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OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Efficacy of Bevacizumab-Based Terapy in Patient With Metastatic or Recurrent Cervical Cancer: Real Life Data

Metastatik veya Nüks Serviks Kanserli Hastalarda Bevacizumab Bazlı Tedavinin Etkinliği: Gerçek yaşam Verisi

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ÖZET

Amaç: Bu çalışmanın amacı metastatik serviks kanseri (SK) tanısı konulan hastalarda bevacizumab (BEV) bazlı tedavilerin güvenliğini ve etkinliğini, gerçek yaşam verileri baz alınarak değerlendirmektir.

Gereçler ve Yöntem: Bu çalışma, retrospektif gözlemsel bir analiz içermektedir. Çalışmaya Ocak 2012-Aralık 2022 tarihleri arasında Tıbbi Onkoloji bölümünde BEV tedavisi alan metastatik SK tanılı hastalar dahil edilmiştir.

Bulgular: Bu çalışmaya ortalama yaşı 51 (medyan: 21-78) ve tedavi sonrası ortalama takip süresi 16,6 ay olan 40 hasta dahil edildi. Yaygın metastatik bölgeler arasında %72,5 (n=29) lenf nodu, %55 (n=22) periton, %35 (n=14) akciğer, %22,5 (n=9) karaciğer ve %15 (n=6) kemik yer almaktadır. Tedavi yanıtlarına ilişkin olarak hastaların %12,5'inde (n = 5) tam yanıt , %45'inde (n = 18) kısmi yanıt , %17,5'inde (n = 7) stabil yanıt, %25'inde ise (n = 10) progresyon saptandı. Medyan progresyonsuz sağkalım 8,5 ay (%(95% CI: 6.838 – 10.295) ve genel sağkalım ise 16,3 ay (95% CI: 11.305 – 21.362) olarak bulundu. Kemik metastazı varlığı (p=0,024) ve obezite (p=0,020) sağkalım sonuçlarını etkileyen istatistiksel olarak anlamlı faktörlerdir. Yaş, patoloji alt grupları, metastatik bölge sayısı, tümör gradı, başlangıç evresi, tedavi öncesi cerrahi ve radyoterapi, ve BEV ile eşzamanlı uygulanan sitotoksik ajan türü gibi çeşitli faktörlere bağlı olarak genel sağkalım sonuçlarında istatistiksel olarak anlamlı bir fark bulunmadı (p > 0.05).

Sonuç: Metastatik SK tanılı hastaların prognozu kötüdür. BEV'in kemoterapi ajanlarıyla kombinasyonları bu hasta grubunun tedavisinde etkili ve güvenlidir.

Anahtar Kelimeler: Serviks kanseri, bevacizumab, kemoterapi

ABSTRACT

Aim: This study's goal is to evaluate the safety and efficacy of bevacizumab (BEV)-based therapies in patients with metastatic cervical cancer (CC) using real-life data.

Materials and Methods: This study constitutes a retrospective observational analysis. Patients diagnosed with metastatic CC who received BEV treatment in the Medical Oncology department between January 2012 and December 2022 were included in the study.

Results: This study encompassed 40 patients, with a median age of 51 years (range: 21-78), and a median follow-up duration post-treatment of 16.6 months. Predominant metastatic sites included the lymph nodes 72.5% (n=29), peritoneum 55% (n=22), lungs 35% (n=14), liver 22.5% (n=9) and bones 15%(n=6). Regarding treatment responses, 12.5% (n = 5) of patients achieved complete response , 45% (n = 18) achieved partial response, 17.5% (n = 7) had stable disaese, and 25% (n = 10) experienced disease progression. The median progression-free survival was found 8.5 months (95% CI: 6.838 – 10.295), and the median overall survival was 16.3 months (95% CI: 11.305 – 21.362). The presence of bone metastasis (p=0.024) and obesity (p=0.020) are statistically significant factors affecting survival outcomes. There were no statistically significant differences in survival outcomes due to several factors, including age, pathology classification, number of metastatic sites, tumor grade, initial staging, previous surgeries and radiotherapy before starting therapy, and the type of cytotoxic agents administered with BEV (p > 0.05).

Conclusions: Metastatic CC has a challenging prognosis. Combinations of BEV with chemotherapy agents are effective and safe in the treatment of this patient group.

Keywords: Cervical cancer , bevacizumab, chemotherapy

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INTRODUCTION

Cervical cancer (CC) is the fourth most common malignancy among women worldwide after breast, colorectal and lung cancers, with 600,000 new cases and 340,000 deaths annually (1). While the incidence of CC has considerably diminished in developed countries due to cytologic screening and HPV vaccination campaigns, it still remains the predominant gynecological malignancy (2). In the management of primary CC, therapeutic approaches encompass surgical interventions for early-stage disease and the utilization of concurrent cisplatin chemotherapy (ChT) combined with pelvic radiation therapy for locally advanced lesions (3). Additionally, even the progress in the prevention and detection of CC is huge, individuals identified with advanced or recurrent stages experience unfavorable prognoses. In the United States, the 5-year survival rate for CC diagnosed at the locally advanced stage is 57%. Yet, for those categorized as stage IV, the rate diminishes to 16% or lower, and for recurrent cases, it dips below 5% (4). In the past, the standard treatment involved cisplatin as a monotherapy, followed by the adoption of a platin and paclitaxel combination (5).

Bevacizumab (BEV), a synthetic antibody against vascular endothelial growth factor, impedes tumor development by suppressing angiogenesis (6). Due to randomized trials, incorporating BEV into ChT regimens has demonstrated favorable results in terms of response rates and overall survival (OS) outcomes (7). Based on these outcomes, current recommendations endorse this regimen as the standard therapeutic approach for metastatic CC (8). Despite these accomplishments, there remains a necessity for innovative therapies to address metastatic CC in both initial and subsequent treatment lines (9).

Randomized prospective trials are essential to ascertain a drug's efficacy and safety. However, since these studies frequently encompass selected patient groups, variations from real-world results are possible. In our research, we aimed to retrospectively assess the safety and efficacy of combining BEV with ChT in patients with metastatic CC, mirroring real-life clinical practices.

MATERIALS AND METHODS

The study was carried out with the permission of the Istanbul University, Istanbul Faculty of Medicine Scientific Research Evaluation and Ethics Committee (Date:13.10.2022, Decision No: 2022/1651). It was conducted in strict adherence to the principles outlined in the Declaration of Helsinki and in accordance with the recommended guidelines for good clinical practice. Retrospective analysis was performed on patients who were hospitalized between January 2012 and December 2022. Individuals diagnosed with metastatic CC and subjected to ChT protocols incorporating BEV were included for this study. All patients received BEV at a dose of 15 mg/kg every three weeks until disease progression, severe toxicity and adequate treatment duration. Patients with insufficient data for statistical evaluation were omitted from the study. Comprehensive demographic and clinical information, encompassing age at diagnosis, familial history, stage, histological findings, perioperative interventions, the count of BEV cycles administered, specific ChT protocols, radiotherapy regimens, surgical procedures, and associated toxicities, were conducted from the medical database. This information was meticulously documented and organized for subsequent analysis.

Clinical and radiological evaluations were performed at approximately two-three month intervals to determine the effectiveness of the treatment. Utilizing the Response Evaluation Criteria in Solid Tumors guidelines as a reference, treatment outcomes were segmented into four categories: complete response (CR), partial response (PR), stable disease (SD), and progressive disease. Using this classification, we determined the optimal response exhibited by patients according to the set criteria. The overall response rate (ORR) was derived from the combined instances of CR and PR. Concurrently, the disease control rate (DCR) was ascertained by encompassing cases categorized as CR, PR, and SD. Progression-free survival (PFS) was determined as the time from initiation of BEV treatment to progression.The time from beginning BEV to death from any cause was defined as OS. An univariate analysis was executed to examine the influence of clinicopathological factors on OS. A multivariate analysis was conducted, incorporating both the notable factors identified in the univariate analysis of this study and those recognized as significant in the current literature. To ensure precise and trustworthy data, patient statuses were verified by cross-referencing with the Ministry of Health's death registration system.

Survival curves were generated employing the Kaplan-Meier methodology. The log-rank test was utilized to conduct univariate analysis. The Cox regression model was employed for multivariate analysis to determine the independent impacts of different variables on the desired outcomes. Statistical evaluations were performed utilizing SPSS version 25 (IBM Corp., Armonk, NY, USA).

RESULTS

The current study included 40 patients diagnosed with metastatic CC. The median age of the patients was 51 years (range, 21–78 years). Based on pathological features, 82.5% (n = 33) of the patients were diagnosed with squamous carcinoma, 10% (n = 4) exhibited adenocarcinoma, 5% (n = 2) clear cell carcinoma, and 2.5% (n = 1) presented with the adenosquamous subtype. The predominant sites of metastatic spread included the lymph nodes at 72.5% (n=29), peritoneum at 55% (n=22), lungs at 35% (n=14), liver at 22.5% (n=9), bones at 15% (n=6) and brain at 2.5% (Table 1). Prior to receiving BEV treatment, 75% (n = 30) underwent definitive radiotherapy, while 45% (n=18) had surgical interventions. Among the participants, 17.5% (n=7) underwent perioperative ChT. Additionally, approximately 32.5% of the patients, equivalent to 13 individuals, had received palliative ChT before initiating BEV. After BEV treatment, 22.5% (n = 9) of patients received palliative ChT.

Table 1. Clinical and pathological features of the patients.

Characteristics		n (%)
Age at diagnosis	<50 years	17 (42.5)
	≥50 years	23 (57.5)
Pathologic subtypes	Squamous	33 (82.5)
	Adenocancer	4(10)
	Clear cell	2 (5)
	Adenosquamous	1 (2.5)
Grade status	Grade 1-2	30 (75)
	Grade 3	10 (25)
BMI (kg/m^2)	<19	1 (2.5)
	19-25	11 (27.5)
	25-30	17 (42.5)
	>30	11 (27.5)
Stage at diagnosis	Stage 1	6 (15.0)
	Stage 2	14 (35.0)
	Stage 3	10 (25.0)
	Stage 4	10 (25.0)
Sites of metastasis	Liver	9 (22.5)
	Periton	22 (55.0)
	Lungs	14 (35.0)
	Bone	6 (15.0)
	Brain	1 (2.5)
	Lymphadenopathy	29 (72.5)
	Others	9 (22.5)
The number of metastatic sites	≤ 2 sites	19 (47.5)
	> 2 sites	21 (52.5)
Surgeries prior to bevacizumab	Yes	18 (45.0)
	No	22(55)
Radioterapy before bevacizumab based terapy	No	8 (20)
	Definitive	30 (75)
	Palliative	2 (5)
Perioperative chemoterapy before bevacizumab based terapy	No	33 (82.5)
	Yes	7 (17.5)
Chemotherapy regimens used in combination with bevacizumab	Paclitaxel + Carboplatin	17 (42.5)
	Cisplatin + Paclitaxel	15 (37.5)
	Gemcitabine +Carboplatin	2 (5.0)
	Gemcitabine + Cisplatin	1 (2.5)
	Weekly Paclitaxel	3 (7.5)
	Others	2 (5.0)
Palliative chemotherapy before Bevacizumab	No	27 (67.5)
	Yes	13 (32.5)
After bevacizumab treatment	Chemotherapy	9 (22.5)
	Other (HT, Surgery, RT)	3 (7.5)

Table 2. Responses to bevacizumab-based treatment in metastatic or recurrent cervical cancer.

	Total n=40 n (%)
Response ratios	
Complete response	5 (12.5)
Partial response	18 (45)
Stable disease	7 (17.5)
Progression	10 (25.0)
Objective response ratio	23 (57.5)
Disease control ratio	30 (75)

Table 3. Grade >2 side effects of bevacizumab-based therapy

Variables	n = 40 n (%)
Hypertension	7(17.5)
Proteinuria	1(2.5)
Fistula	2(5)
Thromboembolic events/hemorrhage	4(10)
Febrile neutropenia	2 (5)
Congestive heart failure	0

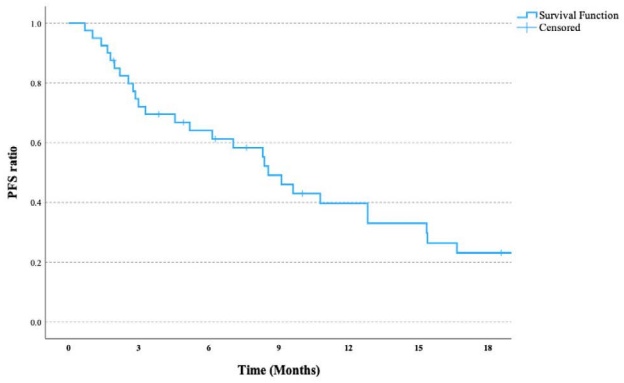

Figure 1. Kaplan–Meier curve of progression-free survival in patients with metastatic cervical cancer treated with chemotherapy plus bevacizumab

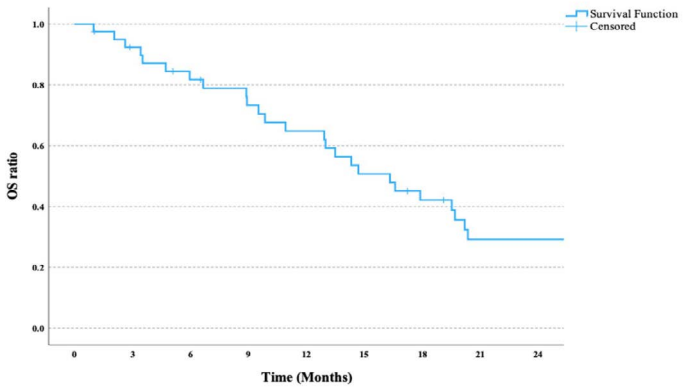

Figure 2. Kaplan–Meier curve of overall survival in patients with metastatic cervical cancer treated with chemotherapy plus bevacizumab

Table 4. Univariate analysis for survival analysis

		Total N	Ex N	Survivors N	Survival rate (%) (24 months)	P-value
Age at diagnosis	<50	17	12	5	29	0.409
	≥50	23	18	5	22	
Obesite	Non-obese	12	9	3	25	0,009**
	Obese	28	21	7	25	
Radioterapy before bevacizumab based terapy	No	8	6	2	25	0,156
	Definitive	30	22	8	27	
	Palliative	2	2	0	0	
Pathologic subtype	Squamose	33	24	9	27	0.080
	Others	7	6	1	14	
Grade status	Grade 1-2	33	24	9	27	0.724
	Grade 3	7	6	1	14	
Primary surgery before bevacizumab	No	22	18	4	18	0.910
	Yes	18	12	6	33	
Palliative chemotherapy before bevacizumab	No	27	19	8	30	0.139
	Yes	13	11	2	15	
Liver	No	31	23	8	26	0,908
	Yes	9	7	2	22	
Peritoneum metastasis	No	18	11	7	39	0.375
	Yes	22	19	3	14	
Lung metastasis	No	26	18	8	31	0.427
	Yes	14	12	2	14	
Bone metastasis	No	34	25	9	27	0,009**
	Yes	6	5	1	17	
Brain metastasis	No	39	29	10	25	0,006**
	Yes	1	1	0	0	
Number of metastatic sites	≤ 2 Sites	13	11	2	15	0.076
	> 2 Sites	18	12	6	33	
Chemotherapy regimens used in combination with bevacizumab	Paclitaxel + Carboplatin	17	13	4	24	0,732
	Paclitaxel + Cisplatin	15	11	4	27	
	Others	8	6	2	25	

Table 5. Multivariate Cox Regression Analysis for Overall Survival

	P-value	HR	95% CI	
			Lower	Upper
Age (<50years vs. ≥ 50)	0,611	1,224	0,561	2,672
Obesite (non-obese vs. obes)	0,020*	2,758	1,175	6,475
Grade (1-2 vs.3)	0,879	0,934	0,387	2,254
Number of metastatic sites (≤ 2 sites vs. > 2 sites)	0,451	1,392	0,589	3,289
Bone metastasis (yes vs. no)	0,024*	3,494	1,179	10,354
Brain metastasis (yes vs. no)	0,401	2,815	0,252	31,446

Multivariate analysis model p-value *p<0,05

The median number of ChT cycles administered in conjunction with BEV was 6 (range, 1–30 cycles). Patients, on average, received 8 cycles of BEV, with the range spanning from 1 to 30 cycles. Regarding the ChT regimens used with BEV, the most prevalent ones included paclitaxel plus carboplatin, used in 42.5% (n = 17) of patients, and cisplatin plus paclitaxel, employed in 37.5% (n = 15). In terms of treatment outcomes, 12.5% (n = 5) of patients accomplished a CR, 45% (n = 18) achieved a PR, 17.5% (n = 7) maintained SD, while 25% (n = 10) faced disease progression. The ORR stood at 57.5% (n = 23), and the DCR was 75% (n = 30), as depicted in Table 2. When it comes to main side effects, roughly 17.5% (n = 7) of patients exhibited hypertension categorized as grade >2. Additionally, proteinuria of grade ≥3 was observed in 2.5% (n = 1) of patients, while gastrointestinal fistula occurred in 5% (n = 2) (Table 3). The cessation of BEV treatment occurred due to disease progression in 72.5% (n = 29) of patients, adverse effects in 7.5% (n = 3), and completion of an adequate treatment duration in 7.5% (n = 3).

Following treatment with BEV, the median follow-up duration was 16.6 months. The median PFS accounted for 8.5 months (95% CI: 6.838 – 10.295), as illustrated in Figure 1, whereas the median OS was 16.3 months (95% CI: 11.305 – 21.362) (Figure 2). The existence of bone metastases emerged as a statistically significant factor associated with lower survival rates (95% CI: 1,179 – 10,354) (p=0.024; p<0.05). Moreover, there were no statistically noteworthy differences in survival outcomes related to various factors, including age, pathology classification, metastatic region count, tumor grade, initial staging, prior chemotherapy surgeries and radiotherapy before starting BEV, and the type of ChT administered alongside BEV (p > 0.05) (Tables 4 and 5).

DISCUSSION

Despite the progress made in screening and diagnostic techniques for CC, a considerable number of cases are diagnosed each year, and a significant proportion of these cases progress to advanced stages (10). For individuals diagnosed with stage IVB disease or those experiencing recurrent disease characterized by metastases across multiple sites particularly those that cannot be encompassed within a single radiation field or metastatic disease that is not responsive to localized treatments, the primary aim of treatment is palliative care. In these advanced scenarios, long-term survival remains a challenge. The introduction of novel targeted therapies, particularly the incorporation of BEV with platinum-based ChT, has led to enhanced OS rates as evidenced by randomized studies involving patients with metastatic CC (11).

In the GOG 240 study, 452 women with metastatic or recurrent cervical carcinoma were randomly assigned to either receive ChT alone or in combination with BEV. The trial demonstrated an enhancement in OS by 3.7 months, with figures of 17 months for those on BEV versus 13.3 months without, regardless of the specific ChT regimen they were receiving concurrently. Additionally, patients administered BEV exhibited superior ORR at 48%, compared to 36% (12). Considering all the above-mentioned findings, this trial advocates for the utilization of ChT in conjunction with BEV as an initial treatment approach for metastatic CC.

In a retrospective investigation by Lee et al., utilizing real-world data, the effectiveness of pairing BEV with platinum-based doublet ChT in managing metastatic CC was examined. The study encompassed 52 patients. Ultimately, the PFS and OS stood at 9.8 months and 15.3 months, respectively. Regarding response rates, the study revealed a CR rate of 15.4%, a PR rate of 34.6%, and a stable response rate of 19.2%. The ORR among these patients was 69% (13). In this real-world analysis, we aimed to explore the effectiveness and safety of approach mainly focused on using BEV for treating recurrent and metastatic CC. According to our findings, PFS was determined to be 8.5 months, OS was 16.3 months, and the ORR was 57.5%. These results are similar to the results of the studies referenced above.

In the research led by Matsumiya et al., the identification of bone metastasis among patients with CC was consistently linked with a diminished OS prognosis (14). Likewise, our study identified bone metastases as a statistically notable factor correlating with decreased OS rates.

In the study of Gross et al., it was observed that survival rates increased in patients diagnosed with CC with a BMI ≥30.

Similarly, in our study, we determined that obese patients had better OS. In our research, the administration of BEV was generally well-received, with predominant grade 3–4 adverse effects encompassing hypertension, proteinuria, thromboembolic incidents, and febrile neutropenia. Only a minimal 7.5% (n = 3) of patients discontinued treatment due to toxicity reasons. These observations align with findings reported in earlier studies (15,16).

This study is subject to certain constraints. The retrospective nature of the design introduced heterogeneity within the patient group, leading to some missing data. Additionally, being a single-center study poses a potential risk of selection bias.

In summary, in real-world clinical settings, BEV-based therapy for recurrent or metastatic CC demonstrates feasibility and tolerability. Additionally, the presence of bone metastases and obesity were found to be statistically significant factors for a survival outcomes in this patient cohort.

Conflict of interest: *Author declares that there is no conflict ofinterest between the authors of the article.*

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