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The efficacy and safety of vinflunine in second-line therapy of patients with disseminated transitional cell carcinoma of the urinary tract in clinical practice

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Objective: *to investigate the safety of vinflunine, the rate and duration of its treatment response, progression-free and overall survival rates in patients receiving this drug in routine clinical practice for first-line chemotherapy (CT) – resistant disseminated transitional cell carcinoma of the urinary tract.*

Materials and methods. *This retrospective observational multicenter study included data on 25 patients with verified disseminated transitional cell carcinoma of the urinary tract who took vinflunine for tumor progression after first-line CT performed in 11 Russian clinical centers in 23 March 2013 to 26 June 2016. The median age of the patients was 60 (44–81) years. Their baseline somatic status was rated as ECOG 0 in 1 (4.0 %) patient, ECOG 1 in 13 (52.0 %) patients, EGOG 2 in 9 (36.0 %), and ECOG 3 in 2 (8.0 %). The most common sites of tumor foci were bones (n = 14, 56.0 %), lymph nodes of different groups (n = 14; 56.0 %), and lung (n = 9; 36.0 %).*

Results. *Adverse reactions were recorded in 24 (96.0 %) cases. The most common types of toxicity were asthenia (n = 19; 76.0 %), anemia (n = 18; 72.0 %), neutropenia (n = 13; 52 %), and nausea (n = 12; 48.0 %). Most adverse events were grades I–II and well controlled. There were no deaths due to adverse events. The best treatment response was regarded as partial in 6 (24.0 %) patients; stabilization and progression were observed in 10 (40.0 %) and 9 (36.0 %) patients, respectively. The median duration of partial response was 5.1 (95 % confidence interval (CI), 0.6–15.0) months; that of stabilization was 3.4 (95 % CI, 1.2–6.3) months. In all the 25 cases, the median progression-free and overall survival rates were 3.7 (95 % CI, 2.1–5.3) and 6.5 (95 % CI, 5.2–7.8) months, respectively. The somatic status was a predictor of overall survival (p < 0.0001).*

Conclusion. *The efficacy and safety of vinflunine in second-line therapy for first-line CT-resistant disseminated transitional cell carcinoma of the urinary tract in unselected patients agree with those previously observed in Phase III randomized trial.*

Key words: *disseminated transitional cell carcinoma of the urinary tract; chemotherapy; vinflunine; progression-free survival; overall survival*

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Introduction

Transitional cell carcinoma of the ureter is a common malignant tumor, one of the ten cancers with the highest morbidity in Russia and Western Europe [1, 2]. Common types of this tumor are sensitive to chemotherapy (CT). Use of regimens based on cisplatin, such as gemcitabine and cisplatin (GC); methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC); paclitaxel, cisplatin, and gemcitabine (PCG), allow to achieve an objective response in 40–70 % of cases [3–5]. However, duration of the response is usually short: In patients with metastatic transitional cell carcinoma of the ureter who received the 1st line therapy, median progression-free survival (PFS) and overall survival (OS) were 8 and 15 months, respectively [6].

In the last 10 years, various drugs in monoregimens and combinations have been studied for treatment of cisplatin-resistant tumors. The trials included possibilities of using paclitaxel [7], protein-bound paclitaxel [8], irinotecan [9], ixabepilone [10], bortezomib [11], pemetrexed [12], oxaliplatin [13], ifosfamide [14], lapatinib [15], docetaxel [16], gefitinib [17], sorafenib [18], sunitinib [19], and pazopanib [20] in this patient category. Among the suggested combi-

nations, regimens including paclitaxel and gemcitabine [21], ifosfamide and gemcitabine [22], and carboplatin and paclitaxel [23] have shown the best results. Nonetheless, despite the effort, the results were more than modest. The rate of objective response in the majority of studies was 10–20 % with median PFS between 6 and 9 months [24].

Vinflunine is a novel Vinca alkaloid. It recently has become available in widespread clinical practice in Russia. The mechanism of action of the drug is based on the disruption of microtubule polymerization during mitosis and induction of apoptosis [25]. The main difference of vinflunine from other Vinca alkaloids is its higher affinity to mitotic, in comparison to axonal, tubulin. This results in reduced neurotoxicity and allows to achieve higher plasma concentration of the drug [26]. Initially, clinical activity of vinflunine in advanced transitional cell carcinoma of the ureter was demonstrated in 2 non-randomized phase II studies [27, 28]. In these protocols, the response rate was 18 and 15 % with median duration of response 9.1 and 6.0 months, respectively. Median PFS and OS were 3.0 and 6.6 months in one study, and 2.8 and 8.2 months in another. These results motivated initiation of a pilot multinational randomized study comparing vinflunine with the best maintenance therapy for urothelial transitional cell carcinoma in patients with progression after cisplatin-based CT [29]. The trial included 370 patients, and vinflunine showed statistically insignificant advantage over maintenance therapy: 6.9 and 4.6 months, respectively (risk ratio (RR) 0.88; 95 % confidence interval (CI) 0.69–1.12; $p = 0.287$). However, analysis of the factual treatment groups showed statistically significant advantage of vinflunine in respect to OS (6.9 and 4.3 months, respectively; $p = 0.04$), as well as response rate (16 and 0 %; $p = 0.0063$), disease control (41.1 and 24.8 %; $p = 0.0024$), and median PFS (3.0 and 1.5 months; $p = 0.0012$). The duration of objective response to vinflunine therapy was 7.4 (95 % CI 4.5–17.0) months. In this study, long-term survival data for follow up duration above 45 months confirmed advantages in the vinflunine group compared to the control group (median OS was 6.9 and 4.6 months, respectively) [30]. Based on these results, vinflunine became the first drug approved for use in cisplatin-resistant advanced transitional cell carcinoma of the ureter.

We performed a retrospective observational multicenter study to evaluate toxicity, rate and duration of response, PFS, and OS in patients receiving vinflunine in routine clinical practice for treatment of advanced transitional cell carcinoma of the ureter resistant to the 1st line CT.

Materials and methods

The retrospective observational multicenter study included data on 25 patients with verified advanced transitional cell carcinoma of the ureter who received vinflunine due to cancer progression after the 1st line CT from 23.03.2013 to 26.06.2016 at 11 clinical centers in the Russian Federation. Median age was 60 (44–81) years. Ratio between men and women was 4:1. The primary tumor was localized in the bladder in 21 (84.0 %) patients, in the renal pelvis in 4 (16.0 %) patients. Diagnosis of transitional cell carcinoma was verified in all 25 (100 %) patients. Before vinflunine therapy, the primary tumor was fully removed in 9 (36.0 %) patients, including 3 (12.0 %) patients with cancer of the renal pelvis; removal of metastases of transitional cell carcinoma was performed in 6 (24.0 %) cases. In 12 (48.0 %) observations, external beam therapy was preformed before CT (radical – 5 (20.0 %), adjuvant – 6 (24.0 %), palliative – 1 (4.0 %)).

Before vinflunine, all patients received CT based on cisplatin ($n = 20$; 80.0 %), carboplatin ($n = 4$; 16.0 %)), or paclitaxel ($n = 1$; 4.0 %). On average, in the 1st line of treatment, 2 (1–6) therapy courses were completed. Response to the 1st line CT was considered partial in 3 (12.0 %) patients; stabilization was observed in 15 (60.0 %) patients, progression – in 7 (28.0 %) patients. Median duration of tumor control for the 1st line CT (sum of partial responses and stabilizations) was 7 (3–17) months. In all patients, radiologically confirmed progression of the disease was observed after the 1st line therapy.

In 1 (4.0 %) case, vinflunine therapy was indicated for nonoperative local recurrence of bladder cancer, in 24 (96.0 %) cases it was indicated for metastases. In the majority ($n = 20$ (80.0 %)) of patients, multiple metastases were observed. One localization of tumor lesions was diagnosed in 5 (20.0 %) patients, more than 1 – in 20 (80.0 %) patients. The most common were metastases in the bones ($n = 14$; 56.0 %), different lymph nodes ($n = 14$; 56.0 %), and lungs ($n = 9$; 36.0 %). In 18 (72.0 %) patients, tumor lesions were measurable. At the time of the start of vinflunine therapy, the ECOG performance status was 0 in 1 (4.0 %), 1 – in 13 (52.0 %), 2 – in 9 (36.0 %), 3 – in 2 (8.0 %) patients (Table 1).

All 25 patients received vinflunine therapy. The initial dose was calculated in accordance with the instructions for use: 320 mg/m^2 ($n = 6$; 24.0 %), 280 mg/m^2 ($n = 13$; 52.0 %), or 250 mg/m^2 ($n = 6$; 24.0 %). Median number of therapy cycles was 4 (1–7).

Medical data of the patients were formalized in the form of electronic tables. Duration of PFS was the period from the start of vinflunine therapy to the date of progression registration or patient»s death due to transitional cell carcinoma. Overall survival was calculated from the start of vinflunine therapy to the date of the last examination or patient»s death of any cause. Response to treatment was evaluated by the attending doctor; in case of existing measurable tumor lesions the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 were used [31]. Objective response was any full or partial response; disease control rate was full, partial responses or disease stabilization for at least 3 months. Adverse events were any unfavorable symptoms and diseases, as well as higher intensity of previous symptoms, observed after the start of vinfl-

unine therapy in patients included in the study. Severity of adverse events was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0 [32].

Statistical analysis of the results was performed using the usual statistical methods and commercially available software. OS and PFS were calculated using the Kaplan-Meier estimator, differences in survival were evaluated using the log-rank test.

Results

At the time of completion of the medical data collection in June of 2016, 21 (84.0 %) patients had completed vinflunine therapy, 4 (16.0 %) patients were continuing treatment. In 17 (68.0 %) patients, tumor progression was reported; 9 (36.0 %) patients died of transitional cell carcinoma. Median vinflunine therapy duration was 2.1 (1–18) months.

Table 1. *Characteristic of patients with advanced transitional cell carcinoma of the ureter receiving vinflunine after progression during the 1st line of chemotherapy*

Characteristic	Number of patients (n = 25)	
	n	%
Age, median (min–max), years	60 (44–81)	
Sex:		
male	20	80.0
female	5	20.0
Location of the primary tumor:		
bladder	21	84.0
renal pelvis	4	16.0
Radical removal of the primary tumor	9	36.0
Previous beam therapy	12	48.0
Previous chemotherapy:		
based on cisplatin	20	80.0
based on carboplatin	4	16.0
paclitaxel	1	4.0
Number of tumor lesions:		
solitary	5	20.0
multiple	20	80.0
Number of locations of tumor lesions:		
1	5	20.0
> 1	20	80.0
Location of tumor lesions:		
bones	14	56.0
lungs	9	36.0
pelvic lymph nodes	8	32.0
retroperitoneal lymph nodes	3	12.0
liver	3	12.0
soft tissues	2	8.0
mediastinal lymph nodes	2	8.0
inguinal lymph nodes	1	4.0
local recurrence	1	4.0
ECOG:		
0	1	4.0
1	13	52.0
2	9	36.0
3	2	8.0

Adverse events were reported in 24 (96.0 %) of 25 cases. The most common types of toxicity were general (76.0 %), hematological (72.0 %), and gastrointestinal (48.0 %). Symptoms of general toxicity included asthenia (n = 19; 76.0 %), weight loss (n = 4; 16.0 %), edema (n = 2; 8.0 %), and myalgia (n = 2; 8.0 %); hematological toxicity presented as anemia (n = 18; 72.5 %), neutropenia (n = 13; 52.0 %), and thrombocytopenia (n = 8; 32.0 %). The main adverse events in respect to the gastrointestinal tract were nausea (n = 12; 48.0 %) and constipation (n = 11; 44.0 %). In most cases, severity of the adverse events was grade I–II, and they were easily controlled. Grade III adverse events were associated with hematological toxicity: anemia (n = 3; 12.0 %), neutropenia (n = 9; 36.0 %); additionally, grade III adverse events included constipation in 1 patient, pneumonia in 1 patient, and hypertensive crisis in 2 patients. The only grade IV adverse event was anemia in 1 patient (Table 2). There were no deaths due to adverse events associated with vinflunine therapy. Dose reduction was necessary in 2 (8.0 %) cases, treatment cancellation in 1 (4.0 %) patient due to grade IV anemia.

The best response to treatment was partial response in 6 (24.0 %) patients; stabilization was reported in 10 (40.0 %) patients, progression – in 9 (36.0 %). Disease control (partial response or stabilization) was achieved in 16 (64.0 %) patients. Among 18 patients with measurable lesions, partial response was observed in 5 (20.0 %), stabilization in 6 (24.0 %), progression in 7 (28.0 %). Median duration of partial response in 6 patients was 5.1 (95 % CI 0.6–15.0) months, median duration of stabilization in 10 patients was 3.4 (95 % CI 1.2–6.3) months, median disease control in 16 patients was 3.7 (95 % CI 0.5–14.7) months.

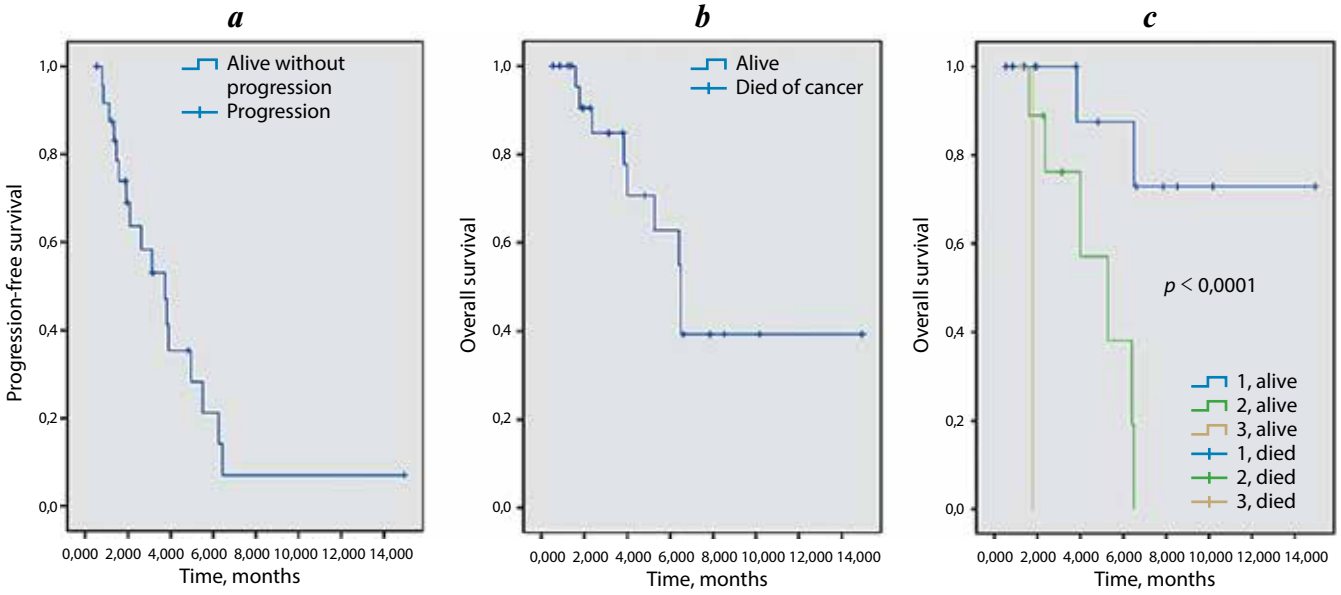
Median PFS (see Figure *a*) and OS (see Figure *b*) of all 25 patients were 3.7 (95 % CI 2.1–5.3) and 6.5 (95 % CI 5.2–7.8) months, respectively. Univariate analysis has shown a significant correlation between a decrease in median OS and the initial ECOG status (ECOG 0–1 – not reached, ECOG 2–5.3 months, ECOG 3–1.8 months; $p < 0.0001$) (see Figure *c*). Furthermore, there was a statistically insignificant decrease in OS in patients with a primary tumor of the renal pelvis (from 6.4 to 3.8 months; $p = 0.670$) and a non-removed primary tumor (from 6.4 to 1.9 months; $p = 0.157$). We haven»t observed any correlation between OS and the number and localization of metastases, as well as with the use of cisplatin in the 1st therapy line (Table 3).

Discussion

The problem of treatment of transitional cell carcinoma of the ureter remains unsolved. Modern drug therapy regimens don»t result in a significant increase in OS in this patient category. Consequently, the majority of patients

Table 2. *Adverse events associated with vinflunine therapy in patients with advanced transitional cell carcinoma of the ureter receiving vinflunine after progression during the 1st line of chemotherapy*

Toxicity	Adverse event	Total		Grade I–II		Grade III–IV	
		n	%	*n*	%	*n*	%
Hematological	Anemia	18	72.0	14	56.0	4	16.0
	Neutropenia	13	52.0	4	16.0	9	36.0
	Thrombocytopenia	8	32.0	8	52.0	0	0.0
Laboratory	Increased level of pancreatic amylase	1	4.0	1	4.0	0	0.0
General	Asthenia	19	76.0	19	76.0	0	0.0
	Weight loss	4	16.0	4	16.0	0	0.0
	Edema	2	8.0	2	8.0	0	0.0
	Myalgia	2	8.0	2	8.0	0	0.0
Immune	Infection	1	4.0	0	0.0	1	4.0
Cardiovascular	Arterial hypertension	2	8.0	0	0.0	2	8.0
Gastrointestinal	Constipation	11	44.0	10	40.0	1	4.0
	Nausea	12	48.0	12	48.0	0	0.0



Survival of patients with advanced transitional cell carcinoma of the ureter receiving vinflunine after progression during the 1st line of chemotherapy: a – progression-free survival; b – overall survival; c – overall survival depending on the initial performance status

with tumor progression doesn»t receive effective treatment after the 1st line CT.

In our small retrospective study, we have shown that vinflunine is an effective and satisfyingly tolerable agent for treatment of transitional cell carcinoma of the ureter progressed after the 1st line CT. Effectiveness of vinflunine achieved in an unselected patient population is comparable to results of a phase III randomized study. In our series, rate of objective response of 24 % was a little higher than the result of the phase III clinical trial (16 %) [29]. Disease control was also more frequent among our patients (64 %) than in the registrational study (41 %) [29]. It should be noted, that results of our series of observations are almost identical to the results of other retrospective studies. In the study by D. Castellano et al. (2014), which included 102 unselected patients receiving vinflunine in the 2nd therapy line for

Table 3. *Survival of patients with advanced transitional cell carcinoma of the ureter receiving vinflunine after progression during the 1st line of chemotherapy*

Group	Median survival (95 % CI min.–max.), months	*p*
All patients (PFS)	3.7 (2.1–5.3)	–
All patients (OS)	6.5 (5.2–7.8)	–
Patients (OS) in respect to		
location of the primary tumor: bladder renal pelvis	6.4 (6.3–6.7) 3.8 (3.6–5.0)	0.670
presence of the primary tumor: not removed fully removed	6.4 (6.3–6.6) 1.9 (1.7–2.1)	0.157
previous chemotherapy, based on cisplatin not based on cisplatin	6.4 (6.3–6.6) 5.2 (4.9–6.4)	0.615
solitary tumor multiple tumors	3.8 (0.5–7.2) 6.5 (6.3–6.6)	0.456
1 location of tumor lesions > 1 location of tumor lesions	6.4 (4.9–7.8) 6.4 (4.7–6.8)	0.789
ECOG 0–1 2 3	 Not reached 5.3 (2.5–8.0) 1.8 (0.0–1.9)	< 0.0001

Note. *PFS stands for progression-free survival. OS stands for overall survival*

treatment of transitional cell carcinoma of the ureter, the rates of objective response and disease control were 24.4 and 65.7 %, respectively [33]. In a similar study by A. Hegele et al. (2013) the rate of objective response in 77 patients was 23.4 % [34]. J. Medioni et al. (2013) also obtained a similar result (22 %) for vinflunine therapy in 134 patients [35]. It is possible that high vinflunine effectiveness in the wide clinical practice is associated with less scrutinous evaluation of the treatment response which was performed in every clinic in accordance to their internal standards, and there wasn»t a centralized evaluation of the radiological examination results.

Same as in the study of D. Castellano et al. (2014), the number of vinflunine therapy courses (4) was higher in our study [33] that in the pilot trial (3) [29]. Mean number of treatment courses in the series by J. Medioni et al. (2013) was even higher: 5 [35]. In our opinion, this fact emphasizes the favorable safety profile of the drug in unselected patients who have a higher incidence of concomitant diseases and worse performance status compared to patients included in a clinical protocol. Thus, in our series 44 % had ECOG performance status > 1. Even in wide clinical practice of the Spanish authors, only 8.1 % of patients had ECOG status 2, and patients with ECOG status 3 didn»t receive treatment [33].

Vinflunine toxicity profile noted in our study corresponded to the registration data. Despite the high incidence of all adverse events (96 %), it»s necessary to emphasize that the majority of them were grade I–II and were easily controlled. Dose reduction and cancellation of vinflunine due to toxicity were necessary only in 2 and 1 patients, respectively. The rate of some vinflunine-specific severe adverse events was lower in our study compared to the randomized phase III study, including constipation (4 and 16 %), nausea (0 and 2.8 %), and neutropenia (36 and 50 %) [29]. As expected, our results are similar to the results of the Spanish retrospective series where these values were 5.9, 2.0, and 12.8 %, respectively [33].

Median PFS in our patients (3.7 months) is comparable to the results of the phase III study (3.0 months) [29]. In other retrospective studies, PFS varied from 3.9 to 4.9 months [33, 35]. OS in our study was almost the same as in the registrational study (6.5 and 6.9 months, respectively) [29], but lower than in the studies by A. Hegele et al. (7.7 months) [34], J. Medioni et al. (8.2 months) [35], and D. Castelllano et al. (10 months) [33]. Supposedly, this result is associated with a larger number of patients with lower performance status in our series of observations.

According to the registrational study data, presence of visceral metastases, low performance status (ECOG > 0), and anemia (hemoglobin < 10 g/l) are unfavorable prognostic factors for OS in patients with cisplatin-resistant transitional cell carcinoma of the ureter [36]. Small sample size didn»t allow us to validate this model. However, even in such a small series of observations, we were able to confirm the correlation between the performance status and OS. Therefore, it's extremely important to start the 2nd line therapy as soon as possible. Similar data were obtained by D. Castellano et al. (2014) [33].

Of note are improved treatment results in patients with previously removed primary tumor and bladder cancer, even though these observations didn't reach statistical significance. These facts require further research.

Our study has several shortcomings associated with retrospective inclusion of patients, absence of clear inclusion criteria, small sample size, absence of a control group, routine local evaluation of toxicity and response. Nonetheless, a high percentage of patients with visceral metastases and low performance status who previously underwent intense treatment, including combination therapy, accurately reflects the true structure of patient population with advanced transitional cell carcinoma of the ureter. Despite all obvious shortcomings of our study, our results are similar to the results of other retrospective studies and reproduce in clinical practice vinflunine's effectiveness and toxicity data obtained in the registrational study.

Conclusion

This study confirms effectiveness and safety of vinflunine in the 2nd therapy line of advanced transitional cell carcinoma of the ureter resistant to the 1st line CT. Results

of the study are similar to the previously published data reported during a randomized phase III study and in several large retrospective series of observations. Our study included medical data of unselected patients and confirmed reproducibility of the registrational study results in clinical practice.

We haven't observed any significant differences in vinflunine therapy duration, safety profile, and survival between our study and the randomized trial. These results confirm advisability of using vinflunine in routine practice as the 2nd line CT of advanced transitional cell carcinoma of the ureter.

REFERENCES

1. Kaprin A.D., Starinskiy V.V., Petrova G.V. Status of oncologic assistance to the population of Russia in 2015. Moscow, 2015.
2. Siegel R., Naishadham D., Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63(1):11–30.
3. von der Maase H., Sengelov L., Roberts J.T. et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23(21):4602–8.
4. Roberts J.T., von der Maase H., Sengeløv L. et al. Long-term survival results of a randomized trial comparing gemcitabine/cisplatin and methotrexate/vinblastine/doxorubicin/cisplatin in patients with locally advanced and metastatic bladder cancer. Ann Oncol 2006;17:118–22.
5. Bellmunt J., von der Maase H., Mead G.M. et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin inpatients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012;30(10):1107–13.
6. Clark P.E., Agarwal N., Biagioli M.C. National Comprehensive Cancer Network (NCCN): Bladder cancer. J Natl Compr Canc Netw 2013;11(4):446–75.
7. Vaughn D.J., Broome C.M., Hussain M. et al. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. J Clin Oncol 2002;20(4):937–40.
8. Ko Y.J., Canil C.M., Mukherjee S.D. et al. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase II study. Lancet Oncol 2013;14(8):769–76.
9. Beer T.M., Goldman B., Nichols C.R. et al. Southwest Oncology Group phase II study of irinotecan in patients with advanced transitional cell carcinoma of the urothelium that progressed after platinum-based chemotherapy. Clin Genitourin Cancer 2008;6(1):36–9.
10. Dreicer R., Li S., Manola J., et al. Phase II trial of epothilone Banalog BMS-247550 (ixabepilone) in advanced carcinoma of the urothelium (E3800): a trial of the Eastern Cooperative Oncology Group. Cancer 2007;110(4):759–63.
11. Rosenberg J.E., Halabi S., Sanford B.L. et al. Phase II study of bortezomib inpatients with previously treated advanced urothelial tract transitional cell carcinoma: CALGB 90207. Ann Oncol 2008;19(5):946–50.
12. Galsky M.D., Mironov S., Iasonos A. et al. Phase II trial of pemetrexed as second-line therapy in patients with metastatic urothelial carcinoma. Invest New Drugs 2007;25(3):265–70.
13. Winquist E., Vokes E., Moore M.J. et al. A Phase II study of oxaliplatin in urothelial cancer. Urol Oncol 2005;23(3):150–4.
14. Witte R.S., Elson P., Bono B. et al. Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. J Clin Oncol 1997;15(2): 589–93.
15. Wülfing C., Machiels J.P., Richel D.J. et al. A single-arm, multicenter, open label phase 2 study of lapatinib as the second-line treatment of patients with locally advanced or metastatic transitional cell carcinoma. Cancer 2009;15(13):2881–90.
16. McCaffrey J.A., Hilton S., Mazumdar M. et al. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 1997;15(5):1853–7.
17. Petrylak D.P., Tangen C.M., van Veldhuizen P.J. et al. Results of the Southwest Oncology Group phase II evaluation (study S0031) of ZD1839 for advanced transitional cell carcinoma of the urothelium. BJU Int 2010;105(3):317–21.
18. Dreicer R., Li H., Stein M. et al. Phase II trial of sorafenib in patients with advanced urothelial cancer: a trial of the Eastern Cooperative Oncology Group. Cancer 2009;115(18):4090–5.
19. Gallagher D.J., Al-Ahmadie H., Ostrovnaya I. et al. Sunitinib in urothelial cancer: clinical, pharmacokinetic, and immunohistochemical study of predictors of response. Eur Urol 2011;60(2):344–9.
20. Pili R., Qin R., Flynn P.J. et al. A phase II safety and efficacy study of the vascular endothelial growth factor receptor tyrosine kinase inhibitor pazopanib in patients with metastatic urothelial cancer. Clin Genitourin Cancer 2013;11:477–83.
21. Meluch A.A., Burris H.S., Greco F.A., Hainsworth J.D. Gemcitabine and paclitaxel combination therapy in transitional cell carcinoma of the urothelium. Eur J Cancer 2000;36:30–3.
22. Milowsky M.I., Nanus D.M., Maluf F.C. et al. Final results of sequential doxorubicin plus gemcitabine and ifosfamide, paclitaxel, and cisplatin chemotherapy in patients with metastatic or locally advanced transitional cell carcinoma of the urothelium. J Clin Oncol 2009;27(25):4062–7.
23. Kouno T., Ando M., Yonemori K. et al. Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. Eur Urol 2007;52(4):1115–22.
24. Sonpavde G., Sternberg C.N., Rosenberg J.E. et al. Second-line systemic therapy and emerging drugs for metastatic transitional-cell carcinoma of the urothelium. Lancet Oncol 2010;11(9):861–70.
25. Braguer D., Barret J.M., McDaid H., Kruczynski A. Antitumor activity of vinflunine: effector pathways and potential for synergies. Semin Oncol 2008;35:13–21.
26. Coderch C., Morreale A., Gago F. Tubulin-based structure-affinity relationships for antimitotic Vinca alkaloids. Anticancer Agents Med Chem 2012;12(3):219–25.
27. Culine S., Theodore C., De Santis M. et al. A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containingregimen. Br J Cancer 2006;94(10):1395–401.
28. Vaughn D.J., Srinivas S., Stadler W.M. et al. Vinflunine in platinum pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase II study. Cancer 2009;115(18):4110–7.
29. Bellmunt J., Théodore C., Demkov T. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009;27(27):4454–61.
30. Bellmunt J., Fougeray R., Rosenberg J.E. Long-term survival results

of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patient safter failure of platinum-based chemotherapy. Ann Oncol 2013;24(6): 1466–72.
31. Eisenhauer E.A., Therasse P., Bogaerts J. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
32. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc. htm.
33. Castellano D., Puente J., de Velasco G. et al. Safety and effectiveness of vinflunine in patients with metastatic transitional cell carcinoma of the urothelial tract after failure of one platinum-based systemic therapy in clinical practice. BMC Cancer 2014;14:779.
34. Hegele A., de Geeter P., Goebell P. et al. Vinflunine in routine practice for the treatment of advanced or metastatic urothelial cell carcinoma in Germany. Eur J Cancer 2013;49(Supp. 2):669.
35. Medioni J., Guillot A., Spaeth D. et al. Historical data in real life from patients treated by vinflunine for an advanced or metastatic urothelial carcinoma: Results of the CURVE study. Eur J Cancer 2013;(Suppl. 2):646–7.
36. Bellmunt J., Choueiri T.K., Fougeray R. et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 2010;28(11):1850–5.