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Original Article

Maintenance treatment with gemcitabine have a promising activity on metastatic bladder cancer survival

Gemsitabin ile idame tedavisinin metastatik mesane kanseri sağkalımında ümit verici bir aktivitesi vardır

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ABSTRACT

Objective: To investigate the effects of gemcitabine maintenance treatment on survival in patients with metastatic bladder cancer.

Material and methods: Gemcitabine maintenance monotherapy was administered following the standard platinum-gemcitabine therapy in patients with metastatic bladder cancer. Patients who had responded to standard treatment received maintenance gemcitabine therapy as 1000 mg/m^2 on days 1 and 8 every three weeks until progression or development of unacceptable toxicity. The following clinical factors were noted: performance status, age, sex, stage, site of metastasis, choice of cisplatin-gemcitabine or carboplatin-gemcitabine, response rates to the initial chemotherapy. Progression- free survival (PFS) and overall survival (OS) for standard treatment, and following gemcitabine monotreatment and for maintenance gemcitabine therapy were calculated using Kaplan–Meier method.

Results: A total of 88 patients with metastatic bladder cancer treated between February 2009 to October 2015 were evaluated retrospectively and 23 patients (26.1%) who had responded to six cycles of platinum-gemcitabine treatment were included in this study. Maintenance gamcitabine was administered for a median of 7 times (range 3–14 times). Grade 3 hematotoxicity according to the criteria of the Common Terminology Criteria of Adverse Events was observed in 7 (30.4%) patients. Median PFS of patients was 46 (range: 30-82) weeks for platinum-based treatment plus maintenance gemcitabine therapy. A higher median PFS was obtained in patients who were <65 year-olds, without organ metastasis with objective response rate, however, it was statistically insignificant.

Conclusion: Gemcitabine maintenance therapy in metastatic bladder cancer patients who did not shown progression after the standard platinum-gemcitabine treatment contributes to survival and presents low toxicity profile, when compared to historical controls.

Keywords: Bladder cancer; gemcitabine; maintenance therapy; metastasis.

ÖZ

Amaç: Metastatik mesane kanserli hastalarda, idame gemsitabin tedavisinin sağkalım üzerindeki etkisini araştırmak.

Gereç ve yöntemler: Gemsitabine idame tedavisi, metastatik mesane kanserli hastalara, standart platin-gemsitabin tedavisinin ardından uygulandı. Standart tedaviye yanıtı olan hastalar, idame gemsitabin tedavisini 1000 mg/m^2, 1. ve 8. gün 3 haftada 1 olmak üzere, progresyona ya da kontrol edilemeyen toksisiteye gelişinceye kadar aldı. Şu klinik faktörler not edildi: yaş, cinsiyet, metastaz bölgesi, sisplatin-gemsitabin ya da karboplatin-gemsitabin seçimi ve ilk tedaviye cevap oranı. Standart tedavi ve sonrası verilen gemsitabin için ve sadece idame gemsitabin için progresyonsuz sağkalım (PSK) ve genel sağkalım (GS), "Kaplan-Meier yöntemi" kullanılarak hesaplandı.

Bulgular: Şubat 2009 ile Ekim 2015 yılları arasında 88 metastatik mesane kanserli hasta retrospektif olarak tarandı ve çalışmaya 6 kür platinum-gemsitabin tedavisine cevaplı 23 hasta (%26,1) dahil edildi. İdame gemsitabinin median uygulanma sayısı 7 (3-14) idi. "Common Terminology Criteria of Adverse Events" kriterlerine göre 3. derece hematoksisite, 7 hastada (%30,4) gözlendi. Platin bazlı tedavi ve idame gemsitabin için median PSK 46 hafta (30-82), sadece idame gemsitabin için 22 hafta (10-56) idi. 65 yaş altı, objektif cevap oranı sergileyen ve organ metastazı olmayan hastalarda, daha yüksek median PSK süresi elde edildi fakat bu istatistiki olarak anlamlı değildi.

Sonuç: Standart platinum bazlı tedavi sonrası progrese olmayan hastalarda idame gemsitabin tedavisi, tarihi kontrolleri ile kıyaslandığında, metastatik mesane kanserinde sağkalıma katkıda bulunur ve düşük bir toksisite profili vardır.

Anahtar Kelimeler: Mesane kanseri, gemsitabin, idame tedavi, metastaz

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Introduction

Bladder carcinoma is a curable disease with the application of some treatment modalities in early stage, while it is one of the most agressive disease in advanced stage. Since 1990, the combination of methotrexate-vinblastine-doxorubicin-cisplatin (MVAC) has been considered as standard first-line treatment in metastatic bladder cancer.[1] However, a high toxicity profile of MVAC chemotherapy leads the way to new therapeutic requests in this field. Gemcitabine is an active and safe monotherapy option for the treatment of metastatic bladder cancer and it is more active when combined with platinum-based agents.[2,3] The first multicenter, randomized phase III study comparing gemcitabine-cisplatin (GC) with MVAC in patients with advanced bladder cancer was published in 2000. Accordingly, GC provided a similar survival advantage compared to MVAC with a better safety and tolerability profile (median time to progression (TTP): 7.4 vs. 7.4 months, respectively.[4] Supporting studies which were published following this study have suggested that GC is not inferior to MVAC.[5-8]

Consecutive studies reported low response rates both with GC and MVAC (49-65%, and 46-65%, respectively).[9,10] So, triple chemotherapy regimens were applied, however, they were more toxic and less effective.[1] The combination of cisplatin with taxanes provided promising effectiveness with improved overall response rate (ORRs) of 50-70 percent[11-14], but it remained inferior to the MVAC as shown by a phase III randomized study (ORR was 37.4% vs. 54.2% p=0.017, TTP was 6.1 vs. 9.4 months, p=0.003).[15] Moreover, after failure of cisplatin-based first-line therapy, there have been just a few agents such as eribulin, taxanes, vinflunine, and pemetrexed which resulted in a low response rate about 7 to 38%.[16-19] In addition to low survival rates obtained with these agents, disease progression inavoidable occurs just after discontinuing the first-line chemotherapy. Consequently, it is necessary to find more effective and tolerable treatments to delay disease progression and improve survival in advanced bladder cancer.

Prolonging the platinum-based chemotherapy could be one option for increasing the progression-free survival (PFS) rate, however, bone marrow suppression and nephrotoxicity are its limitations. In this regard, maintenance treatment for patients who had responded to dual platinum combination chemotherapy gains significance. In the present sudy, we evaluated the maintenance treatment with gemcitabine in patients with advanced bladder carcinoma after standard chemotherapy.

Material and methods

Study design

Patients were recruited in a single center of our university oncology hospital. This retrospective study was conducted in compliance with the ethical principles according to the Declaration of Helsinki and it was approved by the Independent Ethics Committee of Gaziantep University. We hypothesized that mainenance treatment with gemcitabine contributes a survival advantage for patients with bladder cancer and it is a safe treatment option.

Patients

Patients with histologically proven metastatic transitional cell carcinoma of the bladder were recruited between February 2009 to October 2015. Patients who had undergone systemic chemotherapy or immunotherapy, curative surgery including radical cystectomy or nephroureterectomy were excluded from the study. Patients who received prior local intravesical therapy, radiotherapy or palliative surgery were included in the study. Patients were included according to following criteria; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2, adequate bone marrow reserve, and renal function (creatinine clearance: >60 mL/min), and an estimated life expectancy of at least 3 months.

The following clinical factors were noted: performance status, age, sex, stage, site of metastasis, choice of cisplatin-gemcitabine (CG) or carboplatin-gemcitabine (CaG), response rates to previous chemotherapy, PFS for the first six cycles of treatment with gemcitabine and for maintenance gemcitabine and overall survival (OS). Palliative radiotherapy was allowed for painful bone lesions in the absence of disease progression. Toxicities during the gemcitabine treatment were noted according to National Cancer Institute's Common Toxicity Criteria for Adverse Events (NCI-CTCAE) grading scale version 4.03 (NCI-CTCAE 4.03).

Treatment schedule

Cisplatin-gemcitabine treatment was delivered intravenously (IV) as cisplatin (50 mg/m^2) with gemcitabine (1000 mg/m^2) on days 1 and 8 every three weeks or CaG as carboplatin area under curve (AUC) 5) on day 1 with gemcitabine 1000 mg/m^2 on days 1 and 8 every three weeks were administered for six cycles. Patients who had responded to the treatment regimen were classified in stable disease (SD), partial response (PR) or complete response (CR) categories and received gemcitabine maintenance therapy as 1000 mg/m^2 on days 1 and 8 every three weeks. While prophylactic use of growth factors was not recommended, in the case of grade III-IV toxity the doses of cisplatin, carboplatin and gemcitabine were reduced for 25% according to type of toxicity. Treatment was repeated as gemcitabine maintenance therapy until the documented disease progression, unacceptable toxicity, an increase in ECOG PS of one level or the need to delay chemotherapy more than 3 weeks were noted.

Response evaluation

Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. The first computed tomography (CT) scan or ^{18}F-FDG PET/CT was performed

prior to treatment and follow-up CT scans or ^{18}F-FDG PET/CT were performed every 9 weeks (every three cycles) or in case of clinically suspected progression. PFS was defined as the interval between the beginning of chemotherapy to progression or discontinuation of treatment due to any cause. Responses were confirmed at least after 3 cycles (9 weeks). OS was defined from the date of diagnosis until death. CR was defined as the disappearance of all signs of cancer in response to treatment. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, or in the extent of cancer in the body in response to treatment. SD was defined as neither sufficient decrease in tumor burden to qualify for PR nor sufficient increase to qualify for PD. PD was defined as at least a 20% increase in the sum of the longest diameter of target lesions.

Statistical analysis

Kaplan–Meier method was used to calculate survival analyses. Median ± standard errors were specified as descriptive statistics, and evaluation of risk factors for first-line PFS, OS was estimated using hazard regression model. Hazard ratios (HRs) and corresponding confidence intervals (CIs) were calculated using Cox's proportional hazards model. P<0.05 was accepted as statistically significant.

Results

Eighty-eight patients with advanced bladder cancer were evaluated retrospectively. Eight (11.3%) of these patients were female. Response rate after platinum-gemcitabine treatment was 42 percent. Twenty-three patients without disease progression after treatment were included in this study and maintenance treatment with gemcitabine was initiated. Patient characteristics were shown in Table 1. Median 7 (range: 3-14) cycles of gemcitabine were administered. Only one of patients included in the study was female. Median age was 66 (range: 50-82) years. Median PFS of patients was 48 (range: 30-82) weeks for platinum- based treatment plus gemcitabine maintenance therapy. Median PFS, and OS for only gemcitabine maintenance therapy were 26 (range: 10-56), and 73 (range: 30-132) weeks, respectively.

After standard platinum-gemcitabine treatment, SD, PR and CR were observed in 6, 15 and 2 patients respectively. According to responses (SD, PR, CR) to gemcitabine maintenance treatment median PFS times were 20 weeks (95% confidence interval (CI): 10.3-29.6), 28 weeks (95% CI: 17-38), and 43 weeks (endpoint was not reached) respectively (p=0.675). Median PFS was 30 (95% CI: 23.3-36.6) vs. 26 (95% CI:15.8-36.1) weeks for the patients <65, and >65 years old, respectively (p=0.306).

Seven patients had bone, muscle or lymph node metastasis, the remaining patients had visceral metastases including lung and liver metastases. All of visceral metastasis were multiple. For gemcitabine treatment, median PFS of the patients without and with visceral metastasis was 34 (95% CI: 29.3-38.6) vs. 22 (95% CI: 20.2-23.7) weeks (p=0.482).

Table 1. Patient characteristics

	n (%)
Sex	
Male	1 (4.3)
Female	22 (95.6)
Median age (range)	66 (50-82)
Metastatic site	
Lung	11 (47.8)
Liver	4 (17.3)
Only bone	5 (21.7)
Others	2 (8.6)
Efficacy of prior chemotherapy	
Stabilized the disease	6 (26.0)
Partial remission	15 (65.0)
Complete remission	2 (8.6)
Main treatment	
Cisplatin with gemcitabine	11 (47.8)
Carboplatin with gemcitabine	12 (52.1)

When we compared the patients who received carboplatin plus gemcitabine (n=12) or cisplatin plus gemcitabine (n=11), median PFS 30 weeks (95% CI: 18.1-41.8) vs. 22 weeks (95% CI: 13.3-30.6) p=0.335 and median OS 74 week (95% CI: 56.2-91.7) vs. 60 weeks (95% CI: 44.8-75.1) weeks were estimated without any statistically significant difference between groups (p=0.508).

Grade 2 anemia (n=1; 4.3%), Grade 2 (n=4; 17.4%), 3 (n=3; 13%) and 4 (n=2; 8.7%) thrombocytopenia, Grade 2 (n=3; 12%), 3 (n=2; 8.7%) and 4 (n=1; 4.3%) neutropenia were detected in respective number of patients. Seven (30.4%) patients developed grade ≥3 myelotoxicity during gemcitabine maintenance treatment.

Discussion

Maintenance treatment used for many cancer types such as breast, lung, prostate, and ovarian cancers to provide extended response is a significant treatment tool in the management of advanced cancer.[20-26] Urothelial cancer is the most agressive disease and have a low response rate especially after the first-line therapy in its advanced stage. The treatment break for patients who responded to first-line therapy is generally short-term for about 2 to 3 months and it leads to rapid clinical progression and deterioration.[27] Moreover, clinical deterioration might not allow usage of second-line therapy in such patients. In

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this regard, chance of extended response and safe treatment with maintenance treatment should not be missed out. Maintenance therapy is defined as the continuation of a treatment after achieving a clinical response to standard chemotherapy.[28] In the current study, we evaluated efficiency of gemcitabine maintenance treatment which was administered to sustain tumor response of first-line platinum-gemcitabine treatment and delay disease progression. The study had not a placebo arm due to its retrospective design and daily practice of our center. Therefore, we compared our findings with the historical controls. We showed that administering gemcitabine provided a delayed disease progression with a low toxicity profile consistent with the results of limited number of similar studies.[27,29]

Gemcitabine maintenance treatment is also a valuable agent for the patients with squamous cell lung cancer who responded to platinum-gemcitabine chemotherapy. However, despite the improvement in PFS with gemcitabine, according to some studies this PFS advantage did not reflect on OS.[30] Moreover, gemcitabine maintenance treatment was only a useful treatment option for lung cancer patients with good performance status and patients who demonstrated an objective response to platinum-gemcitabine.[31] So, possible response rate is low and benefit is insufficent for patients who presented stable disease following the first-line chemoterapy for lung cancer. Thus, parameters predicting the benefit of maintenance therapy gain importance for the proper selection of maintenance treatment, best supportive care or second-line chemotherapy for many cancer types. In our study, we showed that patients with stable disease after platinum based treatment and older patients aged >65 years showed shorter progression free survival with gemcitabine maintenance treatment. In this regard, these parameters can predict the benefit which might be gained from gemcitabine maintenance treatment in bladder cancer.

Muto et al.[27] compared gemcitabine maintenance treatment and placebo in patients with urothelial carcinomas who received MVAC or GC as the first-line therapy. The patients had lung (36%), liver (36.4%) and bone (27.3%) metastases. Sixty four percent of the patients underwent radical surgery. Seventy-six percent of the patients had stable disease and 9% of the patients demonstrated partial and complete response to first-line treatment. Accordingly, after pretreatment, the median time to progression for the maintenance group was 12.0 months, and 2.0 months for the placebo group ($p<0.001$). When our study was compared with this study, we obtained lower PFS rates with gemcitabine because of patients' characteristics of this study, for instance 63.6% of the patients had undergone radical surgery. Grade 3 or above hemathologic adverse events according to NCI-CTCAE were seen in 27.3% of the patients, consistent with our study. Visceral metastasis, the response rate of prior chemotherapy, and gemcitabine maintenance therapy were significantly independent prognostic factors for survival in univariate and multivariate analyses. In our study, higher median PFS rate was also obtained in patients who were <65 years old, with objective response rate and without organ metastasis ($p>0.05$). Statistically insignificant results obtained in our study might be related to low number of patients in our study.

Gemcitabine maintenance treatment following cisplatinbased combination chemotherapy were retrospectively evaluated in 38 patients with surgically treated advanced urothelial carcinoma, and maintenance treatment provided an additional 5-year OS which was statistically significant in patients who was entirely treated with surgery.[29] Median age was 66 (33-80) years. Fifteen percent of the patients had metastatic disease. Seventy-nine percent of patients presented with stable disease, and 8% of the patients demonstrated disease regression after the main chemotherapy. Different from Muto et al.[27] study and our study, presence of visceral metastasis was not identified as a prognostic factor in this study. In this regard, gemcitabine maintenance treatment after surgical treatment modality was used in two studies, which prolonged the survival. In this regard, gemcitabine maintenance treatment is a reasonable treatment option for patients who had undergone surgery and who are not suitable for surgery in order to delay disease progression.

Any agent with proven effectiveness for the maintenance treatment of bladder carcinoma, has not been available until now. Sunitinib, an oral inhibitor of multiple receptor tyrosine kinases, was used as maintenance treatment without any favourable effect in bladder carcinoma.[32] Immune therapy is also emerging as a promising new treatment option in bladder cancer.[33,34] Ipilimumab, the monoclonal antibody which targets cytotoxic T-lymphocyte–associated antigen 4, was administered as maintenance treatment after CG. Although mean survival time of 14.6 months was achieved, it was not better than historical controls and had a worse toxicity profile.[35] IMvigor 210 trial assessed atezolizumab, an anti–PD-L1 monoclonal IgG1 antibody, as the first-line therapy in patients who are ineligible for platinum-based therapy with a median OS of 14.8 months.[36] We obtained a median OS of 17 months in our study. Although immunotherapy and maintenance immunotherapy have a promising effectiveness in the treatment of bladder carcinoma, platinum-based chemotherapy is still the standard treatment for platinum –treatment responsive patients.

The most important limitations of the study were its retrospective design and low number of patients. Because bladder cancer is one of cancers with low-response rates, the number of patients in our study was as low as in other studies in the literature. As shown in our study, gemcitabine maintenance therapy is still the treatment that provides the longest progression-free survival for the patients after 6 cycles of standard therapy based on literature findings. However, there is a need for prospective studies performed with other options, such as cessation of treatment until progression or comparison with other second-line chemotherapy.

In conclusion, we showed that gemcitabine maintenance therapy for the patients who responded to platinum-based therapy delayed the disease progression with low toxicity profile when compared to historical controls. Gemcitabine maintenance therapy in metastatic bladder cancer is the single agent with proven efficiency contributing to survival.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University School of Medicine.

Informed Consent: Written informed consent was not taken before or after the treatment from patients or patients' parents who participated in this study because the data were collected retrospectively.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan ya da hastaların ailelerinden retrospektif olarak veriler tarandığından dolayı alınmamıştır.

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