



Metronomic Capecitabine as a salvage therapy in advanced Gastric cancer

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Abstract: Recently, for treatment of different types of tumors, metronomic chemotherapy, as cytotoxic agents are administered with a continuous low doses. **Aim:** We aimed to investigate the efficiency and safety of treatment with metronomic capecitabine in patients suffering from advanced gastric tumor. **Methods:** Patients with advanced gastric tumor who progressed on first line chemotherapy for their metastatic disease were treated with 500 mg /m² capecitabine, twice daily continuously for 28days, followed by a 7-day rest period, every 5 weeks) till progression or significant toxicity. Computed tomography scanning is used for assessment of cancer response by applying response evaluation criteria in solid cancers. **Results:** Forty one patients were enrolled. The overall response rate (partial response and complete response) was 21.95% (9/41), and cancer control percentage (overall response and stable disease) was 63.41% (26/41). Median time to progression (TTP) was 9 months. The 1-year PFS (progression free survival) rates were 30.7%. 18 months was the median overall survival (OS). The OS rates within 1 and 2 years were 74.7% and 16.8%, respectively. The furthest common treatment-related side effect was the hand-foot syndrome, presenting in 39.02% (16/41) of patients and only one case (2.44%) with grade 3 toxicity hand-foot syndrome. Diarrhea was recorded in 17.08% of patients (7/41) with 4.88% (2/41) of them had a grade 2 toxicity. **Conclusion:** Metronomic capecitabine was efficient and well tolerated as save therapy in patients suffering from advanced gastric tumor.

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1. Introduction

Despite the decreasing incidence of gastric tumor, it remain one of the highest disease-leading death[1]. Most of patients complaining from disease progression [2, 3]. It was reported that 50% of patients treated with curative surgery relapse within 5 years [4, 5].

Systemic chemotherapy is palliative, and median overall survival (OS) is 1 year but palliative chemotherapy still superior to best supportive care for improving OS and quality of life [6, 7]. Usually palliative chemotherapy consists of a platinum and fluoropyrimidine combined with anthracycline or taxanes [6, 8, 9].

Patients with poor performance can be treated with single-agent chemotherapy[10]. Second-line therapy with irinotecan or docetaxel also effective [9].

Metronomic chemotherapy is repeated (weekly, several times a week, or daily) or continuous giving of chemotherapeutic agents with minimal doses, without extended drug free breaks. This method of treatment will increase the antiangiogenic action of chemotherapeutic agents with significant reduction in toxicity[11].

Capecitabine is an oral pyrimidine analog which is effective in both adjuvant and palliative treatment of gastric cancer [12-15]. The broad margin of safety profile of capecitabine, in addition to its pharmacokinetic properties enable it an appropriate drug for metronomic administration.

We initiated our study of metronomic capecitabine as a salvage treatment in advanced gastric cancer. Progression-free survival (PFS) and safety profile were the primary endpoints of this work. The second end points were overall survival and tumor response.

2. Patient and methods

The current work is a prospective single-arm phase II single-institution study, carried out in Clinical Oncology Department, Tanta University Hospital between February 2015 and February 2018, the protocol was approved by the Ethics Committee in Faculty of Medicine, Tanta University, and before the beginning of treatment all patients signed an informed consent.

Forty one patients suffering from advanced gastric cancer (AGC) confirmed by pathological examination with at least one significant lesion included in this study. All Patients characterized with distant metastases and progressed on first line treatment for metastatic disease (neoadjuvant and/or adjuvant chemotherapy were not taken in consideration during treatment lines for metastatic disease).

Eligible cases aged between 18-75 years, Karnofsky (KF) performance status (PS) of ≥ 60 , satisfactory investigations: (WBC count $\geq 3.5 \times 10^9/L$, hemoglobin ≥ 10 g/dL), platelets $\geq 100 \times 10^9/L$, and ANC count $\geq 1.5 \times 10^9/L$, liver function (transaminases less than 2 x upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL) and renal function (creatinine clearance ≥ 60 mL/min).

Exclusion criteria include cases with leptomeningeal metastasis, dementia or any psychiatric condition that would affect understanding the informed consent. Exclusion patients criteria: suffering from mal absorption disorders, previously administered capecitabine, gastrointestinal disease rendering oral absorption of drugs, individuals suffering from 2nd malignancy or uncontrolled medical illness (e.g. significant cardiac disease and immune-compromised states). Also, all chemotherapy, radiotherapy, and/or targeted therapy had to be superseded at least 8 weeks before start of protocol therapy. Patients were followed up until April 2019.

Treatment

Patients treated with oral doses of capecitabine metronomic (500mg/m², twice daily) on an outpatient clinic, 28 days of therapy were representing one cycle of treatment. Every treatment cycle, normal organ functions and sufficient hematological picture were assured. Side effects were supervised along the study. All recorded toxicities must completely cured, except fatigue and alopecia. In case of the symptoms of toxicities did not respond to therapy, must left for 1- 2 weeks for resolving. The treatment with capecitabine metronomic therapy must be stopped in cases of advancement of illness or in a high-grade of toxicities.

Assessment

The response to the treatment was assayed post 3 cycles of therapy. Pre- and on-treatment watching composed of valuation of body weight and vital signs, performance status, medical clinical case history, neurological and physical examination, radiological imaging and laboratory investigation. Measures of partial response (PR), complete response (CR), progressive disease (PD) and stable disease (SD) were according to the criteria of RECIST 1.1[16], with the overall response rate, involving partial response and complete response.

Treated patients were evaluated for adverse side effects through laboratory and clinical estimations per

3 weeks and heart checking, by ECHO, per 3 months. The grade of toxicity and adverse side effects were determined according to NCI-CTC criteria, version 4.0 [17].

Overall-survival (OS) rate was determined from the onset of initial therapy to the onset of the last follow-up or death. Progression-free survival (PFS) was determined from the onset during and post the therapy to the onset of appearance of disease progression or mortality without progression of disease. SPSS [Statistical package] (version 21) and the Kaplan-Meier [21] were used for assessing survival rate. The 95% confidence intervals were calculated with the precise method. *P* values ≤ 0.05 were considered significant.

3. Results

Forty one patients diagnosed with relapsed AGC and confirmed pathologically were enrolled in this work. The patients' demographic and clinical characteristics were recorded in table 1.

The mean age of patients at time of diagnosis was 51.9 \pm 12.3 years (range 30–74 years), males representing 58.5% (24/41) and females representing 41.5% (17/41) of patients. The most of cases had poorly differentiated or signet ring carcinoma (63.4%) and well to moderately differentiated carcinoma represents (36.6%). Maximum of the cases (85.3%) had karnofsky performance status score of ≥ 80 . Twenty cases (48.4%) presented with liver metastasis, five patients (12.2%) with bone metastasis and 4 patients (9.8%) with lung metastasis while lymph node metastases represent 29.3%. Seven patients (17%) received first line combination chemotherapy in the adjuvant setting and 20 (48.8%) patients administered adjuvant chemoradiation. All cases at the initiation of the study had metastatic gastric carcinoma.

Treatment Administration

All patients administered 500 mg capecitabine metronomic orally (twice a day, for 28 days, followed by 7 days free every 5 weeks).

Response to Treatment

In the first 17 patients 9 out 41 patients in this work, responses were noticed that hopeful proceeding. 21.95% (9/41) was the overall response rate, and tumor control rate (overall response and stable disease) was 63.41% (26/41) according to the RECIST criteria (Table 2). All objective responses were reported at least 4 weeks post 1st observation.

Toxicity

The main adverse reactions detected in the 41 cases are tabulated in table (3). The symptoms of toxicity were mild and manageable. Not recorded any hematologic toxicity of grade 3/4.

The most common adverse effect recorded in the current study was hand-foot syndrome which was

found in 39.02% (16/41) of cases. Eight (19.51%) of cases were of Grade 1, whereas, grade 2 were 7 cases (17.07%) and one case (2.44%) with grade 3 toxicity hand-foot syndrome, which was resolute to grade 0/1 with rest at bed and administration of symptomatic therapy (pyridoxine and topical urea/lactic acid-based cream). Diarrhea was recorded among 7 cases (17.08%), and 4.88% (2/7) of them had a grade 2 toxicity. Other grade 1/2 non-hematologic toxicities recorded were 9.76%(4 cases) anorexia/nausea, vomiting in 2 patients (4.88%), mucositis in 8 patients (19.51%) and fatigue in 12 patients (29.27%). Mild grade one toxicities were observed as sensory neuropathy/elevated liver enzymes in one patient and hyperbilirubinaemia in 2 patients (4.88%).

NO patients required hospitalization. Dose reduction to 75% of the dose in one patient with G3 hand foot syndrome after the 7th cycle till the last cycle (12th). Due to diarrhea (grade two) in 2 cases and grade 1 liver dysfunction in 2 patients the dosage were delayed for one week. The median number of treatment cycles was 5 cycles ranging from 2 to 12 cycles.

Survival

Regular follow-up for all patients were performed. The median follow-up period was 15 months rang (7-28) months.

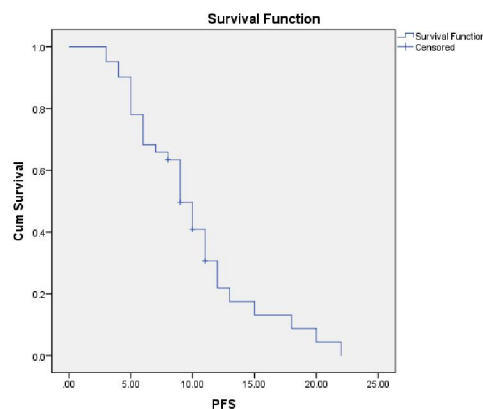
Nine months (95% CI; 7.6–10.4 months) was the reported median time to progression (TTP) (Fig.1). The 1-year PFS was 30.7% (Fig.1).

Eighteen months (95% CI; 15.42- 20.58 months) was the reported median overall survival (OS) (Fig.2). The 1 and 2 years OS were averaged 74.7% and 16.8%, respectively (Fig.2).

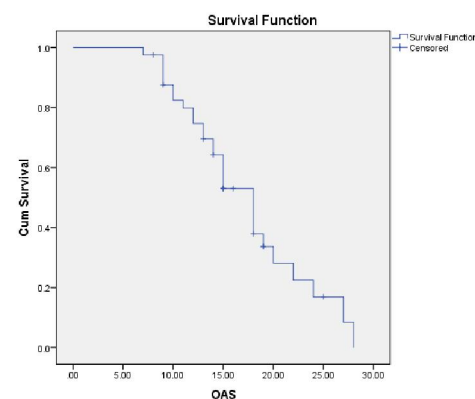
At time of analysis, there were 28 (68.3%) deaths and 13(31.7%) still surviving.

Univariate and multivariate analyses were used for evaluation of factors related to survival. Involved metastatic sites, tumor grade, number of metastatic

sites and response to maintenance treatment significantly affected overall survival, in multivariate analysis, only response to treatment (P=0.033) was independent prognostic factor (Tables 4,5).



Kaplan–Meier curve of progression-free survival (PFS) for patients with AGC



Kaplan–Meier curve of overall survival (OAS) for patients with AGC.

Table (1): Patients' and tumor characteristics as well as initial treatment modality (N=41).

patients characteristics	No. of patents (n=41) (%)
Age (years)	
Mean±SD	51.9±12.33
Range	30-74
Sex	
Male	24(60)
Female	17(40)
Karnofsky performance status	
60	3 (7)
70	6(15)
80	15(36)
90	11 (27)
100	6(15)
Tumor location	
Proximal	21(51)

patients characteristics	No. of patents (n=41) (%)
Distal	20(49)
Metastatic sites	
Liver	35(85.4)
Lung	15(36.6)
Bone	5 (12)
LN	38(92.7)
Number of metastatic sites in the study group	
Single	8 (20)
Double	25 (60)
Three or more	8 (20)
Tumor grade	
Well and moderately differentiated	15 (36)
Poorly differentiated and signet ring	26 (64)
HER/2 expression	
Negative	37 (90)
positive	4 (10)
Adjuvant treatment	
Chemotherapy	7(17)
Chemoradiation	20 (48.8)

Table (2): Tumor Response to Treatment (N=41)

Tumor Response	No.	%
Complete response	0	0
Partial response	9	21.95
Stable disease	17	41.46
Progressive disease	15	36.59

4. Discussion

Advanced gastric cancer (AGC) is aggressive disease. Several studies have shown that chemotherapy is associated with good tolerance and an improved in overall survival (OS) or time-to-progression (TTP) [6, 18, 19]. Though, there is no favorite standard regimen of 2nd line chemotherapy for treatment of AGC [20, 21].

Currently under research bevacizumab which is a VEGF-A-blocking mAb which are used in a trial for treatment of gastric cancer. Many phase II trials joining bevacizumab with various chemotherapeutic agents were performed on treatment-naïve or pretreated individuals with GEJ or AGC tumor, showed initially promising outcomes [22-24].

Several trials were carried out for treatment of advanced gastric cancer by using epidermal growth factor receptor (EGFR)-targeted agents [25-27]. EGFR inhibitors have demonstrated efficacy in combination with other chemotherapeutic agents, such as 5-FU, leucovorin, and irinotecan [28].

There are many researches which investigate the role of capecitabine in patients with advanced and/ or metastatic gastric cancer [29, 30].

One of the drugs which are used is capecitabine which composed of fluoropyrimidine carbamate which given orally and acts as a prodrug 5-fluorouracil (5-FU) and mimics constant infusion of 5-FU [31]. Most of patients usually prefer oral route treatment than intravenous chemotherapy as a non-intensive method [32].

For treatment of different kinds of advanced tumors, metronomic chemotherapy as a single agent are dealt by many investigators in their studies and demonstrating activity in the treatment of breast cancer and advanced gastrointestinal tract cancers after previous treatment failure [33, 34]. In preclinical models some metronomic treatments can have potent as anticancer impacts in comparison with relevant maximum tolerated dose (MTD) treatments, in spite of being minimal in toxicity[35].

Due to the wide range of metronomic capecitabine dose which are ranging from a 1/10 to a 1/3 of the maximum tolerated dose [36], we planned this phase II trial to study the efficiency and tolerability of 500mg/m², metronomic capecitabine, given a twice daily as salvage therapy in AGC patients formerly administered 1st line chemotherapy for metastatic disease.

Basing on our knowledge, this study is considered the first prospective trial to evaluate metronomic capecitabine in treatment of patients suffering from AGC in Egypt.

In the current work, the overall response rate (partial response and complete response) was reached 21.95% (9/41), and 63.41% (26/41) was the tumor control rate (overall response and stable disease). This was comparable to the results of the He S et al. [19] study in which between the 43 cases treated for 1 cycle at least, 9 patients attained PR (20.9% response rate). Whereas, SD, progressive disease and DCR were averaged 30.2% (13/43 patients); 48.8% (21/43 patients) and 51.1%, respectively. Also our results were comparable with the results of Steinbild et al [37] which evaluated the efficacy and safety of metronomic treatment of advanced cancer patients, and showed that nearly 30% of patients, with AGC, had stable disease post 3 months of treatment [37].

The overall acceptable tolerability of metronomic capecitabine was established in the current study [19].

Most of adverse effects of this treatment recorded along the current study were mild. Hematologic toxicity of Grade 3–4 was not observed in the current study. Hand-foot syndrome (HFS), was the most common adverse event, occurring in 39.02% (16/41) of patients. The maximum of HFS was mild to moderate symptoms and merely 1 patient (2.44%) of Grade 3/4 HFS. Diarrhea was recorded in 7 cases (17.08%) with no one suffered from grade 3 toxicity. Other grade 1 or 2 toxicities reported were nausea in 4 cases (9.76), vomiting in 2 patients (4.88%), hyperbilirubinemia in 2 patients (4.88%), and elevated liver enzymes in 1 patient (2.44%). No patients required hospitalization. Dose reduction to 75% of the dose was recorded in one patient with G3 hand foot syndrome after the 7th cycle till the last cycle (12th). Only 4 patients were subjected for delaying in the dosage for 1 week due to diarrhea (Grade 2), in 2 patients and Grade 1 liver dysfunction (2 patients). The median number of treatment cycles was 5 cycles ranging from 2 to 12 cycles.

Most of toxicities was comparable with that of other previous report of He S et al. [19]. He S et al. [19] investigated the tolerability and clinical efficiency of 500 mg capecitabine (twice a day) in 45 patients with AGC. The overall regimen was well tolerated. (42.2%) of patients were complained from leucopenia (Grades 1, 2 and 3). The more recurrently observed adverse effects were the palmar–plantar erythrodythesia which reached 33.3% of cases ranging from mild to moderate (Grades 1 and 2), with only 1 case (2.2%) of Grade 3 and could be managed with the giving of standard therapy. The present work revealed that the hand-foot syndrome, was the most common treatment-related adverse side effects, presenting in

36.58% (15/41) of patients (Grades 1 and 2), and only 1 case (2.4%) of Grade 3/4. This was comparable to that reported in He S et al. [19] study. Vomiting in He S et al [19] study was also similar (4.4%) to that (4.8%) in our study. Diarrhea in our study was also comparable (17.08%) to that reported (15.5 %) in the study by He S et al [19]. No one in our study suffered from grade 3 diarrhea, as well as in He S et al [19] study no grade 3 or 4 diarrhea was recorded. Again this could be explained by the use of similar doses in He S et al [19] study to that we used in our study. In our study Grade 1 elevation of serum transaminases was reported in only one patient. In He S et al [19] no elevation of serum transaminases was occurred. This difference could be explained by the more prevalence of cirrhotic liver patients among our populations and our study was conducted in metastatic patients including those with liver metastasis (48.8% in our study versus 37.8% in He S et al [19] study).

Genfors D et al [38] found that none of the reported adverse effects were of toxicity-grade III or IV. Most frequent side effects were handfoot syndrome and diarrhea [38]. These results were comparable to our results. Such side effects are very common for capecitabine as mentioned by some researchers [39]. The findings reported by Genfors D et al. [38] showed that low-dose capecitabine is well tolerated. These findings are coordinated with several clinical trials, which have demonstrated that high-grade toxicity is rare due to metronomic chemotherapy and very tolerable [40].

AGC accounts for a disproportionate number of GC deaths; advanced gastric cancer treated by palliative chemotherapy can improve significantly the survival rate, in comparison with the best supportive treatment [41]. At the time of this analysis, in our study, the mortality rate was 68.3% (28/41) of patients, whereas, 15 months rang (7-28) months was the median duration of follow-up. Calvani et al. [42] reported that metronomic capecitabine produced longer median OS survival for AGC patients after failure of previous lines of chemotherapy, particularly when the targets of medical therapy are to achieve disease control and to stop cancer growth without influencing the patient's quality of life [42]. In our study median overall survival (OS) was 18 months, (95% CI; 15.42- 20.58 months). The incidence of occurrence OS rates after 1 and 2 years were reached 74.7% and 16.8%, respectively.

Univariate and multivariate analyses were used for evaluation of factors related to survival. Involved metastatic sites, tumor grade, number of metastatic sites and response to metronomic treatment significantly affected overall survival. In multivariate analysis, only response to treatment turned out to be independent prognostic factor. In a study by He S et al

[3] reported that the median OS was 7.6 months (95% CI 7.0–8.2 months) after a follow-up for a period of 15 months (range 1–25 months). The median over all survival rate was 7.6 months (95% CI 7.0–8.2 months). One year OS was 28.5%. OS rate by a multivariate analysis of 43 cases, was not influenced by metastatic sites, gastrectomy, PS, or response to former lines of chemotherapy [19]. This difference between us and He S et al [19] report could be explained by that their study was conducted in metastatic patients with older age group (the median age of our patients was 51.9 years [range 30-74] versus 74.5 years [range 71–81] for those in He S et al [19] study) and their patients were also heavily pretreated.

The current work proved the overall good efficiency of metronomic capecitabine in the treatment, where 9 months, (95% CI; 7.6 – 10.4 months) was the median time to progression (TTP). The 1-year PFS rates were 30.7%. AGC have been investigated by HeS et al [19] as regard the risk for disease progression after metronomic capecitabine treatment. He reported that 3.6 months (95% CI 3.2–4.0 months) was the median TTP [19]. Again this our better TTP could be explained by that He S et al [19] study was conducted in metastatic patients with older age group (the median age of our patients was 51.9 years [range 30-74] versus 74.5 years [range 71–81] for those in He S et al [19] and their patients were also heavily pretreated.

Our results about the improvement in TTP is comparable to that of study conducted by Calvani et al. [42] who reported that metronomic capecitabine, produced longer median TTP in AGC patients after disappointment of former lines of chemotherapy or in frontline in case of contraindication of the standard chemotherapy, particularly when the targets of medical therapy are to perform disease management and to stop growth of cancer without influencing the quality of patient's life. [42].

However, our data are preliminary trial because of small sample size of participants and the follow up time was relatively short. Larger number of patients and longer duration follow-up period are required in the future studies.

Conclusion

The preliminary finding of the current work revealed that, metronomic capecitabine is a promising regimen for AGC treatment with decreasing in the frequency of disease progression, with tolerable toxicity. Therefore, we recommend that metronomic capecitabine can be used as a substitute tool with tolerable toxicities for patients with AGC. To approve this, a multicenter, meta-analysis and a randomized trial with a large number of patients are necessary.

Conflict of interest:

Authors show no conflict of interest

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