtained from the Karmanos Cancer Institute/ Wayne State University (Detroit, MI) institutional review board. The requirement for informed consent was waived as all identifying information was removed from the data set prior to analysis.

### 2.2 | Patients

Retrospectively, data from patients with histology proven unresectable or R/M HNSCC who were treated with CTX/MTX at the Karmanos Cancer Institute between January 2004 and December 2010 were obtained from the pharmacy database.

Demographic characteristics of age, race, gender, PS, number of prior chemotherapy regimens in the R/M HNSCC, number of CTX/MTX cycles and adverse events (AE) were obtained from electronic medical records.

### 2.3 | Chemotherapy

The regimen consisted of weekly intravenous (IV) MTX 25 mg/m<sup>2</sup> plus IV CTX 400 mg/m<sup>2</sup> loading dose at week one then 250 mg/m<sup>2</sup> weekly maintenance dose. Each cycle consisted of 4 weeks. Concurrent treatment was defined as both agents given together for two cycles.

### 2.4 | Evaluation of response and toxicity

Pre-treatment and follow-up imaging studies (ie CT and/or MRI) were reviewed by an independent institutional radiologist. Response to treatment was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4. Imaging studies which were performed between 7 and 12 weeks after starting CTX/MTX were reviewed and analysed for response. Progression-free survival (PFS) was defined as time from initiation of treatment until disease progression or death. Overall survival (OS) was defined as time from initiation of treatment until death. Patients who remained alive were censored at the date of last contact. Response rate (RR) was defined as the fraction of patients who achieved a partial response (PR) or complete response (CR).

### 2.5 | Statistical analysis

The primary endpoint was to estimate the OS. PFS, RR and AE were assessed as secondary endpoints. Descriptive statistics was used to summarise demographic and baseline characteristics among study populations. Continuous variables were summarised with median and range, while counts and percentages were used to summarise categorical variables. The Kaplan-Meier method was used to describe the distribution of the PFS and

OS after treatment. Univariable logistic regression analyses were performed to evaluate for treatment responses. Univariable and multivariable Cox proportional hazards regression models were fit to assess associations between four prior chosen predictors (age, number of cycles, prior CTX exposure and number of prior lines) and survival benefit (PFS and OS). The proportional hazard assumption was checked, and no violation was found. All statistical analyses were performed using R (<http://www.r-project.org>).

## 3 | RESULTS

A total of 54 patients were included. Median age was 60 years old. Forty (74%) patients were males; 14 (26%) were females. Thirty-one (57%) patients were African American; 22 (41%) were Caucasian. Fourteen (26%) patients had received prior CTX. Twenty-eight (52%) patients had PS 1, and 26 (48%) patients had PS of two or more (Table 1). Table S1 shows the 34 patients who were identified in the pharmacy database for having CTX/MTX ordered, but did not complete two cycles for various reasons. Table S2 summarises the toxicities and cause of death.

### 3.1 | Response to treatment

Twenty-two (41%) patients received CTX/MTX as first-line therapy, while 24 (44%) and 8 (15%) received 1 or 2 prior regimens before to receiving CTX/MTX. Prior chemotherapy regimens include taxanes, platinum, 5-fluorouracil and gemcitabine. The median number of CTX/MTX cycles received was six (range; 2-8 cycles).

Out of 54 patients who completed two cycles of CTX/MTX, 5 (9.2%) had PR, 34 (63.0%) had stable disease (SD), and 15 (27.8%) had progression of disease (PD). Patients who had a rash toxicity of grade 2 or more were more likely to have disease control to CTX/MTX (OR, 10.22; 95% CI, 1.06-92.81;  $P=0.03$ , Table 2).

The median PFS was 2.98 (95% CI, 2.16-4.85 months) and the median OS was 8.66 months (95% CI, 7.02-12.26 months) for all patients. The median PFS in the patients with PS of 1 was 3.30 months (95% CI, 2.66-8.89 months) compared with 2.39 months (95% CI, 1.67-4.89 months) in those with PS of 2 or more (PFS HR, 1.19; 95% CI, 0.66-2.13;  $P=0.60$ ). The median OS in the patients with PS of 1 was 9.98 months (95% CI, 7.97-15.0 months) compared with 6.36 months (95% CI, 4.07-12.6 months) in those with PS of 2 or more (OS HR, 1.36; 95% CI, 0.78-2.36;  $P=0.30$ ). Kaplan-Meier estimates of survival are shown in Figure 1A,B.

The number of cycles received correlated with a smaller risk of death (HR, 0.85; 95% CI, 0.78-0.92;  $P<0.001$  in a univariable analysis) that was independently predictive even after adjusting for age, prior CTX exposure and number of cycles received in a multivariable Cox regression (HR, 0.84; 95% CI, 0.77-0.91; adjusted  $P<0.001$ , Table 3). At the end of the inclusion period, 50 (94%) patients were deceased, 45 (83%) due to their malignancy, 5 (9%) to non-malignancy-related causes and 2 (4%) due to unknown reasons; 2 (4%) were alive.

### 3.2 | Safety and tolerability

Most patients tolerated the regimen well. Twenty-five (46%) and 28 (52%) patients had neither skin rash nor hypomagnesemia, respectively. Holding treatment was defined as treatment withheld for 4 consecutive doses. Treatment was held in only five (9%) patients and that was secondary to toxicities. Only four (7%) and two (4%) patients developed Grade 3 rash and hypomagnesemia, respectively. Twenty-five (46%) had Grade 1-2 rash; 24 (45%) had Grade 1-2 hypomagnesemia (Table S2).

## 4 | DISCUSSION

The mainstay treatment for R/M HNSCC is systemic chemotherapy. Both MTX and CTX have shown single-agent efficacy in this setting,<sup>2,3</sup> but studies of combination CTX/MTX have been limited. Although immune checkpoint inhibition with pembrolizumab and nivolumab has become standard options in platinum-refractory R/M HNSCC, the reported RR is in the range of 13%-16%, PFS of approximately 2 months and OS of approximately 8 months.<sup>4,5</sup> Strategies beyond progression on immunotherapy are in dire need.

Judging by the low proportion of patients who developed Grade 3 AE, in addition to the minimal number of patients for whom treatment had to be held, this regimen appears reasonably tolerable.

In our study, we observed a RR of 9.2% with the combination CTX/MTX. The median PFS and OS for all patients in this study were 2.98 (95% CI, 2.16-4.85 months) and 8.66 months (95% CI, 7.02-12.26 months), respectively. Although our study is limited to its retrospective nature, the RR and PFS are similar to previous reports of CTX with/without platinum in the setting of platinum-refractory R/M HNSCC, which has been reported in the range between 10%-13% and 2.2-2.8 months, respectively.<sup>6</sup> The OS of 8.66 months exceeds the previously reported numbers of 5.2-6.1 months.<sup>6</sup>

Our OS data are comparable to the EXTREME trial, although cross-study comparison requires great caution. When compared with platinum-based chemotherapy plus fluorouracil alone, the EXTREME trial showed that the addition of CTX improved OS from 7.4 to 10.1 months. It must be noted that in EXTREME, patients with Karnofsky performance score <70% were excluded,<sup>3</sup> whereas in our study, 48% of the patients had a PS of 2 or more. Our findings are also comparable to trials investigating CTX/taxane combination for R/M HNSCC.<sup>7,8</sup>

Furthermore, efficacy was noted even in the setting of prior exposure to CTX. CTX/MTX can still be a valid option for patients with prior CTX either in the setting of single agent, other combination or with radiation.

This study is limited due to its retrospective nature. Concurrent CTX/MTX was defined as both agents given together for 2 cycles. Although this was in an attempt to standardise the regimen to provide the utmost efficacy data when other factors, that is, primary site and lines of treatment varied (Table 1), its potential for causing a selection bias is inevitable. The sample size is relatively small and comes from a single institution. However, this study

highlights the safety and efficacy of CTX/MTX for front-line as well as second- and third-line treatment for R/M HNSCC patients. CTX/MTX provides a platinum-free regimen for patients who are unlikely to tolerate platinum, such as those with limited PS which have traditionally been excluded from trials, as well as those with complications from previous platinum. Additionally, given emerging data on the improved efficacy of chemotherapy post-immunotherapy,<sup>9,10</sup> this regimen may be of further interest as a potential salvage treatment post-progression on immunotherapy.

## 5 | CONCLUSION

Our findings highlight the safety and efficacy of CTX/MTX as an option for palliative treatment for R/M HNSCC patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGEMENTS

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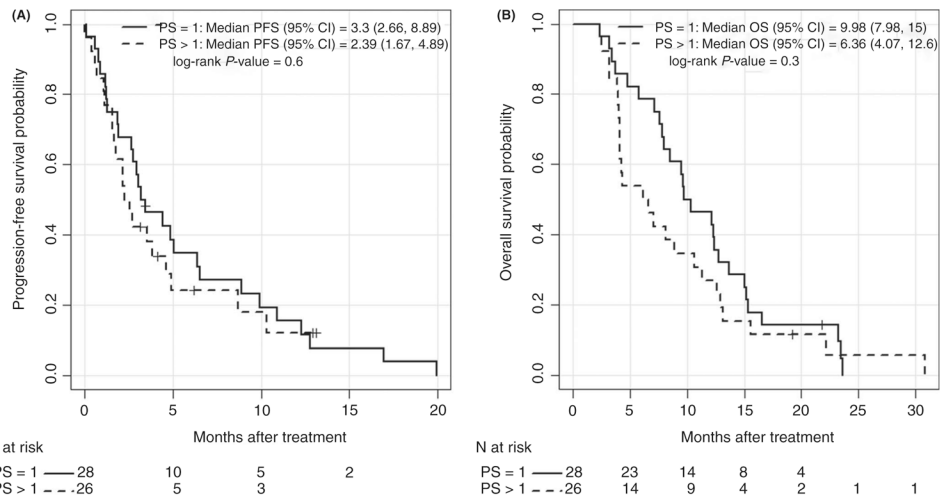
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### Keypoints

- Cetuximab (CTX) and methotrexate (MTX) have both shown single-agent activity in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) but data on CTX/MTX combination is limited.
- We report safety and efficacy data of 54 R/M HNSCC patients treated with concurrent CTX/MTX.
- Median progression-free survival and overall survival were 2.98 months (95% CI, 2.16-4.85 months) and 8.66 months (95% CI, 7.02-12.26 months), respectively.
- Grade 3 rash and hypomagnesemia were observed in four (7%) and two (4%) of patients.
- CTX/MTX combination could be considered as a palliative treatment option for patients with R/M HNSCC.



**FIGURE 1.** A, Kaplan-Meier Progression-free survival (PFS) by PS. B, Kaplan-Meier for Overall Survival (OS) after treatment by PS



TABLE 1

## Patient characteristics

	All (n = 54)
Age at treatment—median (range)	60 (40, 67.75)
Number of cycles—median (range)	6(2, 8.75)
Race—count (%)	
AA	31(57)
EA	22 (41)
Other	1(2)
Gender—count (%)	
Male	40 (74)
Female	14 (26)
Site—count (%)	
Oral cavity: all mouth: lip, molar, gingival ant 2/3 tongue	14 (26)
Oropharyngeal: tonsil, base of tongue, pharynx around oral area	14 (26)
Larynx: supra, infra/sub- and glottic	21 (39)
Hypopharyngeal	2(4)
Unknown primary	3(6)
Received CTX in the past—count (%)	
No	40 (74)
Yes	14 (26)
Number of prior lines of palliative chemo—count (%)	
None	22 (41)
1	24 (44)
2	8(15)
Performance status—count (%)	
1	28 (52)
2	25 (46)
3	1(2)

AA, African American; EA, European American.

**TABLE 2**

Univariable logistic regression analyses for RECIST responses

<b>Univariable</b>		
	<b>OR (95% CI)</b>	<b>Signif</b>
DCR (=CR + PR + SD)		
Number of prior lines of palliative chemo		
None		
1	1.03 (0.16, 8.39)	0.97
Rash		
Grade 1		
Grade 2	10.22 (1.06, 92.81)	0.03
Hypomagnesemia		
Grade 1		
Grade 2	6.67 (0.97, 56.65)	0.05

CI, confidence interval; DCR, disease control rate; OR, odds ratio; Ref., reference; Signif, significance.

**TABLE 3**  
Univariable and multivariable Cox regression analyses for survival benefit (PFS and OS)

	Univariable		Multivariable	
	HR (95% CI)	Signif	HR(95% CI)	Signif
<b>PFS</b>				
Age at treatment	0.99 (0.95, 1.02)	0.44	0.98 (0.95, 1.02)	0.35
Number of cycles	0.97 (0.90, 1.04)	0.43	0.97 (0.90, 1.04)	0.34
Received CTX in the past				
No	Ref.			
Yes	0.84 (0.43, 1.67)	0.63	0.75 (0.37, 1.52)	0.43
Number of prior lines of palliative chemo				
None	Ref.			
1	0.98 (0.54, 1.78)	0.96	0.98 (0.54, 1.77)	0.93
<b>OS</b>				
Age at treatment	0.99 (0.96, 1.02)	0.48	0.98 (0.95, 1.02)	0.34
Number of cycles	0.85 (0.78, 0.92)	<0.001	0.84 (0.77, 0.91)	<0.001
Received CTX in the past				
No	Ref.			
Yes	0.90 (0.48, 1.71)	0.75	0.60 (0.30, 1.20)	0.15
Number of prior lines of palliative chemo				
None	Ref.			
1	1.03 (0.58, 1.83)	0.91	0.91 (0.51, 1.64)	0.76

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; Ref., reference; Signif, significance.