



Comparison of oral capecitabine alone versus platinum combinations in elderly metastatic gastric cancer patients

Serkan Degirmencioglu¹, Olçun Ümit Ünal², Esin Oktay³

1 Pamukkale University School of Medicine, Medical Oncology Department, Denizli, Turkey, ORCID: 0000-0002-1213-2778

2 Tepecik Education and Training Hospital, İzmir, Turkey, ORCID: 0000-0001-7698-3574

3 Adnan Menderes University School of Medicine, Medical Oncology Department, Aydın, Turkey, ORCID: 0000-0002-5974-6339

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Abstract

Objective: Gastric cancer is responsible for a considerable proportion of all cancer-related deaths. Elderly cancer patients are often ignored in prospective studies in which the efficacy of chemotherapy is evaluated, although more than half of all gastric cancer cases are over the age of 70 years. The present study aims to evaluate the efficacy and feasibility of capecitabine-based chemotherapies in geriatric patients with gastric cancer.

Method: A total of 81 patients over the age of 65 years who received chemotherapy for metastatic gastric cancer at two oncology centers between 2012 and 2017 were included in the study. The medical records of the patients were evaluated retrospectively, and the patients and their performance status were evaluated using the American Joint Committee on Cancer staging system and the World Health Organisation scale, respectively.

Results: The mean age was 74 years. The male gender and the adenocarcinoma histological type were seen in higher rates. Most of the patients underwent capecitabine-cisplatin chemotherapy, and the mean follow-up was 42 months. The median overall survival of the groups of patients receiving capecitabine-cisplatin, capecitabine-oxaliplatin and capecitabine was 8 months, 10.7 months and 8.9 months, respectively, indicating no statistically significant differences between the groups ($p=0.467$). The median overall survival of all patients was found to be 8.7 months. The progression-free survival between the different chemotherapy subgroups was not statistically significant ($p=0.59$). The most common side effect was found to be anemia. Grade 3–4 adverse effects were similar between the arms of the study ($p=0.725$). A statistically significant increase was found in the mortality risk with an increased number of metastatic sites in a multivariate analysis ($p=0.001$). No correlation was found between the chemotherapy protocols and mortality risk ($p=0.472$). Adverse effects such as stomatitis, nausea/vomiting, neuropathy, neutropenic fever and nephrotoxicity, independent of chemotherapy, were statistically and significantly associated with the mortality risk ($p=0.045$, $p=0.047$, $p=0.036$, $p=0.02$ and $p=0.049$, respectively).

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Yazışma Adresi / Correspondence: Serkan Degirmencioglu, Pamukkale University Hospital Fahri Goksin Oncology Center 20100 Denizli, Turkey
e-mail: drserkandeg@hotmail.com

Conclusions: Our study results show that adverse effects such as stomatitis, nausea/vomiting, neutropenic fever, nephrotoxicity and neuropathy increase the mortality risk which suggest that particularly oral health care, the application of appropriate antiemetic treatments, the close follow-up of kidney function tests and adequate hydration, protective infection barrier measures and effective treatment of neuropathy associated with chronic diseases are as important as chemotherapy in geriatric cases.

Keywords: Gastric cancer, capecitabine, elderly.

Yaşlı metastatik mide kanserli hastalarda tek başına oral kapesitabin ile platin kombinasyonlarının karşılaştırılması

Öz

Amaç: Mide kanseri, kanser kaynaklı ölümlerin önemli bir kısmını oluşturmaktadır. Tüm mide kanseri olgularının yarısından fazlası 70 yaş üzerinde olmasına rağmen yaşlı kanser hastalar kemoterapi etkinliğinin değerlendirildiği prospektif çalışmalarda kendilerine yer bulamamaktadırlar. Biz bu çalışmada iki onkoloji merkezindeki geriyatrikgastrik kanserli hastalarda kapesitabin bazlı kemoterapilerin etkinliğini ve uygulanabilirliğini araştırmayı amaçladık.

Yöntemler: Çalışmaya iki merkezden metastatik mide kanseri tanısı ile 2012- 2017 yılları arasında kemoterapi alan 65 yaş üzeri hastalar alındı. Hasta dosyaları retrospektif olarak değerlendirildi. Hastalar Amerikan Kanser Komitesi evrelendirme sistemi ve performans statusu Dünya Sağlık Örgütü skalasına göre değerlendirildi.

Bulgular: Çalışmaya alınan 81 hastada ortalama yaş 74 idi. Erkek cinsiyet ve adenokarsinom histolojik tip daha yüksek orandaydı. Hastaların çoğunluğuna kapesitabin-sisplatin kemoterapisi verilmişti. Hastaların ortalama takip süresi 42 aydır. Kapesitabin-sisplatin, kapesitabin-okzaliplatin, kapesitabin kemoterapisi alan grupların median tüm sağ kalım sırasıyla 8 ay, 10,7 ay ve 8,9 ay olarak saptandı, arada istatistiksel fark bulunmadı ($p=0,467$). Tüm hastaların median tüm sağ kalım 8,7 ay bulundu. Kemoterapi alt grupları aralarındaki progresyonsuz sağ kalım farkı istatistiksel olarak anlamlı değildir ($p=0,59$). En sık yan etki anemi olarak saptandı. Grad 3-4 yan etkiler kollar arası benzerdi ($p=0,725$). Çok değişkenli analizde metastatik bölge sayısı ile mortalite riski istatistiksel anlamlı artış göstermiştir ($p=0,001$). Kemoterapi protokolleri ile mortalite riski arası ilişki yoktur ($p=0,472$). Kemoterapiden bağımsız olarak stomatit, bulantı-kusma, nöropati, nötropenik ateş ve nefrotoksisite yan etkileri mortalite riski ile istatistiksel anlamlı ilişki içindedir (sırasıyla $p=0,045$, $p=0,047$, $p=0,036$, $p=0,02$ ve $p=0,049$).

Sonuç: Çalışmamızda evre IV mide kanserli olgularda 8,7 ay tüm sağ kalıma ulaşılmıştır. Kemoterapi alt gruplarında ise hem yan etki hem de sağ kalımlar açısından anlamlı fark yoktur. Stomatit, bulantı-kusma, nötropenik ateş, nefrotoksisite ve nöropati yan etkilerinin mortalite riskini artırması, geriyatrik olgularda özellikle ağız bakımı, uygun antiemetik tedavi uygulanması, böbrek fonksiyon testlerinin sıkı takibi ve yeterli hidrasyon, enfeksiyon açısından koruyucu bariyer tedbirler ve nöropati ilişkili kronik hastalıkların etkin tedavisinin en az kemoterapi uygulanması kadar önem taşıdığını göstermiştir.

Anahtar kelimeler: Mide kanseri, kapesitabin, yaşlı.

INTRODUCTION

Gastric cancer is responsible for a significant proportion of all cancer-related deaths among all cancer types¹. Metastatic gastric cancer (MGC) continues to be a treatment problem among medical oncologists due to its poor prognosis. Several randomized Phase II studies comparing the supportive and combination treatments such as 5-fluorouracil (5FU),

doxorubicin and mitomycin or 5FU, doxorubicin and high dose methotrexate have demonstrated a significantly prolonged overall survival (OS) in favor of chemotherapy groups ranging between 8 and 10 months^{2,3}. Subsequent to these two enlightening studies, various combination chemotherapy regimens were tested in Phase II or Phase III studies of MGC. A Phase III study comparing docetaxel, cisplatin and 5FU (DCF) with cisplatin and a

5FU (CF) reference arm identified significant superior survival of 10.2 months, compared to 8.5 months, and in time to progression (TTP) of 7.2 months over 4.9 months⁴. However, the DCF regimen was found to be associated with high-grade (Grade 3 and 4) toxic effects and has been reported to be a regimen that is difficult to apply in elderly patients with comorbidities.

Capecitabine is an oral fluoropyrimidine carbamate which undergoes a ranked conversion to 5-fluorouracil (5FU)⁵. Conversion to 5FU occurs in several phases, and the final enzyme on the pathway is thymidine phosphorylase, which can be found in much higher concentrations in tumor tissue than in normal tissue. The active form of the drug is mainly in the tumor region⁶. Additionally, capecitabine typically has no cumulative toxicity in long-term use and can be considered appropriate for long-term application. Capecitabine has been demonstrated to be effective in the treatment of MGC as a single-agent or a part of a combination regimen in a series of studies⁷.

More than half of all cases of gastric cancer are in the over 70 years age group, although this group of patients tends to be underestimated in prospective studies in which chemotherapy in MGC is evaluated due to the comorbidities that are common in elderly cancer patients (i.e., diabetes, hypertension, chronic obstructive pulmonary disease, and coronary artery disease) and physiological losses secondary to the ageing process (i.e., impaired kidney and liver function)⁸. Accordingly, in clinical practice, patients with a low performance status receive the best supportive treatment, while patients with a intermediate and good performance status receive monotherapies tolerated better, compared to combined treatments or modified low doses of the combined treatment rather than optimal doses. In the present study, we aimed to evaluate the efficacy and feasibility of capecitabine-based chemotherapies in geriatric patients with gastric cancer.

METHOD

A total of 81 patients over the age of 65 years who received chemotherapy for MGC at two oncology centers between 2012 and 2017 were included in the study. The medical records of the patients were evaluated retrospectively. A written informed consent was obtained from each patient. The study protocol was approved by the local Ethics Board of Non-Interventional Clinical Research (Date: 12/06/2018 and No. 12). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were as follows: 1) pathological diagnosis of MGC in addition to a radiological result; 2) being followed on a regular basis; 3) being over the age of 65 years; 4) no metachronous or synchronous malignancy present (excluding non-melanoma skin cancers); 5) first-line treatment with capecitabine-based chemotherapy (single-agent capecitabine, capecitabine-oxaliplatin combination, or capecitabine-cisplatin combination); and 6) HER2-negative gastric cancer.

The staging and performance status evaluation was performed using the American Joint Committee on Cancer staging system and the World Health Organisation performance status, respectively.

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The elapsed time from the date of first chemotherapy to the date of progression was used in the calculation of progression-free survival (PFS). The time between the date of the first chemotherapy treatment and the date of the last outpatient visit or date of death were used in the calculation of OS. The Kaplan-Meier method was used for the survival analysis. A p value of 0.05 was considered statistically significant.

RESULTS

A total of 81 patients were included in the study. The mean age was 74 years and the male gender was more common. Most of the patients were at the metastatic stage at the time of diagnosis. The most common histological type was evaluated to be adenocarcinoma. Most of the patients received capecitabine-cisplatin chemotherapy. Patient data are presented in Table-I.

Table-I. Baseline characteristics of metastatic gastric cancer patients

Variable	Number of patients (%)
Male	68 (84%)
Female	13 (16%)
Age	74 (65-82)
Histopathological type	
Adenocarcinoma	68 (84%)
Signet ring cell carcinoma	8 (9.8%)
Other	5 (6.2%)
Metastatic stage at time of diagnosis	64 (79%)
Non-metastatic stage at time of diagnosis	17 (21%)
Number of metastatic sites	
1	31 (38.3%)
2	38 (46.9%)
3	12 (14.8%)
Site of metastasis	
Liver	42 (51.9%)
Lung	29 (35.8%)
Peritoneum	9 (11.1%)
Lymph Node	5 (6.2%)
Other	4 (4.9%)
Chemotherapy regimen	
Capecitabine-cisplatin	60 (74.1%)
Capecitabine-oxaliplatin	9 (11.1%)
Capecitabine	12 (14.8%)
Performance status	
0	64 (79%)
1	12 (14.8%)
2	5 (6.2%)

The mean follow-up was 42 months (95% CI, 34.32–53.7). The median OS in the groups that received capecitabine-cisplatin, capecitabine-oxaliplatin and capecitabine was found to be 8 months (95% CI, 6.8–9.2), 10.7 months (95% CI, 9–12.3), and 8.9 months (95% CI, 4.1–13.5),

respectively (Table-II). No statistically significant differences were found between the groups ($p=0.467$). The median OS of all patients was found to be 8.7 months (95% CI, 7.5–8.7). Similarly, no significant difference was found in the PFS between the chemotherapy subgroups ($p=0.59$).

Table-II Overall survival according to chemotherapy regimen

Chemoregimen	Total (n)	Death (n)	Overall survival (month \pm SD)
Capecitabine-cisplatin	60	50	8.033 (6.89–9.22)
Capecitabine-oxaliplatin	9	9	10.7 (9.04–12.35)
Capecitabine	12	10	8.9 (4.23–13.56)
Total	81	69	8.7 (7.51–9.84)

The most frequently seen adverse effect was found to be anemia among all patients. Emesis, nephrotoxicity, anorexia, neutropenia and stomatitis were found to be more common in the capecitabine-cisplatin group. Thrombocytopenia was found to be more common in groups receiving capecitabine-cisplatin and capecitabine-oxaliplatin. Neutropenic fever was seen in a total of six patients – five in the capecitabine-cisplatin group and one in the capecitabine-oxaliplatin group. No statistically significant differences were found between the three treatment arms in terms of Grade 3–4 adverse effects ($p=0.725$). The adverse effects are summarized in Table-III.

A statistically significant increase was found in the mortality risk with an increased number of metastatic sites in a multivariate analysis ($p=0.001$). No association was found between the chemotherapy protocols and mortality risk ($p=0.472$). Adverse effects such as stomatitis, nausea/vomiting, neuropathy, neutropenic fever and nephrotoxicity independent of chemotherapy were statistically and

significantly associated with mortality risk (p=0.045, p=0.047, p=0.036, p=0.02 and p=0.049, respectively). No association was found between the rates of anemia, thrombocytopenia, neutropenia, anorexia, diarrhea and hepatotoxicity and mortality (p=0.464, p=0.899, p=0.195, p=0.246, p=0.153 and p=0.332).

Table-III. Adverse effects

Adverse effect	Capecitabine-oxaliplatin	Capecitabine-cisplatin	Capecitabine
Anemia gr 1-2	6 (66.6%)	52 (86.6%)	7 (58.3%)
Anemia gr 3-4	1 (11.1%)	8 (13.4%)	1 (8.3%)
Neutropenia gr 1-2	2 (22.2%)	22 (53.6)	4 (33.3%)
Neutropenia gr 3-4	1 (11.1%)	5 (8.3%)	0
Low platelet gr 1-2	4 (44.4%)	28 (46.6%)	3 (25%)
Low platelet gr 3-4	1 (11.1%)	2 (3.3%)	0
Stomatitis gr 1-2	4 (44.4%)	50 (83.3%)	2 (16.6%)
Stomatitis gr 3-4	0	0	0
Anorexia gr 1-2	5 (55.5%)	40 (66.6%)	4 (33.3%)
Anorexia gr 3-4	0	2 (3.3%)	0
Emesis gr 1-2	6 (66.6%)	50 (83.3%)	4 (33.3%)
Emesis gr 3-4	0	6 (10%)	0
Diarrhea gr 1-2	1 (11.1%)	14 (23.3%)	2 (16.6%)
Diarrhea gr 3-4	0	3 (5%)	1 (8.3%)
Neuropathy gr 1-2	2 (22.2%)	2 (3.3%)	0
Neuropathy gr 3-4	0	0	0
Hepatotoxicity gr 1-2	1 (11.1%)	1 (1.6%)	0
Hepatotoxicity gr 3-4	0	0	0
Nephrotoxicity gr 1-2	0	32 (53.3%)	0
Nephrotoxicity gr 3-4	0	2 (3.3%)	0

Gr: Grade

DISCUSSION

Gastric cancer is most commonly seen in the elderly population with some 60% of all gastric cancers seen in patients at or over the age of 70 years according to 2017 statistics¹. The treatment protocols applied in young cases based on evidence-based medicine have been used in this patient group, since elderly patients are often excluded from clinical studies. The main drawback of this situation is that with these protocols, adverse effects are more common, and tolerance is lower in the elderly patient group, since comorbidities are more frequent in elderly patients. This finding suggests that elderly patients may tolerate systemic chemotherapy and benefit from it almost as well as younger patients^{9,10}. The results of the present study are consistent with

those of previous studies in literature, and a survival of 8.7 months was achieved independent of the chemotherapy protocol in cases with Stage IV gastric cancer. No significant difference was demonstrated in either adverse effects or OS between the capecitabine alone and the capecitabine and combined platin chemotherapy groups. Therefore, chronological age on its own should not exclude a patient from effective chemotherapy that would improve disease-free survival, quality of life, and OS.

The male gender and the adenocarcinoma subtype were seen in higher rates in the present study, which is consistent with literature¹. In addition, an increased number of sites of metastasis significantly decreased survival in a multivariate analysis. Tan et al. reported that survival was statistically lower in

combined the peritoneal metastasis and distant metastasis arm in their study in which they grouped 470 patients based on the presence of peritoneal metastasis, distant metastasis, and combined peritoneal and distant metastasis¹¹. This suggests to define an increased tumor load in gastric cancer as a poor prognostic factor in the present study, which is also consistent with the findings of previous studies.

The main challenge in the management of elderly gastric cancer patients is to determine whether the expected benefit from the treatment is superior to the treatment risks, and subsequently the selection of the most appropriate drugs or regimen. Advanced stage gastric cancer is more common among the elderly population than in younger patients¹². In addition, tumors located in the cardia with a poorer prognosis have been reported to be seen in higher rates in the elderly population¹³. Algorithms should be developed to aid in the selection of the optimal treatment for elderly patients considering comorbidities, performance status and geriatric functional status. When the adverse effects of all chemotherapy arms were evaluated in the present study, stomatitis, nausea/vomiting, neutropenic fever, nephrotoxicity and neuropathy were found to statistically increase the risk for mortality, which suggests that, particularly oral health care, the application of appropriate antiemetic treatment, the close follow-up of kidney function tests and adequate hydration, protective infection barrier measures and effective treatment of neuropathy associated with chronic diseases are as important as the application of chemotherapy in geriatric cases.

In conclusion, our study results show that no significant difference was found in the PFS and OS between the capecitabine alone and other combination subgroups. This can be considered a preliminary study that needs to be supported with prospective multi-center studies including a larger number of patients.

Conflicts of interest: The authors have no conflict of interests to declare.

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