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Original Article

Cetuximab Plus Methotrexate in Recurrent and/or Metastatic Head-and-Neck Squamous Cell Carcinoma

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Abstract

Background: The effectiveness of cetuximab (CTX) combined with methotrexate (MTX) has not yet been evaluated in patients with recurrent and/or metastatic head-and-neck squamous cell carcinoma (RM-HNSCC). **Materials and Methods:** A retrospective analysis of patients with RM-HNSCC who received 50 mg MTX weekly plus a standard dose of CTX for a maximum of 18 weeks, without maintenance CTX. **Results:** A total of 164 patients were included (cisplatin-sensitive, 88; cisplatin-refractory, 76). Among 58 cisplatin-sensitive patients receiving CTX/MTX as the first-line treatment, the outcomes were 39.7% response rate (RR), 70.7% disease control rate (DCR), 6.0 months of median progression-free survival (PFS), and 9.0 months of overall survival (OS). Among cisplatin-refractory patients, results were 31.6% RR, 51.3% DCR, 4.0 months of PFS, and 6.0 months of OS. Multivariable analyses revealed PFS and OS were not associated with cisplatin-refractory status, age, performance status, or the lines of CTX/MTX treatments. In cisplatin-refractory patients, those with only locoregional-recurrence disease had significantly worse PFS, but this did not affect OS; a similar trend was observed in cisplatin-sensitive patients. **Conclusion:** A CTX/MTX regimen, without maintenance CTX, is a safe and effective palliative treatment for both patients with cisplatin-sensitive or cisplatin-refractory RM-HNSCC. The low adverse events and easy administration makes this treatment a suitable option in various contexts, particularly for cisplatin-unfit or frail patients with RM-HNSCC.

Keywords: Cetuximab, head-and-neck squamous cell carcinoma, metastatic, methotrexate, palliative treatment, recurrence

Introduction

Head-and-neck cancer was the seventh most common cancer worldwide, with 890,000 new cases and 450,000 deaths reported in the 2018 GLOBOCAN estimates.[1]

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The major entity is head-and-neck squamous cell carcinoma (HNSCC) and 60%–70% of these patients present with locally advanced stage (Stage III–IV) disease. Despite advances in diagnosis and treatment, recurrent or metastatic disease (or both) develops in more than 65% of patients with advanced HNSCC.[2] Patients with recurrent and/or metastatic (RM) disease not amenable to salvage surgery and/or radiotherapy, who receive palliative systemic therapy or best supportive care, have a dismal prognosis, with a median survival of 6–9 months.[3]

Adding the epidermal growth factor receptor (EGFR) inhibitor cetuximab (CTX) forwarded the management of RM-HNSCC from CTX alone for cisplatin-refractory disease (disease progression or relapse within 6 months of last cisplatin therapy)[4] to CTX combined platinum/5-fluorouracil doublet (CTX-PF) in EXTREME trial for cisplatin-sensitive disease (disease progression or relapse after more than 6 months from the last dose of cisplatin). The breakthrough EXTREME regimen improved median overall survival (OS) from 7.4 months to 10.1 months when used as a first-line treatment in patients with cisplatin-sensitive RM-HNSCC.[5]

Modern immunotherapy using immune checkpoint inhibitors, such as the anti-programmed cell death protein 1 inhibitors nivolumab and pembrolizumab, showed unprecedented activity in both patients with cisplatin-refractory and cisplatin-sensitive patients with RM-HNSCC. The median OS of patients with cisplatin-refractory RM-HNSCC was improved significantly, from 6.4 months to 8.9 months in the KEYNOTE-040 trial (pembrolizumab),[6] and from 5.1 months to 7.5 months in the CheckMate-141 trial (nivolumab).[7] Pembrolizumab alone or combined with the platinum/5-fluorouracil doublet (KEYNOTE-048) extended the immunotherapeutic activity when used as the first line of treatment in those with cisplatin-sensitive RM-HNSCC. The median OS for the KEYNOTE cohort versus the EXTREME cohort in the total population was noninferior for pembrolizumab alone (11.6 months vs. 10.7 months, hazard ratio [HR] 0.85; 95% confidence interval [CI], 0.71–1.03), but better in those receiving pembrolizumab-PF chemotherapy (13.0 months vs. 10.7 months; HR 0.77; 95% CI, 0.63–0.93; $P = 0.0034$). The improvement in survival was more obvious in patients with combined positive scores (CPS) ≥1 and CPS ≥20.[8]

However, using immunotherapy as the first-line therapy in both cisplatin-refractory and cisplatin-sensitive RM-HNSCC patients involves many potential drawbacks: A low overall response rate (RR) when used alone, rare but potentially life-threatening immune-related adverse events (AEs), the risk of hyperprogression, and high cost.[7,9,10] In real-world practice, the restricted reimbursed regulations and high out-of-pocket burden preclude the greater part of patients with RM-HNSCC from receiving immunotherapies or CTX-based systemic therapies as their first-line therapy. Furthermore, the EXTREME regimen is unsuitable for patients with poor performance status and/or platinum resistance, has substantial toxicity (especially vomiting and diarrhea), and requires intravenous infusion.[5] The TPEx regimen replaced the 5-fluorouracil in the EXTREME regimen with docetaxel (TPExtreme trial); despite the favorable safety profile, OS showed no significant improvement.[11] Besides, the TPExtreme trial enrolled patients with the Eastern Cooperative Oncology Group (ECOG) performance status of 1 or less who also needed systemic granulocyte colony-stimulating factor support at each cycle. In summary, the standard TPExtreme regimen may not be feasible in routine practice, particularly for Asian RM-HNSCC patients, and dosage modification is needed in real-world practice.[12,13]

Methotrexate (MTX) is one of the conventional standard-of-care (SoC) treatments for RM-HNSCC. Despite its lower RR, MTX has proven to have less toxicity and similar OS to the PF doublet in a randomized trial.[14] This study provided the rationale for using MTX in place of PF in the EXTREME protocol. Furthermore, the CTX/MTX combination may be more suitable for treating frail or platinum-unfit patients with RM-HNSCC.

Due to regulations, CTX is reimbursed by the National Health Insurance (NHI) of Taiwan for a maximum of 18 weeks. Here, we report the results of a nonmaintenance CTX/MTX combined regimen in both cisplatin-refractory and cisplatin-sensitive RM-HNSCC patients.

Materials and Methods

Study design and patients

This therapeutic cohort study included a retrospective analysis of prospectively collected data of patients with RM-HNSCC treated with CTX/MTX at a single medical center. Eligible patients were aged 18 years or older, with ECOG performance status score of 0–3; adequate bone marrow, hepatic, and renal function; and measurable or evaluable disease. Major exclusion criteria were third space fluid accumulation (e.g. pleura effusion, ascites) or previous receipt of either CTX or MTX. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital at Linkou (approval number: 201901709BO), which granted a waiver of consent because this study involved no additional therapeutic or diagnostic interventions. The waiver did not adversely affect the rights and welfare of the subjects, and all patient data were de-identified before analysis.

Definitions

Tumor sequence was defined as the sequence of the tumor being treated with CTX/MTX because head-and-neck cancer patients may suffer from sequential development of a second primary tumor. Lines of treatment of CTX/MTX were used to refer to treatment lines in the palliative setting only. Systemic therapy included chemotherapy, molecular targeted therapy, and immunotherapy. However, no immune checkpoint inhibitors were used in this study.

Chemotherapy regimen

All patients received standard intravenous 400 mg/m^2 CTX loaded as a 2-h infusion, then 250 mg/m^2 weekly as a 1-h

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infusion; these were co-administered with intravenous 50 mg MTX weekly. The reimbursement regulations for CTX per the Taiwan NHI are a maximum of 18 weeks in patients with controlled disease, with a mid-course evaluation at the 9th week. The 18 weeks' duration is referred to 6 cycles of the tri-weekly EXTREME regimen, but no reimbursement was allowed for maintenance CTX. After 18 weeks of concurrent treatment, patients were given conventional systemic therapy as per the patient's willingness or at the physician's discretion. Unlike the conventional dosage of 40–60 mg/m^2 weekly of MTX in HNSCC patients, we administered a fixed dose of 50 mg MTX (as one vial of a pharmaceutical preparation) in concern of the cross-over toxicity with CTX (e.g., mucositis) at the initial treatment. The subsequent dose adjustment was by physician discretion per any concerned AEs.

Treatment response and adverse events

The response to CTX/MTX was evaluated at the 9th and 18th weeks of treatment, as set by the NHI regulations for reimbursement. Responses were assessed in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1 and/or the PET Response Criteria in Solid Tumors version 1.0.[15] Patients were evaluated using the same image modality throughout the CTX/MTX course. The time-to-event endpoints were calculated from the date of beginning CTX-MTX. Progression-free survival (PFS) (until disease progression or death) and OS (until death) were determined. The overall RR was defined as the percentage of patients achieving a complete response (CR) or partial response (PR). The disease control rate (DCR) was defined as the percentage of patients achieving CR, PR, or stable disease. AEs were evaluated and graded weekly according to the Common Terminology Criteria of AEs 4.03.

Statistical analysis

Patient characteristics were presented as mean ± standard deviation for age and *n* (%) for other characteristics, therapeutic course, posttherapeutic response, and AEs. Treatment cycles and durations were shown as median (range, minimum/maximum). Differences between the two patient groups (cisplatin-sensitive vs. cisplatin-refractory) were compared using the two-sample *t*-test for age, Pearson Chi-square test or Fisher's exact test for other categorical variables, and Mann–Whitney *U*-test for treatment cycles and duration. Kaplan–Meier curve analysis was performed to compare the OS and PFS between groups and by clinical characteristics. Results were presented as survival curves with the corresponding median with 95% CIs and *P* values using the log-rank test. Multivariable Cox regression analysis was performed to evaluate the OS and PFS between cisplatin-sensitive and cisplatin-refractory groups based on patient characteristics. Results were shown as HRs with 95% CIs and *P* values. All statistical assessments were two-tailed and considered statistically significant at $P < 0.05$. All data were analyzed using IBM SPSS statistical software version 18 for Windows (IBM Corp., Armonk, New York, USA).

Results

Patient baseline demographic and clinical characteristics

A total of 164 consecutive patients with RM-HNSCC treated with CTX/MTX between May 2016 and November 2019 were enrolled and followed until September 2020. The median follow-up duration was 8 (range 0–36) months. Table 1 shows the baseline characteristics, including ECOG performance scores, tumor sites, extent of disease, and receipt of CTX/MTX treatment for the overall population, and for cisplatin-refractory (46.3%, $n = 76$) and cisplatin-sensitive patients (53.7%, $n = 88$). The cisplatin-sensitive group had a greater proportion of patients with de novo metastases (20.5% vs. 0%), and the cisplatin-refractory group had a greater proportion of patients with disease progression after upfront radiotherapy (± systemic therapy) (44.7% vs. 3.4%). All other disease characteristics were comparable between the two groups.

Therapeutic course, compliance, response, and adverse events

The therapeutic course of CTX/MTX treatment was comparable between the two groups. The median duration of CTX/MTX treatment was 3 months (range 0–7) in the cisplatin-sensitive group and 2.3 months (range 0.3–8) in the cisplatin-refractory group. The rates of disease control achieved at the 9th and 18th weeks of CTX/MTX were 61.4% and 37.5% in the cisplatin-sensitive group and 53.9% and 39.5% in the cisplatin-refractory group, respectively [Table 2].

The RR and DCR of the cisplatin-sensitive group were 36.4% and 64.8%, respectively, which were comparable to the 31.6% and 51.3%, respectively, of the cisplatin-refractory group [Table 2]. There was a trend of higher hospitalization rates during the CTX/MTX treatment in the cisplatin-sensitive group (43.7% vs. 30.3%, $P = 0.077$) [Table 2]. Overall mortality, progression rates, and median OS were 84.1%, 88.5%, and 8 months (95% CI, 6.8–9.1), respectively, for all patients. Kaplan–Meier curve analysis for OS and PFS is shown in Figure 1. Median PFS in the cisplatin-sensitive group was significantly longer (5 months; 95% CI, 4.2–5.7) compared to that of the cisplatin-refractory group (4 months; 95% CI, 2.3–5.6, $P = 0.046$) [Figure 1b]. In the 88 cisplatin-sensitive patients, 58 (66.0%) received CTX/MTX as the first-line treatment for their RM-HNSCC. They had an RR of 39.7%, a DCR of 70.7%, a median OS of 9.0 months, a median PFS of 6.0 months, and a 1-year survival rate of 32.8%.

The overall incidence of Grades 3–4 AEs for CTX/MTX was 22.6% (37/164). Nine (10.2%) and 6 (7.9%) patients developed Grades 3–4 AEs of skin and nail in the cisplatin-sensitive and cisplatin-refractory groups, respectively [Table 3].

Subgroups and multivariable analysis

Results of multivariable Cox regression analysis for survival benefits (OS and PFS) are shown in Table 4. After adjustment for age at treatment, treatment cycles, ECOG performance scores, lines of CTX/MTX treatment, and disease stage (locoregional only or metastatic only), the multivariable Cox regression

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Table 1: Patient's baseline demographic and clinical characteristics

Variable	Total (*n*=164)	Cisplatin-sensitive (*n*=88)	Cisplatin-refractory (*n*=76)	*P*
Sex				0.403
Male	148 (90.2)	81 (92)	67 (88.2)	
Female	16 (9.8)	7 (8)	9 (11.8)	
Age at treatment (years)				
Mean±SD	56.3±10.0	58.8±10.3	53.5±8.9	0.001*
Age >65	28 (17.1)	21 (23.9)	7 (9.2)	0.013*
ECOG performance status				0.279
0	1 (0.6)	0	1 (1.3)	
1	130 (79.3)	66 (75)	64 (84.2)	
2	27 (16.5)	18 (20.5)	9 (11.8)	
3	6 (3.7)	4 (4.5)	2 (2.6)	
Tumor subsite				0.060
Oral cavity	95 (57.9)	51 (58)	44 (57.9)	
Oropharynx	33 (20.1)	17 (19.3)	16 (21.1)	
Hypopharynx	21 (12.8)	10 (11.4)	11 (14.5)	
Larynx	8 (4.9)	8 (9.1)	0	
Other	7 (4.3)	2 (2.3)	5 (6.6)	
Tumor sequence				0.330
1st	108 (65.9)	55 (62.5)	53 (69.7)	
≥2nd	56 (34.1)	33 (37.5)	23 (30.3)	
Context of disease				<0.001*
s/p neoadjuvant therapy	4 (2.4)	1 (1.1)	3 (3.9)	
s/p RT_MDT	37 (22.6)	3 (3.4)	34 (44.7)	
Relapse after S_MDT	70 (42.7)	42 (47.7)	28 (36.8)	
Relapse after RT_MDT	35 (21.3)	24 (27.3)	11 (14.5)	
De novo metastasis	18 (11)	18 (20.5)	0	
Disease stage				0.227
Only locoregional	81 (49.4)	46 (52.3)	35 (46.1)	
Locoregional and distant metastasis	59 (36.0)	33 (37.5)	26 (34.2)	
Only distant metastasis	24 (14.6)	9 (10.2)	15 (19.7)	
Line of CTX/MTX treatment				0.672
1st	113 (68.9)	58 (65.9)	55 (72.4)	
2nd	34 (20.7)	20 (22.7)	14 (18.4)	
≥3rd	17 (10.4)	10 (11.4)	7 (9.2)	
Received post-CTX/MTX systemic therapy	117 (71.3)	63 (71.6)	54 (71.1)	0.939

*P<0.05 significance. Data are presented as mean±SD for age and *n* (%) for others; differences between two groups were compared using two-sample *t*-test for age and Pearson Chi-square test/or Fisher's exact test for other categorical variables. s/p neoadjuvant therapy: Progression after neoadjuvant systemic therapy (no surgery or RT), s/p RT_MDT: Progression after upfront RT (± systemic therapy), Relapse after S_MDT: Relapse after upfront surgery and adjuvant RT (± systemic therapy), Relapse after RT_MDT: Relapse after upfront RT (± systemic therapy), *De novo* metastasis: Newly diagnosed advanced and/or metastatic disease, Systemic therapy included chemotherapy, molecular targeted therapy, and immunotherapy, Tumor sequence indicated the sequence of the tumor being treated. SD: Standard deviation, ECOG: Eastern Cooperative Oncology Group, RT: Radiotherapy, S: Surgery, MDT: Multidiscipline treatment, CTX/MTX: Cetuximab-methotrexate

analysis revealed that disease control kept beyond 9 cycles of CTX/MTX (vs. <9 cycles) was predictive of better OS and PFS in both groups. Disease control kept beyond 18 cycles (vs. <18 cycles) of CTX/MTX correlated with better OS and PFS in all cohorts and with PFS in the cisplatin-sensitive group. Those cisplatin-refractory patients with locoregional only recurrence had a significantly worse PFS (but not OS). A similar trend was observed in cisplatin-sensitive patients.

Discussion

The present study showed that the CTX/MTX combination, even without maintenance CTX, is a safe and effective palliative treatment for patients with both cisplatin-refractory and cisplatin-sensitive RM-HNSCC.

Compared with other CTX/MTX studies, the present study enrolled more patients and found a more favorable treatment response. Ham *et al*. compared 30 patients who received CTX/MTX as the first-line treatment for RM-HNSCC with a control group of 15 patients who received MTX monotherapy. The reported PFS was notably higher at 4.5 months in the CTX/MTX group compared to the MTX-only group at 2.0 months; however, OS (8 months), toxicity, and quality of life did not significantly differ between groups.[16] Sukari *et al*. treated 54 patients with RM-HNSCC using CTX/MTX

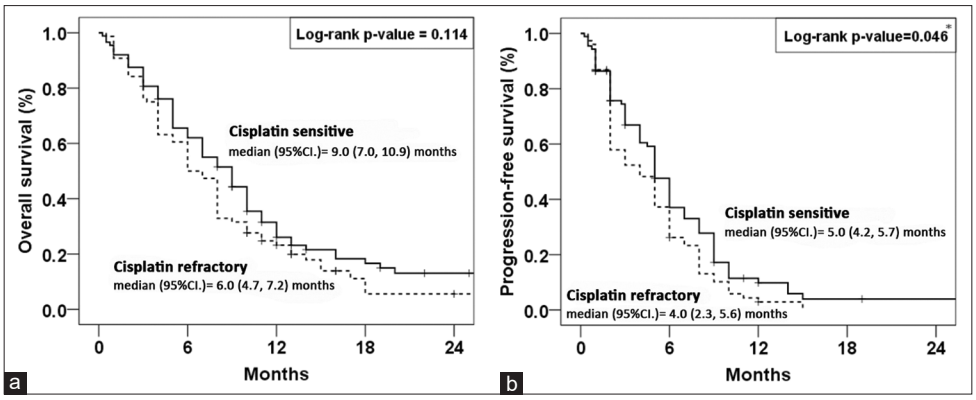

Figure 1: Kaplan–Meier curve analysis of (a) overall survival and (b) progression-free survival between cisplatin-sensitive and cisplatin-refractory patients. Solid lines refer to cisplatin-sensitive patients; dotted lines refer to cisplatin-refractory patients; +, censors. Results are presented as median (95% confidence interval) with a *P* value via log-rank test. *Significant difference between the two groups. CI: Confidence interval

Table 2: Therapeutic course and response to cetuximab-methotrexate treatment

Variables	Total (*n*=164)	Cisplatin-sensitive (*n*=88)	Cisplatin-refractory (*n*=76)	*P*
CTX/MTX cycles				
Median (range)	11 (1–26)	13.5 (1–25)	10 (1–26)	0.735
>9 cycles, *n* (%)	95 (57.9)	54 (61.4)	41 (53.9)	0.337
≥18th cycles, *n* (%)	63 (38.4)	33 (37.5)	30 (39.5)	0.796
Duration of CTX/MTX (months)				
Median (range)	3 (0–8)	3 (0–7)	2.3 (0.3–8)	0.383
Best response, *n* (%)				0.131
CR	17 (10.4)	9 (10.2)	8 (10.5)	
PR	39 (23.8)	23 (26.1)	16 (21.1)	
SD	40 (24.4)	25 (28.4)	15 (19.7)	
PD	55 (33.5)	22 (25.0)	33 (43.4)	
NA	13 (7.9)	9 (10.2)	4 (5.3)	
Overall response rate (CR+PR)	56 (34.1)	32 (36.4)	24 (31.6)	0.519
DCR (CR + PR + SD)	96 (58.5)	57 (64.8)	39 (51.3)	0.081
Hospitalization, *n* (%)	61 (37.4)	38 (43.7)	23 (30.3)	0.077
Survival (months)				
Progression-free survial, median (95% CI)	5 (4.1–5.9)	5 (4.2–5.7)	4 (2.3–5.6)	0.046*
OS, median (95% CI)	8.0 (6.9–9.1)	9.0 (7.0–10.9)	6.0 (4.7–7.2)	0.114

**P*<0.05 significance. Differences between two groups were compared using Pearson Chi-square test for categorical variables and Mann–Whiney *U*-test for treatment cycles and durations and Log-rank test for progression-free duration. CTX/MTX: Cetuximab-methotrexate, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progression disease, NA: Not available, CI: Confidence interval, OS: Overall survival, DCR: Disease control rate

and achieved a RR of 9.2% with an OS of 8.6 months and a PFS of 2.9 months.[17] Of note, these studies did not compare data between cisplatin-refractory and cisplatin-sensitive cohorts. Our more favorable treatment response may be due in part to the characteristics of our cohort, such as the proportion of patients with *de novo* metastatic disease who received no prior radiotherapy or chemoradiation for their primary disease (11%), those with an ECOG performance status of 0–1 (79.9%), and those with HNSCC as the first tumor (65.9%). However, despite the wide use of MTX, the potential pharmacokinetic interaction with CTX when used in combined therapy remain unclear. One *in vitro* study in human conditionally immortalized proximal tubule epithelial cells suggested CTX was able to attenuate MTX cytotoxicity, possibility by downregulating organic anion transporters 1 and breast cancer resistance protein while upregulating multidrug resistance protein 4 through an EGFR-mediated regulation of PI3K-AKT and MAPKK-ERK pathways.[18] This finding may be inconsistent with the current effect of the CXT/MTX combination. Further research into the potential synergy and mechanisms related to co-medication is required to better understand how to use combination therapies to effectively manage R/M HNSCC and prevent AEs.

Amongst the 88 cisplatin-sensitive patients in the present study, 58 (66.0%) patients received CTX/MTX as the first-line treatment for their RM-HNSCC. The outcomes of these 58 patients compared to those reported for the CTX-PF regimen in the EXTREME trial were RR, 39.7% versus 36%; DCR, 70.7% versus 81%; median OS, 9.0 versus 10.1 months; median PFS, 6.0 versus 5.6 months; grades 3–4 AEs, 24.2%

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Table 3: Adverse events

	Cisplatin sensitive ($n=88$)		Cisplatin-refractory ($n=76$)		Significance between 2 groups	
Adverse events	**Any grade, *n* (%)**	**Grade 3 or 4, *n* (%)**	**Any grade, *n* (%)**	**Grade 3 or 4, *n* (%)**	**Any grade**	**Grade 3 or 4**
Any event	86 (97.7)	21 (23.9)	74 (97.4)	16 (21.1)	-	-
Anemia	81 (92)	6 (6.8)	70 (92.1)	8 (10.5)	0.989	0.397
Liver dysfunction	43 (48.9)	3 (3.4)	40 (52.6)	5 (6.6)	0.630	0.473
Mucositis	37 (42)	5 (5.7)	26 (34.2)	1 (1.3)	0.304	0.218
Thrombocytopenia	21 (23.9)	6 (6.8)	18 (23.7)	0	0.979	NA
Neutropenia	18 (20.5)	6 (6.8)	12 (15.8)	3 (3.9)	0.441	0.507
Renal insufficiency	10 (11.4)	0	6 (7.9)	0	0.455	NA
Diarrhea	6 (6.8)	0	5 (6.6)	0	0.951	NA
Vomiting	1 (1.1)	0	0	0	1.000	NA
Skin	66 (75)	8 (9.1)	57 (75)	6 (7.9)	1.000	0.785
Nail	32 (36.4)	1 (1.1)	27 (35.5)	0	0.911	NA

Differences between the two groups were compared using the Pearson test/or Fisher's exact test. NA: Not assessed

Table 4: Multiple cox-regression analysis of overall survival and progression-free survival

Variables	ALL		Cisplatin-sensitive		Cisplatin-refractory	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
OS analysis						
Cisplatin refractory (vs. cisplatin-sensitive)	1.40 (0.97–2.02)	0.071	-		-	
CTX/MTX >9 cycles (vs. ≤9 cycles)[a]	0.38 (0.24–0.60)	<0.001*	0.45 (0.23–0.88)	0.020*	0.23 (0.11–0.49)	<0.001*
CTX/MTX >18 cycles (vs. ≤18 cycles)[b]	0.56 (0.34–0.94)	0.027*	0.60 (0.31–1.17)	0.134	0.51 (0.22–1.20)	0.123
Age at treatment, >65 years (vs. ≤65 years)	0.78 (0.46–1.34)	0.374	0.51 (0.26–1.02)	0.057	1.89 (0.76–4.67)	0.171
ECOG performance status 2–3 (vs. 0–1)	1.27 (0.82–1.98)	0.280	1.39 (0.78–2.46)	0.264	1.78 (0.81–3.89)	0.150
≥2nd line of CTX (vs. 1st line)	0.86 (0.56–1.34)	0.505	0.65 (0.35–1.19)	0.164	1.54 (0.74–3.24)	0.252
Not only locoregional disease (vs. only)	1.36 (0.93–1.99)	0.117	1.54 (0.90–2.64)	0.114	1.34 (0.75–2.37)	0.325
Not only metastatic disease (vs. only)	1.09 (0.65–1.86)	0.739	2.17 (0.92–5.07)	0.076	1.24 (0.59–2.57)	0.572
Post-CTX/MTX systemic treatment (vs. no)	0.40 (0.26–0.62)	<0.001*	0.34 (0.18–0.64)	0.001*	0.48 (0.23–1.00)	0.050
Progression-free survival analysis						
Cisplatin refractory (vs. cisplatin-sensitive)	1.35 (0.94–1.92)	0.104	-		-	
CTX/MTX >9 cycles (vs. ≤9 cycles)[a]	0.17 (0.10–0.29)	<0.001*	0.21 (0.10–0.42)	<0.001*	0.11 (0.05–0.27)	<0.001*
CTX/MTX >18 cycles (vs. ≤18 cycles)[b]	0.52 (0.33–0.84)	0.007*	0.42 (0.22–0.80)	0.009*	0.58 (0.27–1.25)	0.163
Age at treatment, >65 years (vs. ≤65 years)	0.77 (0.47–1.25)	0.289	0.73 (0.39–1.34)	0.726	0.79 (0.30–2.09)	0.627
ECOG performance status 2–3 (vs. 0–1)	1.13 (0.74–1.72)	0.564	1.37 (0.79–2.38)	0.261	0.82 (0.38–1.76)	0.606
≥2nd line of CTX (vs. 1st line)	1.04 (0.69–1.56)	0.861	0.83 (0.47–1.44)	0.505	1.55 (0.77–3.14)	0.225
Not only locoregional disease (vs. only)	1.72 (1.18–2.51)	0.005*	1.69 (0.98–2.92)	0.059	2.05 (1.16–3.61)	0.013*
Not only distant metastatic disease (vs. only)	1.33 (0.78–2.26)	0.296	0.71 (0.31–1.63)	0.423	2.03 (0.98–4.24)	0.058
Post-CTX/MTX systemic treatment (vs. only)	0.84 (0.54–1.31)	0.440	0.74 (0.39–1.42)	0.364	0.98 (0.49–1.97)	0.958

*P<0.05 significance, [a]CTX/MTX >9 cycles indicates CTX/MTX >9 and ≤18 cycles cycles in multivariate analysis, [b]CTX/MTX ≤18 cycles indicates CTX/MTX >9 and ≤18 cycles in multivariate analysis. Systemic therapy included chemotherapy, molecular targeted therapy, and immunotherapy.
HR: Hazard ratio, CI: Confidence interval, CTX/MTX: Cetuximab/methotrexate, ECOG: Eastern Cooperative Oncology Group, OS: Overall survival, ALL: Includes both cisplatin-sensitive and cisplatin-refractory group

versus 82%; grades 3–4 skin reactions, 8.6% versus 9%; and 1-year survival rate, 32.8% versus ~40% [Table 5]. One possible explanation for the lower effectiveness in our study relative to CTX-PF could be the lack of maintenance CTX in the current study, as per Taiwan NHI regulations. In the EXTREME trial, after 18 weeks of scheduled therapy and with controlled disease, CTX maintenance was administered to 45% of patients for a median of 11 weeks. Furthermore, in the Taxane-CTX-cisplatin regimen, 60%–70% of patients received CTX maintenance for 11–14 weeks, resulting in an OS of around 14 months.[11,13,19] It seems that CTX maintenance yields a longer survival period. Twenty-three (23/58, 40%) of our patients with residual reimbursed CTX (from AE-related reduced dose intensity) had an extended CTX/MTX treatment for a median of two cycles (range 1–7). Whether an unconstrained and efficacy-based reimbursement after 18 weeks of CTX can improve the CTX/MTX outcomes of our patients warrants further investigation. However, in comparison with the PF regimen in the EXTERME trial, our CTX/MTX treatment showed higher RR (39.7% vs. 20%), DCR (70.7% vs. 60%), median OS (9.0 vs. 7.4 months), and median PFS (6.0 months vs. 3.3 months); fewer grades 3–4 AEs (24.2% vs. 76%) and grades 3–4 skin reactions (8.6% vs. 9%); and a slightly better 1-year survival rate (32.8%

Table 5: Comparisons with the standard of care in phase III trials and clinical studies using cetuximab/methotrexate combination

Patients	Trials	Regimen	*n*	Best response, percentage (95% CI)		Survival (months); 1-year survival (%)			Adverse events	
				Response	Disease control	Median PFS (95% CI)	Median OS (95% CI)	Percentage (95% CI)	Any (%)	Grades 3–5 (%)
Cisplatin sensitive	Extreme[5]	CTX-PF	222	36 (29–42)	81 (75–86)	5.6 (5.0–6.0)	10.1 (8.6–11.2)	~40	-	82
	Extreme[5]	PF	220	20 (15–25)	60 (53–67)	3.3 (2.9–4.3)	7.4 (6.4– 8.3)	~30	-	76
	KEYNOTE-048[8]	CTX-PF	278	36	88	5.2 (4.9–6.0)	10.7	44		83
	The present study	CTX-MTX*	58	39.7 (27–53)	70.7 (57–82)	6 (4.9–7.0)	9 (7.6–10.4)	32.8 (20.3–45.3)	96.6	24.2
Cisplatin refractory	CheckMate 141[7,9]	SoC[a]	121	5.8 (2.4–11.6)	41.3 (32.9–50.2)	2.3 (1.9–3.1)	5.1 (4.0–6.0)	16.6 (8.6–26.8)	77.5	35.1
	KEYNOTE-040[6]	SoC[b]	248	10.6 (6.6–14.5)	-	2.3 (2.1–2.8)	6.9 (5.9–8.0)	26.5 (21.2–32.2)	84	36
	The present study	CTX-MTX	76	31.6 (21.4–43.3)	51.3 (39.6–63)	4.0 (2.3–5.6)	6.0 (4.7–7.2)	23.2 (23.1–23.3)	97.4	21
Cisplatin unfit	Ham *et al*., 2020[16]	CTX-MTX	30	13.6	-	4.5 (0.9–23.2)	8 (0.9–23.8)	-	100	46.7
Nonspecified[c]	Sukari *et al*., 2019[17]	CTX-MTX	54	9.2	72.2	2.9 (2.1–4.8)	8.6 (7.0–12.2)	-	-	11

*1st line CTX-MTX *n*=58, [a]SoC in CheckMate 141: CTX 12.4%; MTX 43.0%, docetaxel 44.6%, [b]SoC in KEYNOTE-040: CTX 29.4%; MTX 26.2%, docetaxel 44.4%, [c]Received CXT in the past: 26%. CTX: Cetuximab, MTX: Methotrexate, PFS: Progression-free survival, OS: Overall survival, CI: Confidence interval, PF: Cisplatin/5-fluorouracil, SoC: Standard of care

vs. ~30%) [Table 5]. Our study demonstrated that using a combination of CTX/MTX has favorable efficacy in terms of both efficacy and AEs, making it applicable in various contexts, particularly in cisplatin-unfit or PF-unfit RM-HNSCC patients.

Among cisplatin-refractory patients in the present study, even though the therapeutic outcomes were not as effective as with immunotherapy with nivolumab (CheckMate 141)[7,9] or pembrolizumab (KEYNOTE-040),[6] the CTX/MTX provided higher RR (31.6% vs. 5.8%–10.6%), DCR (51.3% vs. 41.3%), and median PFS (4.0 vs. 2.3 months), but not median OS (6.0 months vs. 5.1–6.9 months) in comparison to SoC (CTX, MTX, or docetaxel alone) in both immunotherapy trials. The rate of occurrence of grades 3–5 AEs in those receiving CTX/MTX (21%) was also lower than the 35%–36% of those receiving SoC. Docetaxel, which is more effective but also more toxic than CTX and MTX, was used as the SoC in 44.5% of patients in both trials, which may account for the above results. However, the high vulnerability to severe neutropenia in Asian patients receiving docetaxel precludes its common use in Asian patients.[12,13] In CheckMate 141, the proportion of patients receiving docetaxel versus MTX as SoC in the global cohort was 44.6% versus 43.0%, but it was 18.2% versus 72.7% in Asian patients.[20] Considering the current results, CTX/MTX may provide a practical choice for patients with docetaxel-unfit, cisplatin-refractory RM-HNSCC. Nevertheless, taxanes remains an alternative partner to combine with CTX.[21] In trials with about half of the cohorts being cisplatin-refractory patients, CTX-paclitaxel (60–80 mg/m^2 weekly) showed an RR of 38%–55%, a PFS of 3.9–6.0 months, and an OS of 7.6–16.8 months.[22-24]

In terms of safety in the use of a CTX/MTX combination regimen, fewer AEs occurred in the present study compared to those reported in other trials.[5,6,16,17,25] Skin reactions, hypomagnesemia, and hepatotoxicity were the major AEs reported in other CTX/MTX studies.[16,17] The major CTX-related AE in the current trial was dermatitis, and no grades 3–4 AEs such as renal insufficiency, diarrhea, or vomiting were reported in either cisplatin-refractory or cisplatin-sensitive patients. No hypomagnesemia occurred in our patients; however, patients were not routinely monitored for this condition so that the incidence rate may have been underestimated.

Multivariable analyses showed that the survival outcomes of those receiving CTX/MTX were not correlated with being cisplatin-refractory or not, age ≥65 or not, CTX/MTX as the first-line treatment or not, or ECOG performance status 0–1 versus 2–3 [Table 4]. These results suggest that CTX/MTX can be used in RM-HNSCC patients in variable contexts. The disease state of locoregional only disease carried a worse PFS, but not OS, in cisplatin-refractory patients and a trend in cisplatin-sensitive patients. In cisplatin-sensitive patients in the TPExtreme trial, CTX-P-Taxotere provided a better PFS than CTX-PF in patients with locoregional-only disease.[11]

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However, in the KEYNOTE-048 trial, pembrolizumab ± PF showed no OS or PFS benefit compared to CTX-PF in patients with locoregional-only disease.[26] Although it is presumed that patients with locoregional disease may need treatment with higher RR to prevent lethal airway or dysphagia events in the setting of RM-HNSCC, the inconsistent results between studies indicate the need for further clarification.

We must mention that NHI regulations limit CTX administration to 18 cycles, even if no progression is noted. Therefore, unlike in clinical trials that provide patients with maintenance CTX, no maintenance CTX was provided in our study. In addition, the NHI in Taiwan reimburses neither for immunotherapy nor for other molecular-targeted therapy after treatment with CTX; therefore, there were no patients who received immunotherapy after CTX/MTX. The only nonchemotherapy treatment given after the CTX-MTX in our study cohort was afatinib (in one patient) and erlotinib (in two patients). We assume that any post-CTX/MTX therapy was of limited efficacy and had an insignificant impact on survival. Our study provides evidence of the effect of modified treatment protocol (i.e., limiting CTX treatment cycles) and the real-life situation when patients cannot afford continuous maintenance CTX or immunotherapy to control their disease.

The present study has several limitations, including its retrospective study design and single medical center setting, which may limit inferences of causation and generalization of results to other locations or populations. Matched controls or controls receiving other regimens were not used; instead, we compared results with data from other clinical trials. While this method yields adequate comparisons, it does not constitute the use of a control group that may have helped to validate the main measures. Furthermore, as mentioned in the discussion above, reimbursement regulations of the Taiwan NHI do not allow CTX maintenance therapy after 18 weeks, which may have influenced therapeutic decision-making.

Conclusion

CTX/MTX combination therapy, even without the use of maintenance CTX, is a safe and effective palliative treatment for patients with both cisplatin-refractory and cisplatin-sensitive RM-HNSCC. Similar efficacy is found in CTX/MTX treatment response, OS, and PFS between the first line and subsequent lines of treatment, as well as between patients with different ECOG performance scores. Although this regimen has not been shown to be as effective as current first-line immunotherapy, it is more effective than the SoC chemotherapy (CTX, MTX, or docetaxel alone) for cisplatin-refractory disease and may be as effective as the PF regimen for cisplatin-sensitive RM-HNSCC patients. Given the emerging studies on the improved efficacy of chemotherapy postimmunotherapy, further study is warranted to investigate the potential of using combination CTX/MTX as a safe and effective palliative treatment for RM-HNSCC in combination with immunotherapy or postimmunotherapy.

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Conflicts of interest

There are no conflicts of interest.

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