



Perioperative immunotherapy for muscle-invasive bladder cancer

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Abstract: Radical cystectomy is the standard of care treatment for patients with localized muscle-invasive bladder cancer (MIBC). However, patients with MIBC experience high rates of relapse despite primary therapy, and perioperative strategy is an important treatment option. Cisplatin-based neoadjuvant chemotherapy was associated with improved prognosis, and adjuvant chemotherapy is also an important option for selected patients. However, perioperative chemotherapy is not effective in some patients. Moreover, the currently recommended perioperative treatment is cisplatin-based chemotherapy; approximately 50% of the patients are ineligible for cisplatin treatment owing to various reasons such as medical comorbidities, poor performance status, and renal insufficiency. The recent success of treatment with immune checkpoint inhibitors (ICIs) suggests that ICIs is the new standard therapy for patients with metastatic bladder cancer. Furthermore, ICIs showed more favorable toxicity profiles than conventional cytotoxic chemotherapy. These results indicate that ICIs may play a role in the treatment of muscle-invasive disease, and many recent studies have been conducted in a perioperative setting. The present review aims to summarize and discuss the current perioperative strategy of immunotherapy focused on ICIs based on recent ongoing clinical trials.

Keywords: Bladder cancer; immunotherapy; perioperative systemic treatment

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Introduction

Bladder cancer is the 12th most common malignancy worldwide, with an estimated 200,000 deaths from this disease every year (1). Owing to early micrometastatic dissemination, patients with muscle-invasive bladder cancer (MIBC) and those with upper tract urothelial carcinoma (UC) experience high rates of relapse despite primary therapy. MIBC has a high metastatic potential at diagnosis but is still often curable with aggressive management. According to current treatment guidelines, cisplatin-based neoadjuvant chemotherapy (NAC) is recommended for patients with cT2-4aN0M0 MIBC, and adjuvant cisplatin-based chemotherapy is selectively recommended for patients with locally advanced (pT3/4) and/or lymph node-

positive disease (2,3). Although the currently recommended perioperative treatment is cisplatin-based chemotherapy, approximately 50% of the patients are ineligible for cisplatin treatment owing to various reasons such as poor performance status, medical comorbidity, and renal insufficiency (4). These patient populations represent those patients in whom there is no effective systemic therapy for treating micrometastatic spread.

To date, for various types of cancers, including bladder cancer, several immunotherapeutic agents—which block immune checkpoints—have been investigated and/or clinically used, such as nivolumab and pembrolizumab that block programmed cell death receptor 1 (PD-1); atezolizumab, durvalumab, and avelumab that block PD-

Table 1 Summary of immune checkpoint inhibitors in metastatic UC

Agent	Treatment line	Number	Phase	Primary endpoint	ORR (%)	Median OS (months)	Median PFS (months)	Grade 3–4 TRAE (%)
Atezolizumab (10)	1	119	2	ORR	23	15.9	2.7	16
Pembrolizumab (11)	1	370	2	ORR	24	–	2.0	15
Atezolizumab (12)	2	310	2	ORR	15	7.9	2.1	16
Pembrolizumab (13)	2	542	3	OS, PFS	21	10.3	2.1	15
Nivolumab (14)	2	265	2	ORR	20	8.7	2.0	18
Durvalumab (15)	2	191	1/2	Safety, ORR	18	18.2	1.5	7
Avelumab (16)	2	249	1b	DLT	17	6.5	1.6	8

UC, urothelial carcinoma; ORR, objective response rate; OS, overall survival; PFS, progression free survival; TRAE, treatment related adverse event; DLT, dose limiting toxicity.

ligand-1 (PD-L1); and ipilimumab and tremelimumab that block cytotoxic T lymphocyte-associated protein 4 (CTLA-4). Among these, the immune checkpoint inhibitors (ICIs) of atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab have already been approved for clinical use in bladder cancer by the United States Food and Drug Administration (5). These results suggest that ICIs may have a role in the perioperative setting of MIBC, which has recently led to several clinical trials.

Herein, we briefly review immunotherapy that is currently being implemented in the perioperative setting, focusing on ICIs that have been extensively evaluated for MIBC, and discuss the clinical implications of this treatment.

Data searching process

A literature search for current data on perioperative ICIs was conducted using PubMed and ClinicalTrials.gov databases. We searched data using the following combinations of MeSH terms: “urothelial carcinoma” OR “bladder cancer” and “immunotherapy” OR “atezolizumab” OR “nivolumab” OR “ipilimumab” OR “pembrolizumab” OR “avelumab” OR “durvalumab” OR “tremelimumab” and “neoadjuvant” OR “adjuvant” OR “preoperative” OR “postoperative” OR “perioperative.” Prospective and retrospective studies were included. In addition, as immunotherapy is a rapidly developing field, we examined abstracts from major oncology conferences between 2012 and 2019. Moreover, because many perioperative ICI trials are currently ongoing, these clinical trials were included (Clinicaltrials.gov).

Neoadjuvant immunotherapy

Cisplatin-based NAC followed by surgery is the standard of care for MIBC. A previous study showed that NAC with methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy was associated with longer survival of patients with MIBC and without any residual cancer in surgical specimens (6). In another study, NAC with cisplatin, methotrexate, and vinblastine resulted in a significant survival benefit compared with surgery and/or radiotherapy alone in patients with MIBC (7). Cisplatin-based NAC was associated with a pathologic complete response (pCR) rate of 30–40% and a 5% improvement in overall survival (OS) (3,8). However, NAC is performed for only 10–20% of patients, and approximately 50% of patients are ineligible to receive cisplatin; therefore, as it is difficult to administer NAC to all patients, a new treatment strategy is needed (9).

The recent success of treatment with ICIs for UC suggests that ICI is the new standard therapy for UC, especially metastatic UC (*Table 1*). In an open-label, international, phase 3 trial, pembrolizumab was associated with improved OS and low rates of treatment-related adverse events in patients with platinum-refractory advanced UC (13). In the open-label, multicenter, single-arm, phase 2 IMvigor 210 trial (12), patients treated with atezolizumab showed favorable response rates, survival, and tolerability. In the Checkmate 275 study (14), multicenter, single-arm, phase 2 trial, nivolumab was associated with favorable clinical benefit and manageable toxicity in previously treated patients with locally advanced or metastatic UC. Durvalumab and avelumab also showed similar results (15,16). These studies showed an objective response rate of approximately 20%, and the incidence of

Table 2 Summary of clinical trials of neoadjuvant immunotherapy in MIBC

Trial number	Agent	Phase	Population
Signle agent therapy			
NCT02662309	Atezolizumab	2	cT2-T4 N0 unfit for NAC
NCT02451423	Atezolizumab	2	cTa-T4 N0 unfit for NAC
NCT03577132	Atezolizumab	2	cT2-T4 N0-N1
NCT03498196	Avelumab	1/2	cT2-T4a N0 unfit
NCT03406650	Durvalumab	2	cT2-T4 N0-1
NCT02736266	Pembrolizumab	2	cT2-T4 N0
NCT03212651	Pembrolizumab	2	cT2-T4 N0 unfit for NAC
NCT03319745	Pembrolizumab	2	cT2-T4 N0
ICI combination therapy			
NCT02812420	Durvalumab + Tremelimumab	1	cT2-3a N0
NCT03472274	Durvalumab + Tremelimumab	2	cT2-T4 N0-1
NCT03234153	Durvalumab + Tremelimumab	2	cTa-T4 N0 or N + unfit for NAC
NCT02845323	Nivolumab + Urelumab	2	cTa-T4 N0 unfit for NAC
NCT03387761	Nivolumab + Ipilimumab	1b	cTa-T4 N0 or N +
NCT03520491	Nivolumab + Ipilimumab	2	cT2-4a cN0 unfit for NAC
ICI with chemotherapy			
NCT02989584	Atezolizumab + Gemcitabine + Cisplatin	2	cT2-T4a N0
NCT03674424	Avelumab + Chemotherapy	2	cT2-T4 N +
NCT03732677	Druvalumab + Gemcitabine + Cisplatin	3	cT2-T4a N0
NCT03294304	Nivolumab + Gemcitabine + Cisplatin	2	cT2-T4 N0-N1
NCT03558087	Nivolumab + Gemcitabine + Cisplatin	2	cTa-T4 N0
NCT02690558	Pembrolizumab + Gemcitabine + Cisplatin	2	cT2-T4 N0
NCT02365766	Pembrolizumab + Gemcitabine + Cisplatin	2	cT2-T4 N0
ICI with other agents			
NCT03534492	Durvalumab + Olaparib	2	cT2-T4a N0
NCT03518320	Nivolumab + TAR-200	1	cT2-T3 N0-N1
NCT03832673	Pembrolizumab + Epcadostat	2	cT2-T3 N0

MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; ICI, immune checkpoint inhibitor.

treatment-related grade ≥ 3 adverse events was approximately 6–18%. Moreover, several clinical trials evaluated the use of ICIs as first-line treatment for patients who are ineligible for cisplatin treatment. Keynote-052 trial, a multicenter, single-arm, phase 2 study, showed that pembrolizumab has anti-tumor activity and acceptable tolerability in patients with UC who are ineligible for cisplatin treatment (11). In another

single-arm, multicenter, phase 2 study, atezolizumab showed encouraging response rates, survival, and tolerability, supporting its therapeutic use for untreated metastatic UC (10).

Owing to the success of ICIs for treating metastatic cancer, many studies have recently evaluated the efficacy of neoadjuvant ICIs for MIBC (*Table 2*). The recently

published phase 2 PURE-01 trial was designed to assess the efficacy of single-agent, neoadjuvant pembrolizumab for MIBC, in addition to determining the biomarkers (17). Patients were enrolled regardless of their cisplatin eligibility and received three cycles of 200 mg pembrolizumab every 3 weeks before radical cystectomy. The primary endpoint was the pCR. Among the 50 enrolled patients, 27 (54%) had clinical (c)T3 disease, 21 (42%) had cT2 disease, and 2 (4%) had cT2-3N1 disease. All the patients treated with pembrolizumab underwent radical cystectomy. A pCR and downstaging to non-muscle-invasive tumors were observed in 42% and 54% of patients, respectively. A total of 54.3% of the patients with PD-L1 combined positive score (CPS) ≥ 10 showed pCR, whereas only 13.3% of patients with CPS < 10 showed pCR. A significant nonlinear association was observed between pCR and tumor mutation burden, with a cutoff at 15 mutations/Mb. Additionally, pembrolizumab was associated with few immune-related adverse events and did not delay planned surgery, and postsurgical complications were consistent with those observed in the most recent literature about open and robot-assisted procedures (18).

The ABACUS trial (19), a single-arm phase 2 study, investigated the efficacy and safety of 2 cycles of atezolizumab (1,200 mg q3weeks) prior to cystectomy for MIBC (T2-4N0M0). In total, 69 patients who refused or were ineligible for cisplatin-based NAC were included. The pCR rate was 29%, and 39% of cases were downstaged to non-muscle-invasive disease. A total of 40% of patients with PD-L1-positive disease ($\geq 5\%$ immune cells with SP142 antibody) showed pCR, whereas 10% of those with PD-L1-negative disease showed pCR. Moreover, sequential biomarker analysis showed an increase in PD-L1 and CD8 expression after treatment with atezolizumab. Only one patient experienced significant progression during neoadjuvant atezolizumab treatment. Neoadjuvant atezolizumab treatment was also safe and feasible. Surgical complications (Clavien-Dindo grade 3 or 4) were observed in 10% of patients.

Recent trends in immunotherapy include combination treatment of ICIs with other agents such as cytotoxic agents, other immunotherapy, and target agents, as evaluated in small prospective studies. Hoimes *et al.* presented the results of a phase Ib/II study of neoadjuvant pembrolizumab and chemotherapy for MIBC at ESMO 2018 (20). Patients with cT2-4aN0M0 UC or mixed histology were included in cohort I (cisplatin-eligible) or cohort II (cisplatin-ineligible). Pembrolizumab 200 mg q3 weeks was administered on day

8 for five doses, with cisplatin (70 mg/m²) on day 1 and gemcitabine (1,000 mg/m²) on days 1 and 8 of a 21-day cycle, for four cycles, followed by radical cystectomy with node dissection. The median number of doses of pembrolizumab, cisplatin, and gemcitabine was 5, 4, and 8, respectively. During phase Ib of the study, no dose-limiting toxicities were observed in six patients. Grade 3/4 cytopenia was observed in 57% of patients. One patient did not undergo surgery due to grade 4 thrombocytopenic purpura. The rate of pathologic downstaging was 60%, and it was not correlated with the baseline PD-L1 level.

The pilot results of durvalumab with tremelimumab (anti-CTLA-4) in patients with high-risk MIBC who were ineligible for cisplatin-based NAC were presented in ASCO 2019 (21). In this single-arm study, neoadjuvant durvalumab with tremelimumab was administered to patients with localized, high-risk MIBC (cT2–T4a) who were ineligible for cisplatin-based NAC. Among 28 enrolled patients, 21 patients have completed cystectomy. Of the 21 included patients, 9 (43%) had pCR, and 14 (67%) showed downstaging of disease. Of 28 patients, 5 (17%) developed grade 3 immune-related toxicity, and 2 (7%) experienced a delay in surgery of >30 days. Immune profiling of baseline peripheral blood indicates that patients with pCR have a significantly lower frequency of a Th2 subset than patients with upstaging of disease. In addition, gene expression profiling analysis of baseline tumor tissues revealed a significantly less immunosuppressive microenvironment in patients with pCR than in patients with upstaging of disease.

A NEODURVARIB trial, open-label phase II single-arm trial about the combination of durvalumab and olaparib prior to surgery for resectable MIBC, was presented in ASCO 2019 (22). The primary endpoint is to assess the impact of neoadjuvant treatment with durvalumab plus olaparib in the molecular profile of MIBC. Durvalumab 1,500 mg q 4 weeks and olaparib 150 mg bid orally from 6 to a maximum of 8 weeks pre-cystectomy was administered. This trial is ongoing, and the result is not yet reported.

Adjuvant immunotherapy

The role of adjuvant chemotherapy for bladder cancer is still unclear. Although several studies have been conducted regarding the use of adjuvant chemotherapy for bladder cancer, the trials failed or were terminated prematurely owing to poor study design and limited patient recruitment (23,24). The largest trial (25) that compared adjuvant cisplatin-based combination chemotherapy after radical

Table 3 Summary of clinical trials of adjuvant immunotherapy in MIBC

Study	Study ID	Phase	Agent	Control	N	Primary endpoint	Secondary endpoint	Upper tract	Cisplatin based NAC	Estimated primary completion date
AMBASSADOR	NCT03244384	3	Pembrolizumab	Observation	739	OS, DFS	OS and DFS PD-L1 (+) and (-) groups	Included	Included	February, 2019
Checkmate 274	NCT02632409	3	Nivolumab	Placebo	700	DFS	(I) OS; (II) NUTRFS; (III) DSS	Included	Included	November, 2020
Imvigor010	NCT02450331	3	Atezolizumab	Observation	809	DFS	(I) OS; (II) DSS; (III) DMFS; (IV) NUTRFS	Included	Included	January, 2020

MIBC, muscle-invasive bladder cancer; NAC, neoadjuvant chemotherapy; OS, overall survival; DFS, disease free survival; PD-L1, programmed death ligand 1; NUTRFS, non-urothelial track recurrence free survival; DSS, disease specific survival; DMFS, distant metastasis free survival.

cystectomy with deferred chemotherapy for pathologic (p)T3–pT4 or N + M0 UC of the bladder showed longer progression-free survival but no significant improvement in OS. In 2010, a Spanish group published the results of a preliminary study that compared adjuvant paclitaxel, gemcitabine, and cisplatin with observation for resectable high-risk MIBC (23). This study was prematurely terminated owing to poor recruitment, with 142 patients randomized (74 to the observation arm and 68 to the adjuvant chemotherapy arm). In that study, OS and disease-free survival (DFS) were significantly more prolonged in the adjuvant chemotherapy arm than in the observation arm. However, as the study was prematurely terminated, the results were very limited.

Another trial was performed by an Italian group (24). This study evaluated the benefit of adjuvant gemcitabine with cisplatin versus surgery alone in patients with MIBC. This study did not show any improvement in the OS and DFS of the adjuvant arm compared to the observation arm. However, as only 200 patients were actually registered in the clinical trial instead of the planned 600 patients, the clinical implications were limited.

Adjuvant chemotherapy has some limitations in clinical fields. Many patients who underwent surgery are more likely to be ineligible for adjuvant cisplatin-based chemotherapy owing to impaired renal function or poor performance status after surgery. Moreover, a substantial number of patients received NAC before surgery but still had persistent muscle-invasive disease. In such cases, sequential postoperative cisplatin-based chemotherapy is

often impossible.

ICI results in fewer toxicities than conventional cytotoxic chemotherapy as well as low kidney metabolization, which is an advantage in patients with decreased renal function. Moreover, considering the benefits currently shown for metastatic disease, adjuvant immunotherapy can be another option instead of adjuvant chemotherapy.

Three major phase 3 trials about adjuvant ICIs are currently ongoing (*Table 3*). The results of the three studies have not been reported to date. These studies included patients who did not receive NAC as well as those who had persistent muscle-invasive disease after NAC. Moreover, these trials are unique because they include patients with upper-tract UC. These trials are all about single ICI agent.

Neoadjuvant versus adjuvant immunotherapy

To date, there is no consensus on whether neoadjuvant or adjuvant immunotherapy is appropriate. Neoadjuvant treatment has several advantages (26). First, it enables response monitoring and provides prognostic information. In addition, neoadjuvant treatment downstages the tumor, allowing for less extensive surgery, thereby reducing postoperative complications. Finally, it uses pCR as a surrogate marker of recurrence-free survival and OS. Moreover, NAC might be better tolerated than adjuvant treatment following surgery, owing to the relevant post-surgery morbidity that might prevent reasonable adjuvant treatment (27,28).

The advantages of neoadjuvant immunotherapy may

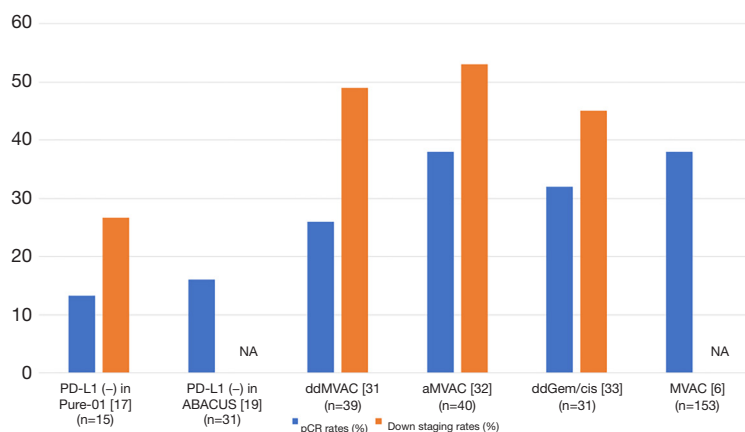


Figure 1 Summary of rates of pCR and downstaging in neoadjuvant chemotherapy and immunotherapy. PD-L1, programmed death ligand 1; NA, data not shown in reference; ddMVAC, dose dense MVAC; aMVAC, accelerated MVAC; ddGEM/Cis, dose dense Gem/cis.

be owing to the hypotheses explained below. Tumor-infiltrating lymphocytes are most often the cells that express the targets for ICIs, and there is an abundance of tumor antigens available for cross-priming at the time of immunotherapy (29). A previous pre-clinical study (30) showed the higher therapeutic efficacy of neoadjuvant than adjuvant immunotherapy to eradicate distant metastases after tumor resection. These hypotheses suggest that immunotherapy may be more likely to be appropriate in the neoadjuvant setting than in the adjuvant setting. However, the major challenge for using a single ICI is the short window of opportunity before surgery that maintains the chance of achieving a cure without delaying the timing for optimal surgery. According to the Keynote 052 trial (11), in untreated patients with metastatic disease, the objective response rate after single ICI was 20%, and approximately 40% of patients showed progressive disease as the best response. Therefore, unresponsiveness to neoadjuvant ICI alone can be a major hurdle because it can lead to treatment failure. Accordingly, biomarker-driven neoadjuvant ICI may be necessary in the future. The above-mentioned ABACUS (19) and PURE-01 (17) studies about neoadjuvant ICI showed improved response rates in the PD-L1-positive group. However, the pCR and downstaging rates were lower in the PD-L1-negative patients than in the patients who were previously treated with cisplatin-based NAC (*Figure 1*) (6,17,19,31-33). Another important challenge associated with the use of neoadjuvant ICIs is the occurrence of perioperative complications. This is in line with the fact that neoadjuvant “cytotoxic chemotherapy” is currently a standard treatment, but it is not often performed

owing to the possibility of perioperative complications.

To date, there is no study which has focused on the perioperative complications that may be associated with neoadjuvant ICIs in patients with MIBC. The RAZOR study compared the efficacy of robot-assisted cystectomy and open radical cystectomy, and showed that robotic cystectomy was non-inferior to open cystectomy considering the 2-year progression-free survival (18). In this study, the surgical complications were evaluated on the basis of the Clavien-Dindo classification system, and there is no significant difference in the incidence of surgical complications between the robotic and open cystectomy approaches. Comparing indirectly these results with the perioperative complications observed in the ABACUS (19) and PURE-01 (17) trials, there was no numerically significant difference between neoadjuvant ICIs and surgery without neoadjuvant ICI (*Table 4*). This finding suggests that the effect of neoadjuvant ICIs on perioperative complication may not be different when surgery is performed without neoadjuvant ICI. Nevertheless, as these comparisons are not performed directly, further studies should be performed. Moreover, treatment-related adverse events (TRAEs) from ICIs should be considered before surgery. Recently, many studies evaluating the use of ICIs for many cancers have shown the occurrence of TRAEs owing to ICIs. TRAEs due to ICIs for UC have been estimated in several previous studies on ICIs for metastatic disease, and the incidence of grade 3 or higher TRAEs was approximately 15% (10-13,34).

In the ABACUS (19) and PURE-01 (17) studies, the incidence of grade 3 or higher TRAEs of ICIs was 11% and 6% respectively, which are lower numerically than the

Table 4 Summary of perioperative complication in surgery with or without neoadjuvant ICI

Perioperative complication	Study			
	ABACUS (19)	PURE-01 (17)	RAZOR-robot (18)	RAZOR-open (18)
Grade 0 (%)	48	50	33	31
Grade 1–2 (%)	45	20	45	47
Grade 3–4 (%)	17	30	19	19

Perioperative complication was assessed using the Clavien-Dindo classification system grade. ICI, immune checkpoint inhibitor.

incidence of TRAEs when ICIs were used to treat metastatic disease. In the PURE-01 (17) study, the most frequent all-grade AE was thyroid dysfunction (18%), and there were three patients (6%) with grade 3 TRAEs that caused pembrolizumab discontinuation. There were a few delayed immune-related AEs, including pyrexia (6%), pruritus (6%), and xerostomia (4%). All of the latter AEs occurred within 2 months postoperatively, and three patients required corticosteroid treatment. It is impossible to compare these results directly. But considering that ICI were administered for relatively short courses to MIBC patients in neoadjuvant setting than metastatic disease, it can be inferred that the incidence of TRAEs owing to neoadjuvant ICIs may not differ significantly from that observed in other studies that were performed for metastatic disease. Further studies should be performed. Furthermore, the above-mentioned studies [i.e., the ABACUS (19) and PURE-01 (17) trials] are on single ICI, and future studies on combination strategies will show different toxicity profiles; accordingly, careful observation and management of TRAEs will be required before performing the surgical approach.

Adjuvant treatment with ICIs has some advantages, including not delaying the timing of definitive local treatment. It can also reduce the incidence of postoperative complications owing to neoadjuvant ICIs. Moreover, in some cases, the pathological stage is higher than the preoperative stage, thereby resulting in the need for adjuvant strategy. Accordingly, adjuvant immunotherapy may also be an important option for selected patients.

Predictive biomarkers for perioperative immunotherapy

Currently, there are no standard predictive biomarkers of ICI in the perioperative setting as well for metastatic disease. Therefore, we discuss some potential biomarkers that indirectly have been studied in trials in metastatic

disease.

Although PD-L1 expression has been studied in many clinical trials, there has been no conclusion till date regarding its use as a predictive biomarker. Previous studies regarding metastatic disease showed different results in the prognosis according to PD-L1 expression (10-14,34,35). These different results may be due to the diversity of the methods currently used for scoring PD-L1, the different cutoff values of PD-L1 expression, intratumoral/intertumoral heterogeneity, and dynamic changes in PD-L1 expression (36). Moreover, because up to 10% of cases with low PD-L1 expression can show response to ICI, PD-L1 expression alone is very limited as a predictive biomarker.

The mutation burden has also extensively studied recently. Cancers with higher rates of somatic mutations showed better responses to immunotherapy (37-39). In both the cohorts in the IMvigor 210 UC trial, a higher mutational load was correlated with a greater response to and longer OS after atezolizumab, and these associations were independent of PD-L1 expression (10,12). However, more research is needed to determine whether the response can be accurately predicted by using only the tumor mutation burden. A recent study suggested the heterogeneity of tumor antigens and tumor mutation burden as biomarkers (40).

Gene expression (mRNA) subtype was also studied as a biomarker. TCGA analysis of RNA-seq data from 129 tumors identified four clusters (clusters I–IV) as biomarkers (41). Cluster I (papillary-like) was enriched in tumors with papillary morphology and FGFR3 alteration. Clusters I and II are similar to luminal A breast cancer, with the expression of urothelial markers such as GATA3. Cluster III is similar to basal-like breast cancer and head and neck squared cell carcinoma. Cluster IV is similar to cluster III, but with features of the surrounding stroma and muscle. The IMvigor 210 cohort 2 trial showed that the response rates to atezolizumab were significantly

higher in the luminal cluster II subtype than in the other subtypes (12). In contrast, cluster III showed the highest response rates to nivolumab in the Checkmate 275 trial (14). However, the gene expression data of those two trials are not publicly available, and the methodology for assigning TCGA clusters was not revealed. Therefore, the results should be interpreted cautiously.

Although recent research indicated several potential biomarkers such as DNA damage repair and immune gene signatures, these biomarker studies were performed in the metastatic setting; the pathophysiology differs between the localized and metastatic settings. Therefore, the results of large-scale phase 3 studies that are ongoing or scheduled in the future in the perioperative setting need to be verified.

Conclusions

The introduction of ICIs changed the treatment landscapes for bladder cancer. In particular, ICIs became a new standard treatment option for patients with metastatic disease who are refractory or ineligible to platinum, owing to the better survival benefits and relatively low toxicity compared to other conventional cytotoxic chemotherapy. These results indicate that ICIs may play a role in the treatment of muscle-invasive disease, with many recent studies conducted in the perioperative setting.

Till date, there is no consensus on whether neoadjuvant or adjuvant immunotherapy is appropriate, and it is not clear whether a single ICI or ICIs in combination with other agents is more appropriate. In addition, as treatment in the perioperative setting increases the curative rate, various parameters should be considered, such as the medical condition, optimal surgery timing, and predictive biomarkers, while selecting the treatment strategy. To date, many trials are currently ongoing, and most of the results have not yet been reported. We hope that the results of these trials will provide clarifications about the above-mentioned issues.

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