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Optimization of systemic treatment in patients with bladder, ureter, and renal pelvis cancer — expert opinion of the Polish Society of Clinical Oncology

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According to the authors and editors, the study contains the best justified principles of diagnostic and therapeutic procedures based on evidence, with the level and category of recommendations indicated. Guidelines should be interpreted in the context of an individual clinical situation. Guidelines do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of refunding individual procedures should be established. The quality of scientific evidence and categories of recommendations are defined according to the following criteria:
1. The quality of scientific evidence
I — Evidence from appropriately planned and conducted randomized clinical trials or meta-analyses of randomized clinical trials
II — Evidence from appropriately planned and conducted prospective observational studies (cohort studies without randomization)
III — Evidence from retrospective observational or case-control studies
IV — Evidence from experience gained in clinical practice and/or expert opinions
2. Recommendation categories
A — Indications confirmed unambiguously and absolutely useful in clinical practice
B — Probable and potentially useful indications in clinical practice
C — Individually determined indications

Introduction

Management of patients with urothelial cancer can pose a significant challenge, related not only to the constantly rising prevalence but also to the increasing number of treatment options. There are 5,600 new urothelial cancer cases in Poland every year, with 3,000 deaths (data for 2021). In the last decade, there has been enormous progress in the systemic treatment of patients with urothelial cancer, including both perioperative treatment and systemic treatment of advanced disease. The introduction of immune checkpoint inhibitors (ICIs), antibody-drug conjugates (ADCs), and small-molecule tyrosine kinase inhibitors (TKI) into the clinical armamentarium

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has significantly improved the prognosis of patients with urothelial cancer. Numerous available systemic treatment options (Tab. 1) and therapeutic algorithms (Fig. 1–3) pose a challenge for oncologists in conducting optimal and maximally personalized therapeutic management both in intensive, relatively short radical as well as inlong-term, multi-stage, palliative treatment. This article presents the current position of the Polish Society of Clinical Oncology experts regarding optimal systemic treatments in patients with urothelial cancer.

Table 1. Chemotherapy regimens used for treatment of urothelial cancer (all drugs are administered intravenously unless otherwise noted)

Therapy regimen	Regimen details	Frequency of administration
ddMVAC	Day 1: Methotrexate 30 mg/m^2 Day 2: Vinblastine 3 mg m^2 Doxorubicin 30 mg/m^2 Cisplatin 70 mg/m^2	Every 2 weeks with G-CSF support
aaMVAC	Methotrexate 30 mg/m^2 Vinblastine 3 mg/m^2 Doxorubicin 30 mg/m^2 Cisplatin 70 mg/m^2	Every 2 weeks with G-CSF support
ddGP	Gemcitabine 2500 mg/m^2 Cisplatin 70 mg/m^2	Every 2 weeks with G-CSF support
GP	Gemcitabine 1000 mg/m^2 day 1, 8. Cisplatin 70 mg/m^{2}day 1	Every 21 days
GP (with split dose cisplatin)	Gemcitabine 1000 mg/m^2 day 1, 8. Cisplatin 35 mg/ m^{2}day 1, 8.	Every 21 days
GC	Gemcitabine 1000 mg/m^{2}day 1, 8. Carboplatin AUC 4–5 day 1.	Every 21 days
GC (with split dose carboplatin)	Gemcitabine 1000 mg/m^2 day 1, 8. Carboplatin AUC 2 day 1, 8.	Every 21 days
GPx	Gemcitabine 1000 mg/m^2 day 1, 8. Paclitaxel 80 mg/m^2 day 1, 8.	Every 21 days
Monotherapy	Docetaxel 75 mg/m^2	Every 21 days
	Docetaxel 50 mg/m^2	Every 14 days
	Paclitaxel 175 mg/m^2 (3-hour infusion)	Every 21 days
	Paclitaxel 80 mg/m^2	Every 7 days
	Gemcitabine 1000 mg/m^2 day 1, 8, 15.	Every 28 days
Avelumab	Avelumab 800 mg/m^2	Every 14 days
Pembrolizumab	Pembrolizumab 200 mg	Every 21 days
	Pembrolizumab 400 mg	Every 42 days
GCN	Gemcitabine 1000 mg/m^2 day 1, 8. Cisplatin 70 mg/m^2 day 1. Nivolumab 360 mg day 1.	Every 21 days (6 cycles)
	Nivolumab maintenance 480 mg	Every 28 days
Erdafitinib	First course Day 1–14: erdafitinib 8 mg/d p.o. Day 15–18: erdafitinib 9 mg/d p.o. (if serum phosphorus concentration < 5.5 mg/dL and no ocular complications ≥ G2) Subsequent courses Erdafitinib 9 mg/days 1–28.	Every 28 days
EV	Enfortumab vedotin 1.25 mg/kg (maximum 125 mg) day 1, 8, 15.	Every 28 days
EVP	Enfortumab vedotin 1.25 mg/kg (maximum 125 mg) day 1, 8. Pembrolizumab 200 mg day 1.	Every 21 days
SG	Sacituzumab govitecan 10 mg/kg day 1, 8.	Every 21 days

aa, dd — dose density; G-CSF — granulocyte colony-stimulating factor); p.o. — *per os*

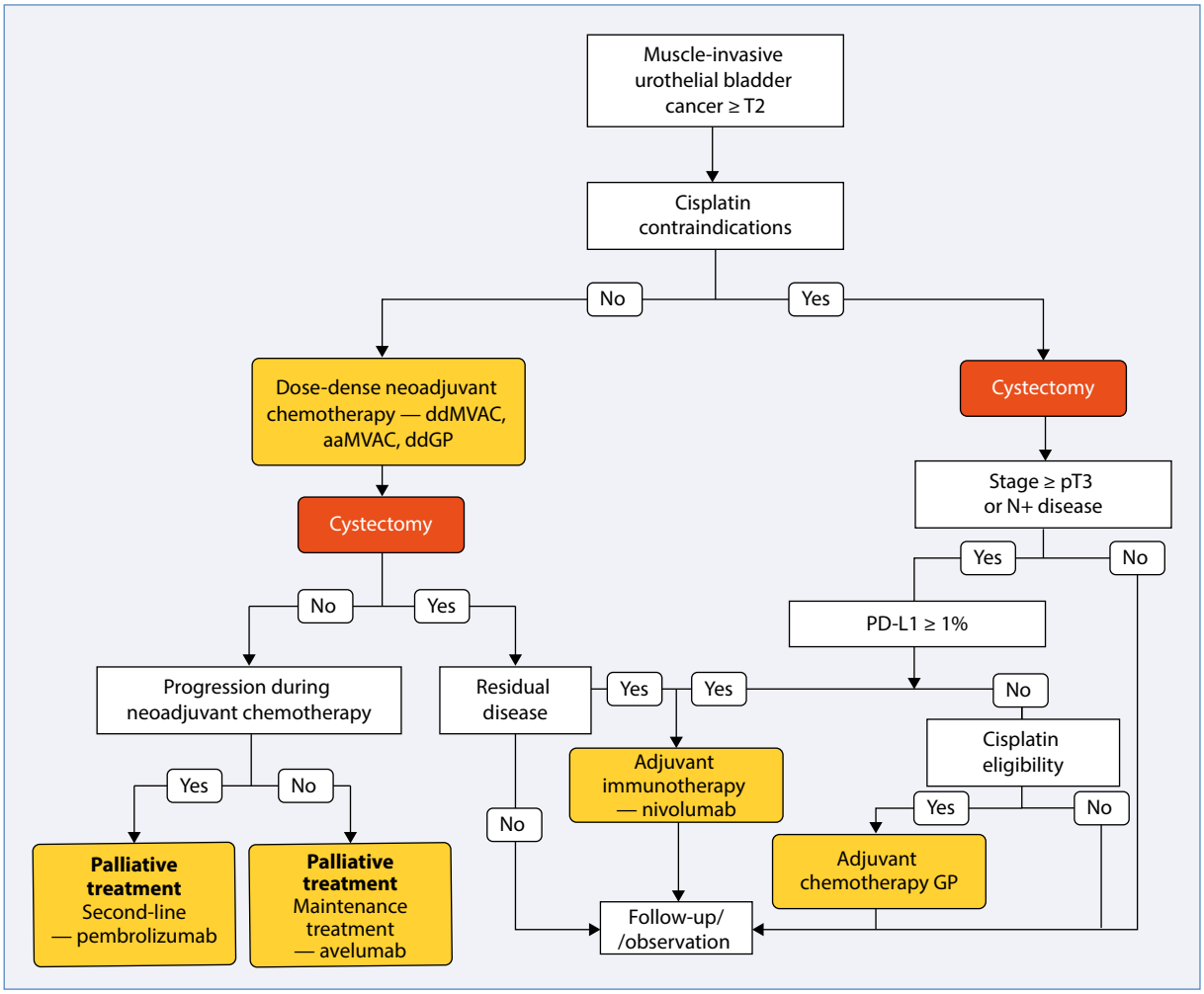

Figure 1. Algorithm for treatment with radical intention in patients with urothelial bladder cancer; aa, dd — dose density; GP — gemcitabine in combination with cisplatin; MVAC — combination of cisplatin, methotrexate, vinblastine, and doxorubicin; PD-L1 — programmed cell death ligand 1

Preoperative treatment

Neoadjuvant chemotherapy of urothelial cancers

Radical cystectomy with lymphadenectomy remains the basic therapeutic strategy for patients with muscle-invasive urothelial bladder cancer [1]. Despite its extensiveness and mutilating nature, it offers a chance for permanent recovery — the greater, the less initially advanced the cancer. In patients with no cancer cells in the postoperative specimen, the chances of 5- and 10-year disease-free survival (DFS) are 92% and 86%, respectively, and in patients with carcinoma *in situ*, these rates are 79% and 74%, respectively. In the case of muscular layer involvement without invasion of perivesical tissues, the 5- and 10-year DFS rates are 89% and 87%, respectively, and in the case of only microscopically detected infiltrations of perivesical tissues (pT3a), the DFS outcomes decrease to 78% and 76%, respectively. In patients with macroscopic invasion of perivesical tissues (pT3b stage), these rates drop to 62% and 61%, respectively, and when tumor invades adjacent organs (pT4 stage), they are only 50% and 45%, respectively. Additionally, more than 23% of patients present with initial lymph node involvement, which significantly worsens the prognosis. In patients with the N+ disease, the 5- and 10-year DFS rates are 35% and 34%, respectively [2]. To improve the outcomes of patients with ≥ T2 urothelial bladder cancer, neoadjuvant chemotherapy has been introduced into clinical practice.

For many years, preoperative treatment was based on chemotherapy regimens routinely used in the palliative settings in patients with advanced urothelial cancer, including MVAC (cisplatin, methotrexate, vinblastine, and doxorubicin), as well as gemcitabine in combination with cisplatin (GP) or carboplatin (GC) regimens [3].

In a study conducted by the Southwest Oncology Group (SWOG), the Eastern Cooperative Oncology Group (ECOG), and the Cancer and Leukemia Group (CALGB)

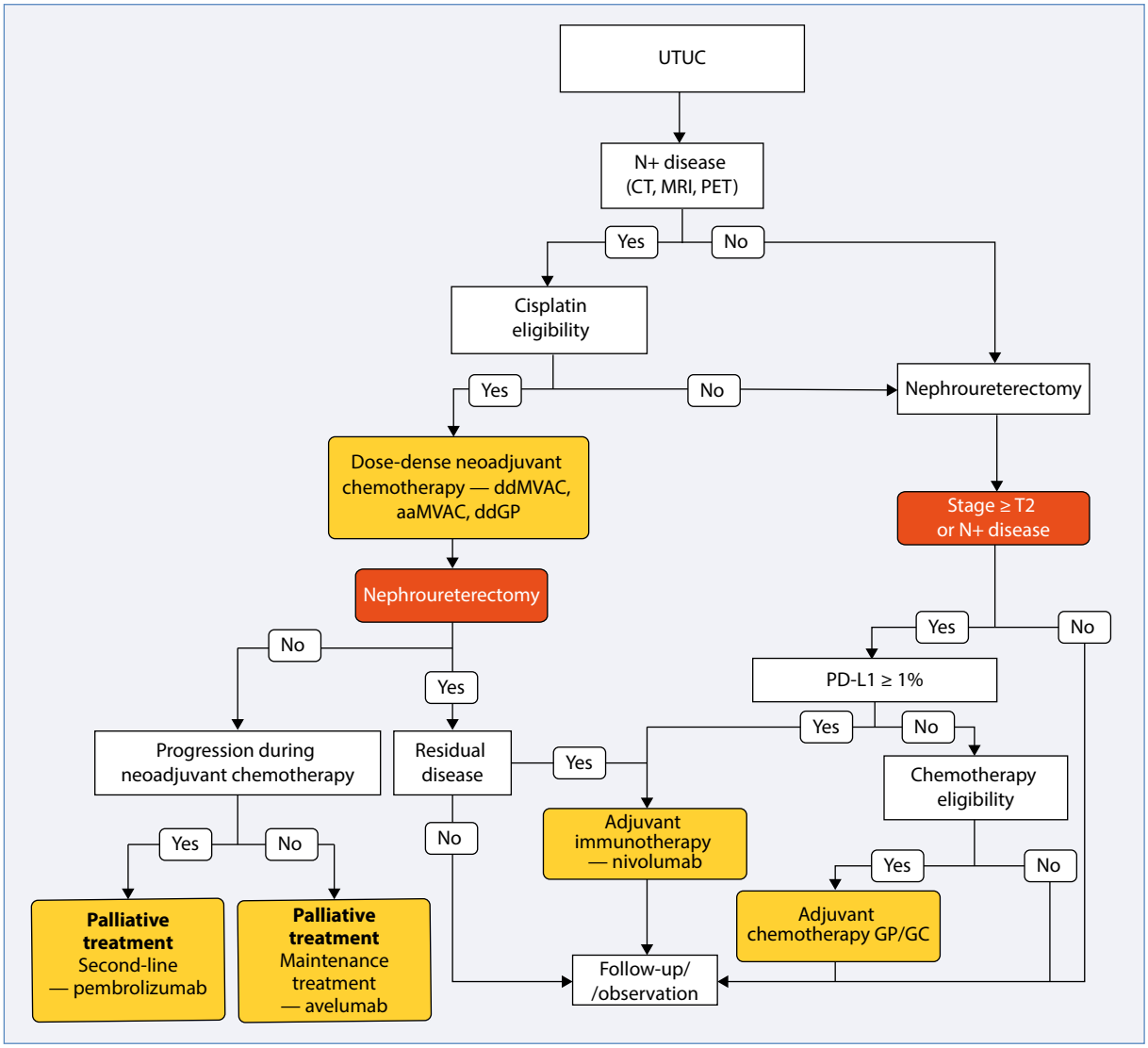

Figure 2. Algorithm of treatment with a radical intention in patients with upper tract urothelial cancer (UTUC) (ureter, renal pelvis); aa, dd — dose density; GP — gemcitabine in combination with cisplatin; GC — gemcitabine in combination with carboplatin; MRI — magnetic resonance imaging; MVAC — combination of cisplatin, methotrexate, vinblastine, and doxorubicin; PD-L1 — programmed cell death ligand 1; PET — positron emission tomography; CT — computed tomography

in patients with operable T2–T4a N0 urothelial bladder cancer, 3 cycles of MVAC increased median overall survival (OS) from 46 months (cystectomy alone) to 77 months (preoperative chemotherapy followed by cystectomy) [4].

Another multicenter study evaluating the effect of neoadjuvant treatment based on an MVC regimen (methotrexate, vinblastine, and cisplatin) showed a 5.5% reduction in the risk of death in patients undergoing preoperative chemotherapy only if all three drugs were administered [5]. There was no effect of neoadjuvant treatment based on cisplatin alone or on cisplatin and methotrexate combination [6–8].

A 2016 meta-analysis summarized the results of fifteen studies involving 3,285 urothelial bladder cancer patients. Preoperative treatment with GP or MVAC/MVC regimens was associated with an absolute improvement in OS by 8% and an absolute increase in the 5-year OS rate by 8% (from 45 to 53%). That meta-analysis also again demonstrated that preoperative cisplatin monotherapy does not improve prognosis. This analysis also compared MVAC and GP regimens. The pathological complete response (pCR) rate for the GP regimen was 25.7%, and for the MVAC regimen, 24.3%, which did not differ significantly. However, the MVAC regimen showed a trend toward improvement in OS [9].

The current standard of preoperative management of urothelial bladder cancer stems from the data obtained in a phase III study (GETUG/AFU V05 VESPER),

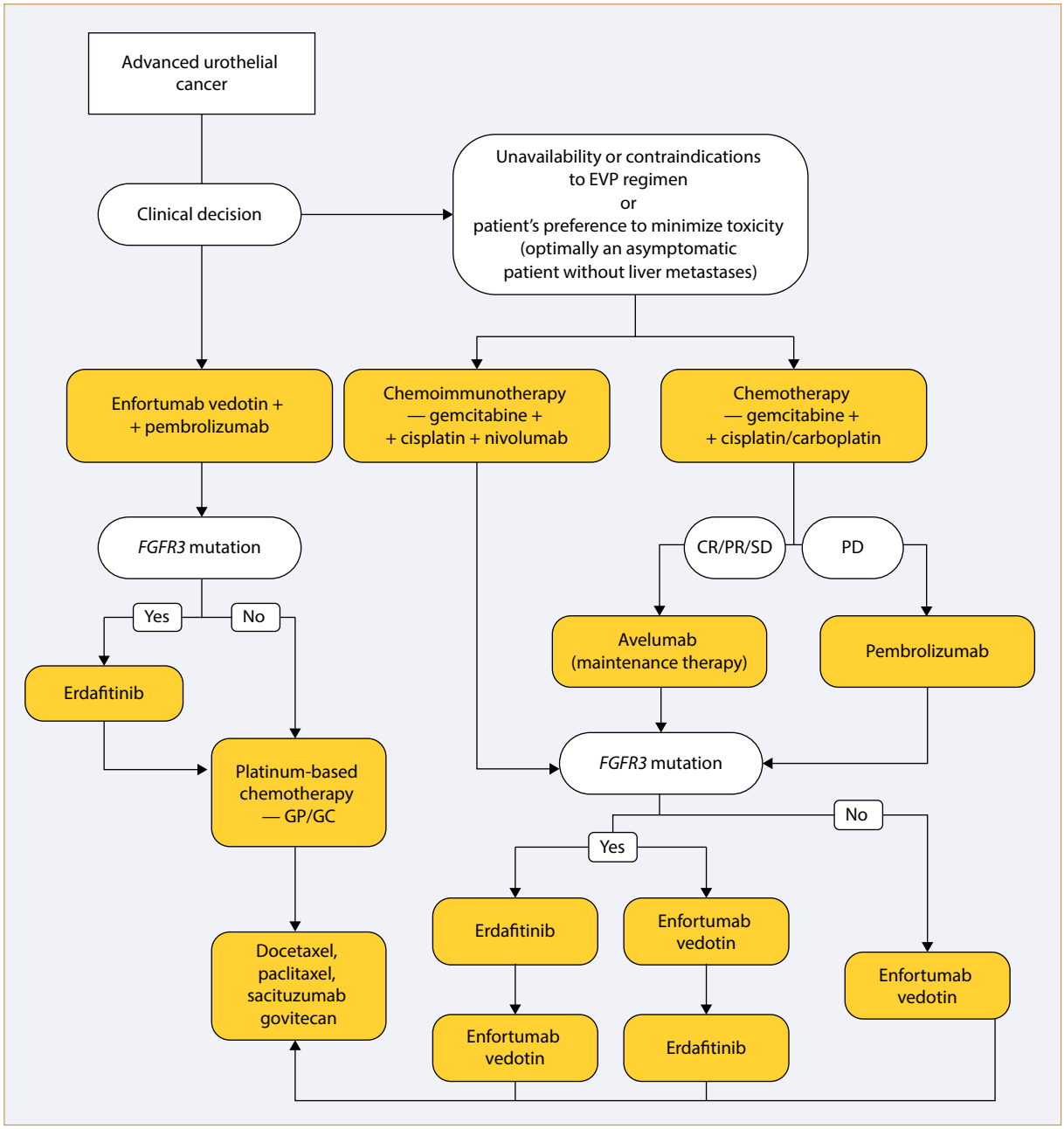

Figure 3. Algorithm for palliative treatment in patients with urothelial cancer; CR — complete response; GP — gemcitabine in combination with cisplatin; GC — gemcitabine in combination with carboplatin; PD — progressive disease; PR — partial response; SD — stable disease

which compared dose-dense MVAC chemotherapy regimen (ddMVAC; 6 courses every 2 weeks) with a GP regimen (4 courses every 3 weeks) used pre- (89% of patients) or postoperatively (11% of patients) in 493 patients with urothelial bladder cancer (≥ T2). The preoperative use of the ddMVAC regimen was associated with a significant increase in the pCR rate (from 36% to 42%), downstaging < ypT2 (from 49% to 63%), and limitation of the disease extent to the bladder wall (from 63% to 77%). Neoadjuvant chemotherapy with ddMVAC compared with GP was associated with a significant improvement in the 5-year OS rate (66% *vs.* 57%), which translated into a significant reduction in the relative risk of all-cause death by 29% (HR = 0.71; 95% CI 0.52–0.97) and death due to bladder cancer by 45% (HR = 0.55; 95% CI 0.39–0.78). The algorithm of perioperative management for patients with urothelial bladder cancer is presented in Figure 1.

In patients with contraindications to anthracyclines, the regimen of choice is a dose-dense GP regimen (ddGP), which, in a randomized study, in patients with advanced urothelial cancer, showed the same activity as ddMVAC in terms of OS, progression-free survival (PFS), and objective response rate (ORR) with significantly better tolerability [10]. In a phase II study, the ddGP regimen used in a neoadjuvant setting led to pCR in 32% of patients and to downstaging (< ypT2) in another 13%. However, a frequent occurrence of thromboembolic episodes (23% of patients) caused a premature study closure [11]. This observation indicates the need for better monitoring of thrombotic risk in patients qualified for the ddGP regimen, with a possible introduction of antithrombotic prophylaxis in high-risk patients.

The optimal number of neoadjuvant chemotherapy courses remains an important issue, especially in the case of the anthracycline-containing ddMVAC regimen. In earlier, small studies, the number of cycles was limited to 3–4 courses and, in the GETUG/AFU V05 VESPER study, to six. Undoubtedly, administering six courses of chemotherapy poses a significant burden for patients, especially the elderly and those with comorbidities (especially with preexisting heart conditions). In the VESPER study, 60% of patients received all six courses of preoperative ddMVAC chemotherapy compared with 84% in the GP arm [12]. Subgroup analysis showed that the maximum benefit from preoperative ddMVAC treatment was achieved by patients who received a dose of cisplatin equivalent to at least four full courses of chemotherapy (≥ 270 mg/m^2) [13].

Neoadjuvant chemoimmunotherapy for urothelial bladder cancer

A recently published neoadjuvant phase III trial (NIAGARA) compared four cycles of GP combined with durvalumab to four cycles of GP alone [14]. Patients in the chemoimmunotherapy arm received up to 8 cycles of durvalumab postoperatively. In total, 1063 patients with muscle-invasive urothelial bladder cancer were randomized in a 1:1 ratio to chemoimmunotherapy or chemotherapy. The dual primary endpoints were pCR and event-free survival. Neoadjuvant treatment was completed by 78.7% and 74.0%, and radical cystectomy was performed in 88.0% and 83.2% of patients in experimental and control arms, respectively. The pCR rate was 37.3% and 27.5% in the chemoimmunotherapy and chemotherapy arms, respectively, but the differences were not statistically significant. The estimated event-free survival was 67.8 in the durvalumab group and 59.8% in the GP group, which was associated with a significant reduction in the relative risk of progression, recurrence, not undergoing radical cystectomy, or death from any cause (HR for EFS = 0.68; 95% CI 0.56 to 0.82). Chemoimmunotherapy also led to a significant improvement in the relative risk of death compared to chemotherapy alone — (HR = 0.75; 95% CI 0.59 to 0.93) with the 24-month OS of 82.2.% and 75.2% in the experimental and control arms, respectively.

Despite the positive outcomes in the NIAGARA study, the practical implementation of these results remains highly controversial. First, the chemotherapy regimen used in the study was suboptimal since the VESPER study equivocally demonstrated the inferiority of GP compared to the ddMVAC. Second, in the VESPER, the ddMVAC regimen significantly improved the pCR rate compared to GC, which was not seen when the durvalumab was combined with GC in NIAGARA. Third, patients treated with ddMVAC in the VESPER study also had significantly better outcomes in terms of EFS and OS without any adjuvant treatment (unlike the NIAGARA study, where adjuvant durvalumab was required). Fourth, patients with residual disease after neoadjuvant treatment should be routinely offered adjuvant nivolumab.

Recommendations

— Preoperative chemotherapy is the standard of care for patients with muscle-invasive urothelial bladder cancer (stage ≥ T2) (I, A).
— Carboplatin should not be used in neoadjuvant treatment (I, A).
— ddMVAC is the recommended preoperative treatment regimen (I, A).
— aaMVAC and ddGP are optional preoperative treatment regimens (II, A).
— Preoperative treatment should last 8–12 weeks (4–6 courses) (I, A).
— In the case of regional lymph node involvement (N+ disease) in patients qualified for radical cystectomy, preoperative treatment should be conducted similarly to patients without lymph node involvement to complete 6 courses of chemotherapy (III, B).
— Preoperative treatment does not increase the risk of postoperative complications and does not worsen the prognosis (I, A).
— Patients diagnosed with rare forms of bladder cancer should be qualified for treatment/therapeutic management on an individual basis, optimally within clinical trials (III, B).
— Neoadjuvant chemoimmunotherapy based on the combination of gemcitabine, cisplatin, and durvalumab cannot be recommended as a therapeutic option due to the suboptimal comparator arm in NIAGARA study (I, B)

Neoadjuvant chemotherapy of non-urothelial bladder cancer

The available evidence on preoperative treatment is mainly devoted to patients with the most common form of urinary tract malignant neoplasm, i.e., urothelial cancer. The optimal management of patients with non-urothelial histology is still under discussion. The relatively low incidence of these tumors precludes conducting conclusive clinical trials. A study published in 2017 analyzed data from the National Cancer Database for 2,018 patients who underwent radical cystectomy for bladder cancer with less common histologies. Patients were allocated to groups with micropapillary or sarcomatoid variants of urothelial cancer, squamous cell carcinoma, adenocarcinoma, neuroendocrine cancer, and other rare forms. The authors concluded that patients with neuroendocrine cancer benefited from neoadjuvant chemotherapy in terms of OS. In the case of tumors with micropapillary, sarcomatous, or adenocarcinoma differentiation, preoperative chemotherapy reduced the incidence of tumor spread beyond the organ borders, which, however, did not translate into OS improvement. In patients with squamous cell carcinoma, preoperative chemotherapy was completely ineffective [15].

Neoadjuvant treatment of upper tract urothelial cancer

There are no randomized phase III trials on the role of neoadjuvant therapy in upper tract urothelial cancer (UTUC) involving the renal pelvis and ureter due to their relatively low incidence. However, retrospective analysis indicates comparable activity of systemic therapy in UTUC and urothelial bladder cancer. It has been shown that in the group of patients with UTUC receiving preoperative chemotherapy, the postoperative local tumor stage is lower than in the group undergoing primary surgery. Fourteen percent of patients who received neoadjuvant chemotherapy achieved complete pathological response [16]. Other authors also reported downstaging and pCR in patients with UTUC receiving neoadjuvant therapy, with the therapeutic response rate reaching 80% [17, 18]. It has also been suggested that preoperative treatment significantly prolongs cancer-specific survival, and in some studies, overall survival improvement has also been observed [19–21]. However, a major limitation of the aforementioned studies is their retrospective nature. A prospective phase II study including 30 patients with UTUC assessed the efficacy of multidrug systemic treatment with cisplatin [or carboplatin in the case of low glomerular filtration rate (GFR) values]. This study showed a complete pathological remission rate of 14%, with 60% of patients with the post-treatment disease stage not exceeding ypT1 [22].

In a single-arm phase II study, 57 patients with UTUC (cT2–cT4a N0/X) received 4 cycles of preoperative GP chemotherapy (with fractionated cisplatin). The use of GP chemotherapy resulted in pathological responses in 63% of patients, including pCR in 19%. The 2- and 5-year PFS rates were 89% and 72%, respectively, while the 2- and 5-year OS rates were 93% and 79%, respectively. In patients with pCR, the 2-year PFS and OS rates were 100% [23].

There is no doubt that, similarly to urothelial bladder cancer, regional lymph node involvement in patients with UTUC is associated with unfavorable prognosis. For many years, the N+ disease was a clear indication to refrain from radical surgical treatment. As already mentioned, currently, the regional lymph node involvement in patients with urothelial bladder cancer does not disqualify them from radical treatment provided that neoadjuvant chemotherapy is used.

At the 2023 ASCO Genitourinary Cancer Symposium, Jawtani et al. [24] presented the National Cancer Database analysis results. The authors identified 862 patients with N+ UTUC, of whom 362 received preoperative chemotherapy before radical nephroureterectomy and 500 received adjuvant chemotherapy after nephroureterectomy. Preoperative chemotherapy was associated with significantly better overall survival, with a median OS of 47.1 months (neoadjuvant) and 20.2 months (adjuvant). In a multivariate analysis, only the sequence of perioperative treatment was associated with a significant change in the prognosis in terms of OS (HR = 1.38; 95% CI 1.14–1.68) [24]. The results of this analysis support considering preoperative chemotherapy (based on standard neoadjuvant cisplatin-based regimens) in patients with N+ UTUC. The perioperative management algorithm in patients with UTUC is presented in Figure 2.

Recommendations

— Patients with UTUC without radiological evidence of regional lymph node involvement are candidates for nephroureterectomy (I, A).
— In UTUC patients with N+ disease diagnosis based on imaging studies, standard preoperative chemotherapy may be considered (III, B).

Adjuvant treatment

Adjuvant chemotherapy for urothelial bladder cancer

Patients with urothelial bladder cancer and UTUC who have undergone radical surgery require full imaging diagnostics before qualification for adjuvant treatment due to the high risk of early recurrence. Despite the potentially radical nature of the surgical procedure, the 5-year OS rate in the group of patients with urothelial

bladder cancer (pT4 pN+ M0) who have not undergone neoadjuvant chemotherapy is 50–60%. In all patients with urothelial cancer not receiving preoperative treatment, adjuvant therapy should be considered after excluding disease dissemination, based on chest, abdomen, and pelvis computed tomography evaluation (CT) [25, 26].

There has been a long-lasting debate on the rationale for adjuvant chemotherapy in patients with bladder cancer. Data from randomized, often prematurely closed clinical trials provide equivocal evidence to support the routine use of adjuvant chemotherapy. The largest phase III trial (EORTC 30994) demonstrated a significant reduction in the risk of disease recurrence (DFS) in patients receiving the GP regimen compared with deferring treatment until recurrence (HR = 0.54; 95% CI 0.4–0.73; p < 0.0001); however, it has not translated into a significant improvement of OS (HR = 0.78; 95% CI 0.56–1.08; p = 0.13) [27].

Multiple, early meta-analyses show an improvement in DFS with adjuvant chemotherapy and suggest an improvement in OS in patients after radical cystectomy with risk factors for recurrence, provided that cisplatin-based chemotherapy is used. A meta-analysis of 10 studies, including 1,183 patients comparing platinum-based adjuvant chemotherapy with cystectomy alone, suggested a significant improvement in OS (HR = 0.82; 95% CI 0.70–0.96) [28].

According to the adopted criteria, patients with stage ≥ pT3 and/or pN1 are eligible for adjuvant platinum-based chemotherapy, and this treatment should be started within 90 days of surgery. It is recommended that 3–4 courses of adjuvant chemotherapy be administered with the GP regimen, and carboplatin is not recommended. If the patient is not eligible for cisplatin-based chemotherapy, no other adjuvant chemotherapy is recommended [25, 26, 29, 30]. It should be noted that the decision on adjuvant treatment should take into consideration the patient's performance status (PS), expected survival time, comorbidities, and patient's preferences. Patients should be informed about limited evidence regarding the long-term benefits of adjuvant chemotherapy [30, 31].

Adjuvant treatment of atypical bladder neoplasms

In patients with invasive urothelial bladder cancer of mixed histology (squamous, glandular, or sarcomatous differentiation) who have not received preoperative treatment, standard adjuvant platinum-based chemotherapy should be considered. In pure squamous bladder cancer, neither neoadjuvant nor adjuvant chemotherapy is recommended [25, 26, 31].

Adjuvant chemotherapy of UTUC

Only one randomized clinical trial (POUT) evaluated the role of adjuvant chemotherapy (4 × GP or GC) in UTUC patients after radical surgery. In that study, in a population of 261 patients, a statistically significant reduction in the risk of recurrence by 45% (DFS HR = 0.55; 95% CI 0.38–0.80; p = 0.0001) was demonstrated, with a clear trend towards reducing the risk of death by 32% (HR = 0.68; 95% CI 0.46–1.00; p = 0.049). Subgroup analysis of OS showed a very clear superiority of the cisplatin regimen (HR for OS = 0.57; 95% CI 0.33–0.97) over the carboplatin regimen (HR for OS = 0.87; 95% CI 0.50–1.53) compared to observation alone, which again indicates the critical role of cisplatin in the perioperative treatment of patients with urothelial cancer. Based on the POUT study, adjuvant chemotherapy is recommended in all patients with histologically confirmed UTUC in stages pT2–T4 N0–3 M0 who did not receive preoperative treatment. Four cycles of GP chemotherapy are recommended, and treatment should be initiated within 90 days of nephroureterectomy. In selected patients (with abnormal renal function), replacing cisplatin with carboplatin may be considered; however, the limited evidence of benefits from such therapy should be highlighted.

Adjuvant immunotherapy of urothelial bladder cancer and UTUC

Immunotherapy with checkpoint inhibitors is used in the palliative treatment of patients with advanced urothelial cancer. The therapy has a favorable safety profile and improves prognosis. For this reason, several phase III studies evaluating the role of adjuvant immunotherapy (based on atezolizumab, nivolumab, or pembrolizumab) in patients after radical surgery have been conducted [32].

The first published phase III study (IMvigor010), including 809 patients, evaluated the role of adjuvant atezolizumab in patients with stage pT3–4a, pN+ (cystectomy alone) or ypT2–Ta or ypN+ (after preoperative chemotherapy). This study failed to demonstrate a significant improvement in DFS (HR = 0.89; 95% CI 0.74–1.08) with atezolizumab [33].

Another phase III study (CheckMate 274) evaluated the efficacy of 1-year nivolumab therapy compared with placebo in patients with high-risk urothelial bladder cancer and UTUC after radical surgery. The study included patients who had received prior preoperative chemotherapy (in the case of ypT2–ypT4a and/or ypN+ disease) and who had undergone surgery alone (pT3–pT4a and/or pN+) [34]. Nivolumab significantly reduced the risk of recurrence (HR for DFS = 0.71; 95% CI 0.58–0.86), with median DFS of 22.0 months (nivolumab) and 10.9 months (placebo). There was also a clear trend towards improved OS (HR = 0.76; 95% CI 0.61–0.96), with a median OS of 69.5 months (nivolumab) and 50.1 months (placebo), which, due to data immaturity, could not confirm a significant reduction in the relative risk of death. Patients with prior

Table 2. Prognosis of patients qualified for first-line systemic treatment — updated Bellmunt risk score

Risk factors	1-year survival rate				
1. Performance status (ECOG > 0) — 1 point		0 points	1 point	2 points	3+ points
2. Anemia (Hgb < 10 g/dL) — 1 point 3. Liver metastases — 1 point	OS	63%	44%	21%	15%
4. CRP > 30 mg/L — 1 point	PFS	26%	14%	7%	6%

CRP — C-reactive protein; ECOG — Eastern Cooperative Oncology Group; Hgb — hemoglobin; OS — overall survival; PFS — progression-free survival

preoperative treatment and with programmed cell death ligand 1 (PD-L1) expression ≥ 1% seemed to benefit significantly more from adjuvant immunotherapy, both in terms of DFS and OS [34].

In a similarly designed AMBASSADOR study, 1-year adjuvant treatment with pembrolizumab was assessed in 739 patients. The use of adjuvant immunotherapy was associated with a significant reduction in the risk of disease relapse (HR for DFS = 0.69; 95% CI 0.54–0.87), with median DFS of 29.0 (pembrolizumab) and 14.0 months (placebo). Contrary to CheckMate 274, in the AMBASSADOR study, patients without PD-L1 expression seemed to benefit more from pembrolizumab [35].

Recommendations

— Adjuvant chemotherapy based on gemcitabine in combination with cisplatin should be considered in patients with pT3/4 and/or pN+ urothelial bladder cancer after radical cystectomy if they no neoadjuvant chemotherapy has been used and there are no contraindications to cisplatin (II, B).
— In patients with urothelial bladder cancer with contraindications to cisplatin-based adjuvant chemotherapy, the use of carboplatin-based chemotherapy is not recommended.
— Patients with urothelial bladder cancer or UTUC who have residual disease after preoperative chemotherapy should receive adjuvant immunotherapy with nivolumab.
— In patients with UTUC after radical nephroureterectomy without preoperative chemotherapy, adjuvant chemotherapy based on the GP (or GC) regimen should be used (I, A).
— In patients with bladder cancer and UTUC with postoperative stage pT3–pT4a and/or pN+ disease, who did not receive preoperative chemotherapy, adjuvant immunotherapy with nivolumab may be used instead of chemotherapy, provided PD-L1 expression is ≥ 1% (II, B).

Palliative systemic treatment of patients with urothelial cancer

About half of urothelial cancer patients experience disease recurrence after curative treatment, which usually manifests as distant metastases. Limited local recurrence is observed in about 30% of patients and primarily disseminated disease in about 10% of patients [36].

Systemic treatment is the basic therapeutic strategy for patients with metastatic urothelial cancer. Therapy qualification requires a thorough and comprehensive assessment of performance status, organ function, and comorbidities [37]. The modified Bellmunt risk score is useful in assessing the prognosis of patients qualified for first-line palliative treatment (Tab. 2) [38].

First-line treatment

Combination of immunotherapy and antibody-drug conjugate

The EV-302 study evaluated the combination of enfortumab vedotin with pembrolizumab (EVP) in the first-line treatment of patients with advanced urothelial cancer [39]. The study included 886 patients randomized 1:1 to either EVP administered until progression (pembrolizumab for up to 35 courses) or conventional chemotherapy — 6 courses of GP/GC (with optional maintenance therapy with avelumab — used in 32% of patients). The combination of pembrolizumab with enfortumab vedotin was associated with a significant improvement in PFS compared to chemotherapy (HR = 0.45; 95% CI 0.38–0.54), with median PFS of 12.5 months (EVP) and 6.3 months (chemotherapy). The experimental treatment also significantly reduced the risk of death (HR = 0.47; 95% CI 0.38–0.58), with a median OS of 31.5 months (EVP) and 16.1 months (chemotherapy). In addition to significantly improving patient prognosis, EVP was also associated with significantly higher objective (ORR) and complete response (CR) rates — 67.7% and 29.1% (EVP) *versus* 44.4% and 12.5% (chemotherapy), respectively. Disease control, including objective responses and disease stabilization, was observed in 86.5% (EVP) and 78.2% (chemotherapy) patients. Compared to EVP, patients receiving chemotherapy had a higher incidence of grade (G) 3–4 bone marrow suppression-related adverse events (neutropenia, anemia, thrombocytopenia). On the other hand, in patients receiving EVP, long-term adverse events such as sensory neuropathy, skin lesions, diarrhea, and hyperglycemia were more frequent. The analysis of the quality of life (QoL) of patients participating in

the EV302 study presented at the 2024 ASCO Annual Meeting did not show any deterioration in patients receiving the EVP regimen compared to standard chemotherapy. The palliative therapy algorithm, including the EVP regimen in patients with advanced urothelial cancer, is presented in Figure 3.

Treatment of cisplatin-eligible patients

In all patients with advanced urothelial cancer, including those eligible for treatment with cisplatin, EVP therapy should be considered as an initial treatment option whenever available (currently, in many countries, including Poland, this strategy is not reimbursed) [39]. However, taking into account the continuous (until progression) treatment with enfortumab vedotin plus pembrolizumab combination, the risk of long-term adverse events associated with EVP, and the limitations of the pivotal EV302 study (a small percentage of patients receiving maintenance treatment with avelumab), simultaneous chemoimmunotherapy or chemotherapy with maintenance immunotherapy may still be considered a viable option in selected patients. Optimal candidates for chemoimmunotherapy or chemotherapy with maintenance immunotherapy may be patients with a good prognosis (0 points according to the updated Bellmunt risk score), especially those asymptomatic patients with no contraindications to cisplatin (Fig. 3).

In a phase III study [40], which compared the GP regimen with the standard (not dose-dense) MVAC regimen, no difference in efficacy was observed between the two treatment arms (median OS of about 14 months), with significantly better tolerability of doublet regimen [40]. In the EORTC30924 study, the efficacy and tolerability of ddMVAC and MVAC regimens were compared, showing a higher ORR with ddMVAC (72%) compared to classic MVAC (58%). The median PFS was 9.5 (ddMVAC) *vs.* 8.1 months (MVAC), respectively. Although the median OS was 15 months in both groups, the 5-year OS rate was higher with ddMVAC (21.8%) than with MVAC (13.5%). Another form of intensified palliative chemotherapy is a dose-dense GP (ddGP) regimen. The phase III study by Bamias et al. compared ddMVAC with the ddGP regimen in the first-line treatment of patients with advanced urothelial cancer. The ddGP regimen included gemcitabine (2,500 mg/m^2), and cisplatin (70 mg/m^2) administered every 2 weeks with prophylactic use of granulocyte colony-stimulating factor (G-CSF). The study showed no difference between the two regimens regarding the ORR, PFS, or OS. However, it showed a lower risk of febrile neutropenia (0% *vs.* 8%), a lower probability of premature treatment discontinuation (3% *vs.* 13%), and a higher chance of administering at least six chemotherapy cycles (85% *vs.* 63%) in the ddGP arm [41]. Based on the results of the above studies, in cisplatin-eligible patients, first-line palliative treatment should be based on the GP or the ddGP regimen, the latter especially when an immediate and deep response to first-line treatment is necessary [42].

Platinum-based chemotherapy in patients with suboptimal renal function

In patients with good performance status, without significant comorbidities and GFR of 40–60 mL/minute/1.73 m^2, a split dose of cisplatin (35 mg/m^2, day 1 and 8, every 21 days) plus gemcitabine (1000 mg/m^2, day 1 and 8) may be considered [43, 44]. However, all cisplatin-ineligible patients should be offered the EVP regimen in first-line (if available).

First-line immunotherapy

Concurrent chemoimmunotherapy

A phase III (CheckMate 901) study compared chemoimmunotherapy [gemcitabine + cisplatin + nivolumab (GCN)] with chemotherapy alone (GP regimen) in 608 patients with advanced urothelial cancer. In both arms, patients received six cycles of chemotherapy (± nivolumab) followed, in the experimental arm, by nivolumab administered until progression, unacceptable toxicity, or up to 24 months. The GCN regimen was associated with a significant increase in the ORR — 57.6% (GCN) *vs.* 43.1% (GP), including CR in 21.7% and 11.8% of patients, respectively. The GCN regimen significantly improved PFS (HR = 0.72; 95% CI 0.59–0.88) and OS (HR = 0.78; 95% CI 0.63–0.96) compared with chemotherapy alone [45]. A subgroup analysis of the CheckMate 901 trial presented at the 2024 ASCO Annual Meeting focused on patients (18% of the general population) with lymph node-only metastases [46]. The use of GCN was associated with a surprisingly high CR rate in patients with pelvic or retroperitoneal lymph node involvement — 63% (GNC) *vs.* 34% (GP). Furthermore, CR was maintained for 12 and 24 months in 70% and 65% of patients on GCN and 32% and 0% on GP regimen, respectively. The median PFS in patients with lymph node-only metastases was 30.5 months (GCN) *vs.* 8.8 months (GP) (HR for PFS = 0.38; 95% CI 0.22–0.66). Grade 3–4 adverse events were observed in 61.8% of patients (GCN) and 51.7% (GP), and in each arm, one patient died due to adverse events (due to sepsis in the GCN arm and due to acute renal failure in the GC arm).

Maintenance immunotherapy after chemotherapy

Patients who achieved at least disease stabilization after 4–6 cycles of chemotherapy based on a gemcitabine+platinum combination (GP, GC) should be offered a maintenance therapy with avelumab (treatment must be initiated within 4–10 weeks of completing chemotherapy). In the phase III JAVELIN Bladder 100 study,

such treatment significantly increased median OS from 14.3 months (best supportive care after chemotherapy) to 21.4 months (maintenance immunotherapy after chemotherapy) [47]. The benefit from maintenance therapy was observed regardless of the PD-L1 expression, presence of visceral metastases, platinum compound used in first-line chemotherapy (carboplatin, cisplatin), or response to chemotherapy. Immune-related adverse events (irAE) occurred in 29% of patients in the experimental arm, with 7% of ≥ G3 [48].

Special patient populations

Patients with contraindications to platinum derivatives

The management of patients who are not eligible for platinum-based chemotherapy depends on their performance status and comorbidities. For many years, the basic therapeutic option in advanced urothelial cancer patients with absolute contraindications to cisplatin was the use of carboplatin [49], albeit with its known lower antitumor potential [50]. In patients with contraindications to either cisplatin or carboplatin, the combination of gemcitabine with paclitaxel [51] or gemcitabine monotherapy [52] can be considered. In patients who are not eligible for platinum-based chemotherapy but demonstrate high PD-L1 expression, stand-alone immunotherapy based on atezolizumab (PD-L1 ≥ 5%) [53] or pembrolizumab [combined positive score (CPS) ≥ 10] may be considered [54]. Objective response rates in this population reach 23–29%, including 7–9% of CR [53, 54]. The optimal treatment for patients who are not eligible for cisplatin or platinum derivatives is the EVP regimen (if available) [39].

In patients with intermediate performance status (ECOG 2) with significant comorbidities (including chronic kidney disease with GFR < 30 mL/min/1.73m^2) and poor performance status (ECOG ≥ 3), best supportive care is recommended due to expected poor treatment tolerance and lack of benefit of systemic treatment [49, 55].

Patients with non-urothelial tumors

Malignant urinary tract neoplasms with histological structures other than urothelial carcinoma are rare (approx. 10% of cases), which is a reason for the lack of established treatment standards. Patients should be consulted in tertiary centers, and the treatment strategy should be established within an interdisciplinary team. Patients should be enrolled in clinical trials whenever possible. Palliative systemic treatment of patients with mixed histology tumors (i.e., urothelial cancer with the presence of micropapillary, squamous, sarcomatous, or glandular components) is the same as in the case of pure urothelial carcinoma [56]. In the case of squamous cell carcinoma, chemotherapy based on paclitaxel plus ifosfamide plus cisplatin combination (TIP) should be considered [57, 58]. Patients with adenocarcinoma should be administered regimens used for the treatment of gastrointestinal adenocarcinomas (mainly FOLFOX regimen based on a combination of 5-fluorouracil, leucovorin, and oxaliplatin) [59] or with a TIP regimen [60]. A similar approach as in adenocarcinoma is considered in patients with advanced urachal carcinoma (90% presenting with adenocarcinoma histology) [57, 59–62]. In the case of small cell or neuroendocrine carcinoma, chemotherapy regimens used in the treatment of patients with small cell lung cancer, which are based on etoposide and cisplatin or carboplatin combinations, are recommended [63, 64].

Patients with recurrence after curative systemic treatment

Making decisions regarding palliative systemic treatment is especially difficult in patients with disease recurrence shortly after radical systemic treatment (pre- or postoperative). This is because clinical trials either excluded patients with early relapse or the subpopulations of such patients were very small.

In clinical practice, it should be assumed that patients with disease recurrence ≥ 6 months after pre- or postoperative chemotherapy or ≥ 12 months after adjuvant immunotherapy should be treated as treatment-naïve patients. On the other hand, in patients with relapse occurring earlier than 6 months after the completion of chemotherapy or earlier than 12 months after the completion of adjuvant immunotherapy, first-line palliative treatment should be based on a different therapeutic strategy.

The EVP regimen should be considered in patients who relapsed within 6 months of completing pre- or postoperative chemotherapy (not receiving adjuvant immunotherapy). If the EVP regimen is not available, pembrolizumab-based immunotherapy should be initiated.

In patients who relapsed within 12 months of completing postoperative immunotherapy, chemotherapy based on gemcitabine+platinum combinations (GC or GP) should be considered with the option of maintenance avelumab-based immunotherapy if disease control is achieved.

Patients not receiving local treatment after neoadjuvant treatment.

Patients with urothelial cancer who have not (for any reason) undergone curative local treatment after neoadjuvant chemotherapy should be treated as patients with advanced disease and receive/continue standard palliative treatment. In patients without progression after neoadjuvant chemotherapy, it is reasonable to consider maintenance immunotherapy (avelumab) within 4–10 weeks after completion of chemotherapy. Although the JAVELIN Bladder 100 study included

only patients with disease control achieved with gemcitabine and platinum combination, maintenance treatment with avelumab should also be offered to patients who achieved disease control after ddMVAC or aaMVAC regimens. Another option for patients treated with neoadjuvant chemotherapy who have not undergone surgery is close surveillance with the introduction of first-line systemic treatment (GP/GC → avelumab or GCN) if disease progression occurs after at least 6 months of completing preoperative treatment or the introduction of second-line immunotherapy (pembrolizumab) in the case of progression occurring within 6 months.

Recommendations

— In patients with metastatic urothelial cancer, performance status, organ function, and comorbidities should be considered upon qualification for first-line systemic treatment (II, A).
— The combination of enfortumab vedotin with pembrolizumab is the treatment of choice in most patients with advanced urothelial cancer (I, A).
— In patients with asymptomatic metastatic urothelial cancer, with a good prognosis (0 points according to the updated Bellmunt risk score) and without contraindications to cisplatin, concurrent chemoimmunotherapy (GCN) or chemotherapy (GP/GC) with avelumab maintenance treatment may be considered (I, B).
— In patients with metastatic urothelial cancer, with no access to the EVP regimen, chemotherapy based on the classic GP regimen or a dose-dense regimen (ddGP) should be used (I, B).
— In patients with metastatic urothelial cancer with contraindications/lack of access to the EVP regimen and contraindications to cisplatin treatment, the GC regimen is recommended (I, B).
— Only the best supportive care is recommended in patients with ECOG performance status 2 with clinically significant comorbidities and with ECOG performance status ≥ 3 (I, A).
— In patients with disease relapse/dissemination ≥ 6 months after perioperative chemotherapy completion or ≥ 12 months after adjuvant immunotherapy, palliative treatment should be performed as in treatment-naïve patients (III, B).

Second-line treatment

Immunotherapy after first-line chemotherapy

In a phase III clinical trial (KEYNOTE-045), pembrolizumab was compared with single-agent chemotherapy (docetaxel, paclitaxel, or vinflunine). The study enrolled 542 patients with advanced urothelial cancer who had failed prior platinum-based therapy. Patients could receive up to two prior lines of palliative chemotherapy or perioperative platinum-based chemotherapy alone if relapse occurred within 12 months of therapy completion. Pembrolizumab significantly increased the ORR to 21.1% (including 7.0% CR) *vs.* 11.4% in the chemotherapy arm (including 3.3% CR). Although no significant difference was observed in the reduction of relative risk of progression or death (HR for PFS = 0.96; 95% CI 0.79–1.16), the 2-year PFS rates were 12.4% (pembrolizumab) *vs.* 3.0% (chemotherapy). Pembrolizumab was also associated with a significant 30% reduction in the relative risk of death (HR = 0.70; 95% CI 0.57–0.85).

Other immune checkpoint inhibitors have been approved by regulatory agencies for the treatment of patients after failure of platinum-based chemotherapy based on the results of single-arm phase II studies. Nivolumab used in a CheckMate 275 study, in a population of 270 patients, allowed for objective responses in every fifth patient (19.6%), with median PFS and OS of 2.0 and 8.74 months, respectively [65]. In turn, durvalumab was approved based on a phase I/II study involving 191 patients with advanced urothelial cancer. In the analyzed population, durvalumab led to 17.8% of objective responses (including 3.7% CR). The median PFS and OS were 1.5 and 18.2 months, respectively [66]. Two years after the positive US Food and Drug Administration (FDA) decision, durvalumab approval for palliative treatment was withdrawn due to unfavorable results of phase III studies in earlier lines of treatment of urothelial cancer. The registration of atezolizumab after the failure of platinum-based chemotherapy was also based on the results of a phase II study (IMvigor 210) [67]. In this trial, atezolizumab allowed for 26% of objective responses in 220 patients, but median OS and PFS in the entire study population were not reported [68]. To precisely verify the benefits of atezolizumab in the second and subsequent treatment lines in patients with advanced urothelial cancer, a phase III study (IMvigor 211) was conducted. This trial enrolled 931 patients randomly assigned to atezolizumab or chemotherapy (paclitaxel, docetaxel, or vinflunine) arms [69]. Atezolizumab failed to improve prognosis compared with chemotherapy, with median OS of 11.1 months (atezolizumab) and 10.6 months (chemotherapy) (HR = 0.87; 95% CI 0.63–1.21). In March 2021, the FDA withdrew the approval of atezolizumab for the treatment of patients with advanced urothelial cancer after platinum-based chemotherapy failure.

Treatment after immunotherapy failure

Enfortumab vedotin

Enfortumab vedotin (EV) is a conjugate of an antibody recognizing an adhesion protein (Nectin-4), which is highly expressed on the surface of urothelial cancer

cells, and the cytotoxic drug monomethyl auristatin E, an inhibitor of microtubule polymerization. The phase III (EV-301) study included 608 patients with advanced urothelial cancer after failure of platinum-based chemotherapy and immunotherapy with ICIs. Patients were randomly assigned to the EV arm or control arm (paclitaxel, docetaxel, or vinflunine) [70]. The use of EV was associated with a significant reduction in the relative risk of death by 30% (HR = 0.70; 95% CI 0.56–0.89), with median OS of 12.88 months (EV) and 8.97 months (chemotherapy). A significant improvement in PFS was also observed (HR = 0.60; 95% CI 0.51–0.75), with medians of 5.55 months and 3.71 months in the experimental and control arms, respectively. The treatment with EV compared with chemotherapy was associated with a significantly higher ORR — 40.6% *vs.* 17.9%, including CR rates of 4.9% *vs.* 2.7%, respectively. Disease control, including disease stabilization, was achieved in 71.9% of patients in the experimental arm and 53.4% in the control arm. Adverse events were similar in both arms — the rate of grade G1–4 and G3–4 AEs was 94% and 51% in the EV arm and 92% and 50% in the chemotherapy arm, respectively. Typical adverse events for ADC were skin reactions (rash and severe skin reactions), occurring in 40% of patients (grade G3–4 in 15%), hyperglycemia (6% of patients), and peripheral neuropathy, occurring in 46% of patients (including grade G3–4 in 5%). Peripheral neuropathy included both sensory (44% of patients, including G3-4 – 4%) and motor neurons (7% of patients, including G3–4 — 2%) [70].

FGFR tyrosine kinase inhibitor

The luminal I subtype of urothelial cancer is characterized by low immunogenicity and low expression of PD-L1 in the tumor microenvironment, which are reasons for the generally low sensitivity of this cancer subtype to standard immunotherapy [71]. However, luminal I tumors often demonstrate abnormalities in the *FGFR2/3* genes encoding the fibroblast growth factor receptor [72]. Mutations and fusions in the *FGFR2/3* genes activate signaling pathways that determine the development and progression of the neoplastic disease. In about 20% of patients with urothelial cancer and 37% of patients with UTUC, *FGFR2/3* gene abnormalities can be found. Erdafitinib, an oral FGFR1–4 receptor tyrosine kinases inhibitor, was evaluated in the phase III THOR trial. The study included 266 patients with *FGFR3* gene disorders (no patients with *FGFR2* gene disorders were identified during recruitment) who progressed after at least one previous chemotherapy regimen and immunotherapy with PD-1 or PD-L1 inhibitors. Patients were randomized 1:1 to the group receiving erdafitinib or chemotherapy (vinflunine or docetaxel). The use of erdafitinib significantly improved OS and PFS. The median OS was 12.1 months (erdafitinib) and 7.8 months (chemotherapy), which resulted in a 36% reduction in the risk of death (HR = 0.64; 95% CI 0.47–0.88). The median PFS was 5.6 months in the erdafitinib arm and 2.7 months in the chemotherapy arm (HR = 0.58; 95% CI 0.44–0.78). The use of erdafitinib was associated with typical class-specific adverse events like hyperphosphatemia (≥ G3 — 5.2%), stomatitis (≥ G3 — 8.1%), nail disorders (≥ G3 — 11.1%), skin disorders (≥ G3 — 11.9%) and ocular disorders including central serous retinopathy (≥ G3 — 4.4%).

Treatment after EVP regimen failure

There is no established treatment option with a confirmed efficacy for patients with progression after first-line EVP treatment. However, taking into account the mechanisms of action of cytotoxic drugs other than auristatin monomethyl, which are active in urothelial cancer, it seems reasonable to consider standard platinum-based chemotherapy in such patients. A standard GP regimen should be considered (or GC regimen in the case of cisplatin contraindications) for patients without contraindications to platinum derivatives. In patients with urothelial cancer with *FGFR3* mutation, the use of erdafitinib as a second-line treatment may be considered.

Recommendations

— The treatment of choice for advanced urothelial cancer patients after failure of platinum-based first-line chemotherapy is pembrolizumab-based immunotherapy (I, A).
— In patients after first-line EVP failure, chemotherapy based on gemcitabine and platinum derivative combination (III, B) or erdafitinib in the case of *FGFR3* gene rearrangement (I, A) should be used.
— In advanced urothelial cancer patients who received chemotherapy in combination with immunotherapy (concurrently or sequentially), EV (I, A) or erdafitinib in the case of *FGFR3* gene rearrangements (I, A) should be used in the second line.
— In patients with advanced urothelial cancer who have failed platinum-based chemotherapy and who cannot receive either immunotherapy or EV, single-agent chemotherapy with paclitaxel, docetaxel, or vinflunine (I, B), or combination regimens of paclitaxel plus gemcitabine, paclitaxel plus carboplatin should be considered (II, B).

Further treatment lines

In patients with good performance status, in whom available therapeutic options, including novel drugs (immunotherapy, EV, possibly erdafitinib) and platinum-based chemotherapy in combination with gemcitabine have been exhausted, there is a possibility of

using chemotherapy based on paclitaxel, docetaxel, or vinflunine. In a phase III study, vinflunine used in the second-line treatment after platinum-based chemotherapy failure resulted in objective responses in 8.6% of patients and disease control in 41.1% of patients compared to only 24.8% of patients achieving disease stabilization (without objective responses) in the BSC group [73]. The final analysis of the study results, including only patients who met the protocol criteria, showed that the use of vinflunine was associated with a significant reduction in the relative risk of death by 22% (HR = 0.78; 95% CI 0.61–0.96), with median OS of 6.9 months (vinflunine) and 4.3 months (symptomatic treatment). Taxanes and vinflunine have been used in recent years as comparators in studies assessing the efficacy of pembrolizumab, EV, and erdafitinib in second and third-line systemic treatment. The use of vinflunine or taxanes resulted in objective responses in the second-line setting in about 11% of patients (KEYNOTE-045, THOR) and in the third-line setting in 18% of patients (EV301), with a median OS of about 7.5 months (KN-045, THOR) and 9 months (EV301).

Sacituzumab govitecan

The phase II TROPHY-U-01 study evaluated sacituzumab govitecan (SG), a conjugate of antibody (anti-TROP2) and cytotoxic drug (topoisomerase-1 inhibitor), which was used in 113 patients with metastatic urothelial cancer after failure of prior platinum-based chemotherapy and immunotherapy with ICIs. SG was associated with objective responses in 27% of patients and disease stabilization in 34%. Disease control of fewer than 6 months was achieved in 37% of patients. The median PFS was 5.4 months, and the median OS was 10.9 months.

Recommendations

- In patients who have failed first-line chemotherapy and second-line immunotherapy, EV should be used (I, A); in patients with *FGFR3* gene rearrangement, erdafitinib should be used (I, A).
- In patients with *FGFR3* gene rearrangement, after failure of platinum-based chemotherapy, immunotherapy, EV, or erdafitinib should be used in the subsequent treatment lines (II, B).
- In patients in good performance status who failed previous treatment lines of platinum-based chemotherapy and targeted therapies (immunotherapy, EV, and possibly erdafitinib), the use of sacituzumab govitecan may be considered (II, B).
- In patients in good performance status, after the failure of previous treatment lines of platinum-based chemotherapy and targeted therapies (immunotherapy, EV, sacituzumab govitecan, and possibly erdafitinib), monotherapy with paclitaxel, docetaxel, or vinflunine may be considered (II, B).

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