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"TO EVALUATE THE ADVERSE EFFECTS OF TEGAFUR URACIL AS METRONOMIC CHEMOTHERAPY IN PREVIOUSLY TREATED ADVANCED HEAD & NECK CANCER PATIENTS – A RETROSPECTIVE STUDY"

Medical Science

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ABSTRACT

Background: Head and neck squamous cell carcinoma (HNSCC) arising in the oral cavity, oropharynx, larynx, and hypopharynx was the seventh most common cancer worldwide in 2018. It accounts for about 3.9% of all new cancers and approximately 3.8% of all cancer deaths. India has the largest number of oral cancer cases and one-third of the total burden of oral cancer globally. Oral cancer poses a serious health challenge to the nations undergoing economic transition. Fluoropyrimidines are usually well tolerated; most patients only experience slight myelotoxicity (in bolus IV injections) or light-to-moderate gastrointestinal toxicity, such as mucositis and diarrhoea as well as hand and foot syndrome, especially when using protracted techniques of administration **Methods:** This retrospective clinical study is conducted in the department of Radiotherapy, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh. The 4 year data from 1 January 2016 to 1 January 2020 of Tegafur Uracil use in head & neck cancers as metronomic chemotherapy is collected, studied and analyzed. **Findings:** Carcinoma Buccal mucosa was predominant in most of the patients i.e. 33.3%, GBS was seen involved in 6 patients, Anterior 2/3rd Tongue, alveolus, larynx was involved in 5 patients each. Adverse effects of oral Tegafur-Uracil was observed in 14 patients, Grade 1 Nausea and Vomiting was complained by 3(21.4%) patients, oral mucositis in 1(7.1%), Neutropenia 1 (16.6%), Anemia in 2(14.2%), Anorexia in 5(35.7%). **Interpretation:** As a metronomic maintenance regimen, tegafur–uracil was well tolerated with minimal adverse effects. We suggested tegafur–uracil as a maintenance therapy of choice for patients with LA HNSCC.

KEYWORDS

Chemotherapy, Head & Neck cancer, Residual, Adverse Effects, Tegafur-uracil.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) arising in the oral cavity, oropharynx, larynx, and hypopharynx was the seventh most common cancer worldwide in 2018. [1] It accounted for about 3.9% of all new cancers and approximately 3.8% of all cancer deaths. Globally, oral cancer ranks sixth among all types of cancer. India has the largest number of oral cancer cases and one-third of the total burden of oral cancer globally. Oral cancer poses a serious health challenge to the nations undergoing economic transition. [2] In India, around 77,000 new cases and 52,000 deaths are reported annually, which is approximately one-fourth of global incidences. [3] As compared to the west, the concern of oral cancer is significantly higher in India as about 70% of the cases are reported in the advanced stages (American Joint Committee on Cancer, Stage III-IV). Oral cavity cancer includes tumors of the following Site: buccal mucosa, retromolar triangle, alveolus, hard palate, anterior two-thirds of tongue, floor of mouth, and mucosal surface of the lip. Early detection and treatment improves the prognosis of oral cancer.

The treatment of locally advanced disease varies according to the anatomical location and involves multidisciplinary care, including surgery, radiotherapy, and chemotherapy. Unfortunately, locally advanced disease carries a high risk of recurrence and distant, metastasis, with a poor prognosis (five-year overall survival (OS), <50%). [4][5] Therefore, further prevention of recurrence and distant metastasis is crucial for survival improvement, in advanced HNSCC patients. Metronomic chemotherapy is a maintenance therapy with continuous and dose-dense administration of chemotherapeutic drugs in lower doses (a tenth to a third of the maximum tolerated dose). Several mechanisms of action of metronomic therapy have been proposed, including inhibition of the nutrition supply for tumor growth, obstruction of tumor angiogenesis, immune system modulation, and cellular dormancy mechanisms. [8]It can directly affect tumor cells, tumor progenitors, and neighboring stromal cells. Additionally, it is believed to decrease metastasis. The concept of metronomic chemotherapy has been applied to several malignant diseases, including breast cancer, lung cancer, prostate cancer, ovarian cancer, colorectal cancer, and nasopharyngeal carcinoma. [9] Tegafur–uracil, an active agent used as metronomic adjuvant chemotherapy, is a 4:1 molar mixture of uracil and tegafur. [10] Tegafur is a prodrug of fluorouracil, which is gradually converted to fluorouracil (5-FU) by the hepatic cytochrome P-450 enzymes. Uracil is a reversible inhibitor of the fluorouracil- degrading enzyme dihydropyrimidine dehydrogenase, the enzyme responsible for fluorouracil catabolism. Its administration can achieve a stable plasma 5-FU concentration with a low toxicity profile. [11] To date, tegafur–uracil has been widely used in several malignancies, including lung cancer, gastric cancer, colorectal cancer, breast cancer, and head and neck cancer. The antitumor effects of tegafur—uracil as a metronomic agent in advanced oral cancer and nasopharyngeal carcinoma have been documented in previous studies.

METHODOLOGY

Method: This retrospective clinical study is conducted in the department of Radiotherapy, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh. All patients were diagnosed with LA HNSCC (stage III or non-distant metastatic stage IV). Patients were either treated with curative surgery with adjuvant CRT or definitive concurrent CRT. The 4 year data from 1 January 2017 to 1 January 2021 of Tegafur-Uracil use in locally advanced head & neck cancers as metronomic chemotherapy is collected, studied and analyzed. The data was entered in Microsoft excel and it was analysed by SPSS 22.0 version.

Oral Tegafur–Uracil was given at a daily dose of 100–224 mg 1 capsule twice a day (200-448mg per day) started 1 month after completion of definitive treatment (chemotherapy, surgery, radiotherapy, CCRT) . The evaluation of disease status included disease inspection, laboratory tests, and radiological studies.

Patient Inclusion Criteria

1) All Histopathological proven cases of squamous cell carcinoma of head & neck.
2) All previously treated stage 3; stage 4 head & neck cancers.

3) All proven cases of oral cavity, maxilla, larynx who are previously treated with definitive chemotherapy, Radiotherapy or surgery.

Major Variables

1. Age
2. Gender
3. Tumour location
4. Treatment Failure
5. Adverse effects

FINDINGS

This retrospective clinical study is conducted in the department of Radiotherapy, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh. The 4 year data from 1 January 2017 to 1 January 2020 of Tegafur Uracil use in locally advanced head & neck cancers as metronomic chemotherapy is collected, studied and analyzed. Total 36 patients were registered under this study. The results are as follows:

Age

24 out of 36(66.6%) patients were in below 45 years age group whereas 12 out of 36(33.3%) patients belonged to >45 years age group.

Table I Age wise distribution of IPD patients

Age Range(yr)	<45	>45
N= 36	24(66.6%)	12(33.3%)

Gender

28 out of 36(77.7%) patients were male whereas female population was 22.2%, no patients of transgender community was reported.

Table II Gender wise Distribution of IPD patients

Gender	Male	Female	Transgender
N=36	28(77.7%)	8(22.2%)	0

Tumor Location

Carcinoma Buccal mucosa was predominant in most of the patients i.e. 33.3%, GBS was seen involved in 6 patients, Anterior 2/3rd Tongue, alveolus, larynx was involved in 5 patients each. Soft Palate, Base of Tongue and tonsil was involved in 1 patient each.

Table III Tumor Location Wise distribution of patients

Tumor Location	Buccal Mucosa	Gingivobuccal sulcus	Anterior 2/3rd Tongue	Alveolus	Larynx	Soft Palate	Base of Tongue	Tonsil
N=36	12(33.3%)	6(16.6%)	5(13.8)	5(13.8)	5(11.1%)	1(2.7%)	1(2.7%)	1(2.7%)

Treatment failure

Treatment failure is seen among 8 patients, Local recurrence at their primary tumor site was observed in 4 patients (50%) ,Regional lymph nodes metastasis was seen in 3(37.5%), and Distant metastasis was found in 1 patient.

Table IV Treatment failure

Treatment Failure	Local Recurrence	Regional Lymph Metastasis	Distance Metastasis
N=8	4(50%)	3(37.5%)	1(12.5%)

Table VIII Adverse effects

Adverse Effects	Nausea, Vomiting	Oral mucositis	Anemia	Nuetropenia	Diahorrea	Skin Rash	Anorexia	Neuropathy
N=14	3(21.4%)	1(7.1%)	2(14.2%)	1(16.6%)	5(11.1%)	1(7.1%)	5(35.7%)	1(2.7%)

Adverse effects

Adverse Events of oral Tegafur-Uracil was observed in 14 patients, Grade 1 Nausea and Vomiting was complained by 3(21.4%) patients, oral mucositis in 1(7.1%), Neutropenia 1 (16.6%), Anemia in 2(14.2%), Anorexia in 5(35.7%), neuropathy was seen in 1 patient only.

DISCUSSION

The anticancer mechanism of 5-FU lies in its inhibition of thymidylate synthase, reducing the synthesis of thymidylate and subsequently, the synthesis of DNA and RNA. It has become the most commonly used anticancer agent, and is widely administered to treat gastric, colorectal, pancreatic, and breast cancer. The absorption of orally administered 5-FU is very poor because it is rapidly degraded by dihydropyrimidine dehydrogenase (DPD) in the intestine. [12] Orally administered agents with better absorption have been developed. Tegafur is the precursor of 5-FU, and its administration results in the prolonged elevation of blood 5-FU levels. It is slowly converted to 5-FU through the P-450 enzyme system and thymidine phosphorylase in tumor tissues. Uracil itself is a component of nucleic acids, and has neither pharmaceutical efficacy nor toxicity. It is a natural pyrimidine that must be metabolized by DPD; it can thus compete with 5-FU for DPD, thereby slowing down its degradation and extending its effective duration and availability. [13] A number of clinical trials have shown that orally administered UFUR adjuvant chemotherapy is effective. Some reports compared the results of orally administered UFUR/leucovorin combination with intravenously injected 5-FU/leucovorin and concluded that they had similar efficacies, although oral administration resulted in fewer side effects.

Jiun-ShengLin, Chieh-YuanCheng, Chung-JiLiu et al used oral UFUR as a postoperative adjuvant treatment for OSCC. The disease-free survival rate was ~9% higher than that of untreated patients, indicating that 5-FU can control OSCC effectively via oral administration. [13]

In Taiwan, cisplatin/fluorouracil (5-FU) is still the most common regimen for R/M HNSCC. Recently, triple combination therapy in the induction setting for locally advanced HNSCC has shown a high response rate. Therefore, triple combination regimens were examined in R/M HNSCC. However, the continuous 96-hour infusion of 5-FU is inconvenient for patients. An oral 5-FU prodrug, UFUR, combined with cisplatin has demonstrated similar activity as continuous-infusion 5-FU in R/M HNSCC. [14]

According to study by **Hsieh, MY., Chen, G., Chang, DC.** ***et al.*** The metronomic adjuvant chemotherapy oral tegafur– uracil was administered to advanced oral cancer patients after standard treatment, improving 5-year overall survival, disease-free survival, and disease-specific survival rates. The toxicity and adverse effects were mild and did not reach grade 4 or 5 toxicity. The optimal dosage of tegafur–uracil was 300 or 400 mg/day as long as patients were able to tolerate the side effects of tegafur–uracil. [15]

CONCLUSION

In head and neck squamous cell carcinoma (HNSCC), more than 60% of patients presenting with locally advanced disease carries a high risk of recurrence and distant metastasis, with a poor prognosis (five-year overall survival (OS), Therefore, further prevention of recurrence and distant metastasis is crucial for survival improvement in advanced HNSCC patients. In this retrospective study, we investigated the outcomes of metronomic chemotherapy with Tegafur–Uracil in locally advanced HNSCC (LA HNSCC). We concluded that adding Tegafur–Uracil after curative surgery with adjuvant chemoradiotherapy or definitive concurrent chemoradiotherapy significantly improved the overall survival in patients with LA HNSCC. As a metronomic maintenance regimen, Tegafur–Uracil was well tolerated with minimal adverse effects. We suggest Tegafur–Uracil as a maintenance therapy of choice for patients with LA HNSCC.

REFERENCES

1. Bray F, Ferlay J et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 2018, 68, 394–424.
2. Gupta B, Bray F, Kumar N, Johnson N.W. Associations between oral hygiene habits, diet, tobacco and alcohol and risk of oral cancer: a case–control study from India. *Cancer Epidemiol.* 2017; 51:7–14.
3. Laprise C, Shahul H.P, Madathil S.A., Thekkepurakkal A.S et al. Periodontal diseases and risk of oral cancer in Southern India: results from the HeNCe Life study. *Int. J. Canc.* 2016;139:1512–1519.
4. Chow L.Q.M. Head and Neck Cancer. *N. Engl. J. Med.* 2020; 382:60–72.
5. Braakhuis B.J., Brakenhoff R.H., Leemans C.R. Treatment choice for locally advanced head and neck cancers on the basis of risk factors: Biological risk factors. *Ann. Oncol.* 2012; 23(Suppl. S10): x173–x177.
6. Vives, M, Ginesta M, Gracova K et al. Metronomic chemotherapy following the maximum tolerated dose is an effective anti-tumour therapy affecting angiogenesis, tumour dissemination and cancer stem cells. *Int. J. Cancer* 2013, *133*, 2464–2472.
7. Simsek, C.; Esin, E.; Yalcin, S. Metronomic Chemotherapy: A Systematic Review of the Literature and Clinical Experience. *J. Oncol.* 2019, *2019*, 5483791.
8. De Felice, F.; Benevento, I.; Musella, A.; Musio, D.; Tombolini, V. Metronomic chemotherapy in head and neck cancer. *Cancer Lett.* 2017, *400*, 219–222.
9. Gourd, E. Metronomic chemotherapy option for advanced oral cancer. *Lancet Oncol.* 2019, *20*, e614.
10. Wellington, K.; Goa, K.L. Oral tegafur/uracil. *Drugs Aging* 2001, *18*, 935–948, discussion 949–950.
11. Chen, J.H.; Huang, W.Y.; Ho, C.L.; Chao, T.Y.; Lee, J.C. Evaluation of oral tegafur-uracil as metronomic therapy following concurrent chemoradiotherapy in patients with

non-distant metastatic TNM stage IV nasopharyngeal carcinoma. *Head Neck* 2019, *41*, 3775–3782.
12. M. Colleoni, A. Rocca, M.T. Sandri, *et al.* Low dose oral methotrexate and cyclophosphamide in metastatic breast cancer: antitumor activity and correlation with vascular endothelial growth factor levels. *Ann Oncol. 2006 Feb*; 17(2):232-8.
13. Jiun-ShengLin, Chieh-YuanCheng, Chung-JiLiu. Oral uracil and tegafur as postoperative adjuvant metronomic chemotherapy in patients with advanced oral squamous cell carcinoma. *Journal of Dental Sciences 2015*,Volume 10, Issue 4, December 2015, 408-413.
14. Jacobs C, Lyman G, Velez-García E, et al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. *J Clin Oncol.* 1992; 10:257–263.
15. Hsieh, MY., Chen, G., Chang, DC. *et al.* The Impact of Metronomic Adjuvant Chemotherapy in Patients with Advanced Oral Cancer. *Ann Surg Oncol* **25,** 2091–2097 (2018).