

The Gulf Journal of Oncology



Indexed By PubMed and Medline Database

Issue 42, May 2023
ISSN No. 2078-2101



*8th Gulf Week for
Cancer Awareness,
1-7 February 2023*

The Official Journal of the Gulf Federation For Cancer Control

Table of Contents

Original Articles

Identification of the Physiological Dimension and Self-Concept among Husbands of Iranian Women with Mastectomy; a Directed Content Analysis.....	06
Marzieh Beigom Bigdeli Shamloo, Nasrin Elahi, Marziyeh Asadi Zaker, Kourosh Zarea, Armin Zareiyen	
Tumor–Stroma Ratio in ER+/HER2– Breast Cancer: Is it a Tool for Treatment Decision?.....	14
Choukri ELMHADI, Mohammed Allaoui, Meryem Zerrik, Mohammed Oukabli, Rachid Tanz, Mohammed Ichou	
Prevalence of BRCA1 and BRCA2 Mutations Among High–risk Bahraini Patients with Breast Cancer.....	22
Zain Bukamal, Amal AlRayes	
Survival Outcomes of Post–mastectomy Breast Cancer Patients Treated with Hypofractionated Radiation Treatment Compared to Conventional Fractionation –a Retrospective Cohort Study.....	26
Ciniraj Raveendran, Suma Susan Meloot, I Yadev	
Variants of Human Mucin Genes in Clear Cell Renal Cell Carcinoma and their Potential Prognostic and Predictive Values.....	35
Jamal Zekri, Mohammed A. Baghdadi, Abdelrazak Meliti, Turki M. Sobahy, Saba Imtiaz	
Study of Efficacy and Toxicity of Capecitabine Maintenance After Response to Docetaxel, Cisplatin, and 5–Fluoracil–Based Chemotherapy in Advanced Carcinoma Stomach.....	40
Udip Maheshwari, Pankaj Goyal, Varun Goel, Nivedita Patnaik, Venkata Pradeep babu koyyala, Krushna Chaudhari, DC Doval, Vineet Talwar	
EGFR Expression in Gallbladder Carcinoma in North Indian Population.....	47
Vikash, Vikas Kailashiya, Mohan Kumar, Puneet	
Does the Nightmare of Distressing Complications of Groin Dissection Over with “River Flow” Incision? – Experience of 240 Dissections from Tertiary Referral Oncology Centre,India.....	53
M D Ray, J R Jeena Josephin, Premanand N	

Review Article

Peptic Ulcer Disease and its Treatments and Risk of Pancreatic Cancer: a Meta–analysis.....	61
Nasser Alkhashaym, Goot Albuainain, Tuqa A AbuShaheen, Mohammed Y. Alshami, Ali S Almutairi, Ayman Ahmed Sakr, Ayat S Almuhayshi	

Case Reports

Treatment Process of Primary Prostate Leiomyosarcoma: A Rare Case Report.....	70
Denis Cetin, Mustafa Murat Mdk, Mustafa Mustafayev, Burcak Karaca	
Metastatic Small Cell Carcinoma of a Male Breast: A Case Report and Review of the Literature.....	74
Nadin Shawar Al Tamimi, Yousra Bennouna, Mohammed El Fadli, Rhizlane Belbaraka	
A Rare Tumor in Adulthood: Extrapneumatic Pancreatoblastoma.....	79
Ugur Topal, Begm alm Grbz, Hasan Bektas	

Conference Highlights/Scientific Contributions

News Notes.....	84
Advertisements.....	86
Scientific events in the GCC and the Arab World for 2023.....	87



Original Article

Study of Efficacy and Toxicity of Capecitabine Maintenance After Response to Docetaxel, Cisplatin, and 5–Fluracil–Based Chemotherapy in Advanced Carcinoma Stomach

Udip Maheshwari¹, Pankaj Goyal¹, Varun Goel¹, Nivedita Patnaik², Venkata Pradeep babu koyyala¹, Krushna Chaudhari¹, DC Doval¹, Vineet Talwar¹

1. Department of Medical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, India

2. Department of Pathology, Rajiv Gandhi Cancer Institute and Research Centre, India

Abstract

Background: Advanced gastric cancer is associated with poor survival despite chemotherapy. Maintenance chemotherapy has been successfully tried in lung cancer and colorectal cancers however there is scarce literature on maintenance therapy in advanced gastric cancer. We report a prospective non–randomized single–arm trial of capecitabine maintenance after response to docetaxel, cisplatin, and 5–Fluorouracil–based chemotherapy.

Methods: 50 patients with advanced gastric cancer, who had achieved response or had stable disease after 6 cycles of Docetaxel, Cisplatin, and 5–Fluorouracil (D 75 mg/m², C 75 mg/m², FU 750 mg/m²/d d1–d5, q3 weeks) chemotherapy were prospectively selected to receive maintenance chemotherapy with capecitabine (1000mg/m² bid d1–d14 q21 days) until progression.

Results: During the median follow–up period of 18 months all patients had progressed, however, there was no treatment–related death, the median time to tumor progression was 10.3 months, with grade 3 and 4 toxicities in 10–15% of patients, and treatment delays in 75% of patients.

Conclusions: Our study has shown that maintenance chemotherapy with capecitabine post–first–line docetaxel, cisplatin, and 5–FU–based chemotherapy is effective and delays tumor progression. However, toxicity was a concern in our study which led to treatment–related delays but without any treatment–related death. Most patients continued therapy till progression.

Keywords: Capecitabine, maintenance, carcinoma stomach, Time to tumor progression

Introduction

Less than a century ago, gastric cancer was the most common cancer throughout the world. The last several decades have demonstrated a gradual decline in the rates of gastric cancer in most populations and across sub–types. And this decline can be attributed in part to improved food preservation,⁽¹⁾ increased accessibility to fresh fruits and vegetables year–round, lower salt diets, the decreased use of tobacco⁽²⁾, and eradication of *Helicobacter pylori* infections in endemic areas.

Although most gastric tumors are declining in incidence, tumors of the gastric cardia and gastroesophageal junction are becoming more frequent and there is a trend of the rising

incidence of non–cardia gastric cancer among American whites between 25 and 39 years of age⁽³⁾ and in the same age group in other western countries^(4,5).

It remains a major public health issue as the fifth most common cancer and the third leading cause of cancer death

Corresponding Author: Dr. Varun Goel,
Consultant, Medical Oncology, Rajiv Gandhi Cancer
Institute and Research Centre, Sector 5, Rohini, New
Delhi–110 085 India. Tel: 9560538081
Email: goelvarundoc@gmail.com

worldwide, accounting for 738,000 deaths (9.7% of the total)^(6,7). Gastric cancer leads to maximum tumor burden measured as disability—adjusted life years lost⁽⁸⁾.

There is substantial geographic variation in the incidence and mortality of gastric cancer, with the highest rates in East Asia and the lowest in North America⁽⁹⁾. *H. pylori* infection, dietary factors, and smoking patterns may contribute to these disparities⁽¹⁰⁾.

The overall incidence of gastric cancer in India is less than worldwide. The age—adjusted rate (AAR) of gastric cancer among urban registries in India is 3.0–13.2 compared to the worldwide AAR of 4.1–95.5⁽¹¹⁾. Although the incidence of gastric cancer in India is high in certain geographical areas (e.g. southern part and northeastern states of the country), where it is comparable to high—incidence areas of the world⁽¹¹⁾.

Gastric cancer is the fifth most common cancer among males and the seventh most common cancer among females in India⁽¹¹⁾. Annually incidence of new gastric cancer cases in India is approximately 34,000, with a male—to—female ratio of (2:1). Symptoms related to gastric cancer arrive late in the natural history of the disease, thus usually present in advanced stages and portend a poor prognosis.

Since the 1970s, there have been notable improvements in the relative 5—year survival rates for gastric cancer, from 15% in 1975 to 29% in 2009 in the United States⁽¹²⁾. The overall 5—year relative survival rate is about 20% in most areas of the world, except in Japan, where 5—year survival rates of above 70% for stages I and II of gastric cancer⁽¹³⁾. Such high survival rates may be due to the effectiveness of mass screening programs in Japan. Advanced and metastatic gastric cancer have dismal prognoses and despite the development of newer surgical techniques and medical management the 5yr survival in advanced gastric cancers is about 3.1%⁽¹⁴⁾. The role of surgery is also limited as only 23% of stage IV gastric cancer patients receiving a palliative gastrectomy are alive one year after surgery⁽¹⁴⁾.

Gastric cancer is a heterogeneous disease that demands continued attention and research concerning prevention, early detection, and novel therapeutic options. The potential for exploration into newer chemotherapeutic drugs and newer approaches and better diagnostics is huge and needs to be tapped. Recently targeted strategies are gaining momentum, with anti—HER 2—based therapy in receptor—positive gastric cancer showing additional survival advantage⁽¹⁵⁾. Perioperative chemotherapy and surgery with or without RT are established as the standard of care treatment in resectable disease and palliative chemotherapy is a standard in the advanced metastatic setting. Even on the standard—of—care chemotherapy, complete response (CR) and partial response (PR), and stable disease (SD)

rates are less and if present not sustained with overall survival (OS) being just around 12 months in advanced gastric cancer⁽¹⁶⁾.

Thus, there is a need for maintenance therapy after induction chemotherapy to sustain the responses attained by induction and to prolong overall survival. Maintenance chemotherapy is an established treatment in lung malignancies⁽¹⁷⁾ and colorectal cancer however, there have been very few studies evaluating the effects of maintenance chemotherapy in advanced gastric cancer. Our study is a pilot study aimed to see the effects of maintenance chemotherapy post 1st line treated advanced stomach cancer which would be the first Indian data of its kind and will give further insight into the management of these cases.

Materials And Methods

Aims and objectives:

This study aims to evaluate the time to tumor progression (TTP) and toxicity profile for Capecitabine maintenance therapy in metastatic gastric cancer post—first—line Docetaxel, cisplatin, and 5—fluorouracil—based chemotherapy.

The current study is a pilot study and is planned prospectively to study the role of maintenance capecitabine in metastatic gastric cancer post—first—line Docetaxel, Cisplatin, and 5—Fluorouracil—based palliative chemotherapy. Patients were enrolled from April 2016 – July 2020 at a tertiary care cancer institute in India.

The study included patients with metastatic stomach cancer presenting at our hospital during the study period, who fulfilled the eligibility criteria.

Inclusion criteria:

(1). 18yrs to 60yrs old patients with metastatic gastric cancer. (2). Patients who had an ongoing response (at least stable disease) on initial treatment with 6 cycles of Docetaxel, Cisplatin, and 5—FU (DCF) based chemotherapy assessed by RECIST criteria 1.1. (3). Patients with Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. (4). Patients with Adequate Hepatic and Renal functions.

Exclusion criteria:

Patients with, Other primary malignancies, pregnant or lactating females, documented brain metastases (brain imaging not required in asymptomatic patients), ECOG 3,4.

Pre—treatment evaluation will be done by following: Detailed medical history and physical exam, Complete blood cell (CBC) count, standard biochemical profile (KFT, LFT, Serum electrolytes), upper GI endoscopy, and radiologic

imaging study for tumor measurement, mostly Chest CT, Abdomen CT and PET scan (if required) will be done as per proforma attached.

Treatment protocol:

Patients who received 6 cycles of Docetaxel, Cisplatin, and fluorouracil (DCF) and are in SD, CR, and PR will be taken. These patients were treated with oral maintenance Capecitabine 1000mg/m² twice a day on D1 to D14 q3 weekly cycle with dose modification as necessary. q3weekly assessment was done till progressive disease. Evaluations before each cycle of therapy include a complete history, physical examination, CBC, and measurement of blood chemistry values.

To start oral chemotherapy, patients were required to maintain a WBC >3000/mm³, ANC>1500/mm³, platelet count > 100000/mm³, and serum creatinine < 1.4mg%. Dose modification delays were allowed for hematologic toxicity, gastrointestinal toxicity, hand–foot syndrome, or any other observed toxicity that precluded chemotherapy administration.

The study's primary objective was to determine the time to tumor progression (TTP) for the patient with metastatic stomach cancer who received maintenance treatment with capecitabine post 1st line docetaxel, cisplatin, and 5 fluorouracil–based palliative chemotherapy. All patients were assessed for response. RECIST response criteria (version 1.1) were used to define the anti–tumor effects; responses were assessed every 3 cycles, just before the subsequent cycle by clinical tumor measurements and documentation of the tumor size of measurable and non–measurable disease, using CT/PET scans. All sites with measurable lesions were followed for the response.

The duration of any grade adverse event was documented according to Common Terminology Criteria for Adverse Events (CTCAE) v.4 Version and managed accordingly.

Statistical analysis:

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. The normality of data was tested by the Kolmogorov–Smirnov test. Statistical tests applied were, Qualitative variables were correlated using Chi–Square test /Fisher's exact test, Kaplan Meier Survival analysis curve was used to find out the time to tumor progression (TTP) and two factors were compared in survival analysis using a log–rank test. A p–value of <0.05 was considered statistically significant. The data was entered in an MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0 (©copyright IBM corporation 1989, 2014).

Results

Patients were enrolled from April 2016 to July 2020 at a comprehensive tertiary care institute in New Delhi. The follow–up duration was 9 months from the enrollment of the last patient. A total of 50 eligible patients fulfilling the inclusion and exclusion criteria were enrolled. At the time of the final analysis, all 50 patients had tumor progression and hence all 50 patients were eligible for survival and toxicity analysis.

Patient characteristics:

The mean age in the whole subset was 52.3 ± 2, for comparison purpose the age groups were divided into <50 yrs and ≥50yrs and 30/50 (60%) of the cases were 50 years or above, and the rest 40% were less than 50 years. 33 of 50 (66%) patients were male compared to 17 of 50 (34%) female. 4 out of 50 (8%) patients were ECOG PS 2 and 2 out of 50 patients were ECOG PS 0 and the rest 44/50 (88%) patients were ECOG PS 1.

Tumor characteristics:

All patients were diagnosed with adenocarcinoma; none had variant histology. The most common histology was moderately differentiated adenocarcinoma accounting for 33/50 (66%). The second most common was poorly differentiated adenocarcinoma, 12/50 (24%), and 5/50 patients had signet ring cell type histology. All patients were metastatic stomach cancer and the most common metastatic site was omentum (44%) and followed closely by the liver (36%). Other sites were distant lymph nodes, lungs, and bone.

At the time of starting maintenance chemotherapy, (day 21 of the initial 6 cycles of Docetaxel, Cisplatin, 5–FU based chemotherapy) the number of patients with partial response, stable disease, and complete response were 18(36%), 30(60%) and 2(4%) respectively.

The average time to completion of initial chemotherapy was 4.27 months. The median time from the end of the initial 6 cycles of Docetaxel, Cisplatin, 5–FU based chemotherapy (day 21 of cycle 6) to the first maintenance dose was 3 days (range, 2 to 8 days), with the majority of patients (95%) initiating maintenance therapy within 7 days.

The total numbers of cycles of Capecitabine maintenance administered were 330. The median numbers of cycles received were 8 (range 2–14). A total of 72 cycles were delayed due to various toxicities. 10/50 (20%) patients received < 4 cycles, 13/50 (26%) patients received 4–6 cycles, and 27/50 (54%) patients received > 6 cycles of

Capecitabine maintenance.

None of the patients on maintenance treatment achieved a complete response. Overall, at best partial response was achieved in the treatment group followed by stable disease.

Survival Analysis:

The final analysis was performed 9 months after the last patient was enrolled in our study. At this point, all the patients on maintenance treatment had progressive disease. The median TTP was 10.3 months (95% CI 8.79–11.79). At the end of 1 year, 20% of patients were progression-free whereas 80% had progressed. (Figure). Patients were divided into two groups based on response to initial Docetaxel, cisplatin, and 5-FU-based chemotherapy. Median TTP in patients with group A (CR+PR) was 10.57 months and in Group B (SD) was 8 months, the difference was not found to be significant ($P=0.108$).

Toxicity analysis:

To detect any adverse effect of Capecitabine maintenance therapy, safety data analysis was done from June 2016 to March 2020. The adverse events were documented according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.1 Version and were managed accordingly. (table 1)

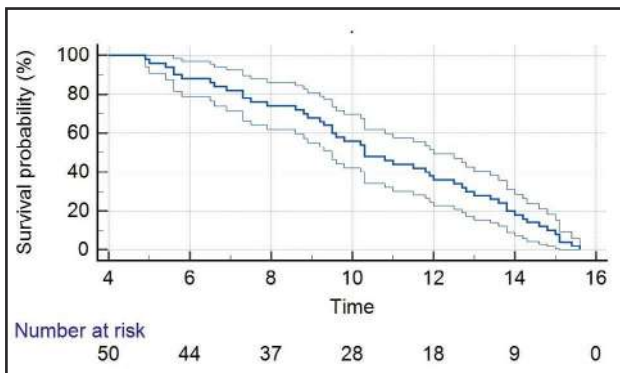


Figure 1. Median TTP for the patients

A total of 72 chemotherapeutic cycles were delayed due to toxicity. Overall Grade 3/4 Toxicity was seen in 24% of patients. The most common toxicity in our study was Hand Foot Syndrome (HFS), seen in 80% of patients followed by gastrointestinal side effects, 76% of patients had diarrhea, 74% of patients had mucositis, 66% of patients had fatigue and 76% and 44% patients had nausea and vomiting respectively and these were lastly followed by hematologic toxicity. There was no grade 4 toxicity seen in the study population, all grade 3 toxicity was seen in 24% of patients. Grade 3 HFS was seen in 20% of patients, and grade 3 diarrhea in 10% of patients. Amongst grade 2 toxicity, diarrhea was most common,

TOXICITY	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Neutropenia	7/50 (14%)	5/50 (10%)	Nil	Nil
Thrombocytopenia	5/50 (10%)	Nil	Nil	Nil
Anemia	5/50 (10%)	5/50 (10%)	Nil	Nil
Diarrhea	10/50 (20%)	23/50 (46%)	10/50 (10%)	Nil
Nausea	25/50 (50%)	13/50 (26%)	Nil	Nil
Vomiting	17/50 (34%)	5/50 (10%)	Nil	Nil
HFS	12/50 (24%)	18/50 (36%)	10/50 (20%)	Nil
Fatigue	28/50 (56%)	5/50 (10%)	Nil	Nil
Mucositis	17/50 (34%)	20/50 (40%)	Nil	Nil

Table 1. Toxicity Profile

seen in (44%) of patients followed by mucositis, seen in (40%) of patients. Grade 1 and 2 HFS were seen in 60% of patients. Neutropenia, thrombocytopenia, and anemia were rare, seen in 24%, 10%, and 20% of patients respectively, and there was no grade 3/4 hematologic toxicity. Lastly, there was no treatment-related mortality, 2 patients had withdrawn consent due to grade 4 toxicity and were not included in the toxicity analysis.

Discussion

Maintenance chemotherapy has been successfully tried in lung cancer (NSCLC) and colon cancer^(17,18), however, in gastric cancer the benefit is still unknown. We aimed to assess the efficacy and safety of capecitabine maintenance therapy in gastric cancer.

Thirty-five percent of gastric cancer presents as metastatic disease and 40% of these cancers recur after curative surgeries⁽¹⁹⁾. The incidence of gastric cancer tends to increase with age with peak incidence at 60–80 years of age⁽²⁰⁾. However, in India, it has been shown that peak incidence is somewhat early in the 4th and the 5th decade, and gastric cancer occurs more commonly in males as compared to females⁽²¹⁾. In our study, the mean age of patients was 52.3 ± 2 , corresponding to earlier presentation in previous studies, and also, males were more commonly affected (65%) than females (35%). In our study, in younger patients (<50yrs) there were significantly greater females than males ($p=0.014$), this has not been reported in any of the previous studies.

Survival in gastric cancer remains dismal with 5 years of survival for advanced gastric cancer is only 3.1%⁽¹⁴⁾.

Chemotherapy remains the standard treatment in metastatic gastric cancer, a meta-analysis confirms the benefit of chemotherapy over the best supportive care⁽²²⁾. Various combination chemotherapies have been tried with response rates ranging from 20% – 50%, some were well tolerated and some were marred with toxicities^(16,23). However, cisplatin and 5-FU-based doublets or triplets remain the standard of care. Median survival with these regimens usually ranges from 8 – 12 months and median TTP (time to tumor progression) from 4–6 months^(16,23). The TAX 325 study by Van Cutsem et al. provided the basis for triplets in advanced gastric cancer with incremental improvement in OS with the addition of taxane (third drug) to cisplatin and 5-FU backbone. It was able to demonstrate a 32% risk reduction for tumor progression with the use of triplets and lead to triplets with taxanes being the standard of care⁽¹⁶⁾. The optimal duration of chemotherapy in metastatic gastric cancer is not defined and in most phase 3 trials chemotherapy has been given till progression or is unacceptable, leading to dose reduction in up to 35–42% of patients⁽²³⁾. Prolonged periods of multi-drug chemotherapy can lead to cumulative toxicity thus de-escalation to maintenance therapy can be considered in these patients to maintain ongoing responses and this has been used successfully in colon cancer as demonstrated by the CAIRO 3 study, which demonstrated a significant PFS advantage⁽¹⁸⁾. Maintenance chemotherapy with capecitabine has been used in an adjuvant setting by Feng et al.⁽²⁴⁾ where they observed improved 3-year DFS when after 8 cycles of XELOX further 8 cycles of capecitabine maintenance were given. However, in metastatic settings maintenance chemotherapy has been rarely used in advanced gastric cancer and there is very scarce literature to support the same, however, we felt the need to evaluate some form of therapy to maintain the responses achieved by initial chemotherapy and with back up of few small studies of efficacy and safety, we conducted this prospective study. In our study, we observed a median TTP of 10.29 months which is better than seen in most studies in metastatic gastric cancer, which did not use maintenance chemotherapy. A similar non-randomized study with a very small no of patients was conducted by Basak Oyan et al., who observed a similar TTP of 10.4 months and median OS of 20.4 months⁽²⁵⁾. In another study of maintenance capecitabine in advanced gastric cancer post-first-line chemotherapy was given in patients after randomization, and they observed a PFS of 11.4 months in the maintenance arm vs 7.1 months in the no-maintenance arm⁽²⁶⁾. When these results are compared to what is achieved in trials with no maintenance arm, they appear to be significant. A multinational randomized prospective study (MATEO

study) of S-1 maintenance therapy in metastatic gastric cancer is ongoing⁽²⁷⁾ and it is likely to provide answers to the usefulness of maintenance chemotherapy.

Factors affecting survival were assessed in various studies, Yang et al. in their study observed many factors affecting survival⁽²⁸⁾. (table 2)

We in our study have observed a significant association of tumor progression with histology, with poorly differentiated variant and signet ring cell histology having significantly worse survival than moderately differentiated and well-differentiated histology (p=0.005). however, we could not see a significant association between gender, site, and age with TTP, which could probably be due to fewer patients.

Toxicity on maintenance chemotherapy has not been a major concern with <5% grade 3/4 toxicity⁽²⁶⁾. In our study,

FACTORS	WORSE median survival	P value
Gender	Male > female	<0.001
Age	Increasing age	<0.001
Site	Lower>body>cardia	0.003
Grade	Poorly differentiated>moderately and well-differentiated	<0.001
Histology	Adenocarcinoma > signet ring cell histology	<0.001

Table 2. Factors affecting survival in stomach cancer

we did not observe any grade 4 toxicity, and no grade 3/4 hematologic toxicity, However, overall grade 3/4 toxicity was seen in 24% of patients mainly consisting of diarrhea and HFS. In a study by Abushullaih S et al., HFS was seen in 68.3 % of patients with colorectal cancer with capecitabine⁽²⁹⁾. Another study by Gómez-Martin C et al. observed around 20% HFS rates in gastric cancer patients with capecitabine as a part of the chemotherapy regimen⁽³⁰⁾. However, in our study have observed around 80% of patients have all grade HFS and 20% have grade 3 HFS. Overall the toxicity was more commonly seen in our study as compared to western literature and was associated with treatment-related delays and dose reductions in chemotherapy. However, there were no treatment-related deaths seen in our patients.

Our study was a single-arm study with less number of patients. However, our results are in line with other studies which have used maintenance therapy in advanced gastric cancer. Larger randomized studies would be needed to confirm the benefit of time to tumor progression seen in our study.

Conclusion:

Our study aimed to observe the efficacy and safety of maintenance therapy in advanced gastric cancer, especially in Indian patients, which has not been reported in India. Very few studies are found in western literature as well. Maintenance therapy offers a chance to prolong meaningful survival in patients with metastatic gastric cancer who anyway have a dismal prognosis. Our study has shown that maintenance chemotherapy with capecitabine post–first–line docetaxel, cisplatin, and 5–FU–based chemotherapy is effective and delays tumor progression. However, toxicity was a concern in our study which lead to treatment–related delays but without any treatment–related death, and most patients continued therapy till progression.

This study ignites a small lantern in a dark room. However, for complete illumination, larger randomized studies would be needed. In aggressive malignancies like advanced metastatic gastric cancer, the small number of cases that do respond to initial therapy, for them maintenance therapy is the need of the hour. However, will capecitabine maintenance fill this void remains to be seen?

Acknowledgments

We thank the Rajiv Gandhi Cancer Institute and Research Centre Hospital Staff, especially people working in the Department of Medical oncology We also thank people working in the Department of Histopathology.

Ethical approval

Ethical approval had been taken by scientific committee, Rajiv Gandhi Cancer Institute and research centre.

Conflicts of interest

nil

No financial support of any form has been taken from any agency for this study.

Competing interests

The authors declare that they have no competing interests.

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