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Second-line Chemotherapy for Advanced Bladder Cancer: Taxanes Versus Vinflunine

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ABSTRACT

Aim: Second-line chemotherapy in advanced urothelial carcinoma (UC) remains a significant clinical challenge, with limited high-level evidence guiding regimen selection. Vinflunine is the only agent approved by the European Medicines Agency for this setting, while taxanes are widely used off-label based on phase 2 data.

Methods: We conducted a retrospective analysis of patients with metastatic bladder cancer treated at Aydın Adnan Menderes University between 2013 and 2022. Eligible patients had received at least three months of second-line chemotherapy with either vinflunine or taxane-based regimens (docetaxel or paclitaxel). Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events were compared between groups.

Results: Among 38 patients receiving second-line therapy, 25 (65.8%) were treated with taxanes and 13 (34.2%) with vinflunine. Median PFS was significantly longer in the taxane group (4.9 vs. 2.2 months; p=0.001). Median OS favored taxanes numerically (13.2 vs. 4.33 months) but did not reach statistical significance (p=0.068). ORR was higher in the taxane group (52% vs. 23.1%), but the difference was not statistically significant (p=0.87). Adverse event profiles were consistent with known toxicities.

Conclusion: This single-center retrospective study suggests that taxane-based regimens may offer superior PFS compared to vinflunine in the second-line treatment of advanced UC, despite the lack of statistically significant OS benefit. Given limitations in access to immunotherapy and targeted agents, cytotoxic chemotherapy remains essential, underscoring the need for further prospective trials to define optimal second-line strategies.

Keywords: Urothelial carcinoma, second-line chemotherapy, taxanes, vinflunine

Introduction

Metastatic bladder urothelial carcinoma (UC) responds well to chemotherapy; therefore, systemic chemotherapy combined with immunotherapy is a preferred treatment. Few studies exist for second-line treatment [1]. Currently, enfortumab-vedotin with pembrolizumab has replaced avelumab immunotherapy maintenance after platinum-sensitive treatment, achieving a 32-month overall survival (OS), with a 68% objective response rate (ORR) [2]. Disease typically advances after 13 months, with the effectiveness of cisplatin-based second-line therapy remaining uncertain. Due to reimbursement issues, cisplatin-based therapies remain first-line treatments. Cisplatin-based treatments like gemcitabine with cisplatin (GC), or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) show survival benefits with 40-70% response rates [3].

Chemotherapy treatments after cisplatin-based therapy failure are usually single-agent therapies, with an ORR of 5-20% and

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median progression-free survival (PFS) of 3-4 months [4,5]. The US Food and Drug Administration has not approved any cytotoxic chemotherapy drugs for second-line treatment. Vinflunine was approved in the second-line treatment by the European Medicines Agency (EMA) in 2009, providing a 2.3-month OS advantage over best supportive care (BSC) [6]. Both docetaxel and paclitaxel are widely used in second-line settings, based on phase 2 data. A study involving 76 patients treated with weekly single-agent paclitaxel reported an ORR of 5-10% and a median OS ranging from 6.9 to 7.2 months [7,8]. In a randomized trial conducted by Choueiri et al. [9], patients receiving docetaxel at a dose of 75 mg/m^2 every three weeks had a median OS of 7 months. Nonetheless, 19% of these patients experienced grade 3/4 hematologic side effects, while 25% encountered grade 3/4 non-hematologic toxicity, including fatigue, infection, and electrolyte imbalances. Recent data indicate that, although immunotherapy agents provide a survival benefit in second-line treatment, they are effective in only about 20% of patients [10].

In second-line treatment, studies have only been conducted against BSC owing to characteristics such as advanced age, comorbidities, and poor performance status of patients. The effectiveness of the treatments used was unclear when compared with each other. The purpose of this research is to assess and contrast the effectiveness of paclitaxel and vinflunine, which are commonly chosen for second-line therapy in advanced bladder cancer.

Methods

Patients diagnosed with advanced-stage bladder cancer who were followed up at the Clinic of Medical Oncology at Aydın Adnan Menderes University Training and Research Hospital between 2013 and 2022 were retrospectively analyzed. The study included patients over the age of 18 years who had been diagnosed with metastatic disease and had received at least three months of second-line chemotherapy. Patient data were retrospectively recorded by reviewing the hospital database and follow-up files. Data on demographics, clinicopathological characteristics, response rates, and survival outcomes were collected in a retrospective manner. Individuals were excluded if they had incomplete data, were lost to follow-up, could not be assessed for response, had a secondary cancer, or had herbal or alternative treatments.

According to RECIST criteria, the time from the initiation of subsequent chemotherapy until radiological progression or date of death was considered PFS. The duration from the start of subsequent treatment to either the final follow-up or the date of death was defined as OS. Adverse events related to drugs were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.Patients were grouped into those receiving vinflunine (n=13) and those receiving taxane-based treatment (docetaxel or paclitaxel) (n=25). The treatment groups were compared in terms of OS, PFS, and ORR.

Following the Declaration of Helsinki guidelines, the Clinical Research Ethics Committee at the Aydın Adnan Menderes University Faculty of Medicine granted approval for the study. (decision no: E-53043469-050.04-764721, date: 11.07.2025).

Statistical Analysis

Data analysis was performed using International Business Machines Corporation Statistical Package for the Social Sciences (SPSS) version 22, a software developed by SPSS Inc.. Clinical and demographic patient characteristics were examined using descriptive analysis. Numerical and categorical variations are presented as percentages (%) and numbers (n). When dealing with continuous data that adhere to a normal distribution, the findings are presented as the mean along with the standard deviation. For data with other distributions, results are presented as median and range. The Kaplan-Meier method was utilized to determine PFS and OS. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using the Cox regression model. Group differences were evaluated using the log-rank test. A p value of less than 0.05 was deemed statistically significant for all analyses.

Results

Out of 102 patients who underwent initial chemotherapy, 38 individuals (37.2%) proceeded to receive a second round of treatment. Among those who underwent second-line chemotherapy, 34 (89.5%) were male. The participants in the study had a median age of 68, ranging from 48 to 82. Only three (7.9%) patients had no history of smoking. Eighteen (47.4%) patients did not receive local treatment and were classified as *de novo* metastatic. The most common visceral organ metastasis was in the lung (n=19). Twelve (31.6%) patients had no other comorbidities. The most commonly used first-line treatment regimen (89.5%) was platinum plus gemcitabine. As a second-line treatment, 25 (65.8%) patients received taxane, and 13 (34.2%) patients received vinflunine. Table 1 presents the baseline characteristics of the patient cohort.

The median OS in the entire treatment group was found to be 6.26 months (standard error=2.99, 95% CI: 0.39-12.13). In the taxane group, the median OS was 13.2 months (standard error=6.23, 95% CI: 0.98-25.4), while in the group receiving vinflunine, the median OS was 4.33 months (standard error=1.07, 95% CI: 2.22-6.44). There was no statistically significant difference in OS between the treatment groups (p=0.068) (Figure 1A). In the entire patient group, the median PFS was determined to be 3.96 months (standard error=0.881, 95% CI: 2.24-5.69). In the taxane group, the median PFS was 4.9 months (standard error=0.687, 95% CI: 3.55-6.24), while in the vinflunine group, the median PFS was 2.2 months (standard error=0.399, 95% CI: 1.42-2.98). The groups exhibited a statistically significant difference (p=0.001) (Figure 1B).

The overall response rate was 42.1% in all patients who received second-line treatment. In the taxane and vinflunine groups, the ORR was 52% (13/25) and 23.1% (3/48), respectively. The

ORR did not show a notable difference in the groups receiving taxane and vinflunine treatments (p=0.87). In the taxane group, the disease control rate was 68% (17 out of 25), whereas in the vinflunine group, it was 23.1% (3 out of 13). The groups did not show any statistically significant differences (p=0.305). After progression on the current treatment, 44.7% (n=17) of the patients received systemic chemotherapy. Table 2 displays the response characteristics of the treatment groups

All individuals initially received platinum-based therapy and were platinum-resistant. For second-line treatment, only patients who received vinflunine (n=13) and taxane (n=25) were compared. The groups treated with taxane and vinflunine demonstrated a statistically significant difference in PFS, with median PFS values of 4.9 months and 2.2 months, respectively (p=0.001). There was no statistically significant difference observed between the groups regarding OS. The median OS was 13.2 months for participants given taxane and 4.33 months for those given vinflunine (p=0.068). The rate of anemia of any grade was 88% and 100% in the taxane and vinflunine groups, respectively. The rates of grade 3-4 anemia were 12% and 0%, respectively (Table 3).

Table 1. Demographic and clinicopathological features of the patients

	All patients n (%)	**Taxan n (%)**	**Vinflunine n (%)**
Gender Female Male	 4 (10.5%) 34 (89.5%)	 23 (92%) 2 (8%)	 11 (84.6%) 2 (15.4%)
Age (median) Min-max	68 (48-82)	69 (50-82)	66 (48-80)
Smoking Yes No	 31(92.1%) 3 (7.9%)	 23 (92%) 2 (8%)	 12 (92.3%) 1 (7.7%)
ECOG PS 0 1 2	 1 (2.6%) 33 (86.8%) 4 (10.5%)	 0 (0%) 22 (88%) 3 (12%)	 1 (7.7%) 11(84.6%) 1 (7.7%)
Comorbid disease Yes No	 26 (68.4%) 12 (31.6%)	 19 (76%) 6 (24%)	 7 (53.8%) 6 (46.2%)
Comorbid disease HT Type-2 DM CAD COPD	 23 (60.5%) 3 (7.9%) 8 (21.1%) 8 (21.1%)	 17 (44,7%) 1 (2.6%) 7 (18.5%) 4 (10.5%)	 6 (15.8%) 2 (5.3%) 1 (2.6%) 4 (10.5%)
Histopathology urothelial carcinoma other	 36 (94.7%) 2 (5.3%)	 24 (96%) 1 (4%)	 12 (92.3%) 1 (7.7%)
De novo metastasis Yes No	 18 (47.4%) 20 (52.6%)	 11 (44%) 14 (56%)	 7 (53.8%) 6 (46.2%)
Metastatic sites Lung Liver Bone Distant lymph node Other	 19 (50%) 4 (10.5%) 14 (36.8%) 33 (86.8%) 5 (13.2%)	 12 (31.5%) 2 (5.3%) 8 (21.1%) 21 (55.2%) 5 (13.2%)	 7 (18.5%) 2 (5.3%) 6 (15.8%) 12 (31.6%) 0 (0%)
First-line CT type Platinum+gemcitabin Platinum+taxan Gemcitabin Other	 34 (89.5%) 1 (2.6%) 1 (2.6%) 2 (5.3%)	 22 (88%) 0 (0%) 1 (4%) 2 (8%)	 12 (92.3%) 1 (7.7%) 0 (0%) 0 (0%)
Second-line CT type Taxan Vinflunine	 25 (65.8%) 13 (34.2%)	 25 (100%)	 13 (100%)

ECOG PS: Eastern Cooperative Oncology Group performance status, CT: Chemotherapy, HT: Hypertension, Type 2 DM: Type 2 diabetes mellitus COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease

Discussion

Although there are only a few phase 3 studies on second-line treatments for locally advanced and metastatic UC, no chemotherapy regimen has proven to be better than the others. This study aimed to share real-world data from a retrospective, single-center experience.

Although an enhanced understanding of molecular pathways in carcinoma treatment has introduced targeted agents, immunotherapies, and antibody-drug conjugates into second-line therapy in recent times, their use remains limited due to countries' reimbursement policies. Therefore, chemotherapy agents are used in a large number of patients. Various chemotherapeutic drugs have been investigated for second-line treatment. Pemetrexed has undergone evaluation in two phase 2 studies. While one study showed a positive response

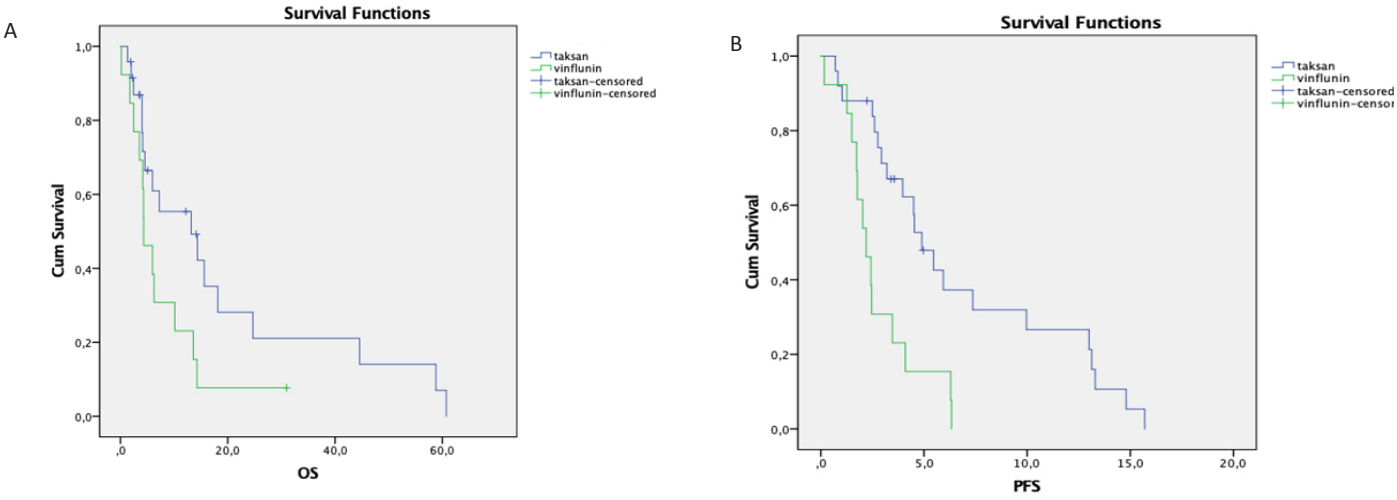

Figure 1. (A) Overall survival curves. B) Progression-free survival curves

Table 2. Objective tumor responses

		Taxan n (%)	Vinflunine n (%)	p
Best response	Complete response	4 (16%)	1 (7.7%)	
	Partial response	9 (36%)	2 (15.4%)	
	Stable response	4 (16%)	0 (0%)	
	Progressive disease	8 (32%)	10 (76.9%)	
Objective response rate		13 (52%)	3 (23.1%)	0.87
Disease control rate		17 (68%)	3 (23.1%)	0.305

Table 3. Most common treatment-related adverse events and hematologic abnormalities

	Taxan				Vinflunine			
Adverse Event	Overall incidence No. of patients (%)		Grade 3 or 4 No. of patients (%)		Overall incidence No. of patients (%)		Grade 3 or 4 No. of patients (%)	
Anemia	22	88	3	12	13	100	0	0
Neutropenia	11	44	0	0	2	15.4	0	0
Thrombocytopenia	8	32	0	0	3	23.1	0	0
Nausea	20	80	0	0	5	38.5	0	0
Diarrhea	17	68	1	4	1	7.7	0	0
Stomotitis	12	48	0	0	1	7.7	0	0
Hepatic enzymes elevation	4	16	1	4	2	15.4	0	0
Rash	0	0	0	0	4	30.8	1	7.7
Neuropathy	17	68	0	0	1	7.7	0	0

(response rate 28% and OS 9.8 months), a negative response were obtained in the other [11,12]. Other chemotherapy agents (such as irinotecan, oxaliplatin, nab-paclitaxel, ixabepilone, ifosfamide, gemcitabine, and combinations like paclitaxel-gemcitabine) have also been studied, resulting in a 10-20% ORR, median PFS ranging from 2 to 3 months, and median OS between 6 and 9 months [13].

Vinflunine is considered an appropriate choice. In a phase 3 second-line study involving 370 patients with advanced or metastatic UC, vinflunine demonstrated an improvement in survival compared to BSC, achieving the primary endpoint with a median survival of 6.9 months versus 4.6 months (HR 0.88, 95% CI: 0.69-1.12) and attained a 9% ORR [6]. It was approved by the EMA and started to be used as second-line therapy. Subsequently, a phase 2/3 cabazitaxel study with vinflunine in the opposite arm was planned. The study began with phase 2, which included 70 patients. The patient characteristics were comparable across both study groups, with neither group exhibiting a complete response to the treatment. A partial response was observed in three patients (13%) receiving cabazitaxel and six patients (30%) receiving vinflunine. The median PFS for cabazitaxel was 1.9 months, whereas for vinflunine, the difference in PFS was statistically significant, with a median of 2.9 months (p=0.039). However, although there was a trend in favor of vinflunine for OS (7.6 vs. 5.5 months), it was not significant, so it could not proceed to phase 3 [14]. In our study, a similar PFS rate (2.2 months) was observed in patients receiving vinflunine.

Taxanes were widely used in Europe as a second-line treatment prior to vinflunine approval, despite the limited responses observed in small phase 2 studies. Paclitaxel was investigated in three phase 2 studies with small patient numbers. In a cohort of 31 patients, the ORR was found to be 10% while the median OS was 7.2 months. However, in the other two studies, the ORR was lower (5-7%) [7]. In a phase 2 trial, docetaxel was assessed; showing an ORR of 13% and a median OS of 9 months [15]. Although no study in the literature directly compares vinflunine to taxanes as second-line treatment, they remain the two most used agents in daily practice. In our study, a statistically significant PFS advantage was observed in patients who received taxanes. Although OS was numerically in favor of taxanes, it was not significant (13.2 months vs. 4.33 months, p=0.068).

Over the past few years, with the increasing use of immunotherapy and targeted therapies, many drugs have been approved for second-line therapy of advanced-stage bladder cancer. For platinum-resistant patients who have not received immunotherapy, pembrolizumab, nivolumab, avelumab, enfortumab vedotin, erdafitinib, and trastuzumab-deruxtecan have been approved by the FDA for use as second-line therapies [16-22]. In a phase 2 trial involving nivolumab, the ORR was 20%, showing no dependence on programmed cell death ligand 1 (PD-L1) expression levels. With a median follow-up period of seven months, the study revealed a notable and enduring OS advantage, with a median OS of nine months for the entire group. Specifically, for participants with PD-L1 expression levels below 1% and those at or above 1%, the median OS was six months and eleven months months, respectively. Additionally, the treatment had a manageable safety profile [16]. The KEYNOTE-045 study evaluated pembrolizumab against randomized chemotherapy options, including paclitaxel, docetaxel, or vinflunine, in patients with advanced UC who had experienced progression after treatment with platinum-resistant therapies. Compared with chemotherapy, pembrolizumab improved OS with a median follow-up of approximately 28 months (mOS 10 vs. 7 months; HR 0.70, 95% CI: 0.57-0.85). The PFS was comparable between the two treatment groups, with median PFS being two months versus three months, and a HR of 0.96 (95% CI: 0.79-1.16). Moreover, the pembrolizumab group experienced fewer adverse side effects [17]. Similarly, an ORR of up to 24% was achieved with avelumab [18].

The effectiveness of enfortumab vedotin, previously confirmed in other research, was assessed in a phase 3 clinical trial (EV-301) involving patients with metastatic UC. The study design was similar to that of the pembrolizumab study. The control arm consisted of investigator-chosen chemotherapy regimens. The results showed that enfortumab vedotin improved both mOS (13 vs. 9 months, HR 0.70) and mPFS (6 vs. 4 months, HR 0.63) [19]. Nevertheless, individuals who experienced progression following maintenance with avelumab were excluded from the study. The incidence of grade ≥3 toxicity for any adverse event was comparable between the two treatment groups, with rates of 52% and 51%, respectively. In a study evaluating erdafitinib, an fibroblast growth factor receptor (FGFR) inhibitor, it was found to be effective compared to chemotherapy in patients with FGFR mutations. Moreover, this study included patients who had previously received immunotherapy. After a median follow-up period of 16 months, erdafitinib demonstrated superior OS and PFS compared to chemotherapy, with a median OS of 12 months versus 8 months (HR 0.64) and a median PFS of 6 months versus 3 months (HR 0.58). Additionally, erdafitinib showed higher ORR (46% compared to 12% with chemotherapy) and complete response rates (7% compared to 1% with chemotherapy) [20]. In another cohort of the study, erdafitinib was compared with pembrolizumab in patients who had not previously received immunotherapy. Similar survival outcomes were observed, with a median follow-up period of 33 months, a median OS of 11 months for each group, and a HR of 1.18 [21]. Fam-trastuzumab deruxtecan was assessed in a basket study involving patients with human epidermal growth factor receptor-2 (HER2) expression.With a median observation of 13 months, the ORR was 39% in 41 patients with advanced bladder cancer. Moreover, patients with IHC 3+ disease exhibited higher ORRs than those with IHC 2+ disease, with rates of 56% compared to 35% [22].

Despite the benefits of antibody-drug conjugates, immunotherapy, and targeted therapies, the need to find effective cytotoxic agents for second-line treatment persists because of limited access to these drugs. Our research underscores this gap in the existing literature by evaluating taxane, a treatment with potential efficacy, against vinflunine,

which is already sanctioned and regarded as the standard treatment. We confirmed the safety profiles of both taxanes and vinflunine and did not detect any novel safety signals.

Study Limitations

Our study is subject to certain limitations. Firstly, its single-center and retrospective nature may introduce biases. The limited patient cohort, the absence of standardized treatment transitions, and the lack of a significant difference in OS despite the observed advantage in PFS may contribute to these biases. To accurately assess OS, larger, prospective, and randomized controlled trials are warranted. In future research, stringent control of treatment transitions is crucial to minimize confounding effects. Additionally, conducting subgroup analyses to identify specific patient populations that may derive greater benefit from this treatment is advantageous.

Conclusion

Although chemotherapy regimens do not show superiority over each other in terms of survival, taxanes have demonstrated a significant PFS benefit over vinflunine administration. The agents used in second-line treatment have only been shown to provide a survival benefit against BSC. For this reason, systemic therapy is recommended as a second-line treatment for all patients with good performance status.

Ethics

Ethics Committee Approval: Following the Declaration of Helsinki guidelines, the Clinical Research Ethics Committee at the Aydın Adnan Menderes University Faculty of Medicine granted approval for the study. (decision no: E-53043469-050.04-764721, date: 11.07.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Pratices: B.D., O.Y.B., Concept: B.D., A.A., Ö.A., Design: B.D., O.Y.B., Data Collection or Processing: A.A, G.Ç., Ö.A., Analysis or Interpretation: B.D., A.A., O.Y.B., Literature Search: B.D., G.Ç., Ö.A., Writing: B.B., G.Ç.

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