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Brief Report

Novel Effective Therapeutic Regimen for Recurrent/Metastatic Head and Neck Squamous Cell Cancer: Concurrent Triple Oral Metronomic Chemotherapy and Immunotherapy

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INTRODUCTION

Head and neck cancer is the sixth most common cancer worldwide and the third most common malignancy in the Indian subcontinent. The median survival is poor and ranges between 6-15 months, depending on patient-related factors.[1] Over the last two decades, immunotherapy has revolutionized the treatment of solid tumors. Head and neck squamous cell cancers (HNSCC) are known to be immunogenic. Immunotherapy with or without chemotherapy has become a standard of care in the management of recurrent and metastatic (R/M) HNSCC in the frontline and subsequent settings.[2–5] In KEYNOTE 048, immunotherapy with chemotherapy was shown to enhance survival in R/M HNSCC irrespective of the programmed death-ligand 1 (PD-L1) status, while immunotherapy alone demonstrated survival advantage in PD-L1 combined positive score greater than 20%.[4] The frontline chemotherapy backbone for KEYNOTE 048 study and before that for the EXTREME study has mostly been platinum and 5-fluorouracil (5-FU).[4,5] It is well-recognized that this particular regimen is fraught with toxicity-related challenges, and most oncologists have moved over to using other chemotherapy backbones (i.e., platinum-paclitaxel or platinum-docetaxel or platinum-nab paclitaxel). Oral metronomic chemotherapy (OMCT) is frequently used in combination regimen of methotrexate, EGFR inhibitor and Cox 2 inhibitor for the treatment of R/M HNSCC in low- and middle-income countries (LMIC), especially in India.[6] OMCT uses frequent low doses of the above oral regimen, given over an extended duration of time, to minimize side effects and maximize response to treatment[7]. In Phase I and II studies of platinum-refractory advanced oral cancer, triple-drug OMCT (TOMCT) demonstrated an overall response rate (ORR) of 42.9%, a 3-month progression-free survival (PFS) rate of 71.1%, and a 6-month overall survival (OS) rate of 61.2%.[8] A TOMCT backbone was recently studied in a phase III trial along with low-dose immunotherapy with nivolumab 40 mg flat dose and shown to be beneficial in this combination. The addition of low-dose

immunotherapy to TOMCT resulted in improved OS in heavily pretreated R/M HNSCC patients.[9] Earlier, the same group had presented real-world evidence on flat low-dose nivolumab at 40 mg with a response rate of 23% in R/M HNSCC patients who were unable to afford the standard dose of nivolumab.[9,10] Combining immune checkpoint inhibitor (ICI) therapy with metronomic chemotherapy may create a synergistic effect that augments antitumor immune responses and clears metabolic competition, which results in immune-mediated elimination of therapy-resistant cancer cells.[11]

Although this phase III trial used TOMCT and low-dose immunotherapy as one of the options for R/M HNSCC, standard-dose immunotherapy in combination with TOMCT remains unexplored. Although anecdotal usage of the combination of TOMCT with standard-dose immunotherapy is popular in India and remains one of the standard regimens for R/M HNSCC, published data with this combination is nonexistent. Here, we present 10 cases of R/M HNSCC treated with a novel regimen combining TOMCT and standard-dose immunotherapy (Table 1).

METHODS

Here, we report a retrospective case series of patients treated between 2017 and 2023 in the Division of Precision and Medical Oncology at Sir H N Reliance Foundation Hospital and Research Centre, Mumbai, India. We included patients with recurrent/metastatic head and neck cancer, responders were identified and reviewed for duration of response, outcomes, and toxicity for the combination treatment of standard-dose immunotherapy and TOMCT. PD-L1 expression in archival, formalin-fixed tumor samples was assessed in the laboratory using the assay (PD-L1 by IHC/Ventana SP263/Dako 22C3 assay) and characterized by the combined positive score (CPS), defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells $\times 100$; a minimum of 100 viable tumor cells must have been present for the specimen to be considered evaluable.

This study was exempt from ethical committee review, as a retrospective clinical chart review of de-identified data. Informed consent was waived.

RESULTS

Ten case charts were reviewed for a combination of standard-dose immunotherapy and TOMCT experience. All patients received TOMCT (Table 2) along with standard-dose immunotherapy, with six patients receiving nivolumab at 3-mg/kg dosage and four patients receiving pembrolizumab at 200 mg per treatment at flat dosage. The TOMCT consisted of weekly oral methotrexate, twice daily celecoxib, and once daily EGFR inhibitor, all given orally. The details of the therapy given are outlined in Table 2. The dosage range for oral methotrexate varied from 10–20 mg once weekly and was dosed consistently for each patient. Celecoxib at 200 mg twice daily was well-tolerated by most patients. The EGFR tyrosine kinase inhibitors (TKI) given were gefitinib in six patients, erlotinib in three patients, and afatinib in one patient. Treatment duration ranged from 24–60 months (median: 35.5 months).

All 10 patients had a radiological complete response to the combined treatment. The PFS range was 12–63 months, with a median (IQR) of 30 (24) months. The OS range was 12–63 months, with a median (IQR) of 33 (24) months. The survival analysis shows that PFS was equal to OS as the patients had durable responses and were alive and when given a durable complete response, immunotherapy was stopped. Five patients quit TOMCT therapy due to mucositis and diarrhea from TKI or targeted therapy. One patient quit treatment as a result of immune-mediated toxicity (immune-mediated nephritis).

DISCUSSION

Immunotherapy with or without chemotherapy, has transformed outcomes in R/M HNSCC.[2–5] Key clinical trials are summarized in Table 3. The phase III KEYNOTE-048 trial[5] established a new paradigm for first-line treatment in patients with R/M HNSCC. Based on this study, either pembrolizumab with or without chemotherapy is the first choice for these patients. CheckMate 141 established nivolumab as an immunotherapy option in the second-line treatment of R/M HNSCC[2,12].

The practice of combining chemotherapy and immunotherapy was first established in non–small cell lung cancer (NSCLC) with the KEYNOTE-021[13] study, which investigated pembrolizumab with different chemotherapy regimens in this group of patients. Furthermore, the combination of pembrolizumab with platinum and pemetrexed showed a significantly higher response rate, PFS, and OS compared with chemotherapy alone in KEYNOTE-189,[14] a phase III trial in advanced non-squamous NSCLC. The success of these trials has led to the establishment of combination chemo-immunotherapy as a standard approach in several different solid tumors and brought about a paradigm shift in the management of advanced solid tumors in general.[13,14]

Oral metronomic therapy involves administration of combination of drugs in a repetitive, low-dose, continuous manner, without any treatment-free interval and over a period of time. OMCT is known to cause a decrease in angiogenesis and an increase in immune activation.[11,15] OMCT is effective on the heterogeneous population of tumor cells, thus eliciting the immune system and turning the nonresponsive “cold” tumor into a responsive “hot” tumor immunologic phenotype.[15] OMCT results in competition for nutrients between tumor and immune cells to be reduced via gradual removal of tumor cells. This would facilitate tumor infiltration by cytotoxic immune cells.[15–16] ICI therapy results in sustained immune cell activation, allowing the effective elimination of therapy-resistant cells as the

Table 1. Clinical characteristics and responses with recurrent/metastatic head and neck cancers treated with a combination of immunotherapy and triple oral metronomic chemotherapy (ICI-TOMCT)-based regimens

Age (Sex)	Diagnosis	PD-L1	Prior Treatment	ICI + TOMCT	Duration	PFS + OS	Remarks
55 y (M)	Squamous cell carcinoma of buccal mucosa	PD-L1 +ve, TPS 4-5% by Ventana SP263	• Surgery • Adjuvant radiotherapy 6 cycles of carboplatin + paclitaxel + cetuximab • Disease progression	• Nivolumab 3 mg/kg once every 2 wk • Celecoxib 200 mg twice daily • Methotrexate 15 mg once weekly • Gefitinib 250 mg once daily	ICI: 24 mo TOMCT: 12 mo	PFS: 48 mo OS: 48 mo	• Complete response • TOMCT stopped at 12 • mo due to mucositis, diarrhea, and rash • ICI stopped at 24 mo
81 y (M)	Squamous cell carcinoma of lateral pharyngeal wall	PD-L1 expression unknown	• Surgery • Adjuvant radiotherapy • Disease progression	• Nivolumab 3 mg/kg once every 2 wk • Celecoxib 200 mg twice daily • Methotrexate 15 mg once weekly • Gefitinib 250 mg once daily	ICI: 36 mo TOMCT: 6 mo	PFS: 60 mo OS: 60 mo	• Platinum resistant • TOMCT stopped at 6 mo due to oral mucositis and diarrhea • ICI stopped at 36 mo • Achieved complete response
60 y (M)	Squamous cell carcinoma of left maxilla	PD-L1 expression unknown	• Surgery • 6 cycles of carboplatin + paclitaxel + cetuximab • Disease progression	• Nivolumab 3 mg/kg once every 2 wk • Celecoxib 200 mg twice daily • Methotrexate 15 mg once weekly • Erlotinib 100 mg once daily	ICI: 24 mo TOMCT: 24 mo	PFS: 30 mo OS: 30 mo	• Complete response • Therapy stopped at 24 mo
65 y (M)	Squamous cell carcinoma of buccal mucosa	PD-L1 expression unknown	• Surgery • Adjuvant radiotherapy • 6 cycles of carboplatin + paclitaxel + cetuximab • Disease progression	• Nivolumab 3 mg/kg once every 2 wk • Celecoxib 200 mg twice daily • Methotrexate 15 mg once weekly • Erlotinib 100 mg once daily	ICI: 24 mo TOMCT: 8 mo	PFS: 30 mo OS: 36 mo	• Complete response • TOMCT stopped after 8 mo due to development of grade 3 oral mucositis • ICI stopped at 24 mo
49 y (M)	Squamous cell carcinoma of tongue	PD-L1 +ve, TPS 60% by Ventana SP263	• Surgery • 3 cycles of carboplatin + paclitaxel + cetuximab on disease progression • Interval debulking surgery • Adjuvant radiotherapy alone • Disease progression	• Pembrolizumab 200mg once every 3 wk • Celecoxib 200 mg twice daily • Methotrexate 10 mg once weekly • Gefitinib 250 mg once daily	ICI: 22 mo TOMCT: 22 mo	PFS: 24 mo OS: 24 mo	• Complete response • Patient stopped therapy at 22 mo

Table 1 continues on next page

Table 1. Continued

Age (Sex)	Diagnosis	PD-L1	Prior Treatment	ICI + TOMCT	Duration	PFS + OS	Remarks
54 y (M)	Squamous cell carcinoma of maxilla	PD-L1 +ve,70%–80% by IHC	• Surgery • Chemo–radiotherapy with weekly cisplatin • Disease progression	• Pembrolizumab 200 mg once every 3 wk • Celecoxib 200 mg twice daily • Methotrexate 10 mg once weekly • Gefitinib 250 mg once daily	ICI: 12 mo TOMCT: 12 mo	PFS: 19 mo OS: 19 mo	• Complete response • Patient stopped therapy at 12 mo
42 y (F)	Squamous cell carcinoma of retro-molar trigone	PD-L1 expression unknown	• Surgery + observation • Disease progression	• Nivolumab 3 mg/kg once every 2 wk • Celecoxib 200 mg twice daily • Methotrexate 10 mg once weekly • Gefitinib 250 mg once daily	ICI: 30 mo TOMCT: 30 mo	PFS: 30 mo OS: 30 mo	• Complete response • Therapy ongoing
68 y (M)	Squamous cell carcinoma of the right maxillary sinus	PD-L1 +ve TPS 90% by Dako 22C3	• Surgery • Adjuvant chemoradiotherapy with weekly cisplatin • Salvage surgery • Disease progression	• Pembrolizumab 200 mg once every 3 wk • Celecoxib 200 mg twice daily • Methotrexate 15 mg once weekly • Afatinib 30 mg once daily	ICI: 22 mo TOMCT: 13 mo	PFS: 42 mo OS: 42 mo	• Complete response • Stopped TOMCT at 13 mo due to oral mucositis • Stopped ICI at 22 mo
47 y (M)	Squamous cell carcinoma of left retromolar trigone	PD-L1 +ve TPS 10% by Dako 22C3	• Definitive chemo-radiotherapy with weekly cisplatin • 3 cycles of docetaxel + cisplatin + 5Fu + cetuximab • Disease progression	• Pembrolizumab 200 mg once every 3 wk • Celecoxib 200 mg twice daily • Methotrexate 20 mg once weekly • Erlotinib 100 mg once daily	ICI: 18 mo TOMCT: 9 mo	PFS: 63 mo OS: 63 mo	• Complete response • TOMCT stopped at 9 months due to severe recurrent mucositis • ICI stopped at 18 months due to immune mediated nephritis
50 y (M)	Metastatic keratinizing squamous cell carcinoma left parapharyngeal space	PD-L1 CPS: 29% by Ventana SP263	• Surgery (Neck dissection) + CTRT • Surgery + adjuvant radiotherapy • Disease progression • Salvage surgery	• Nivolumab 3 mg/kg once every 2 wk • Celecoxib 200 mg twice daily • Methotrexate 10 mg once weekly • Gefitinib 250 mg once daily	ICI: 12 mo TOMCT: 12 mo	PFS: 12 mo OS: 12 mo	• Complete response • Therapy ongoing

ICI: immune checkpoint inhibitors; TOMCT: triple oral metronomic chemotherapy; PFS: progression-free survival; OS: overall survival; TPS: tumor proportion score; CTRT: concurrent chemoradiotherapy; CPS: combined positive score; PD-L1: programmed cell death ligand 1; +ve: positive.

Table 2. Treatments included in immunotherapy and triple oral metronomic chemotherapy

Drug	Dose	Frequency	No. of Patients
Immune checkpoint inhibitors			
Nivolumab	3 mg/kg	Once every 2 wks	6
Pembrolizumab	200 mg	Once every 3 wks	4
Tyrosine kinase inhibitors			
Gefitinib	250 mg	Once daily	6
Erlotinib	100 mg	Once daily	3
Afatinib	30 mg	Once daily	1
Celecoxib	200 mg	Twice daily	10
Methotrexate	10 mg	Weekly	4
	15 mg		5
	20 mg		1

immune cells are now able to infiltrate the tumor core better after the OMCT has worked on the outer surface of the tumor. The combination of two therapeutic modalities, OMCT and ICI therapy, creates a synergistic effect[16] (Fig. 1).

TOMCT has yielded promising results in R/M HNSCC, with ease of delivery, improved quality of life, limited side effects, and improved outcomes, especially in platinum-refractory patients.[8,17,18]

Although the phase III study by Patil et al.[1] was practice changing for the usage of immunotherapy in LMICs, it was a reminder that we lacked data regarding the outcomes of combining standard-dose immunotherapy and TOMCT. In KEYNOTE 048, grade 3 or worse all-cause adverse events occurred in 164 (55%) of 300 treated participants in the pembrolizumab alone group, 235 (85%) of 276 in the pembrolizumab with chemotherapy group, and 239 (83%) of 287 in the cetuximab with chemotherapy group.[5,19] Patil et al.[9] reported findings in a randomized clinical trial of low-dose nivolumab in advanced head and neck cancers. This trial reported grade 3 and above adverse events as 46.1% (35, $n = 76$) in oral metronomic therapy plus low-dose nivolumab[9,20]. Compliance with chemotherapy is an issue that needs to be considered. In platinum-based concurrent chemoradiotherapy or palliative chemotherapy,

Table 3. Clinical trials in recurrent/metastatic head and neck cancer

Trial Title and Registry ID	Phase	No. of Patients and Treatment Groups	Outcome Measures
OMCT "Low-cost oral metronomic chemotherapy versus intravenous cisplatin in patients with recurrent, metastatic, inoperable head and neck carcinoma: an open-label, parallel-group, non-inferiority, randomised, phase 3 trial"[17] Trial ID: CTRI/2015/11/006388	III	422 patients Oral metronomic chemotherapy group: 213 patients Intravenous cisplatin group: 209 patients	PFS 3.23 vs 1.63 mo OS 7.5 vs 6.1 mo
Keynote-048 "Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study"[5] Trial ID: NCT02358031	III	882 patients Pembrolizumab alone: 301 patients Cetuximab + chemotherapy (EXTREME): 300 patients Pembrolizumab + Chemotherapy: 281 patients	Pembrolizumab alone: ORR 17%, OS 11.6 mo vs EXTREME: ORR 36%, OS 10.7 mo Pembrolizumab + Chemotherapy: ORR 36%, OS 13 mo vs EXTREME: ORR 36%, OS 10.7 mo
Checkmate-141 "Nivolumab for recurrent squamous-cell carcinoma of the head and neck"[2] Trial ID: NCT02105636	III	361 patients Nivolumab: 240 patients SOC: 121 patients	Nivolumab: ORR 13.3%, OS 7.5 mo SOC: ORR 5.8%, OS 5.1 mo
Keynote -040 "Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study"[4] Trial ID: NCT02252042	III	495 patients Pembrolizumab: 247 patients SOC: 248 patients	495 patients Pembrolizumab: ORR 14.6%, OS 8.4 mo SOC: ORR 10.1%, OS 6.9 mo
Flat-dose Nivolumab "Real-world data of use of nivolumab in platinum refractory head and neck cancers"[30]	Retrospective	42 patients	RR 23.1%, PFS, median OS 6.7 mo (3.4-8.8) Median PFS 2.3 mo (0.6-4.02)
Low dose Nivolumab + OMCT "Low-dose immunotherapy in head and neck cancer: a randomized study"[9] Trial ID: CTRI/2020/11/028953	III	151 patients	RR 69.2% PFS 6.57 mo OS 6.7 vs 10.1 mo

OMCT: oral metronomic chemotherapy; PFS: progression-free survival; OS: overall survival; ORR: overall response rate; RR: response rate; SOC: standard of care.

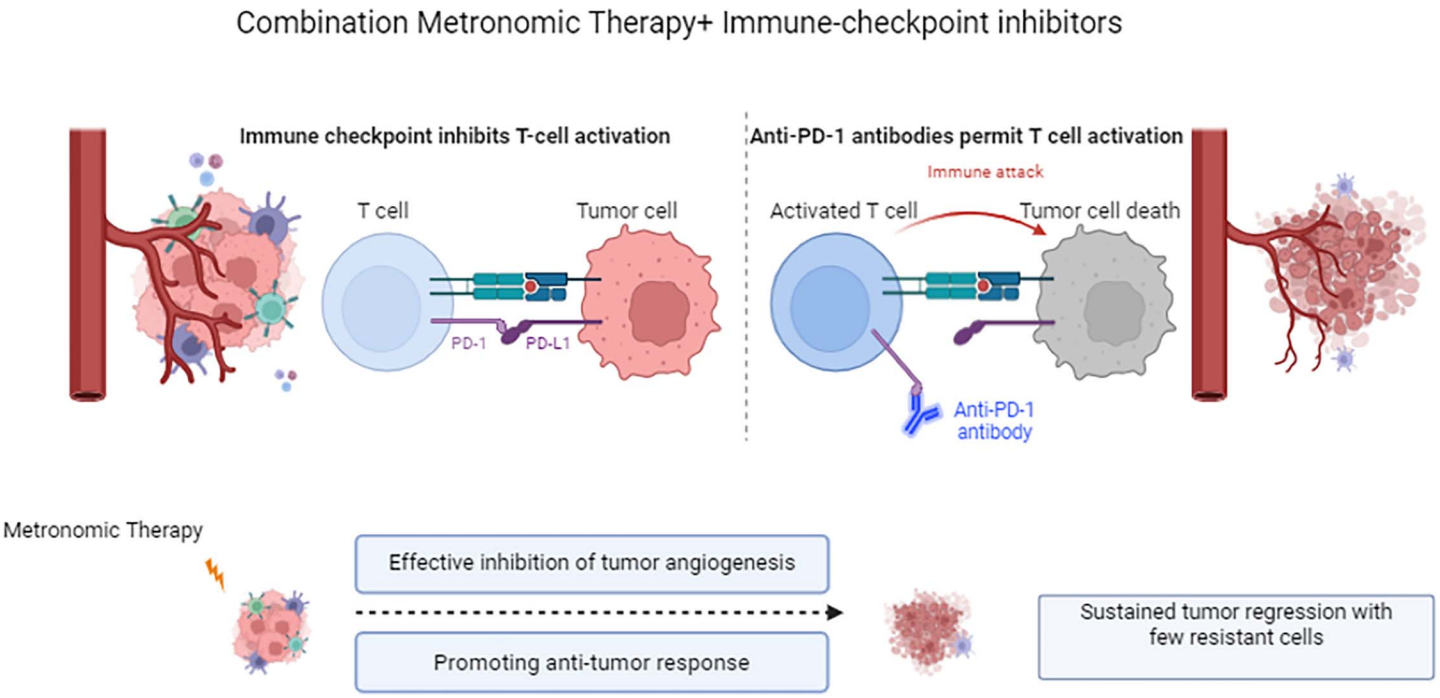

Figure 1. Schematic representation of mechanism of action of metronomic chemotherapy and immunotherapy on tumors. This figure was created with BioRender.com.

administration of the maximum tolerated dose of cisplatin (100 mg/m^2 every 3 weeks) is generally considered a gold standard regimen; however, it is also considered to be associated with significant toxicities.[21] Metronomic chemotherapy in head and neck cancer has been studied extensively in a multicenter, prospective, single-center study by Sultania et al.[22] studied the feasibility of metronomic therapy in advanced oral cancer and the compliance rate was reported to be 89.8%. Here, we report 10 cases of R/M HNSCC that responded well to concurrent treatment with standard-dose immunotherapy and TOMCT.

There are limitations to our study. First, there may have been a selection bias as this study was performed at a single institution using a cohort that mainly consisted of patients with recurrent/metastatic head and neck cancer, and responders were included in the study, therefore the results may not be widely applicable for all patients. All 10 cases had radiologic complete responses on follow-up imaging, irrespective of the PD-L1 status, which was largely unknown at the time of treatment allocation, in all patients. The addition of standard-dose immunotherapy to TOMCT improved outcomes in this cohort of patients. The development of immunotherapy has improved survival in solid tumors, yet it is not available to most people in LMICs who might benefit from it.[23,24] All patients were able to afford standard-of-care full-dose immunotherapy; however, we have not performed a formal cost-effective analysis, which could be a future area of study.

CONCLUSION

Head and neck/oral cancer is common in many parts of the world and is associated with poor median survival for which novel therapeutic combinations are urgently needed. Integrating clinical trial findings into oncology practice requires consideration of several factors, such as immediate symptom relief, short- versus long-term benefits, toxicity, quality of life, logistics, and financial burden. The major challenge in adopting the KEYNOTE-048 regimen with platinum and 5-FU with pembrolizumab in a community-based practice combination is 5-FU–related toxicity and central venous access for infusion therapy in frail patients with poor nutrition. Oral metronomic chemotherapy is a proven alternative to standard-of-care chemotherapy options, especially in post-platinum failure scenarios. In our case series of 10 patients, standard-dose immunotherapy and OMCT were a well-tolerated and effective regimen with low rates of adverse events. All 10 patients had a radiologic complete response and the combination appeared to improve survival outcomes. Therefore, the combination of TOMCT with standard-dose immunotherapy is an appealing option for further study. We suggest a prospective study of standard-dose immune checkpoint inhibitors with TOMCT as a next step. Larger randomized controlled trials are necessary to establish the efficacy and safety of this combination therapy.

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