Original Article
Middle East Journal of Cancer; January 2025; 16(1): 99 - 107

Clinical Benefits of Metronomic Chemotherapy in Platinum-Refractory, Recurrent, and Metastatic Head and Neck Squamous Cell Carcinoma

Amira Elwan*♦, MD, Adel Bakry, MD, Mohamed Eesa***, MD, Hoda Ismail***, MD, Mohamed Abdelmohsen Alnemr***, MD**

**Clinical Oncology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt*
***Medical Oncology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt*
****Otorhinolarngology-Head and Neck Surgery Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt*

Please cite this article as: Elwan A, Bakry A, Eesa M, Ismail H, Alnemr MA. Clinical benefits of metronomic chemotherapy in platinum-refractory, recurrent, and metastatic head and neck squamous cell carcinoma. Middle East J Cancer. 2025;16(1): 99-107. doi: 10.30476/mejc.2024.101525.2034.

Received: January 28, 2024;
Accepted: June 19, 2024

Abstract

Background: Patients with platinum-refractory disease who experience early treatment failure of head and neck squamous cell carcinoma (HNSCC) exhibit a dismal prognosis. Metronomic chemotherapy is a promising treatment schedule in clinical practice for HNSCC. Oral metronomic chemotherapy with methotrexate, celecoxib, and capecitabine regimens was effective because of overcoming drug resistance and antiangiogenesis effects. We aimed to improve treatment outcomes of recurrent, platinum–resistant, and metastatic HNSCC.

Method: In this prospective clinical trial, 94 patients diagnosed with advanced/recurrent HNSCC were enrolled. Patients received triple therapy, including capecitabine, methotrexate, and celecoxib. The multidisciplinary team evaluated treatment toxicity, response, progression-free survival (PFS), and overall survival (OS). Kaplan Meier curve was used to show the survival/Wilcoxon signed-rank test.

Results: The most common observable toxicity findings were grade 1 plus grade 2 fatigue in 49 (52.1%), oral mucositis in 40 patients (42.5%), and anemia in 37 patients (39.4%) in the absence of notified grade 3 or 4 toxicities. 20 patients out of 94 exhibited complete responses (CRs). One and two-year PFS rates were 16% and 11.7%; and one and two-year OS were 21.3% and 17 %, respectively. Two median years PFS was 4 months, and two median years OS was 8 months (SPSS 16.0 for Windows, Wilcoxon signed-rank test, P value ≤ 0.05 is significant).

Conclusion: Capecitabine, methotrexate, and celecoxib combined chemotherapy are effective and tolerable in treating platinum-refractory, recurrent, and metastatic HNSCC with non-inferior clinical outcome results, especially in poor societies.

Keywords: Squamous cell carcinoma of head and neck, Refractory, Methotrexate, Celecoxib, Metronomic chemotherapy

♦Corresponding Author:
Amira Elwan, MD
Clinical Oncology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
Email: Toamira_elwan@yahoo.com

Introduction

Head and neck cancers rank as the seventh most prevalent type of cancer on a global scale.[1] In Egypt, 30% of adults are current smokers.[2] HPV is associated with the risk for head and neck squamous carcinoma (HNSCC) among Egyptian population.[3] Patients with platinum-refractory disease with early head and neck cancer treatment failure show a poor prognosis. Within six months of platinum-refractory disease, a progression occurs upon receiving definitive treatment, including first-line platinum-based chemotherapy; early failure is a treatment failure within one month of local therapy.[4]

Metronomic chemotherapy is a promising treatment schedule in clinical practice for various cancer types, including oral cavity squamous carcinoma.[5–11] These treatments overcome drug resistance and have antiangiogenesis effects.[12,13] The addition of Celecoxib augment the antiproliferative action of methotrexate (MTX).[14]

Triplet erlotinib, MTX, and celecoxib therapy are effective in recurrent oral cavity cancers. Chemotherapy combinations are warranted in patients with an expected poor outcome.[15]

The combined therapy of MTX and celecoxib shows cost-effectiveness and convenience. The treatment has diminutive toxicity profile and provides a reasonably better quality of life, pain control and survival benefits in patients with advanced/recurrent HNSCC.[16]

Oral metronomic chemotherapy with MTX, celecoxib, and capecitabine regimens was effective.[17] Combined chemotherapy with MTX and Celecoxib provides better tolerability and acceptable clinical outcomes comparable with capecitabine alone or keeping supportive treatment solely in patients with metastatic, recurrent, and advanced HNSCC. Combined chemotherapy improves the quality of life.[18] Mateen et al. reported the combination efficacy of oral MTX and capecitabine in progressed HNSCC. The treated patients for six months had 18% two-year progression-free survival (PFS) and 40% two-year overall survival (OS).[19]

Therefore, the present study aimed to improve treatment outcome of recurrent/platinum–resistant and metastatic HNSCC.

Material and Methods

We studied 94 recurrent, resistant, and metastatic HNSCC cases in a prospective clinical study from January 2021 to December 2023. A written informed consent was obtained from all participants, and the Ethical Research Committee of the Faculty of Medicine, Zagazig University, approved the study (Approval No.:9102). The study was conducted according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria

Patients with documented squamous cell carcinoma of head and neck pathology had progressed within one month of surgery/radiation or six months of platinum-based systemic therapy and were planned for palliative chemotherapy, patients aged ≥18 years, an Eastern Cooperative Oncology Group performance status of ≤ 2, presence of measurable disease defined per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[20] and accepted organ functions.

Exclusion criteria

Patients were fit for palliative surgery or re-irradiation, nasopharyngeal origin. We excluded patients with uncontrolled comorbidities, electrocardiography abnormalities or history of cardiac problems, previous target therapy proposal, patients with incomplete data in medical records, and patient refusal.

Pre- and post-metronomic therapy assessments were done by full history, physical examination, and endoscopies such as nasopharynx laryngoscopy in some situations; radiological evaluation was performed (e.g., head and neck ± chest computed tomography with contrast, head and neck magnetic resonance with contrast ± positron emission tomography/computed tomography scan (PET/CT) to assess patient status).

Triple therapy protocol

Capecitabine: An oral dose of 500 mg was administered daily/12 hours, starting on Days 1-14, with 100 mg celecoxib capsule orally, twice

Table 1. Clinicopathological features of head and neck squamous cell carcinoma in 94 patients

Characteristics	(N=94)		Characteristics	(N=94)	
	N	%		N	%
Age			**Tumor site**		
Median (59)					
Range (44-70)					
≤ 60	59	62.80	Oral cavity	24	25.50
> 60	35	37.20	Oropharynx	13	13.80
Sex			Larynx	48	51.10
Male	84	89.40	Hypopharynx	6	6.40
Female	10	10.60	Others	3	3.20
ECOG			**Disease extent**		
1	31	33	locoregional	81	86.20
2	63	67			
Smoking index			Locoregional+metastatic	13	13.80
0	11	11.70	**Prior chemotherapy**		
1 - 400	40	42.60	Platinium	67	71.30
> 400	43	45.70	Combination platinum + taxens	27	28.70
Tobacco chewer			**Prior radiotherapy**		
No	76	80.90	Yes	88	93.60
Yes	18	19.10	No	6	6.40
Tumor size			**Chemotherapy line number**		
Mean (4.68 ± 1.6)					
≤ 4 cm	45	47.80	1	67	71.30
> 4 cm	49	52.20	≥ 2	27	28.70
Treatment indication					
Definitive treatment intent	54	57.40			
palliative treatment intent	40	42.60			

Categorical variables were expressed as numbers (percentages). Continuous variables were expressed as mean ± SD. ECOG: Eastern Cooperative Oncology Group; Platinium: Cisplatin or carboplatin; Taxens: Paclitaxel or Docetaxel; N: Number

daily, and weekly oral MTX 15 mg /m^2 1 hour before food. The patients received their treatment until uncontrolled toxicity or disease progression.

The treatment response was evaluated three months later; toxicity and survival data were collected from the patient's medical records and by direct patient contact and follow-up at the Clinical Oncology, Medical Oncology, and Otorhinolaryngology-Head and Neck Surgery Departments. Toxicity was evaluated by teamwork according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0.[21]

Tailored surgery post triple therapy involved total laryngectomy, permanent tracheostomy, partial or complete pharyngectomy, unilateral or bilateral neck dissection, and reconstruction in feasible conditions.

Statistical analysis

Continuous variables are mean ± SD, median (range), and categorical variables are a number (percentage). OS was calculated as the time from diagnosis to death or the most recent follow-up contact (censored). At the same time, PFS was the patient's most recent follow-up contact, known as progression-free. The authors used the Wilcoxon signed-rank test to test PFS during pre- and post-regimen treatment; *P*-value ≤ 0.05 was considered significant. SPSS 16.0 for Windows (IBM Inc., Chicago, IL, USA) was used.

Results

Most patients 59/94 (62.8%) aged ≤ 60, 84 /94 patients were male. 63/94 patients were ECOG 2. 43/94 patients were heavy smokers with a smoking index > 400, 40 patients were of a smoking index within 1-400, only 18 patients were tobacco chewer. Tumor size was > 4 cm in 49 patients. The most predominant cancer site was the larynx followed by the oral cavity. Loco regional disease extent was observed in 81 patients, prior platinum therapy we offered for 67 patients, and radiotherapy was delivered in 88 patients (Table 1).

Toxicity outcome

The most common observable toxicity findings

were grade 1 plus grade 2 were fatigue in 49 (52.1%), oral microsites in 40 patients (42.5%) and anemia in 37 patients (39.4%), raised liver enzymes in 29(30.8%) patients, diarrhea in 25 patients (26.5%), dysphagia in 23 patients (24.4%). No grade 3 or 4 toxicities were notified (Table 2), so there was no treatment interruption; the triplet combination was tolerable and affordable for our patients and medical treatment was described for such side-effects and were all controlled.

Response and survival outcome

In the pretreatment, the median PFS was two months, while in the post-treatment regimen, one and two-year PFS rates were 16% and 11.7%, and one- and two-year OS were 21.3% and 17 %, respectively. Two median years of PFS was four months, and two median years of OS was eight months. PFS in the post-treatment was superior to the pretreatment PFS with statistical significance ($P < 0.001$); also, 20 out of 94 exhibited CR, and 24 patients exhibited partial response. In comparison, 32 out of 94 showed stable disease, and 18 patients exhibited progressive disease. The treatment response was assessed three months after the therapy began (Table 3, Figures 1 and 2).

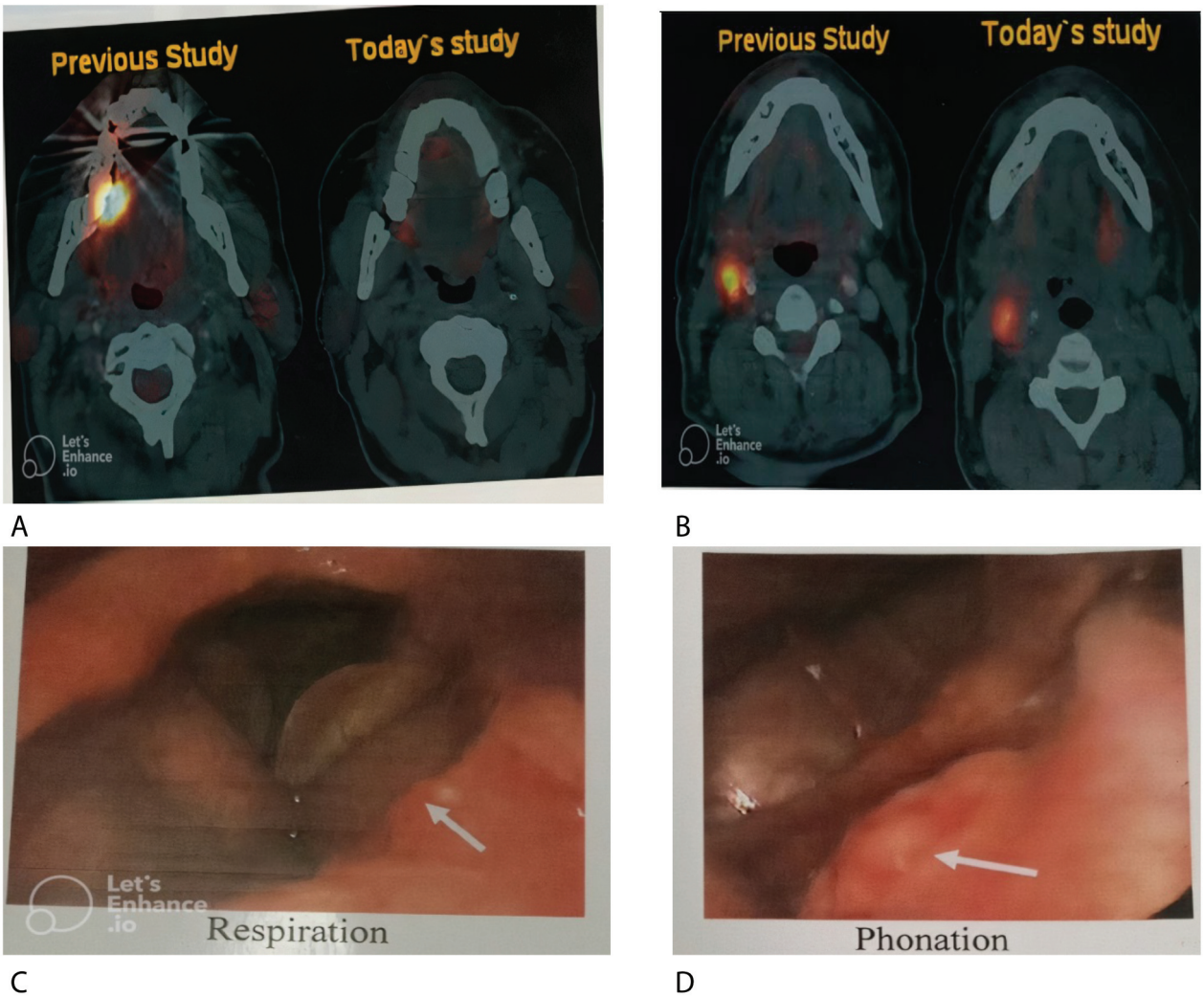

Figure 1. (A, B): Positron emission tomography and computed tomography (PET-CT) scan of a 59 years old male presented with tongue carcinoma shows complete resolution of previously enhancing hyper metabolic soft tissue lesion at the right lateral aspect of the proper hemi tongue, metabolic regression of the previously detected hyper metabolic upper deep cervical lymph node. (C, D): Telescopic video-laryngoscopy showed that multiple, irregular, reddish supraglottic swellings invade the upper part of the inner surface of the epiglottis, both ventricular bands, aryepiglottic fold, bilateral balloon shaped swellings of both vocal folds with unhealthy and markedly congested mucosa in a 49 years old male patient.

Discussion

This prospective study proves that triple therapy included 94 recurrent HNSCC patients who were not eligible for salvage resection or re-irradiation. Treatment consisted of an oral metronomic schedule of capecitabine, celecoxib, and MTX. In the present study, the most common observable toxicity findings were grade 1 plus grade 2 fatigue in 49 (52.1%), oral mucositis in 40 patients (42.5%), and anemia in 37 patients (39.4%). 29 patients (30.8%) had elevated liver enzymes. We did not notify grade 3 or 4 toxicities, and there was no dose reduction or treatment interruption.

The results of metronomic chemotherapy were better than intravenous chemotherapy schedules in palliative conditions.[14]

Table 2. The toxicity profile of head and neck squamous cell carcinoma in 94 patients

Toxicity	Any N (%) G1+G2
Diarrhea	25 (26.50)
Dysphagia	23 (24.40)
Fatigue	49 (52.10)
Hand foot syndrome	12 (12.70)
Oral mucositis	40 (42.50)
Anemia	37 (39.40)
Neutropenia	9 (9.50)
Thrombocytopenia	5 (5.30)
Raised liver enzymes	29 (30.80)
Raised creatinine	10 (10.60)
Raised bilirubin	5 (5.30)

Categorical variables were expressed as numbers (percentage). G1: Grade 1 toxicity; G2: Grade 2 toxicity; N: Number

Vijay Patil et al.[22] treated 213 patients and reported adverse events in a MTX and celecoxib combination treatment protocol. Dose reductions

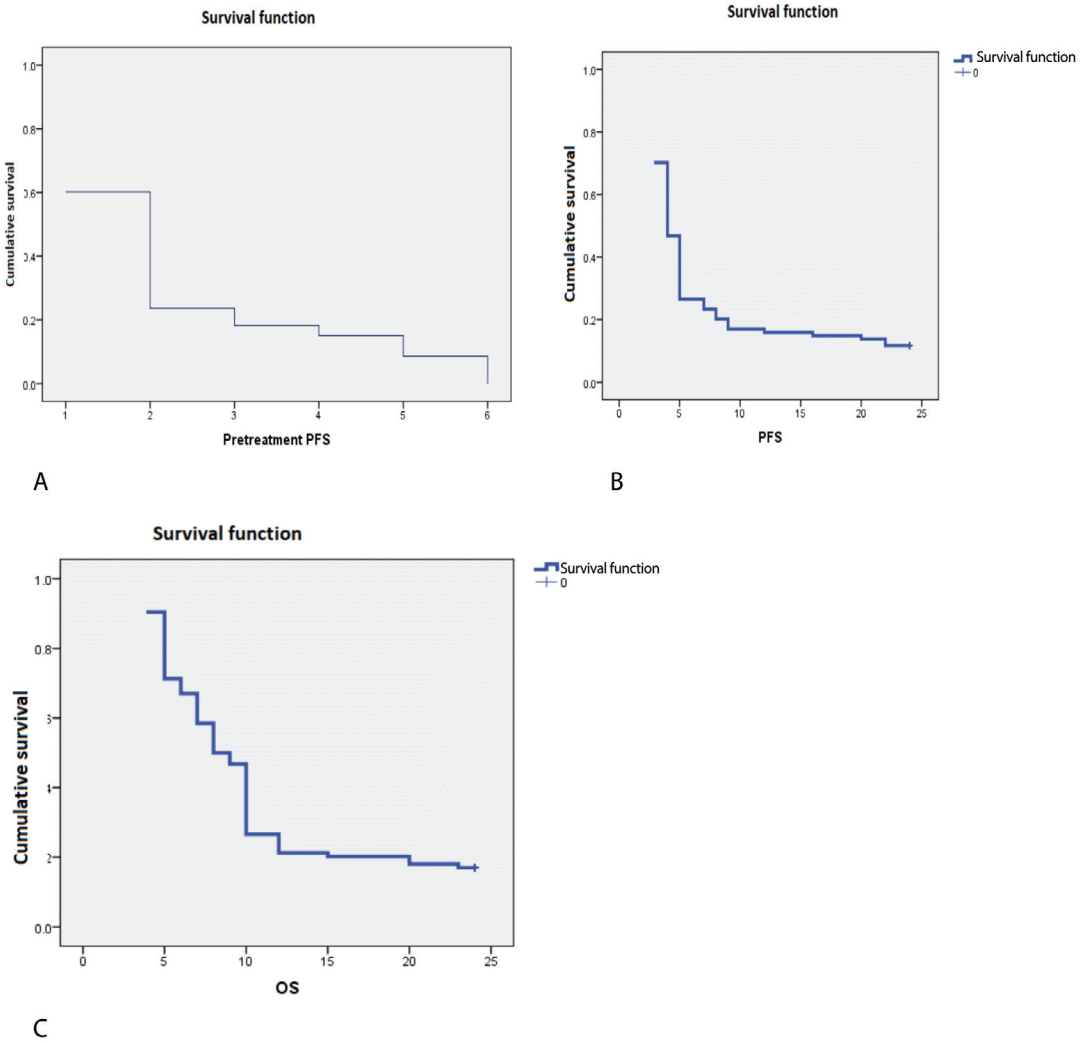

Figure 2. Kaplan Meier plot: (A and B) show pre- and post-treatment PFS; C) shows OS in 94 patients.
PFS: Progression-free survival; OS: Overall survival

were in two patients with diarrhea. The patients had mucositis, myelosuppression, and transaminitis, and stopped treatment in ischemic cardiac events. 19 patients (9%) underwent dose interruptions, 11 (5%) patients had adverse events, and eight (4%) patients were non-compliant. They stopped combined chemotherapy due to toxic profile in five (2%) patients. Permanent discontinuation of oral metronomic chemotherapy was in such conditions as seizure disorder, transaminitis, myelosuppression, pneumonia, cardiac ischemia, and the development of active pulmonary tuberculosis.

Adverse events data were notified by Vijay M et al.[15] Out of 88 patients, 75 patients (85.2%) were tired, and 71 patients (80.7%) showed both rash and anemia. The most common grade 3 to 4 adverse event was hyponatremia in 13 patients, 14.8%, and five patients, 5.7 %, showed raised ALT. They reduced the dose in 12 patients (13.6%). They reduced MTX dose in 10 patients (11.4%), erlotinib in nine patients (10.2%), and celecoxib in eight patients (9.1%).

De Felice et al. reported no severe adverse events. There is debate on the impact of metronomic chemotherapy on tumorigenesis and prognosis.[23]

Salvage surgery remains the cornerstone of managing recurrent HNSCC.[24] V. Patil et al. emphasize that acute adverse events were reported in all patients. The patients received oral weekly MTX and celecoxib in 6 administered cycles. Toxicities were mucositis (25%), odynophagia (25%), dysphagia (32.7%), hyponatremia (30.8%), hypomagnesemia (9.6%) and anemia (61.5%).[25]

Harsh et al. observed that five patients had grade 3+4 mucosal toxicity, 18 had grade 1+2 mucosal toxicity and five patients showed grade 1+2 diarrhea. The study included 84 patients. Treatment was metronomic 15 mg MTX m2 once /week and oral 200 mg celecoxib twice daily. The therapy provides a reasonably better quality of life with pain control and diminutive toxicities.[16]

Annie Kanchan Baa et al.[26] studied (erlotinib + MTX +5-fluorouracil) regimen. Toxicity profiles, such as rash, fatigue, and mucositis were everyday toxicities presented in 23 patients (65%), 14 patients (40%), and nine patients (25.7%), respectively. Five patients (14.2%) showed grade 3 rash, and two (5.7%) showed grade 3 diarrhea.

Table 3. The clinical outcome, including treatment response and survival analysis of head and neck squamous cell carcinoma in 94 patients

Clinical outcome	N = 94
Treatment response	N (%)
CR	20 (21)
PR	24 (26)
SD	32 (34)
PD	18 (19)
Progression (post-treatment)	N (%)
No	11 (11.70)
Yes	83 (88.30)
PFS (pre-treatment)	
Median (months)	2
Range (months)	1.76 – 2.23
PFS (post-treatment)	
Median (months)	4
(Range) 95% CI	3.50 – 4.40
Death	N (%)
Yes	78 (83)
No	16 (17)
Overall survival	
Median (months)	8
(Range) 95% CI	7– 8.90

Continuous variables were expressed as mean (95% confidence interval (CI)); Categorical variables were expressed as numbers (percentage). CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; PFS; Progression-free survival; OS: Overall survival

Ferris RL et al. and Harrington KJ et al. studied access to immune checkpoint inhibitors such as nivolumab in HNSCC. Patients treated with nivolumab had better outcomes and fewer toxicities compared with physician's choice,[27,28] in addition to becoming a new standard for patients with relapsed refractory HNSCC.[29]

Toxicity profile differences reported in the present study compared with other studies were due to variances in the sample size and combination schedules, dose variations, and patient comorbidities.

We found that 20 patients out of 94 (21%) exhibited CR, 24 (26%) patients exhibited partial response, 32 patients out of 94(34%) exhibited stable disease, and 18 (19%) patients exhibited progressive disease.

Parikh et al. studied 15 patients who received metronomic oral MTX, celecoxib, and erlotinib. They reported two patients with CR, seven patients showed partial response, four patients showed stable disease, and two patients showed

progressive disease. However, they delivered palliative radiotherapy and curative radiotherapy to 11 patients before metronomic chemotherapy.[30] Harsh et al.[16] studied metronomic MTX, celecoxib combination. They noted 56% stable disease, partial response in 11%, and progressive disease in 27% of patients. They reported a 67 % clinical benefit rate (partial response + stable disease), while we reported 60% (partial response + stable disease) in the present study.

Annie Kanchan et al. reported that the 3-month overall response rate was 45.7%, partial was 45.7% in 16 patients, eight patients 22.86% had stable disease, 11 patients 31.4% had progressive disease of a total of 35 patients with intravenous MTX and 5Fu combination with erlotinib triplet schedule as intravenous administration ensuring compliance.[26]

Vijay M et al. achieved an overall best of 42.9% response rate (RR) (95% confidence interval (CI), 33.2% to 53.1%; n = 39).[15] They emphasized on combining erlotinib, MTX, and celecoxib results in favorable response rates. RR was 19.5%, with a CR rate of 2.4% reported by Patil et al., achieved by nivolumab as a single agent in patients with relapsed/ refractory advanced HNSCC.[31] In contrast, Choudhary J et al. achieved a response rate of 23% in a retrospective cohort of patients with relapsed HNSCC who received a 40 mg flat dose of nivolumab.[32]

Patil V et al. reported an improved response rate with adding low-dose nivolumab to oral MTX, celecoxib, and erlotinib.[33]

In the present study, one- and two-year PFS rates were 16 and 11.7%, and one- and two-year OS were 21.3 and 17 %, respectively. The two-year median PFS was four months, and the median OS was eight months. In agreement with Vijay Patil et al., the median PFS was 3·13 months. Other studies showed that the median OS was 7·5 months.[22] Parikh et al. reported a median PFS of 4.9 months, consistent with the present study. Median OS was 6.3 months in metronomic therapy in the study of 60 patients offered paclitaxel (80 mg/m^2) weekly and cetuximab versus metronomic celecoxib plus MTX.[30]

PFS was five months, and OS was nine months, as Annie Kanchan Baa et al. reported,[26] with better survival outcomes than the current results.

Parikh et al. showed that cetuximab-based chemotherapy significantly improved OS (P = 0.031) compared with metronomic combined chemotherapy in recurrent/metastatic settings.[30] While superior outcome with patients treated with nivolumab compared with docetaxel, MTX, or cetuximab combinations OS, 7.7 vs. 5.1 months; 1-year survival rate (34 vs. 19.7%).[27,28]

Oral metronomic chemotherapy with MTX, celecoxib, and erlotinib had shown low PFS (range, 2.5–3 months) and OS (range, 5.6–8 months).[4]

Pembrolizumab monotherapy was approved in combination with chemotherapy in the KEYNOTE-048 study. The study showed an improved OS compared with the standard of care (EXTREME; cetuximab + platinum + 5 - fluorouracil) regimen.[34]

Mateen et al. studied 72 patients who underwent oral 2.5 mg twice weekly MTX and 500 mg twice daily capecitabine for six months at least. Patients had 18 % two-year PFS and 40 % OS.[19]

Response rate and survival outcome variations were due to different metronomic schedule considerations. The authors wish for more publications, prospective studies with large sample sizes, chemotherapy combinations ± target, or immune therapy alone. Unfortunately, the absence of a comparative group was one of the study limitations during the COVID-19 pandemic. Combinations are warranted and standard of care for patients with relapsed refractory HNSCC. However, authors wish for good interpreted therapeutic efficacy, quality of life, survival outcome, tolerable toxicity, and on the other hand, budget affordability in poor developing countries.

Conclusion

Capecitabine, MTX, and celecoxib combined therapy are effective and tolerable in treating platinum-refractory, recurrent, and metastatic HNSCC with non-inferior clinical outcome results and gains, especially in poor societies and within the era of high target therapy cost.

Acknowledgments

We would like to thank the patients who participated in this study.

Funding

None declared.

Authors' Contribution

AE: Designed the study, performed the statistical analysis, results' interpretation, designed the figures, performed patients' clinical assessment and follow-up as well as writing this manuscript with assistance from AE, AB, ME, MA, and HI. AE, AB, and MA were involved in planning, organization, supervision and reviewing of the work, and the writing final manuscript. All authors discussed the results, commented on the manuscript, and contributed to the writing of the final manuscript.

Conflict of Interest

None declared.

References

1. Menezes FDS, Fernandes GA, Antunes JLF, Villa LL, Toporcov TN. Global incidence trends in head and neck cancer for HPV-related and -unrelated subsites: A systematic review of population-based studies. *Oral Oncol.* 2021;115:105177. doi: 10.1016/j.oraloncology.2020.105177.
2. Fouda S, Kelany M, Moustafa N, Abushouk AI, Hassane A, Sleem A, et al. Tobacco smoking in Egypt: a scoping literature review of its epidemiology and control measures. *East Mediterr Health J.* 2018;24(2):198-215. https://doi.org/10.26719/2018.24.2.198.
3. Moawad MHED, Shalaby MM, Sadeq MA, Al-Jafari M, A'amar JW, Alsayed O, et al. Insights into head and neck cancer research in Egypt: A scoping review. *Cancer Treat Res Commun.* 2023;37:100782. doi: 10.1016/j.ctarc.2023.100782.
4. Patil VM, Noronha V, Joshi A, Pinninti R, Dhumal S, Bhattacharjee A, et al. Metronomic chemotherapy in platinum-insensitive failures and/or early failures post-multimodality management in oral cancers. *Indian J Med Paediatr Oncol.* 2015;36(3):161-5. doi: 10.4103/0971-5851.166725.
5. Filippi R, Lombardi P, Depetris I, Fenocchio E, Quarà V, Chilà G, et al. Rationale for the use of metronomic chemotherapy in gastrointestinal cancer. *Expert Opin Pharmacother.* 2018;19(13):1451-63. doi: 10.1080/14656566.2018.1512585.
6. Cazzaniga ME, Cortesi L, Ferzi A, Scaltriti L, Cicchiello F, Ciccarese M, et al. Metronomic chemotherapy in triple-negative metastatic breast cancer: The future is now? *Int J Breast Cancer.* 2017;2017:1683060. doi: 10.1155/2017/1683060.
7. Lambrescu I, Fica S, Martins D, Spada F, Cella C, Bertani E, et al. Metronomic and metronomic-like therapies in neuroendocrine tumors—Rationale and clinical perspectives. *Cancer Treat Rev.* 2017;55:46-56. doi:10.1016/j.ctrv.2017.02.007.
8. Woo IS, Jung YH. Metronomic chemotherapy in metastatic colorectal cancer. *Cancer Lett.* 2017;400:319-24. doi:10.1016/j.canlet.2017.02.034.
9. Romiti A, Falcone R, Roberto M, Marchetti P. Tackling pancreatic cancer with metronomic chemotherapy. *Cancer Lett.* 2017;394:88-95. doi:10.1016/j.canlet.2017.02.017.
10. Romiti A, Falcone R, Roberto M, Marchetti P. Current achievements and future perspectives of metronomic chemotherapy. *Investig New Drugs.* 2017;35(3):359-74. doi:10.1007/s10637-016-0408-x.
11. Gourd E. Metronomic chemotherapy option for advanced oral cancer. *Lancet Oncol.* 2019;20(11):e614. doi:10.1016/S1470-2045(19)30623-0.
12. Kerbel RS. A decade of experience developing preclinical models of advanced- or early-stage spontaneous metastasis to study antiangiogenic drugs, metronomic chemotherapy, and the tumor microenvironment. *Cancer J.* 2015;21(4):274-83. doi: 10.1097/PPO.0000000000000134.
13. Natale G, Bocci G. Does metronomic chemotherapy induce tumor angiogenic dormancy? A review of available preclinical and clinical data. *Cancer Lett.* 2018,432:28-37. doi:10.1016/j.canlet.2018.06.002.
14. Patil VM, Noronha V, Joshi A, Muddu VK, Dhumal S, Bhosale B, et al. A prospective randomized phase II study comparing metronomic chemotherapy with chemotherapy (single agent cisplatin), in patients with metastatic, relapsed or inoperable squamous cell carcinoma of head and neck. *Oral Oncol.* 2015;51(3):279-286. doi: 10.1016/j.oraloncology.2014.12.002.
15. Patil VM, Noronha V, Joshi A, Dhumal S, Mahimkar M, Bhattacharjee A, et al. Phase I/II study of palliative triple metronomic chemotherapy in platinum-refractory/early-failure oral cancer. *J Clin Oncol.* 2019;37(32):3032-41. doi: 10.1200/JCO.19.01076.
16. Harsh KK, Maharia SR, Nirban RK, Khatri P, Beniwal S, Kumar HS, et al. Metronomic palliative chemotherapy in locally advanced, recurrent and metastatic head-and-neck cancer: A single-arm, retrospective study of a regional cancer center of North India (Asia). *J Cancer Res Ther.* 2020;16(3):559-64. doi: 10.4103/jcrt.JCRT_702_18.
17. Péron J, Polivka V, Chabaud S, Poupart M, Ceruse P,

Ramade A, et al. An effective and well-tolerated strategy in recurrent and/or metastatic head and neck cancer: successive lines of active chemotherapeutic agents. *BMC Cancer.* 2014;14:504. doi: 10.1186/1471-2407-14-504.
18. Nautiyal V, Kumar V, Arora A, Gupta M, Mehra S, Bansal S, et al. Assessment of quality of life in recurrent and metastatic head and neck cancer after oral metronomic chemotherapy: A prospective interventional study. *J Clin Diagn Res.* 2021; 15(7):XCo1-XCo5. doi:10.7860/JCDR/2021/48916.15089.
19. Mateen A, Adil AR, Maken RN, Khan SA, Arif M. Metronomic chemotherapy in recurrent head and neck cancer. *J Clin Oncol.* 2015;33(15_suppl):e17007. doi:10.1200/jco.2015.33.15_suppl.e17007.
20. Ruchalski K, Braschi-Amirfarzan M, Douek M, Sai V, Gutierrez A, Dewan R, et al. A primer on RECIST 1.1 for oncologic imaging in clinical drug trials. *Radiol Imaging Cancer.* 2021;3(3):e210008. doi: 10.1148/rycan.2021210008.
21. Chung AE, Shoenbill K, Mitchell SA, Dueck AC, Schrag D, Bruner DW, et al. Patient free text reporting of symptomatic adverse events in cancer clinical research using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *J Am Med Inform Assoc.* 2019;26(4):276-85. doi: 10.1093/jamia/ocy169.
22. Patil V, Noronha V, Dhumal SB, Joshi A, Menon N, Bhattacharjee A, et al. 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. *Lancet Glob Health.* 2020;8(9):e1213-e1222. doi: 10.1016/S2214-109X(20)30275-8.
23. De Felice F, Musio D, Tombolini V. Head and neck cancer: metronomic chemotherapy. *BMC Cancer.* 2015;15:677. doi: 10.1186/s12885-015-1705-z.
24. Patil VM, Noronha V, Thiagarajan S, Joshi A, Chandrasekharan A, Talreja V, et al. Salvage surgery in head and neck cancer: Does it improve outcomes? *Eur J Surg Oncol.* 2020;46(6):1052-8. doi: 10.1016/j.ejso.2020.01.019.
25. Patil V, Noronha V, Joshi A, Menon N, Mathrudev V, Bhattacharjee A, et al. RMAC study: A randomized study for evaluation of metronomic adjuvant chemotherapy in recurrent head and neck cancers post salvage surgical resection in those who are ineligible for re-irradiation. *Oral Oncol.* 2022;128:105816. doi: 10.1016/j.oraloncology.2022.105816.
26. Baa AK, Sharma A, Bhaskar S, Biswas A, JeeBharti S, Thakar A, et al. A single-arm feasibility phase II study of EMF (erlotinib + methotrexate + 5-fluorouracil) regimen in platinum-refractory recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). *Ecancermedicalscience.* 2022;16:1451. doi: 10.3332/ecancer.2022.1451.
27. Ferris RL, Licitra L, Fayette J, Even C, Blumenschein G Jr, Harrington KJ, et al. Nivolumab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: Efficacy and safety in CheckMate 141 by prior cetuximab use. *Clin Cancer Res.* 2019;25:5221-30. doi:10.1158/1078-0432.CCR-18-3944.
28. Harrington KJ, Ferris RL, Blumenschein G Jr, Colevas AD, Fayette J, Licitra L, et al. Nivolumab versus standard, single?agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): Health-related quality-of-life results from a randomized, phase 3 trial. *Lancet Oncol.* 2017;18:1104-15. doi:10.1016/S1470-2045(17)30421-7.
29. Rajappa SJ, Pinninti R. Real-world evidence with nivolumab in head-and-neck cancer: Access is key! *Cancer Res Stat Treat.* 2022;5(3):541-3. doi: 10.4103/crst.crst_264_22.
30. Parikh PM, Hingmire SS, Deshmukh CD. Selected current data on metronomic therapy (and its promise) from India. *South Asian J Cancer.* 2016;5:37-47. doi: 10.4103/2278-330X.181623.
31. Patil V, Muthuluri H, Choudhary J, Parekh D, Abraham G, Noronha V, et al. Nivolumab in platinum-refractory head-and-neck cancers – Retrospective observational audit from a tertiary cancer center. *Cancer Res Stat Treat.* 2022;5(3):468-73. doi: 10.4103/crst.crst_185_22.
32. Choudhary J, Hemanth K, Ravikrishna M, Patil V, Prabhash K. Real-world data of using nivolumab in platinum-refractory head and neck cancers. *J Clin Oncol.* 2022;40(16_suppl):e18686. doi:10.1200/JCO.2022.40.16_suppl.e18686.
33. Patil VM, Noronha V, Menon NS, Bhattacharjee A, Kumar S, Purandare N, et al. Phase 3 randomized study evaluating the addition of low-dose nivolumab to palliative chemotherapy in head and neck cancer. *J Clin Oncol.* 2022;40(17_suppl):LBA6016. doi:10.1200/JCO.2022.40.17_suppl.LBA6016.
34. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, et al. 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. *Lancet.* 2019;394(10212):1915-28. doi: 10.1016/S0140-6736(19)32591-7. Erratum in: *Lancet.* 2020;395(10220):272. Erratum in: *Lancet.* 2020;395(10224):564. Erratum in: *Lancet.* 2021;397(10291):2252.