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Safety, Feasibility, and Efficacy of Capecitabine Maintenance in Patients With Advanced Gastric Cancer: A Retrospective Study

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Gastric cancer is still one of the cancers with highest mortality. Most patients present with advanced-stage disease. Palliative chemotherapy is usually the only treatment option for patients with advanced gastric cancer (AGC). Maintenance chemotherapy is an evolving concept in medical oncology. Maintenance chemotherapy can be administered with the same drug(s) in the initial regimen or with an alternative agent. In this article, we report our experience with capecitabine as a maintenance agent for patients with AGC. No treatment-related death was observed due to use of capecitabine. Median progression-free survival was 10.4 months, and median overall survival was 19.7 months. Activity and toxicity profile of capecitabine seems favorable as a maintenance agent in AGC. We believe that capecitabine deserves further trials as a maintenance agent for patients with AGC.

Keywords: gastric, cancer, maintenance, capecitabine

INTRODUCTION

Gastric cancer, despite its decreasing incidence, is still one of the cancers with highest mortality.[1] Most patient present with advanced-stage disease.[2,3] Post-surgery recurrence is common even in patients with early-stage gastric cancer. It was reported that ≥50% of patients treated with curative intent surgery relapse within 5 years.[4,5] Systemic chemotherapy is palliative, and median overall survival (OS) is still <1 year.[6,7] Nevertheless, palliative chemotherapy is superior to best supportive care for improving OS and quality of life.[6,7] A small percentage of patients with metastatic disease may benefit from targeted agent trastuzumab.[8] Palliative chemotherapy consists of a platinum backbone and a fluoropyrimidine backbone combined with an anthracycline compound or a taxane compound.[6,9] Patients with poor performance status may be treated with single-agent chemotherapy.[10] Second-line therapy with irinotecan or docetaxel may also be effective, based on a recent trial.[11]

Maintenance chemotherapy is the continuation of chemotherapy after a predefined number of cycles for patients with nonprogressive disease.[12] Continuation maintenance is the use of the drug(s) in the initial chemotherapy regimen.[12] Switch maintenance is using alternative chemotherapeutic or targeted agent.[12] The role of maintenance therapy has been demonstrated in non–small-cell lung cancer[13,14] and colorectal cancer[15] (CRC). Recently, concept of maintenance chemotherapy has been evolving in advanced gastric cancer (AGC). Considering the poor prognosis of AGC, every effort to improve treatment outcome of AGC should be welcomed.

Capecitabine is an oral pyrimidine analog used to treat various type of solid tumors. Its activity has been demonstrated in adjuvant and palliative

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treatment of gastric cancer.[16–19] Capecitabine passes through 3 enzymatic steps in the body before conversion to the active metabolyte 5-fluorouracil. The third step of capecitabine's conversion involves the enzyme thymidine phopsphorylase, which is much more abundant in tumor tissue than in nontumorous tissue.[19] Capecitabine may meet the criteria for being a candidate maintenance agent for AGC, which are safety, efficaciousness, and ease of administration. The cost of capecitabine is reasonable when compared with other agents used for maintenance in lung and CRCs. This study aimed to report our experience with capecitabine maintenance in 10 patients with AGC.

MATERIALS AND METHODS

The study included 11 patients with AGC who was treated at Yeditepe University Hospital Department of Medical Oncology between November 2008 and July 2014. Patients without progression after first-line chemotherapy that include docetaxel, cisplatin, and 5-fluorouracil were eligible for capecitabine maintenance. Patients who received docetaxel, cisplatin, and fluorouracil (DCF) in classical dose or its modified version (mDCF) as first-line treatment were eligible if no progression was detected after completion of scheduled cycles. Classical DCF consists of docetaxel 75 mg/m^2 day 1, cisplatin 75 mg/m^2 day 1, and 5-fluorouracil 750 mg/m^2 days 1–5.[20] The modified regimen was applied biweekly and consisted of docetaxel 40 mg/m^2 day 1, 5-fluorouracil 400 mg/m^2 bolus day 1 plus 1000 mg/m^2 twice daily, folinic acid 400 mg/m^2 day 1, and cisplatin 40 mg/m^2 day 3.[21] The maintenance dose of capecitabine was 1000 mg/m^2 twice daily for 14 days and 7 days break before the beginning of next cycle. Progression-free survival (PFS) was calculated from the day of pathological diagnosis to first evidence of progression or death. OS was calculated from the day of pathological diagnosis to death from any cause or the last visit. Patient data were obtained from computer- and paper-based records. Statistical analysis was performed using Statview for Windows, version 5.0. Survival curves were estimated using the method of Kaplan and Meier.

RESULTS

Patient baseline characteristics are shown in Table 1. In all, 11 patients with AGC were included. Five patients received classical DCF and 6 patients received mDCF. All 11 patients had completed 6 cycles of chemotherapy before the introduction of capecitabine maintenance. The median number of cycles of maintenance capecitabine received was 5 (2–14). During a median follow-up of 20 months, all patients progressed and 9 patients died. Probability of OS and PFS of patients is given in Figure 1. No death or hospitalization for capecitabine toxicity was noted. In all, 1

Table 1. Characteristics of patients included in trial.

Characteristics	n = 11
Age (median)	53 (30–72)
Gender	
Male	6 (%)
Female	5 (%)
Stage at diagnosis	IV (100%)
Location of primary tumor	
Cardia	5
Lesser curvature	2
Corpus	3
Antrum	1
Site of metastasis	
Liver	6
Lung	2
Bone	3
Lymph nodes	5
No. metastatic sites	
1	3
2	6
≥3	2
ECOG performance status	
0	3
1	8
Mucinous tumor	
Yes	4
No	7
HER-2 status	
Positive	0
Negative	7
Unknown	4
First-line chemotherapy	
Classical DCF	5
mDCF	6
Best response to first-line chemotherapy (on CT)	
CR	0
PR	9
SD	2

CT, computed tomography; CR: complete remission; DCF, docetaxel, cisplatin, and fluorouracil; ECOG, Eastern Cooperative Oncology Group; HER-2: human epidermal growth factor receptor-2; PR, partial remission; SD, stable disease.

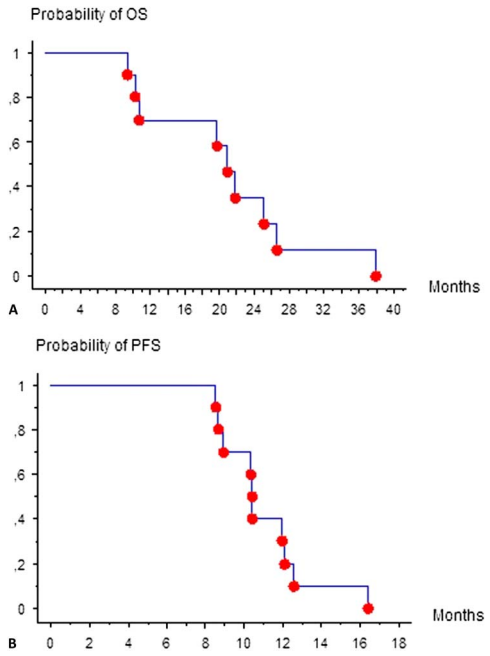

FIGURE 1. Probability of (A) OS and (B) PFS of patients with AGC receiving maintenance capecitabine.

patient developed grade III hand foot syndrome and 1 patient developed grade I hand foot syndrome. Grade II diarrhea and mucositis developed in 1 patient. Mild hematologic toxicity and grade II anemia were detected in 1 patient. Toxicity associated with capecitabine treatment is depicted in Table 2.

Median PFS was 10.4 months (range, 8.5–16.3 months), and median OS is 19.7 months (range, 9.3–37.9 months). The 1-year survival rate was 72.7%, and 2-year OS was 36.4%. Median number of lines of chemotherapy received after capecitabine maintenance was 2 (0–4). In total, 2 patients did not receive further chemotherapy after progression on capecitabine.

Table 2. Toxicities associated with capecitabine treatment.

Grade 2–4 toxicities	n (%)
HFS*	2 (18)
Neutropenia	0
Anemia	1 (9)
Thrombocytopenia	0
Febrile neutropenia	0
Diarrhea	1 (10)
Vomiting	0
Mucositis	1 (9)
Death due to toxicity	0
Hospitalization for toxicity	0

*One patient with grade I and 1 patient with grade III HFS.
HFS, hand foot syndrome.

DISCUSSION

Patients with AGC have poor prognosis.[1] Pallative chemotherapy is more effective than best supportive care. Although the benefit is marginal, combination chemotherapy is preferred over single-agent chemotherapy in patients with AGC. Median OS in patients with AGC is usually ≤1 year. In the landmark REAL-2 trial, epirubicin was combined with various platinum analogs and fluoropyrimidines.[19] In this trial, statistically significant improvement in OS was detected when capecitabine containing arm was compared with 5-fluorouracil-containing arm. Median OS in epirubicin, oxaliplatin, and capecitabine arm was 11.2 months. In V 325 trial, DCF was compared with CF in patients with AGC. In this trial, median OS was 9.2 months.[20] In numerous trials containing irinotecan, median OS was about 11 months.[22,23]

Maintenance therapy is a rapidly evolving issue in medical oncology and primarily used in CRCs and non–small-cell lung cancer. Maintenance therapy can be in the form of chemotherapy or targeted therapy. The maintenance treatment concept is evolving in AGC. Capecitabine seems to be the most appropriate candidate drug for being used as maintenance treatment in patients with AGC, as it is relatively safe, easy to administer, and was demonstrated to be effective as a single agent or in combination with other agents active against gastric cancer. In addition, capecitabine is also less expensive than other agents used for maintenance treatment of lung and CRCs (eg, erlotinib, bevacizumab, cetuximab, and pemetrexed). Qui et al[24] conducted a prospective trial of capecitabine as maintenance treatment in patients with AGC. In that trial, capecitabine maintenance was started after 6 cycles of combination chemotherapy that include capecitabine and oxaliplatin. Capecitabine 2000 mg/m^2 was administered on days 1–14, and the median number of cycles administered as maintenance was 4. Adverse events were mild to moderate and manageable, and no treatment-related mortality was reported. PFS and OS in the maintenance chemotherapy group were 11.4 months and 23 months, respectively. Administration of maintenance chemotherapy was confirmed as an independent prognostic factor for survival based on multivariable regression analysis (hazard ratio, 2.144; 95% CI, P = 0.016). The results of that trial constitute additional evidence of the efficacy and favorable toxicity profile of capecitabine maintenance in AGC.

Another trial involving maintenance chemotherapy with capecitabine in AGC was performed by Gong

et al.[25] Capecitabine maintenance was started after 6 cycles of combination chemotherapy that include capecitabine and paclitaxel. Capecitabine was administered 2000 mg/m^2 on days 1–14. Adverse events were mild, and most common grade 3 and grade 4 toxicities were leucopenia and neutropenia. The maintenance treatment was well tolerated with hand foot syndrome being main toxicity that restricted use of capecitabine. PFS and OS in the whole study population were 188 and 354 days, respectively. Among the 45 patients who received maintenance chemotherapy with capecitabine, OS was 531 days (about 18 months). The researchers reported that no factor was an independent predictor of OS based on multivariate Cox regression analysis.

Wu et al[26] evaluated the tolerance to and activity of cisplatin plus capecitabine in a phase I/II trial, which preferentially includes patients with AGC. Some of the patients with gastric cancer received prolonged maintenance with capecitabine up to 2500 mg/m^2 on days 1–14. Although the number of the evaluable patients with gastric cancer was limited, the treatment protocol seemed to be effective with a time to tumor progression of 5 months and median OS of 28 months. The most common toxicity was neutropenia (grade 3 or 4 in 8% of the patients), fatigue, and hand foot syndrome. No treatment-related death was reported. This study has some limitations, including its retrospective design, a small study population, and inclusion of patients that did not have disease progression during first-line chemotherapy (a favorable group of patients). Therefore, definitive conclusions about maintenance treatment in patients with AGC cannot be made based on the present findings. Nevertheless, we think the therapeutic efficacy and favorable toxicity profile associated with capecitabine should prompt additional research on capecitabine as maintenance therapy in patients with AGC. When considering the poor prognosis of AGC, alternative treatment strategies including agents with favorable toxicity profile that are cost effective (such as capecitabine) deserve further studies.

CONCLUSIONS

Based on the present findings, we think maintenance therapy with capecitabine, in patients with AGC who do not progress on first-line chemotherapy, is feasible. Additional well-designed studies are needed to clarify the role of capecitabine as maintenance in patients with AGC.

All of the patients gave their informed consent before their inclusion in the study.

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