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Research Article

TO EVALUATE THE RESPONSE OF TEGAFUR URACIL AS METRONOMIC CHEMOTHERAPY IN PREVIOUSLY TREATED GYNECOLOGICAL MALIGNANCIES – A RETROSPECTIVE STUDY

Chandrahas Dhruw[1]., Suman Kumar Kujur[1]., Himanshu Gupta[1]., Richa Agarwal Gupta[1]., Anwarul Haque Jafri[1] Suvigya Wadhwani[2] and Akanksha Soni[3]

[1]Dept. Of Radiotherapy, CIMS Bilaspur
[2]Dept. Of ENT CIMS Bilaspur
[3]Department of Pharmacology CIMS Bilaspur Chattisgarh

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ABSTRACT

Background: Gynecological cancers are among the most common cancers in women and hence an important public health issue. Due to the lack of cancer awareness, variable pathology, and dearth of proper screening facilities in developing countries such as India, most women report at advanced stages, adversely affecting the prognosis and clinical outcomes. **Objective**: To evaluate the response of Tegafur- Uracil as metronomic chemotherapy in previously treated gynecological malignancies **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 2017 to 1 January 2021 of Tegafur Uracil use in gynecological cancer is collected, studied and analyzed. **Results**: 52 out of 62(83.8%) patients were in below 45 years age group whereas 10 out of 62(16.1%) patients belonged to >45 years age group. 48 out of 62(77.4%) patients were of carcinoma cervix, 17.7% were of carcinoma ovary and 3 patients suffered from carcinoma endometrium. At sixteen month, 37(59.6%) patients showed CR, PR was seen in 15(24.1%) patients, stable disease was seen in 5(8.06%) whereas progressive disease was found in 5(8.06%) patients. This data showed that at sixteen month 60% patients had complete response to Tegafur- Uracil whereas only 8% patient had progression of disease. Adverse Events of oral Tegafur-Uracil was observed in 27 patients, out of which Grade 1 Nausea and Vomiting was complained by 12(44.4%) patients, oral mucositis in 3(11.1%), Neutropenia 1 (3.7%), Anemia in 1(3.7%), diarrhea in 3 (11.1%), skin rash in 2(7.4%),Anorexia in 4(14.8%) and neuropathy was seen in 1(3.7) patient only. **Conclusion**: 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 all patients of residual and recurrent gynecological cancers.

INTRODUCTION

Ovarian and cervical cancers are the most common gynecological cancers affecting women worldwide and in India. Cervical cancer is on a declining trend, but remains the second most common cancer in women after breast cancer. Every year in India, 122,844 women are diagnosed with cervical cancer and 67,477 die from this disease. [1] Gynecological cancers are among the most common cancers in women and hence an important public health issue. Due to the lack of cancer awareness, variable pathology, and dearth of proper screening facilities in developing countries such as India, most women report at advanced stages, adversely affecting the prognosis and clinical outcomes. Ovarian cancer has emerged as one of the most common malignancies affecting women in India and has shown an increase in the incidence rates over the years. Although cervical cancer is on a declining trend, it remains the second most common cancer in women after breast cancer. 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). [2][3] 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. [4] 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. [5] Tegafur–uracil, an active agent used as metronomic adjuvant chemotherapy, is a 4:1 molar mixture of uracil and tegafur. [6] Tegafur is a prodrug of fluorouracil, which is gradually converted to fluorouracil (5-FU) by the hepatic cytochrome P-450 enzymes. Uracil is a

Corresponding author:* **Akanksha Soni
Department of Pharmacology CIMS Bilaspur Chattisgarh

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. [7] 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 gynecological Malignancies. 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 gynecological malignancies is collected, studied and analyzed. Frequency tables, graphs are used to evaluate and measure the data from the study.

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 gynecological malignancies.
2. All previously treated stage 3; stage 4 gynecological malignancies.
3. All proven cases of ca cervix, ca ovary, ca endomentium who were previously treated with definitive chemotherapy, Radiotherapy or surgery.

Major Variables

1. Age
2. Types of Tumour
3. Response at different phases
4. Treatment Failure
5. Adverse effects

RESULTS

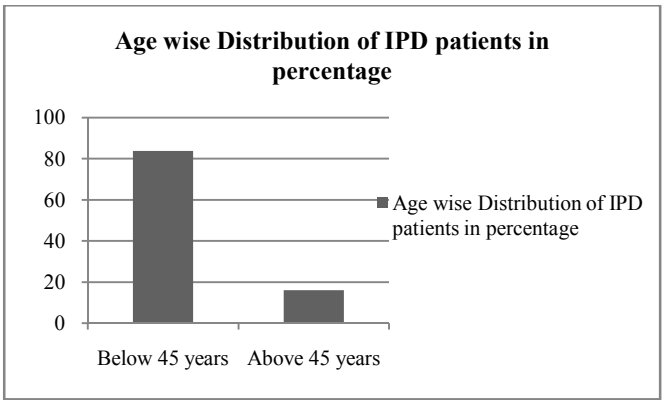
The results are as follows:

Age

52 out of 62(83.8%) patients were in below 45 years age group whereas 10 out of 62(16.1%) patients belonged to >45 years age group. This data showed that patients of below 45 yrs predominantly suffered from gynecological malignancies.

Table I Age wise distribution of IPD patients

Age Range(yr)	<45	>45
N= 62	52(83.8%)	10(16.1%)



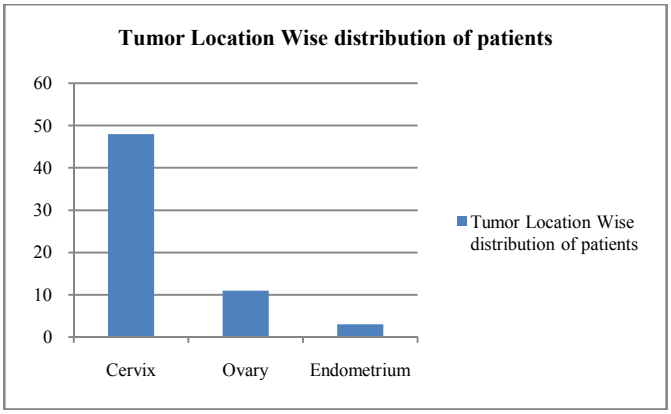
Graph 1

Tumor Location

48 out of 62(77.4%) patients were of carcinoma cervix, 17.7% were of carcinoma ovary and 3 patients suffered from carcinoma endometrium. Carcinoma cervix patients are predominant in our study

Table II Tumor Location Wise distribution of patients

Tumor Location	Cervix	Ovary	Endometrium
N=62	48(77.4%)	11(17.7%)	3(4.8%)



Graph 2

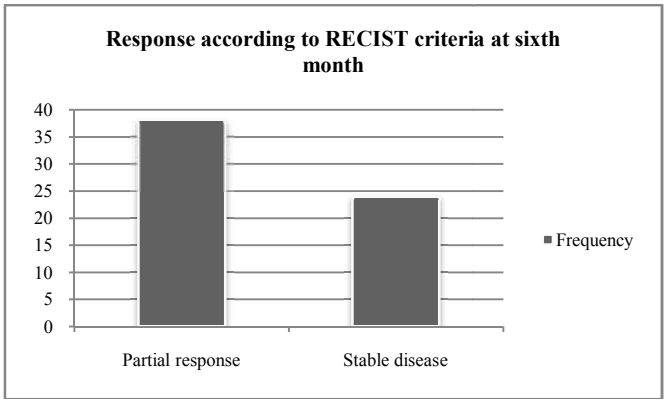
Response

At Sixth Month

At sixth month none of the patients showed complete response, partial response was seen in 38(61.2%) and stable disease was observed in 24 patients (38.7%). This data revealed that recurrent cases of gynecological malignancies are chemosensitive in first six months of treatment.

Table III Response according to RECIST criteria at sixth month

Response	Frequency	Percent
Partial Response	38	61.2
Stable Disease	24	38.7
Total	62	100.0



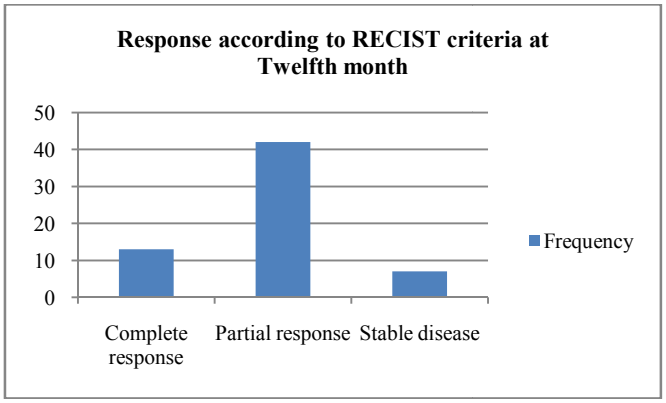
Graph 3

At Twelfth Month

At twelfth month complete response was found in 13 patients (20.9%), partial response was seen in 42(67.7%) whereas stable disease was observed in 7(11.2%) patients. This data depicted that partial response was the predominant treatment response at 12 months and among 7 patients the Tegafur-Uracil proved to be chemoresistant

Table IV Response according to RECIST criteria at Twelfth month

Response	Frequency	Percent
Complete Response	13	20.9
Partial Response	42	67.7
Stable Disease	7	11.2
Total	62	100.0



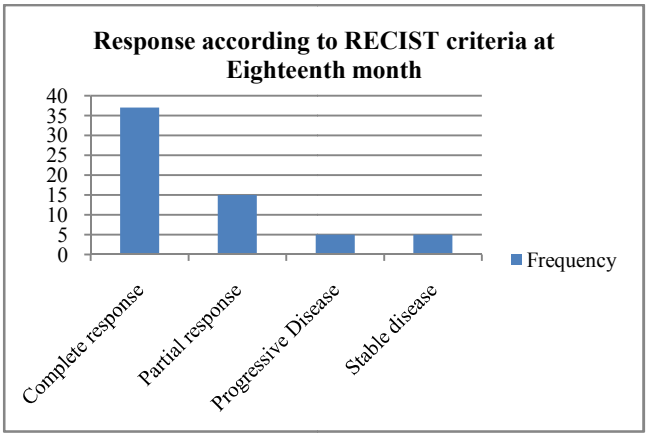
Graph 4

At Eighteenth Month

At eighteenth month 37(59.6%) patients showed CR, PR was seen in 15(24.1%) patients, stable disease was seen in 5(8.06%) whereas progressive disease was found in 5(8.06%) patients. This data showed that at eighteenth month 60% patients had complete response to Tegafur- Uracil whereas only 8% patient had progression of disease.

Table V Response according to RECIST criteria at Eighteenth Month

Response	Frequency	Percent
Complete Response	37	59.6
Partial Response	15	24.1
Progressive Disease	5	8.06
Stable Disease	5	8.06
Total	62	100.0



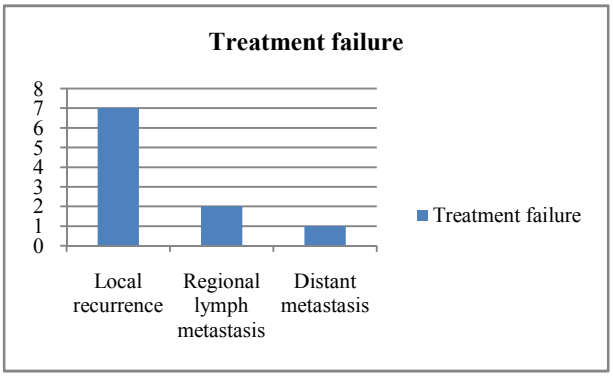
Graph 5

Treatment failure

Treatment failure is found in 10 patients, Local recurrence at primary site was observed in 7 patients (70%) out of which all patients were of carcinoma cervix, Regional lymph nodes metastasis was seen in 2(20%), 1 in ca ovary and 1 in ca endometrium, and Distant metastasis (bone metastasis/ Spinal metastasis) was found in 1 patient (10%) of ca ovary.

Table VI Treatment failure

Treatment Failure	Local Recurrence	Regional Lymph Metastasis	Distant Metastasis
N=10	7 (70%)	2(20%)	1(10%)



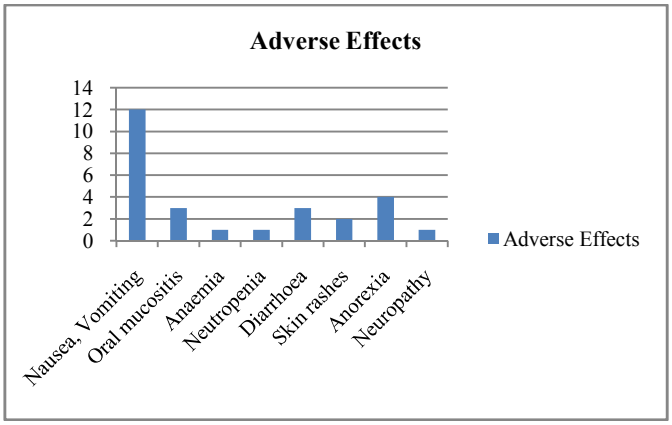
Graph 6

Adverse effects

Adverse Events of oral Tegafur-Uracil was observed in 27 patients, out of which Grade 1 Nausea and Vomiting was complained by 12(44.4%) patients, oral mucositis in 3(11.1%), Neutropenia 1 (3.7%), Anemia in 1(3.7%), diarrhea in 3 (11.1%), skin rash in 2(7.4%),Anorexia in 4(14.8%) and neuropathy was seen in 1(3.7) patient only. Our study depicted that Tegafur-Uracil is well tolerated and only 44% patients had adverse effects.

Table VII Adverse effects

Adverse Effects	Nausea, Vomiting	Oral mucositis	Anemia	Nuetropenia	Diahorrea	Skin Rash	Anorexia	Neuropathy
N=27	12(44.4%)	3(11.1%)	1(3.7%)	1(3.7%)	3(11.1%)	2(7.4%)	4(14.8%)	1(3.7%)



Graph 7

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. [8] 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. [9] 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. ***Isao Sakaguchi, Takeshi Motohara et al*** concluded in their study that High-dose oral UFT maintenance treatment prolonged the disease-free survival and overall survival of patients with uterine cervical cancer, particularly of those with advanced disease. [10] Results of our study are similar with this study. In patients with breast cancer, large clinical trials of UFT-based postoperative chemotherapy conducted in Japan have shown that UFT is useful for the treatment of intermediate-risk patients with no lymph node metastasis. [11]

CONCLUSION

We conclude that adding Tegafur–Uracil after curative surgery with adjuvant chemoradiotherapy or definitive concurrent chemoradiotherapy significantly improved the overall survival in patients of gynecological cancers.

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 of gynecological cancers.

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