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Review

Therapeutic strategies for organ-confined and non-organ-confined bladder cancer after radical cystectomy

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Abstract

Introduction: In patients with muscle invasive or Bacillus Calmette-Guérin refractory urothelial carcinoma of the urinary bladder (UCUB) radical cystectomy represents the standard of care. However, a proportion of patients experience disease progression, local recurrence and/or metastatic disease.

Areas covered: This review provides an overview of available therapeutic strategies after radical cystectomy and examines ongoing clinical trials including cytotoxic chemotherapy and immunotherapy.

Expert commentary: Cytotoxic chemotherapy offers limited benefit in UCUB patients. However, the recent introduction of immunotherapy provides new hope for durable responses or possibly complete cures.

Keywords: Bladder cancer, Radical cystectomy; Immunotherapy; Urothelial Carcinoma; Cisplatin-based chemotherapy; Adjuvant chemotherapy, Neoadjuvant chemotherapy
1. Introduction

Urothelial carcinoma of the urinary bladder (UCUB) is the most common form of urothelial carcinoma and the most common bladder cancer (BC) histotype [1]. In patients with muscle invasive urothelial carcinoma of the urinary bladder (MI-UCUB) the main treatment option is radical cystectomy (RC) [2]. Neoadjuvant chemotherapy (NAC) represents the standard of care in patients with MI-UCUB and its use is supported by European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines in patients with T2a-T4a cN0M0 UCUB [2–4].

Adjuvant chemotherapy (AC) represents an alternative to neoadjuvant therapy. It is less frequently used. Despite the availability and potential use of NAC or AC, a proportion of patients with surgically treated UCUB will experience locally recurrence or distant metastases after RC [5]. In consequence, either induction or salvage systemic therapy may be needed with the goal of providing long term complete responses [2–4]. To date this objective has not been met with the standard systemic chemotherapy [6].

However, recently the introduction of novel immunotherapeutic agents, either as second or first line treatment marked a significant change in the treatment landscape for patients with locally advanced UCUB, or in those who progressed or are unfit for platinum-based chemotherapy [7].

The aim of this review is to summarize current literature on promising immunotherapeutic agents and to provide a brief outline of current standards of care in patients with localized, locally advanced or metastatic UCUB after RC.
2. Literature review

2.1 Therapeutic strategies in locally advanced bladder cancer after radical cystectomy

2.1.1 Adjuvant chemotherapy

The rationale for AC after RC in pT3-4 N1-3 M0 patients is based on poor outcomes with local treatment alone. Indeed, the 5-year overall survival rate decreases from 78% in organ-confined, node-negative UCUB to 45%, when lymph nodes are involved [8]. Prognosis is poorer (25%, 5-year survival) in patients with extra-vesical and concurrently node-positive UCUB [8]. In this context, significant efforts were made to improve the prognosis in those patients. One of the strategies consists of AC after RC. A recent meta-analysis in addition to demonstrate survival benefit of AC over observation, also suggest gemcitabine with cisplatin as the preferred combination treatment [9]. The use of first line RC provides reliable pathological staging and confirm extra-vesical and/or node positive UCUB. Accurate pathological staging at RC reduces the rate of clinical over-staging and helps avoiding chemotherapy after RC in those with organ confined UCUB. Moreover, the sequence of AC after RC might avoid exposure to multiple NAC cycles in the setting of potentially chemotherapy-refractory UCUB. In such individuals, the pivotal effect of RC might be better exploited, when chemotherapy is given as AC instead of NAC. Last but not least, renal function recovery after RC may represent another argument favoring AC in patients unfit for platinum based NAC. Here, initial renal insufficiency may be relieved with urinary diversion and may allow AC use [10,11]. These arguments represent the most common reasons against systematic use of NAC in all non-metastatic MI-UCUB patients [11,12]. However, the main drawback of AC, consists of the fact that up to 30% of AC candidates may suffer of post-operative complications that render them non-eligible for such approach [13].
AC efficacy was examined in several randomized clinical trials (RCTs). Unfortunately, most such trials failed to demonstrate clear survival benefit of AC vs. no AC, due to poor recruitment: 50% or even lower enrolment was recorded in several studies [14–16]. The latter observation undermined the power such RCTs. The largest and most recent phase III trial (EORTC 30994) recruited from April 2002 to August 2008. Overall, 284 pT3-4 pN1-3 M0 UCUB patients were randomly assigned to AC vs. differed chemotherapy at relapse and no significant overall survival (OS) improvement was shown. However, a significantly longer progression free survival (PFS) was recorded in the AC arm [16].

This RCT, similarly to the three other recent RCTs, was limited in power [14–17]. In consequence, it is possible that some patient subgroups might still benefit from AC [16]. Indeed, a meta-analysis of AC trials showed a 23% relative decrease in the risk of death with AC [18]. Based on lower evidence level for AC relative to NAC (level 1a), AC is guideline recommended only in those patients with high-risk disease, who are unfit for NAC prior to RC (grade of recommendation C) [2,18]. Principles of systematic therapies according to NCCN guidelines are resumed in table 1.

Despite the guideline recommendations for AC, Schiffmann et al. showed an overall NAC rate of 6.4%. An increase occurred in more contemporary years [19]. A similar analysis of AC rates after RC for UCUB showed rates ranging from 21.4 to 29.9% [20]. Taken together, these results indicate suboptimal use of NAC prior to RC for UCUB; based on systematic NAC guideline recommendation.

Most recently, Seisen et al. relied on National Cancer Data Base to test the OS benefit from AC in pT3-4 N0-3 UCUB patients treated with RC, who previously received NAC. An OS benefit was documented, when both chemotherapy types were combined. These data
suggest a potential survival benefit from combinatorial use of AC and NAC and this topic warrant further study [21].

2.1.2 Adjuvant radiotherapy

Some evidence suggest that radiotherapy may have a role in patients with locally advanced UCUB [3,22,23]. The rationale for adjuvant radiotherapy in these patients stands from high rates of loco-regional treatment failure after RC and low efficacy of AC after RC [2,23]. Bayoumi et al. relied on a small cohort (N=170) of T3-4 N0-1 M0 BC patients to test the efficacy of adjuvant radiotherapy after RC on OS and disease free survival (DFS). Their results showed improved 5-year DFS after adjuvant radiotherapy. However, no OS benefit was recorded [24]. A historical, randomized trial also showed a DFS benefit for adjuvant radiotherapy after RC vs. RC alone [25]. Furthermore, a more recent randomized controlled trial enrolled 198 patients with locally advanced BC and at least one high risk feature (≥pT3b stage, grade 3 or positive nodes) that were randomized to either postoperative radiotherapy, chemotherapy plus radiotherapy or chemotherapy alone. It showed no significant differences in DFS, distant metastasis-free survival or OS [26]. Despite the discouraging OS results within the above studies, new selection strategies and inclusion criteria were proposed for future RCTs [23]. Specifically, the Bladder Cancer Adjuvant Radiotherapy Trial (BART) a phase III trial that will randomize pT3-4 N1-3 M0 patients to adjuvant radiotherapy vs. RC with or without AC. The study is currently recruiting. The estimated completion date is March 2023 [27].

2.1.3 Adjuvant immunotherapy

Systemic immunotherapy focuses on immune system activation instead of direct cancer destruction. Over the past decades, milestone advances in the treatment of metastastic
cancers have been made with the use of immunotherapy [28]. There is a long tradition of non-specific immune stimulation with intra-vesical Bacillus Calmette-Guerin (BCG) in patients with non-metastatic UCUB, which was pioneered by Morales et al. and is in use since 30 years [29].

The novel approach of systemic immunotherapy for recurrent, locally advanced and metastatic UCUB rests on specific immune cascade activation, aimed at restoring the natural antitumor immunity that is mediated by T-cells [30]. Several other pathways that focus on macrophages, natural killer cells and B-cells are also being explored [30,31].

The vast majority of systemic immunotherapy approaches that have been examined in phase II or III trials focuses on checkpoint blockade [30,32,33]. The latter deactivates the cancer cell-mediated immunosuppression. Specifically, immune checkpoints are signals that regulate most immune responses. Immune response evasion occurs when tumor cells express cell surface ligands to immune checkpoints. Their binding with T-cells receptors results in downregulation of the immune response. New immune therapeutic agents reduce the interaction between T-cell receptors and cancer ligands and restore host’s immune anticancer response [30].

Currently three phase III studies are testing the effect of checkpoint inhibitors in the setting of adjuvant immunotherapy. Specifically, IMvigor010 is a phase III trial designed to evaluate the efficacy and safety of atezolizumab adjuvant treatment compared with observation. Patients are randomized 1:1 between atezolizumab vs. observation after cystectomy or nephroureterectomy. Primary endpoint of the trial is DFS. Secondary endpoints include overall, disease-specific and distant metastasis-free survival [34]. Similarly, CheckMate 274 is a phase III randomized trial that investigates the use of adjuvant nivolumab vs. placebo in
patients with high-risk invasive urothelial carcinoma. Primary endpoint is DFS. Secondary endpoints are non-urothelial tract recurrence-free survival, disease specific survival and OS [35]. Finally, NCT03244384 is a randomized clinical trial (RCT) that will test the effect of pembrolizumab vs. observation in patients with muscle invasive or locally advanced urothelial carcinoma who received surgery. The primary outcome will be DFS and OS [36] (Table 2).

2.2 Therapeutic strategies in metastatic bladder cancer

2.2.1 Local recurrence and progression to metastatic disease and criteria for platinum eligibility

Approximately half of RC patients relapse. Local recurrences account for about 10 to 30% of all relapses. Distant metastases account for the remaining 70-90% [3]. Rink et al. relied on a large (1545 patients who experienced recurrence after RC) multi-institutional (16 international centers) database to investigate the natural history following disease recurrence after RC and to identify prognostic factors that influence cancer-specific survival [37]. Median time from RC to UCUB recurrence was 10 months. In patients who experienced UCUB recurrence, median time to death was also 10 months. Predictors of UCUB mortality after recurrence were higher tumor stages, lymph node metastases, positive surgical margins, female gender, more advanced age and short time interval between RC and recurrence [37].

For either local or distant recurrence, systemic chemotherapy represents the standard of care. Standard of care chemotherapy regimens consist of 1). Methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), 2). high-dose intensity methotrexate, vinblastine, doxorubicin and cisplatin (HD-MVAC) with granulocyte colony-stimulating factor (G-CSF)
support or 3). gemcitabine with cisplatin (GC) [2,3]. Not all relapsed patients represent candidates for systemic cisplatin-based chemotherapy, using eligibility criteria that include comorbidities, performance status and renal function [38] (Box 1).

Bamias et al. recently examined a large multi-institutional database of advanced or metastatic urinary tract cancer patients, whose eligibility criteria for cisplatin-based chemotherapy were reported. Of those, 46% of patients with available data on platinum eligibility status (N=929) had at least one ineligibility criterion [39]. This observation explains at least partially the suboptimal rates of NAC and AC respectively either to or after RC [19,20,39].

In cisplatin ineligible patients, carboplatin-based chemotherapy represent an option. However, non-cisplatin chemotherapy single agent or combination regimens should not be considered in cisplatin eligible patients [2,40].

**2.2.2 First-line systemic chemotherapy**

GC, MVAC and HD-MVAC represent the first line systemic chemotherapy regimens for UCUB [2]. Despite their potential efficacy, survival remains poor in patients with urothelial cancer treated with traditional MVAC or GC dose and schedule [1,2,41]. Results from a phase III RCT that compared GC to MVAC showed no significant differences in median OS, that was of respectively of 14.0 vs. 15.2 months (p=0.66). Similarly, no differences were shown in PFS that was of 7.7 vs. 8.3 months (p=0.63) for GC vs. MVAC, respectively [42].

However, differences in cancer control rates were recorded when HD-MVAC was compared to standard MVAC in a phase III RCT (EORTC30924). On the classic MVAC schedule, doses were delivered in 4 weeks cycles, instead in HD-MVAC cycles lasted 14 days. Over a period of 8 weeks patients on classic MVAC received two cycles, while patients on
the HD-MVAC received four cycles. HD-MVAC patients received also G-CSF [43]. At seven years follow-up of this RCT the median OS was respectively 14.9 vs. 15.1 months in MVAC vs. HD-MVAC (HR:0.76, 95% CI:0.58-0.99, p=0.042). Similarly, in intention to treat analysis PFS also favored HD-MVAC vs. MVAC (9.5 vs. 8.1 months, HR=0.73, 95% CI:0.56-0.95, p=0.017)[44]. Moreover, HD-MVAC was associated with lower toxicity [43]. In consequence, HD-MVAC with G-CSF is considered the standard of care in patients platinum eligible and should be preferred to standard MVAC [3].

Cisplatin-unfit patients were studied in a single phase II/III trial (EORTC30986) that investigated two different chemotherapy regimens, gemcitabine with carboplatin vs. methotrexate and vinblastine with carboplatin (M-CAVI). The median OS was 9.3 vs. 8.1 months in respectively gemcitabine plus carboplatin vs. M-CAVI treated patients (p=0.64). There was also no differences in PFS between the two arms. The PFS was 5.8 vs. 4.2 months in gemcitabine plus carboplatin vs. M-CAVI treated patients (p=0.78)[45]. However, severe acute toxicity was observed in 9.3% of patients receiving gemcitabine with carboplatin and in 21.2% of patients receiving M-CAVI. In consequence, gemcitabine with carboplatin is considered the standard of care in cisplatin-ineligible patients.

2.2.3 Second-line systemic chemotherapy in patients with first-line cisplatin failure

In patients with first-line cisplatin failure, options consist of single or multi-agent regimens other than GC or MVAC (Table 1). Such regimens includes taxanes, gemcitabine, pemetrexed and vinflunine [46]. Vinflunine, a third generation vinca alkaloid showed promising objective response rates (ORR) of 18% in a phase II trial [47]. In a phase III RCT 370 patients were randomly assigned to vinflunine or best supportive care (BSC). In intention to treat analysis, the median OS was 6.9 vs. 4.6 months favor of vinflunine. The
resulting 2 months survival advantage was not statistically significant. However, in the per protocol analysis OS (p=0.04), PFS (p=0.001), disease control (p=0.002) and response rate (p=0.006) were statistical significantly higher in vinflunine treated patients [48]. Based on these data, vinflunine is approved as a second line agent in patients previously treated with cisplatin in Europe, but not in the United States [2,48].

According to NCCN several second line options are recommended in the United States. These include immunotherapy as well as chemotherapy (Table 1). Several trials tested the efficacy of different combination regimens [46]. These options consist of paclitaxel with gemcitabine or paclitaxel with carboplatin. Taxane based combinations yielded response rates of 30 to 70% in single armed phase II trials [46]. Besides taxane based combination therapy, another proposed strategy is to use cisplatin-based second line therapy in patients who previously responded to first line cisplatin-based combination therapy and thus are considered platinum sensitive [46]. Han et al. in a small retrospective analysis investigated the safety and efficacy of MVAC combination as second line regimen for patients who failed first line GC chemotherapy. Overall response of 30% and a median OS of 10.9 months were reported [49].

2.2.4 Post-chemotherapy surgery and treatment of bone metastases

The role of surgery in patients with relapsed or metastatic UCUB after chemotherapy is still unclear. Nonetheless, some investigators suggested long-term disease free survival after surgical treatment either of metastatic sites or of the primary. However, this evidence mostly originates from small, retrospective, uncontrolled institutional studies. Seisen et al. relied on NCDB (1998-2012) to investigate the effect of high intensity local treatment (multi-agent chemotherapy plus RC and/or targeted radiation therapy with ≥50 Gy) vs.
conservative treatment (multi-agent chemotherapy plus transurethral resection of bladder
tumor and/or targeted radiation therapy with <50 Gy) on OS in patients with metastatic
UCUB. Authors showed significantly longer median OS after high intensity local treatment
vs. conservative treatment (median OS respectively, 14.92 vs. 9.95 months) [50].
Furthermore, Patel et al. performed a meta-analysis of 17 studies investigating the role of
metastasectomy in urothelial carcinoma. An OS advantage after metastasectomy vs. non-
surgical treatment was showed (HR: 0.63, 95%CI:0.49-081). However, most of the included
studies were retrospective with high risk of selection biases [51]. Faltas et al. relied on SEER-
Medicare database (N=497) to study OS and complications rates after metastasectomy in
patients with metastatic urothelial cancer. These investigators showed a median OS after
first metastasectomy of 19 months. However, these results were undermined by a 10% rate
of thirty-day mortality [52].
Other multimodality approaches for locally relapsed, locally advanced or metastatic UCUB
include radiotherapy or chemo-radiotherapy, as recommended within the NCCN guidelines.
Specifically, when palliative radiotherapy is administered in metastatic bladder cancer or for
recurrent pelvic tumor, it should be combined with radio-sensitizing chemotherapy (Box 2).
Finally, bone targeted agents should be considered in all patients with metastases to bone
[3].

2.2.5 Emerging role of the immunotherapy
As previously discussed, immune system activity regulation plays a key role in cancer
biology. Nowadays, three principal pathways are acknowledged and exploited to restore the
natural anti-tumor activity of the immune system [32]. The first pathway is the PD-1/PD-
L1/2 axis. PD-1 receptor is expressed on the surface of activated T cells and maintains
peripheral immune tolerance when activated by ligands [32,53]. PD-L1/2 are two ligands expressed in various normal peripheral tissues and may be also expressed in tumor cells. In UCUB there is an overexpression of either the PD-1 and/or its ligands. This results in a suppression of the immune response to UCUB [32,53]. Monoclonal antibodies were developed to prevent the binding of PD-L1/2 ligands to PD-1 receptor. Similarly to PD-1, the cytotoxic T-lymphocyte antigen 4 (CTLA-4) is expressed on the surface of T-cells and has a negative regulatory role on the immune response [30]. Available immune agents for the treatment of relapsed or metastatic UCUB predominantly rely on one or both receptor inhibition (Tables 2-3-4). A third less well described pathway mediating immune response suppression is based on indoleamine-2,3-dioxygenase (IDO1). Here, IDO1 contributes to immunosuppression by converting tryptophan to kynurenines. IDO1 blockade increases level of tryptophan levels and anti-tumor activity [32].

2.2.5.1 PD-L1 inhibitors

Atezolizumab

Atezolizumab was first Food and Drug Administration (FDA) approved in May 2016 for the treatment of patients affected by urothelial carcinoma, based on the results of the phase II clinical trial IMvigor 210 [32,54]. IMvigor 210 (NCT02108652) was a multicenter, single-arm, two cohort trial. Between May and November 2014, 315 patients were enrolled into the study. Of these, 310 received atezolizumab. PD-L1 expression status on infiltrating immune cells (ICs) in the tumor microenviroment was defined according to the percentage of PD-L1 immune cells as IC0 (<1%), IC1 (between 1 and 5%) and IC2/3 (≥5%). Objective response rates were 27, 18 and 15% in respectively IC2/3 group, IC1/2/3 group and overall in all 310 patients [55]. However, IMvigor211, a phase III study comparing atezolizumab vs.
chemotherapy (vinflunine, paclitaxel, docetaxel) in 911 patients with previously treated metastatic urothelial cancer, who progressed during or after platinum-based regimens failed to prove and overall survival benefit of atezolizumab [32,56,57]. The efficacy of atezolizumab was also investigated in first-line setting in cisplatin-ineligible patients. In IMvigor210 (NCT02108652) 123 patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin treatment were recruited. At 17.2 months, the objective response rate was 23%, while the complete response rate was 9%. Median overall survival was 15.9 months [58]. Atezolizumab is NCCN guidelines recommended as first line treatment in patients with locally advanced or metastatic UCUB in cisplatin ineligible patients as well as second line therapy in patients who progressed after standard chemotherapy [3].

**Durvalumab**

Durvalumab is an FDA approved PD-L1 inhibitor recommended as second line treatment in NCCN guidelines [3]. Durvalumab safety and efficacy was first explored in a phase I/II multicenter, open-label study. Durvalumab was administrated to a total of 61 patients. Of all, 40 patients were PD-L1+. All patients harbor either inoperable or metastatic UCUB. The overall objective response rate was 31.0% in 42 response-evaluable patients, 46.4% in the PD-L1+ patients and 0% in the PD-L1- patients [59]. An update of the trial on 191 patients showed an objective response rate of 17.8%, regardless of PD-L1 status. Median PFS and OS were respectively 1.5 and 18.2 months [60]. An ongoing randomized, open-label, multicenter, global phase III trial, (DANUBE; NCT02516241) will evaluate durvalumab with or without tremelimumab vs. standard of care chemotherapy (cisplatin + gemcitabine or
carboplatin + gemcitabine) in patients with treatment-naïve, unresectable and/or metastatic UCUB [61].

*Avelumab*

Avelumab is FDA approved and NCCN guidelines recommended second line treatment [3]. In a phase Ib, multicenter, expansion cohort, avelumab was administered to patients with urothelial carcinoma that progressed after platinum-based chemotherapy regardless of PD-L1 expression. Forty-four patients were treated. At the data cut-off, the confirmed ORR by independent central review was 18.2% [62].

2.2.5.2 PD-1 inhibitors

*Nivolumab*

Nivolumab is FDA approved and NCCN guideline recommended for the second line treatment of patients who progress after platinum-based chemotherapy. Safety and efficacy of nivolumab was first time evaluated in the phase I/II trial CheckMate 032 (NCT01928394). Overall, 78 patients received nivolumab in monotherapy with an objective response rate of 24.4% and a median overall survival of 9.7 months [63]. In the larger CheckMate 275 (NCT02387996) 270 patients received nivolumab and 265 were evaluated for activity. Confirmed objective response was achieved in 28.4% of patients with PD-L1 expression of 5% or more, in 23.8% in those with PD-L1 expression of 1% or more and 16.1% in patients with PD-L1 expression lower than 1% [64].

*Pembrolizumab*

Pembrolizumab is FDA approved and NCCN guideline recommended in first line treatment of patients with locally advanced or metastatic UCUB cisplatin-ineligible and as second line
treatment in patients with progression after first line [3]. The safety and activity of pembrolizumab was first evaluated in KEYNOTE-012 (NCT01848834), a phase Ib basket trial. Overall, 115 patients were screened. Of 61 who resulted PD-L1+, 33 were enrolled in the trial. Full trial analysis was based on data from 27 patients. The ORR was of 26% [65].

In the pivotal phase III randomized clinical trial KEYNOTE-045, 542 patients with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy were randomly assigned to pembrolizumab or chemotherapy (paclitaxel, docetaxel or vinflunine). The median OS was 10.3 months in the pembrolizumab group vs. 7.4 months in the chemotherapy group (p=0.002). The median overall survival in patients with PD-L1 expression over 10% was respectively of 8.0 vs. 5.2 months in the pembrolizumab vs. chemotherapy group [66].

Pembrolizumab was also evaluated as first-line therapy in patients cisplatin-ineligible. KEYNOTE-052 was a phase II, open-label trial that enrolled 370 patients, ORR was 27% and 6% of patients achieved a complete response. PFS and OS at 6 months were respectively 31 and 67% [67].

2.2.5.3 CTLA-4 inhibitors

Ipilimumab

Ipilimumab is an anti-CTLA-4 monoclonal antibody. Ipilimumab alone or in combination is not recommended according NCCN guideline in patients with UCUB [3]. Nonetheless, efficacy and safety of ipilimumab in association with nivolumab was investigated in metastatic urothelial cancer within the phase I/II open-label CheckMate-032 (NCT01928394) study. Pretreated patients with locally advanced or metastatic urothelial carcinoma were
treated with nivolumab 3mg/kg (N=78) or nivolumab 1mg/kg + ipilimumab 3mg/kg (N=26) or with nivolumab 3mg/kg + ipilimumab 1mg/kg (N=104) followed by nivolumab 3mg/kg. [63] Results showed ORR of 38.5% and complete response rate of 3.8% for the 26 patients receiving high dose ipilimumab in association with nivolumab. Conversely, lower confirmed objective response rates were observed in the low dose ipilimumab arm. Median OS was 10.2 vs. 7.3 months in respectively high and low dose ipilimumab group [32,68]. These results encourage to the exploration of new combinations of immunotherapy agents that may led better results than monotherapy [68].

### 2.2.5.4 IDO-1 inhibitors

**Epacadostat**

Epacadostat is an IDO-1 inhibitor that suppress tryptophan conversion to kynurenines [32]. Epacadostat with pembrolizumab were tested in phase I/II open label study ECHO-202/KEYNOTE-037 (NCT02178722). In 40 patients with advanced urothelial carcinoma, previously exposed to platinum therapy (adjuvant or advanced disease setting) or alternative therapy, when platinum therapy was not appropriate. The ORR was 35.0% [69]. However, this combination therapy is not yet recommended [3].

### 2.2.5.5 Main adverse events

The use of immunotherapy is associated with different category of adverse events, relative to systemic chemotherapy. Their presence may require the treatment discontinuation and/or the use of immunosuppressive treatments [33].

Most frequent immune related adverse events are transient and consist of skin manifestation (such as pruritis and/or rash) as well as fatigue. Immune related adverse
events that affect gastrointestinal system consist of colitis, hepatitis and increase of alanine aminotransferase and aspartate aminotransferase [33]. Other immune related adverse events are endocrine adverse events such as hypophysitis [70], as well as hypothyroidism secondary to thyroiditis [71].

CTLA-4 inhibitors are typically associated with the highest incidence of immune related adverse events [33,70,72]. Usually cutaneous toxicity appear 2-3 weeks after treatment initiation. Colitis and hepatitis typically emerge after respectively 5-10 and 12-16 weeks after treatment start. Endocrine adverse events are the latest to be manifested (8-14 weeks). PD1 and PD-L1 inhibitor associate toxicity are less frequent and show less specific temporal distribution [33]. Prevention, monitoring and management of immune adverse events require close patients follow-up. Management of grade 3-4 adverse events may require use of corticosteroids in high dose [72].

3. Conclusion

MI-UCUB represent a lethal disease with poor survival and high recurrence rates, especially in high risk patients. Conventional systemic and local treatment in adjuvant setting showed poor OS results. Moreover, systemic treatments that relied on platinum based combinations failed to provide sustained responses and were only applicable in a proportion of patients. Alternative chemotherapy regimens provided even lower efficacy. The advent of new immunotherapeutic agents offers a new hope for patients with locally advanced or metastatic UCUB, with possibility of durable and complete responses.

4. Expert commentary and five-years view

Over the past several decades and in years to come RC will play a pivotal role in the management of patients with non-metastatic UCUB and for many years to come it would
likely represent the gold-standard treatment modality for patients with non-metastatic bladder cancer. Several modifications that relate to the procedure itself, as well as to additional therapeutic strategies, have been proposed with the intent of improving his efficacy, surgical modifications focused on more extensive lymphadenectomy as an aid to better stage RC patients [73–75]. Moreover, surgical modifications consist of minimally-invasive approaches aimed at decreasing the morbidity associated with RC in properly selected surgical candidates [73–75]. Adjunct systemic strategies that consist of either NAC or AC are recommended by guidelines with the intent of improving survival of RC patients [2–4]. The adherence to these recommendations remains suboptimal and clinicians should be continuously encouraged to improve the rates of adherence, both in North America and Europe.

Several types of cytotoxic systemic therapy are available for use in patients who progress to metastatic stage after RC, as well as in those diagnosed with the novel metastatic disease [2–4]. The efficacy of those approaches provided responses in a relative small proportion of patients. Moreover, use of cytotoxic chemotherapy is associated with significant morbidity and potential mortality. Based on the unmet need for better efficacy and lower morbidity a number of immune-oncology approaches have been examined in patients with unresectable or metastatic UCUB [32].

In the next five-years, the results of ongoing phase III clinical trials examining various immunotherapies will become available. Specifically, three randomized phase III trials are testing the efficacy of different immunotherapeutic agents vs. chemotherapy standard of care in first line: IMvigor-130 [76], KEYNOTE-361 [77], DANUBE [61] in the first line treatment. Moreover, three phase III randomized clinical trials are testing the efficacy of
different immunotherapeutic agents on second line: IMvigor 211 [78], NCT02928406 [79], and KEYNOTE-045. Furthermore, one phase III clinical trials (JAVELINE Bladder 100, NCT02603432) is testing the use of avelumab in patients with locally advance or metastatic urothelial cancer in responders to first line chemotherapy without evidence of progression [80]. Finally, three clinical trials are testing the efficacy of nivolumab (CheckMate-274) [81], atezolizumab (IMvigor 010) [82] and pembrolizumab (NCT03244384) [36] as adjuvant treatment after RC.

These observations indicate a transition from systemic chemotherapy to immunotherapy in patients with locally advanced or metastatic UCUB. The intent of such approach is to provide the highest possible rates of durable and/or complete responses. Current data are highly promising and like in other primaries have shown substantially better cancer control outcomes than those recorded with the most effective chemotherapeutic regimens. Importantly, improvement in cancer control are not undermined by low tolerability. Indeed few if any patients are considered immunotherapy-ineligible, unlike the elevated proportion of those who cannot receive systemic chemotherapy for ineligibility considerations.

**Key issues**

- MI-UCUB represent a lethal disease with poor survival and high recurrence rates, especially in high risk patients.
- Systemic treatments that relied on platinum-based combinations failed to provide sustained responses and were only applicable in a proportion of patients.
- Alternative chemotherapy regimens to standard cisplatin-based chemotherapy regimens provided even lower efficacy.
• The advent of new immunotherapeutic agents offers a new hope for patients with locally advanced or metastatic UCUB, with possibility of durable and complete responses.

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References

Reference annotations

* Of interest
** Of considerable interest


*Authors performed a meta-analyses of RCTs that provides evidence of an overall survival and disease-free survival benefit in patients who receive adjuvant cisplatin-based chemotherapy after radical cystectomy.


Long term results from a pivotal randomized trial on the use of high-dose intensity MVAC and G-CSF vs. standard M-VAC in advanced urothelial tract tumors.


**Results from the phase 2 trial that tested the effect of atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy.**


**Results from a randomized phase III trials that tested the effect of pembrolizumab vs. standard of care chemotherapy in patients with advanced urothelial carcinoma that progresses after platinum-based chemotherapy. The trial showed an improved overall survival after pembrolizumab.**

*Authors report the first pathologically proven cases of hypophysitis secondary to CTLA-4 blockade and provide mechanistic insights into the pathogenesis of a rare condition that may become more common with the use of new immunotherapeutic agents.*


<table>
<thead>
<tr>
<th>Box 1 – Definition of cisplatin-based chemotherapy ineligibility for patients with metastatic urothelial carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO</strong> or <strong>ECOG</strong> performance status of 2, or Karnofsky performance status of 60-70%</td>
</tr>
<tr>
<td>Creatinine clearance less than 60 mL/min</td>
</tr>
<tr>
<td>CTCAE version 4, grade 2 or above audiometric hearing loss</td>
</tr>
<tr>
<td>CTCAE version 4, grade 2 or above peripheral neuropathy</td>
</tr>
<tr>
<td>NYHA class III heart failure</td>
</tr>
<tr>
<td><strong>Abbreviations:</strong> <strong>WHO:</strong> World Health Organization; <strong>ECOG:</strong> Eastern Cooperative Oncology Group; <strong>CTCAE:</strong> Common Terminology Criteria for Adverse Events; <strong>NYHA:</strong> New York Heart Association</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Box 2 - Radiosensitizing chemotherapy given with conventionally fractionated radiation for palliation of metastases or for pelvic recurrence after cystectomy according to NCCN guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>Taxane (docetaxel or paclitaxel)</td>
</tr>
<tr>
<td>5-fluorouracile</td>
</tr>
<tr>
<td>5-fluorouracile and mytomycin</td>
</tr>
<tr>
<td>Capecitabine</td>
</tr>
<tr>
<td>Low dose gemcitabine</td>
</tr>
<tr>
<td>Regimen type</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td><strong>Perioperative chemotherapy (adjuvant or neoadjuvant)</strong></td>
</tr>
</tbody>
</table>
| **Standard** | HD-MVAC with growth factor support for 3 or 4 cycles  
Gemcitabine and cisplatin for 4 cycles  
CMV for 3 cycles |
| **Alternate regimens** | In patients unfit for cisplatin there are no data supporting other perioperative regimen |
| **First line chemotherapy for locally advanced or metastatic disease** | |
| **Standard regimen in cisplatin eligible** | Gemcitabine and cisplatin  
HD-MVAC with growth factor support |
| **Standard regimen in cisplatin ineligible** | Gemcitabine and carboplatin  
Atezolizumab  
Pembrolizumab |
| **Alternate regimens** | Gemcitabine  
Gemcitabine and paclitaxel  
Ifosfamide, doxorubicin and gemcitabine (patients with good kidney function and performance status) |
| **Subsequent chemotherapy for locally advanced or metastatic disease (participations in clinical trials of new agents is recommended)** | |
| **Standard regimens** | Pembrolizumab  
Atezolizumab  
Nivolumab  
Durvalumab  
Avelumab  
Paclitaxel or docetaxel  
Gemcitabine  
Pemetrexed |
| **Alternate regimens** | Nab-paclitaxel  
Ifosfamide  
Methotrexate  
Ifosfamide, doxorubicin and gemcitabine  
Gemcitabine and paclitaxel  
HD-MVAC |

*OS*: Overall survival; *DFS*: Disease free survival; *DSS*: Disease specific survival; *PGC*: paclitaxel, cisplatin and gemcitabine; *GC*: gemcitabine and cisplatin; *MVAC*: methotrexate, vinblastine, doxorubicin and cisplatin; *HD-MVAC*: high dose intensity MVAC; *CMV*: cisplatin, methotrexate and vinblastine
<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Immunotherapy drug</th>
<th>Trial name</th>
<th>Arms</th>
<th>Inclusion criteria</th>
<th>Primary endpoints</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First</strong></td>
<td>Atezolizumab</td>
<td>IMvigor-130 (NCT02807636)</td>
<td>Atezolizumab+Gemcitabine+Carboplatin/Cisplatin vs. Placebo+Gemcitabine+Carboplatin/Cisplatin vs. Atezolizumab Monotherapy</td>
<td>Patients with untreated locally advanced or mUC platinum-based chemotherapy eligible</td>
<td>PFS OS AEs</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>KEYNOTE-361 (NCT02853305)</td>
<td>Pembrolizumab vs. Pembrolizumab+Chemotherapy vs. Chemotherapy (Cisplatin+gemcitabine or Carboplatin+ gemcitabine)</td>
<td>Patients with advanced/unresectable or metastatic urothelial carcinoma who had no prior systemic chemotherapy (adjuvant/neoadjuvant platinum-based chemotherapy allowed if recurrence &gt;12 months)</td>
<td>PFS OS</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>Durvalumab (MEDI4736) + Tremelimumab</td>
<td>DANUBE (NCT02516241)</td>
<td>MEDI4736 + Tremelimumab vs. MEDI4736 vs. Cisplatin or Carboplatin + Gemcitabine</td>
<td>Patients with histologically or cytologically documented, unresectable, Stage IV transitional cell carcinoma of the urothelium who have not been previously treated with first-line chemotherapy</td>
<td>OS</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td><strong>Second</strong></td>
<td>Atezolizumab</td>
<td>IMvigor 211 (NCT02302807)</td>
<td>Atezolizumab vs Chemotherapy (Vinflunine, Paclitaxel, or Docetaxel)</td>
<td>Locally advanced or mUBC who progressed during or following treatment with platinum-containing regimen</td>
<td>OS</td>
<td>Active/Not recruiting</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>KEYNOTE-045</td>
<td>Pembrolizumab vs. Chemotherapy (Vinflunine, Progression or recurrence of OS</td>
<td>OS</td>
<td>Active/Not recruiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>Avelumab</td>
<td>Avelumab plus Best Supportive Care vs. Best Supportive Care alone</td>
<td>Patients with unresectable locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy</td>
<td>PFS</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
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<td>------------------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Nivolumab</td>
<td>Nivolumab vs. Placebo</td>
<td>Patients with invasive urothelial cancer at high risk of recurrence who had radical surgery free of disease</td>
<td>DFS</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atezolizumab</td>
<td>Atezolizumab vs. Observation</td>
<td>Patients with invasive urothelial cancer at high risk of recurrence who had radical surgery free of disease</td>
<td>DFS</td>
<td>Recruiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Pembrolizumab vs. Observation</td>
<td>Patients with muscle-invasive urothelial cancer at high risk of recurrence who had radical surgery free of disease</td>
<td>DFS</td>
<td>Recruiting</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** OS: Overall survival, PFS: Progression free survival, DFS: Disease free survival, AEs: Adverse events
### Table 3 - FDA approved immunotherapies as first line treatment in patients with metastatic urothelial bladder cancer not fit for cisplatin

<table>
<thead>
<tr>
<th>Target</th>
<th>Immunotherapy drug</th>
<th>Trial name</th>
<th>Trial phase</th>
<th>Number of patients treated</th>
<th>Objective response rate</th>
<th>Overall survival</th>
<th>Progression free survival</th>
<th>Any grade adverse event (%)</th>
<th>Grade 3-4 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>Atezolizumab (1,200 mg q3wk)</td>
<td>IMvigor 210 (NCT02108652)</td>
<td>II</td>
<td>119</td>
<td>23%</td>
<td>15.9</td>
<td>2.7</td>
<td>66%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (200 mg q3wk)</td>
<td>KEYNOTE – 052 (NCT02335424)</td>
<td>II</td>
<td>370</td>
<td>27%</td>
<td>-</td>
<td>-</td>
<td>62%</td>
<td>16%</td>
</tr>
</tbody>
</table>

### Table 4 - FDA approved immunotherapies as second line treatment in patients with metastatic urothelial bladder cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Immunotherapy drug</th>
<th>Trial name</th>
<th>Trial phase</th>
<th>Number of patients treated</th>
<th>Objective response rate</th>
<th>Overall survival</th>
<th>Progression free survival</th>
<th>Any grade adverse event (%)</th>
<th>Grade 3-4 adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>Atezolizumab (1,200 mg q3wk)</td>
<td>IMvigor 210 (NCT02108652)</td>
<td>II</td>
<td>310</td>
<td>15%</td>
<td>7.9</td>
<td>2.1</td>
<td>69%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (200 mg q3wk)</td>
<td>IMvigor 211 (NCT02302807)</td>
<td>III-randomized</td>
<td>911</td>
<td>23%</td>
<td>11.1 vs. 10.6</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Durvalumab (10 mg/kg q2wk)</td>
<td>NCT01693562</td>
<td>II</td>
<td>191</td>
<td>17.8%</td>
<td>18.2</td>
<td>1.5</td>
<td>-</td>
<td>6.8%</td>
</tr>
<tr>
<td></td>
<td>Avelumab (10 mg/kg q2wk)</td>
<td>JAVELIN (NCT01772004)</td>
<td>I</td>
<td>44</td>
<td>18.2%</td>
<td>13.7</td>
<td>2.9 (11.6 wk)</td>
<td>65.9%</td>
<td>6.8%</td>
</tr>
<tr>
<td>PD-1</td>
<td>Nivolumab (3 mg/kg q2wk)</td>
<td>CheckMate-032 (NCT01928394)</td>
<td>I/II</td>
<td>78</td>
<td>19.0%</td>
<td>9.7</td>
<td>2.8</td>
<td>81.0%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (200 mg/kg q3wk)</td>
<td>KEYNOTE-012 (NCT01848834)</td>
<td>IIB</td>
<td>27</td>
<td>21.1%</td>
<td>13.0</td>
<td>2.0</td>
<td>100%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab (200 mg/kg q3wk)</td>
<td>KEYNOTE-045 (NCT02256436)</td>
<td>III-randomized</td>
<td>542</td>
<td>21.1%</td>
<td>10.3 vs. 7.4</td>
<td>2.1</td>
<td>60.9%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>

*patients evaluated for activity