Review Article

A narrative review of management of muscle-invasive bladder cancer perioperative period: will continuous and combined treatment be the new trend?

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Background and Objective: With the emergence of immunotherapy and targeted therapies, there are more options for the perioperative period management of muscle-invasive bladder cancer (MIBC), and various types of clinical studies are emerging, leading to the need to explore ways to choose the optimal treatment modality. This review aims to synthesize past and present treatment modalities and to explore future trends in the perioperative period cares of MIBC for the benefit of clinical practitioners.

Methods: A non-systematic, literature search was conducted between March 5, 2023 and November 30, 2023 on PubMed using "perioperative period", "MIBC", "chemotherapy", "radiotherapy", "immunotherapy", "targeted treatment" and "combination" as keywords, along with a search for ongoing clinical studies that were related to the perioperative period of MIBC on classic.clinicaltrials.gov, some latest conference abstracts were also included as references.

Key Content and Findings: The trend towards benefit from adjuvant chemotherapy in perioperative chemotherapy is gradually being recognized. Neoadjuvant immunotherapy, including single-agent immunization, like programmed cell death protein 1 (PD-1) inhibitors, programmed cell death 1 ligand 1 (PD-L1) inhibitors and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, and double-immunization, has been confirmed by several clinical studies to be beneficial to clinical remission rates, and the combination regimen is superior to single-agent therapy. Targeted therapies such as antibody-drug conjugate (ADC) are entering MIBC perioperative studies. Multiple sequential and combination clinical studies are gradually disclosing preliminary data on efficacy and safety.

Conclusions: Immunotherapy would become an essential perioperative treatment for MIBC, and continuous and integrated perioperative management may become the MIBC treatment mode of the future. ADC medicines will also be a hot research focus in the coming years.

Keywords: Perioperative period; muscle-invasive bladder cancer (MIBC); immunotherapy; continuity; combination

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Introduction

With the 12th highest mortality rate in the world, bladder cancer ranks 6th in men and 10th in women as the 10th most common malignant tumor in the world (1). In the United States, bladder cancer accounts for six percent of the morbidity of malignant tumors in male, ranking fourth, and it is only second to the morbidity of prostate cancer in urinary system tumors (2). Most of bladder tumors are non-muscle invasive bladder cancer (NMIBC), with only 25–30% being muscle invasive (3). However, the 5-year overall survival (OS) rate for muscle-invasive bladder cancer (MIBC) was only five percent prior to the development of radical cystectomy (RC) (4). In spite of the fact that the current major therapy for MIBC is RC coupled with pelvic lymph node dissection, up to 50% of patients develop metastatic disease within 2 years of diagnosis (5). Therefore, it is critical to the therapy of MIBC during the perioperative period. In the early stage, chemotherapy is the main means of perioperative treatment. During the perioperative phase, it is standard therapy for MIBC to undergo preoperative chemotherapy. Adjuvant chemotherapy (AC) has also been applied to patients with high-risk recurrence of MIBC. However, at present, there are still problems of efficacy bottleneck and low utilization. With the addition of immunotherapy and various targeted therapies, more options for perioperative treatment have been introduced. By summing up previous and current research advances, this review aims to provide clinicians with new ideas on the choice of perioperative treatment plans and offer a reference for standardizing the management of MIBC in the perioperative period in the future. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-494/rc).

Methods

A non-systematic, literature search was conducted between March 5, 2023 and November 30, 2023 on PubMed using "perioperative period", "MIBC", "chemotherapy", "radiotherapy", "immunotherapy", "targeted treatment" and "combination" as keywords, along with a search for ongoing clinical studies that were related to the perioperative period of MIBC on classic.clinicaltrials.gov. The search strategy is summarized in *Table 1*. Some latest conference abstracts were also included as references. The pertinent inclusion criteria are displayed in *Table 1* and only English language papers were included.

Neoadjuvant chemotherapy (NAC)

RC is a local treatment for non-metastatic MIBC, despite the fact that it is effective in controlling local MIBC lesions, up to 50% of patients will later acquire distant metastases due to undetected micro-metastases (6). Perioperative chemotherapy is created as a result to increase patient survival benefits.

Grossman *et al.* pioneered the use of the methotrexate/vinblastine/adriamycin/cisplatin (MVAC) regimen for NAC in MIBC in the SWOG 8710 study in 1987, this study randomized 317 MIBC patients to the RC alone or MVAC combined with RC groups, and the median survival in the RC alone and RC after NAC groups were 46 and 77 months, respectively (P=0.06) (7). After cisplatin, methotrexate and vinblastine (CMV) regimen before local treatment for MIBC in the BA06 30894 trial, the risk of death was reduced by sixteen percent [hazard ratio (HR): 0.84; P=0.037], which was the largest trial in the NAC (8). A phase III randomized controlled study in Japan illustrated that the NAC set (MVAC) had better OS than the RC set (HR: 0.65, P=0.07), with 34.4% and 9.4% of patients achieving pT0 in the NAC and RC sets, respectively (P=0.001) (9). According to recent research, cisplatin-based NAC followed by RC has an absolute survival rate that is five percent higher than RC alone (10). Hence, cisplatin-based NAC is recommended by several guidelines for the treatment of MIBC patients with pathological staging of cT2-4N0M0, even if it has also been shown in other study that NAC combined with RC does not improve OS in patients with cT2N0M0 MIBC (11). In NAC, carboplatin is not suggested as a cisplatin substitute (12,13).

Since the development of NAC, the most common NAC regimens currently available are dose-dense MVAC (dd-MVAC) and gemcitabine and cisplatin (GC). MIBC patients were randomly assigned to either the six-cycle dd-MVAC group or the four-cycle GC group in the VESPER trial. The dd-MVAC group had a higher pathological complete response (pCR) rate than the GC group (42% *vs.* 36%, P=0.02), severe anemia and grade 3 gastrointestinal adverse events (AEs) were more frequent in the dd-MVAC group (P<0.001) (14). Another phase III randomized controlled trial (RCT) concluded that MVAC and GC had comparable clinical effects, with the GC protocol having better tolerance and safety (15). Similarly, a meta-analysis of 3,116 patients from 18 studies found no statistical difference

Table 1 The search strategy summary

Items	Specification
Date of search	Searches performed between March 5, 2023 and November 30, 2023
Database searched	PubMed
Search terms used	"Perioperative period", "MIBC", "chemotherapy", "radiotherapy", "immunotherapy", "targeted treatment" and "combination"
Timeframe	January 1987 to November 2023
Inclusion and exclusion criteria	Inclusion criteria: • Original studies of RCTs, cohort studies, case-control studies, and case series • Meta-analysis, clinical trial articles, review, systematic review, and conference abstracts related to bladder cancer therapy, especially MIBC perioperative treatment • English-language papers Exclusion criteria: • Main topic not related to MIBC perioperative management • Editorials, letters to editors
Selection process	Selection process was conducted independently by two of the authors (T.L. and S.R.). When there was a disagreement, consensus was obtained by the adjudicating of the senior author (W.H.)

RCT, randomized controlled trial; MIBC, muscle-invasive bladder cancer.

between GC regimen and MVAC regimen in terms of pCR and OS (P=0.69, P=0.87) (16). In general, the GC regimen has fewer side effects and better tolerance than the dd-MVAC regimen, but the latter has a higher rate of local control and clear advantages in pathological reaction. There is currently insufficient evidence to support the application of cisplatin as a single drug in NAC (17).

The timing of NAC use requires attention as chemotherapy toxicity (hematotoxicity, neurotoxicity and nephrotoxicity), disease progression, delayed RC and overtreatment need to be considered. Before cystectomy, Culine *et al.* recommend at least four-cycle of cisplatin-based chemotherapy. And beyond four cycles, there is no clinically significant loss of renal function, but no noticeable improvement in local control (18). Based on the VESPER trial, the current duration of NAC application is mainly 4 to 6 cycles. For bladder cancers with metaplastic histology, there is insufficient evidence to indicate that NAC is beneficial in adenocarcinoma and sarcomatoid variant bladder cancers, and further studies are needed in papillary variant bladder cancers, with a potential benefit in squamous malignancies (19).

Furthermore, not all of the patients can benefit from NAC. NAC also induces delayed RC, raising chemotherapy toxicity and care costs for patients who are unable to profit from it. In recent years, predicting NAC beneficiaries has been a hot topic, and discovering new biomarkers is being researched in a large number of studies that include Genome analysis, molecular subtypes, and so on. A study found that the changes of DNA damage response genes *ATM*, *FANCC* and *RB1* are related to pathological response and OS rate in accelerated methotrexate, vinblastine, adriamycin and cisplatin (AMAVC) group and dose-dense gemcitabine and cisplatin (dd-CG) group (20). Van Allen *et al.* initially investigated a nucleotide excision repair gene, *ERCC2*, which was the only enriched mutation gene (P<0.001) among 25 NAC responders (21). Recently, changes in *FGFR3*, *ERBB2* and *PIK3Ca* have also been discovered to be linked to the response to preoperative chemotherapy (P=0.01) (22). Three subtypes of MIBC were identified by Choi *et al.* in their study of 73 patients: basal tumors, which were invasive but reacted well to NAC; intraluminal tumors, which had a good prognosis; and p53-like subtypes, which did not respond to NAC (23). These biomarkers are yet to be recognized as reliable forecasting tool and e more prospective studies are required to verify its role in the future. The SWOG S1314 study used the co-expression extrapolation (COXEN) method to forecast the

drug sensitivity of tumor cells. COXEN is an algorithm exploited by Dan Theodorescu and his colleagues, and this algorithm forecasts the drug sensitivity of tumor cells based on the *in vitro* drug sensitivity of different cancer cell models previously analyzed. According to the study, the COXEN GEM GC score was substantially associated with the reduction in stage [odds ratio (OR): 2.33, P=0.02] in the combined group (GC and dd-MVAC) and the sensitivity for pT0 and downstaging in this pooled study for the GC COXEN score was 32%, with a specificity of 81%. But the COXEN score specific to a given treatment was unable to significantly predict how well a patient would respond to specific chemotherapy (P>0.05) (24,25). In general, these biomarkers still have high clinical significance and are worthy of development and research.

It is worth noting that patients suffering from bladder cancer tend to be older, have multiple comorbidities, are prone to be infected with coronavirus disease 2019 (COVID-19), and have a higher severity rate. The European Association of Urology (EAU) Surgeons Guide Rapid Response Group provides a priority-based management recommendation for MIBC: patients with cT2-3N0M0 MIBC should refrain from using NAC during the COVID-19 pandemic. This suggestion has also been validated by a meta-analysis that comprised eight studies (26).

AC

AC has following benefits over NAC: initially, prevent postponed surgery; next, select a treatment for high recurrent rick patients to avoid overtreatment based on postoperative pathological stage rather than clinical stage. It does, however, have several evident flaws. For instance, poor patient compliance, missing early systemic therapy for patients with hidden metastases, and the challenge of performing AC since postoperative complications and a delayed healing process (27,28). Now, there is inadequate data to stand up for using AC in comparison to NAC, and there is still a number of disputations in survival benefit brought by AC in several retrospective and small sample prospective studies (29-35). An observational investigation recruited 5,653 patients with pathological stages of pT3-4 and/or lymph node positivity, 23 percent of patients received AC after RC, and AC improved the OS rate (HR: 0.70) (36). The first prospective trial of AC performed by Skinner *et al.* gave four cycles of AC or surgery alone in 91 patients after surgery, in the chemotherapy group, the median survival time was 4 years, while it was just 2 years in the control group (P=0.006) (37). In the SOGUG 99/01 trial, published only in American Society of Clinical Oncology (ASCO), AC [paclitaxel/gemcitabine/cisplatin (PGC)] had a 31% (P<0.001) higher 5-year OS rate than the surgery alone group (27). But the largest AC trial at the moment, a phase III RCT from Italy, immediate *vs.* deferred AC (both GC regimens), illustrated that it was no significant difference in OS between immediate group and deferred group [P=0.24; HR: 1.29; 95% confidence interval (CI): 0.84–1.99] (38). There are all kinds of shortcomings above these studies, such as deficient sample, poor patient cumulative rate, early trial termination and insufficient methodology, resulting in the quality of evidence not very reliable.

Nowadays, multiple meta-analyses endorse that AC improves patient survival. Kim *et al.* included four RCTs exhibited that pooled HRs of progression-free survival (PFS) and OS were 0.48 and 0.63, respectively. In addition, PFS and OS increased proportionally by 17% and 10%, respectively, in patients with locally advanced MIBC (39). A meta-analysis performed in 2005 showed that chemotherapy patients had a survival rate HR of 0.75 (P=0.02) and a 25% lower risk of death than the control group (40). In addition, a latest meta-analysis contained 1,183 patients demonstrated that cisplatin-based AC was beneficial to OS (HR: 0.82; P=0.02), and compared with 50%, the 5-year survival rate improved by 6% to 56%. Moreover, AC was also proved to be able to improve recurrent-free survival (RFS) (HR: 0.71; P<0.001) (41).

Currently, application of cisplatin-based AC in MIBC patients with pathological stages of pT3-T4 and/or lymph node positivity if no NAC has been given was suggested by various guidelines (42). Survival benefit of AC for MIBC patients is being confirmed gradually. Nevertheless, careful design and superior quality prospective trials are needed to offer strong evidence.

Neoadjuvant immunotherapy

RC after NAC based on cisplatin is the standard care for MIBC patients at present, but nearly 50% of patients are not tolerant to cisplatin (43). Among the criteria pioneered by Galsky *et al.* to determine whether a patient is unsuitable for cisplatin chemotherapy are the following: Eastern Cooperative Oncology Group performance status of 2, creatinine clearance less than 60 mL/min, grade ≥2 hearing loss, grade ≥2 neuropathy, and/or New York Heart Association Class III heart failure (44). Immunotherapy has been applied to NMIBC through bladder perfusion in

the past few decades, and the efficacy of immunotherapy in advanced and metastatic bladder tumor has been affirmed in recent years. Five immune-drugs have been recommended by the Food and Drug Administration (FDA) for second-line treatment of locally advanced or metastatic urothelial cancer (45). For instance, according to the most recent IMvigor130 study results in 2023, atezolizumab monotherapy continues to be more tolerable than chemotherapy, and based on these preliminary findings, atezolizumab monotherapy is superior to chemotherapy for first-line treatment of cis-ineligible metastatic urothelial cancer (46). The application of immunotherapy during the preoperative period demonstrated advantages for MIBC patients with cisplatin intolerance.

The first immunotherapy for the preoperative management of MIBC is ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors. Prior to surgery, two cycles of ipilimumab medication were applied to patients with cT1-T2N0M0 urothelial carcinoma, and the study's authors reported optimistic early outcomes: positive urine cytology changed to negative (47). PURE-01 trial is a single-arm clinical study to evaluate the role of pembrolizumab in neoadjuvant treatment of patients with MIBC. Twenty-one patients achieved pCR (42%; 95% CI: 8.2–56.8%), while 27 patients acquired <pT2 stage decline (54%; 95% CI: 39.3–68.2%). Among all grades, thyroid dysfunction is the most common AE, with 6% of AEs classified as grade 3. Besides, the event-free survival (EFS) and OS of intention-to-treat (ITT) population for 36 months are 74.4% and 83.8%, respectively (48,49). Another phase II experiment, the ABACUS trial, assessed the curative effect of two-cycle atezolizumab neoadjuvant therapy in 95 MIBC patients and showed that pCR rate is 31% and 2-year disease-free survival (DFS) and OS rate are 68% and 77%, respectively (43,50). A meta-analysis with 843 patients by synthesizing 22 studies on neoadjuvant immunotherapy indicated that the pCR rate of immune checkpoint inhibitor (ICI) monotherapy and double ICI therapy are 24% and 32.1%, respectively. When it comes to safety, the combined rate of grade ≥3 immune-related AEs (irAEs) were 11.7% (95% CI: 6.5–16.9%) (51). Dual ICI therapy has better efficacy than ICI monotherapy, but irAEs above grade 3 or treatment-related AEs (TRAEs) are also higher (52,53). Specifically, head-to-head studies are required to validate the role of neoadjuvant immunotherapy in the perioperative period of MIBC, whether as an alternative treatment, a treatment of choice, or a supplement to NAC.

It is unclear which biomarkers may forecast the efficacy of neoadjuvant immunotherapy right now. While there was no statistically significant difference between programmed cell death 1 ligand 1 (PD-L1) and RFS, tumor infiltration of FOXP3 and immunotherapy resistance are associated to the prediction of OS in the ABACUS study, the expression of PD-L1 showed a favorable relationship with response in the PURE-01 trial (43,49). $CD8^+$ T cell invasion and circulating tumor DNA (ctDNA) are thought to be connected to survival promotion and the possibility of disease recurrence (43). The optimum regimen and duration of neoadjuvant immunotherapy are thought to require more research, similar to NAC. Although pCR was frequently utilized as the primary endpoint in neoadjuvant immunotherapy studies, it is still unknown if pCR can accurately predict patients' long-term survival.

Adjuvant immunotherapy

Postoperative adjuvant immunotherapy may be advisable for bladder cancer patients with high-risk recurrence, including pT3-T4 pathologic staging, lymph node positivity or intolerance to cisplatin. In CheckMate274, a phase III, multicenter RCT, nivolumab treatment was assigned to 353 patients and placebo treatment to 356 patients. Median follow-up was 20.9 months in nivolumab set and 19.5 months in control set. In the ITT population, compared with the control set, 12-month DFS was 62.8% and 46.6% (HR: 0.70, P<0.001), respectively. In the population with PD-L1 expression ≥1%, HR was 0.55 (P<0.001). The most common TRAE is pruritus (23.1%) (54), and according to 2023 ASCO oral abstract, grade ≥3 TRAEs occurred in 18.2% and 7.2% in the nivolumab and control arm (55). In the IMvigor010 trial, 406 patients were given atezolizumab and 403 patients were observed. The median DFS time of the test set and the observation set were 19.4 and 16.6 months (P=0.24), respectively. The most common grade ≥3 AE was urinary tract infection (56). Although the conclusions of DFS in the two trials were inconsistent, the subgroup analysis showed potential benefits for bladder cancer patients at high-risk of recurrence and $PD\text{-}L1^+$ disease patients. At present, nivolumab has been recommended by FDA for adjuvant treatment of urothelial carcinoma (www.cancer.gov), and we look forward to more information from the study of adjuvant treatment after surgery with immune combination.

Neoadjuvant radiotherapy

Perioperative radiation is used to localize the tumor, lessen tumor burden and decline tumor spread during operation. However, the strength of evidence supporting the application of neoadjuvant radiotherapy is still weak. At this time, even though half of patients were excluded from survival analysis because of incomplete treatment plans, the largest neoadjuvant radiotherapy trial with 475 patients, which compared perioperative radiation and surgery alone, revealed that radiation group had a better complete response (CR) (34% *vs.* 9%) and survival rate (55% *vs.* 32%) than that of surgery alone group (57). Multiple studies disapproved that radiation prior to operation is able to obtain significant improvements (58-60), and the radiation toxicity should be reminded, but some studies believed that using modern radiotherapy technology, intensity-modulated radiation, for example, might efficiently lower the dosage to the digestive structure, potentially improving the risk-benefit of this perioperative treatment (61).

Adjuvant radiotherapy

The benefit of radiation therapy following RC may be that it can be regulated based on pathological parameters, such as a high-risk stage (pT3–T4) and/or a favorable surgical margin (62). Zaghloul *et al.* reported the study of 236 patients with pT3a–4a pathologic stage who received hyper-fractionation radiotherapy or conventional radiotherapy after cystectomy for comparison with simple surgery. The 5-year DFS rate of hyper-fractionation radiotherapy and conventional radiotherapy were 49% and 44% respectively, while that of the simple surgery group was only 25% (63). This study laid the foundation for the application of radiation after surgery in patients with locally advanced bladder tumor. However, it is mentioned that most of tumor type of patients in this study is squamous cell carcinoma. Following cystectomy, another trial compared the effectiveness of bladder cancer patients with local advanced stage between the chemoradiotherapy set and the chemotherapy alone set. It discovered that the 2-year DFS rate of the chemoradiotherapy group and the chemotherapy alone group are 68% and 56%, respectively, and the OS HR in the chemoradiotherapy group is 0.61 (P=0.11) (64). At this moment, larger phase III clinical studies are still required to support the use of adjuvant radiation and adjuvant chemoradiotherapy.

Chemotherapy combined with immunotherapy

There is a synergistic effect between chemotherapy and immunotherapy (65): some chemotherapy drugs can trigger immunogenic cell death (ICD). This ICD promotes the maturation of dendritic cells through the release of damage-associated molecular patterns by tumor cells, and then recruit and activate anti-tumor cells (such as cytotoxic T cells) (66,67). At the same time, cytotoxic drugs can stimulate the effector of the innate immune system, recruit effective natural killer cells and dendritic cells to the tumor site, and enhance the tumor-related macrophage cytotoxicity by producing pro-inflammatory cytokines (68). The platinum-based protocol inhibits the expression of programmed cell death ligand 2 (PD-L2) on dendritic cells and tumor cells by regulating signal sensors and activator of transcription six, and restores the immune stimulation of dendritic cells (69). Consequently, chemotherapy combined with immunotherapy is proposed to be used in patients with MIBC during perioperative period.

The nivolumab paired with GC regimen was employed as a preoperative therapy for MIBC patients in the multicenter BLASST-1 research. Of the 41 patients enrolled, 90% were classified as cT2N0. Patients with N1 disease were included in the 27/41 (65.9%) patients who had the primary endpoint pathologic response rate observed. Twenty percent of all AEs of grade 3 or higher were neutropenia-related (70). Another multicenter study assessed pembrolizumab and GC in combination as preoperative therapy for MIBC patients. After cystectomy, 22 of the 39 patients reached pT2N0M0 with an overall pathological decline rate of 56% and a pCR rate of 36%. Specially, pathologic downstaging (pDS) was associated with significantly prolonged RFS compared to those without. There were 74% of patients reported with grade 3 or higher TRAEs, with hematological complications being the most common AEs of any grade (71). In HCRN GU14-188 study cohort one, the rate of pathologic muscle invasive response (PaIR) rate of neoadjuvant treatment of pembrolizumab combined with GC regimen was 61.1% (72). The pCR rate in the AURA study comparing dd-MAVC + avelumab (A) to GC + avelumab (A) was 54% for dd-MAVC + A and 50% for GC + A (73). A pDS rate of up to 76.5% and a pCR rate of 58.8% were reported in the abstract of the BGB-A317-2002 research, which was published in 2022. TRAEs in grades 3 and above were hematological and no grade ≥3 irAEs occurred (74). With regard to immunotherapy and NAC, Sarkis *et al.*

retrospectively integrated 17 trials with pathological response and pCR rates for the cisplatin-eligible group ranging from 56–75% and 34–66%, respectively. And the efficacy of immune combination therapy surpassed that of single formula immunotherapy (75). However, the majority of the studies were phase II clinical studies with small scale subjects, and more rigorous phase III clinical studies are desired to validate the benefits of immune combination chemotherapy regimens. The research on EV303/EV304 may offer a useful research strategy for the aforementioned defects.

Radiotherapy combined with immunotherapy

Similarly, radiotherapy has been shown to have synergistic effects with immunotherapy, with radiation-induced cell death releasing tumor antigens, contributing to the initiation of anti-tumor cytotoxic T cells, promoting tumor antigen uptake by dendritic cells, and facilitating tumor antigen cross-presentation on major histocompatibility complex (MHC) class I molecules (76). It has been shown that various radiation grading systems and dosages have a range of immunological regulation effects that favor either immune-stimulation or immune-suppression. There are safety concerns with concurrent immunotherapy employing low-level radiation in restricted MIBC (77,78). In the first dose cohort of the PLUMMB trial, patients with MIBC accepted pembrolizumab plus radiation, 3 out of 5 patients suffered grade 3 urinary toxicities. Therefore, the trial has been paused and researcher suggests that caution should be exercised when using high dosage per fraction in the pelvic region along with immunotherapy (79). In spite of the fact that both of chemotherapy and radiation ally with immunotherapy has potential synergistic effects, more compelling evidences are needed to advocate the application of combined regimens in MIBC patients during the perioperative period in order to address the following issues: first, efficacy and safety of combined regimens; second, the best regiments, including dose, type and duration; last, suitable population for medication or radiotherapy.

Novel combined immunization regimen

Moreover, some innovative combined immunization regimens include those that combine programmed cell death protein 1 (PD-1)/PD-L1 inhibitors with CTLA-4 inhibitors, immunotherapy with albumin paclitaxel, immunotherapy with targeted medications, and others. In the NABUCCO study, after receiving two doses each of ipilimumab and nivolumab, 24 patients underwent surgery. Eleven subjects (46%) acquired a pCR, while 14 subjects (58%) had no residual invasive disease (80). Currently targeted drugs have FGFR2, FGFR3, Nectin-4, etc. as their main targets (81). It should be mentioned that in recent years, the efficacy of antibody-drug conjugate (ADC) in the treatment of locally advanced and metastatic urothelial carcinoma has been proven. As reported by the latest progress of RC48-C014 study, disitamab vedotin (RC48) in combination with toripalimab were applied to locally advanced and metastatic urothelial carcinoma, and the objective response rate (ORR) was able to reach 75%. Specially, in patients with PD-L1 combined positive score (CPS) ≥1 and 50% in CPS ≥1, the ORR was able to reach 97.1%. The most common TRAE was anorexia (72%), and the most frequent irAE was pneumonitis (20%) (82).

Similarly, ADC drugs are currently being used to treat NMIBC and MIBC. According to a retrospective study, the CR rate of RC48 monotherapy or RC48 in combination with tislelizumab for the treatment of high-risk NMIBC can reach 73.7%. Grades 3–4 TRAEs were reported in three patients (6.3%), including rash, pruritus, leukopenia, and neutropenia (83). However, the study has not yet disclosed the treatment cycles. EV104 is a phase 1 study of first-in-human of intravesical enfortumab vedotin (EV) (another ADC drug). Four patients and two patients received drug treatment at dose levels of 125 and 250 mg, respectively. There were no grade ≥3 TRAEs and three patients achieved CR (84).

Lately, EV103 research updates the progress of cohort H, in which 22 MIBC subjects were enrolled and 86.4% of them completed all three cycles of EV neoadjuvant therapy. The pCR rate was 36.4% and the most common EV-related TRAEs were fatigue (45.5%). Besides, three subjects died due to AEs unrelated to ADC therapy (85). Higher pCR may arise from the combination therapy regimen and longer medication cycles, but overall safety is still deemed acceptable. It can be seen that ADC drugs are gradually covering the studies on the treatment of bladder cancer at different stages.

More and more investigations on immunotherapy combined with targeted drugs are anticipated to obtain outcomes in the next few years. More ongoing combined immunotherapy trials are showed in *Table 2*. Although chemotherapy combined with immunotherapy has a synergistic and beneficial therapeutic effect, it is required to investigate if immunotherapy is suitable for combination

Table 2 Ongoing combined immunotherapy trials

Regimen of medication combination	NCT	Including population	Sample size	Study regimen	Primary outcome	Study completion date
Chemotherapy combined with immunotherapy	NCT03549715	cT2-4aN ≤ 1M0	121	Durva + dd-MVAC	pCR	Sep. 2025
	NCT02989584	cT2-4aNxM0	54	Atezo + GC	DLT	Dec. 2023
	NCT04871529	cT2-4aN0M0	196	Ave + GCar	pCR	Apr. 2029
	NCT04383743	cT2-4aN0/1M0	17	Pembro + dd-MAVC	pCR	Oct. 2025
	NCT04506554	cT2-3N0M0	71	AMVAC + Nivo	MFS	Nov. 2028
	NCT03558087	cT2-4aN0M0	76	Nivo + GC	pCR	Aug. 2024
Radiotherapy combined with immunotherapy	NCT04543110	cT2-4aN0M0	25	Durva + RT	pCR	Nov. 2024
	NCT05445648	cT2-4aN0M0	65	Tisle +TURBT + RT	pCR	Feb. 2026
	NCT05241340	cT2-4aN0M0	33	Sasan + RT	pCR	Feb. 2025
Novel combined immunization regimen	NCT04876313	cT2-4aN0M0	29	Nivo+ Nab	pCR	Jun. 2025
	NCT02845323	cT2-4N0-2M0	15	Nivo + Ure	Immune response	Dec. 2024
	NCT05328336	cT2-4aNxM0	74	Tisle+ Nab	pCR	Nov. 2025
	NCT05239624	cT2-4aNxM0	23	Pembro + EV	pCR	Jun. 2024

NCT, National Clinical Trial; Durva, durvalumab; dd-MVAC, dose-dense methotrexate/vinblastine/adriamycin/cisplatin; Atezo, atezolizumab; GC, gemcitabine and cisplatin; Ave, avelumab; GCar, gemcitabine and carboplatin; Pembro, pembrolizumab; AMVAC, accelerated methotrexate/vinblastine/adriamycin/cisplatin; Nivo, nivolumab; RT, radiation therapy; Tisle, tislelizumab; TURBT, transurethral resection of bladder tumor; Sasan, sasanlimab; Ure, urelumab; Nab, nab-paclitaxel; pCR, pathological complete response; DLT, dose limiting toxicity rate; MFS, metastasis-free survival; EV, enfortumab vedotin.

therapy regimens, that is, the selection of the population eligible for immunotherapy. The beneficiary population should be selected to be included in the research via biomarkers or immunophenotyping.

Chemotherapy combined with radiotherapy

Certain chemotherapy, such as gemcitabine and cisplatin, are radiation sensitizers (86-88). Several studies have shown that chemotherapy combined with radiotherapy is superior to radiotherapy or chemotherapy alone (64,89,90). Chemoradiotherapy is increasingly being used in bladder preservation regimens. For example, trimodality treatment (TMT), the most recognized bladder preservation regimen, includes chemoradiotherapy and maximum transurethral cystectomy for bladder tumor. Based on strict postoperative follow-up and prompt salvage cystectomy, TMT is able to achieve a similar OS rate and a disease-specific survival (DSS) rate to RC (91,92). The BC2001 experiment, the biggest MIBC organ sparing study, demonstrated that fluorouracil and mitomycin C can be added to radiation to improve local control. Chemoradiotherapy had a 5-year RFS rate of 63% (95% CI: 54–71%), whereas radiotherapy alone had a rate of 49% (95% CI: 41–57%, P=0.004) (89). Koga *et al.* recruited 102 patients who received low-dose chemoradiotherapy before surgery. Forty-one patients attained CR and 29 patients achieved partial response (PR), and the 5-year OS rate was 66% (93). Nevertheless, our experience indicates that patients with a history of radiation therapy are much more likely to acquire intestinal adhesions, which severely limits the chance for orthotopic neobladder to be performed on patients who have not responded well to bladder preservation therapy. In order to investigate more empirical treatment models, future bladder preserving treatments may try to undermine the status of radiation by adding novel medications like ADC or mixing other combination therapy models.

Continuous and combined therapy

With the concept of early diagnosis and treatment in bladder cancer, a continuous and combined treatment paradigm of neoadjuvant therapy followed by RC and adjuvant therapy has been concerned in recent years. At

an early stage, Zargar-Shoshtari *et al.* recruited 161 locally advanced bladder cancer patients and discovered that there was no significant difference in the RFS between NAC followed by RC and AC group and NAC followed by RC group (P=0.78) (94). Patients who had residual illnesses after preoperative chemotherapy experienced a markedly reduced risk of recurrence (HR: 0.35) when AC was utilized, according to the preliminary findings of the retrospective international study (RISC) group of urothelial carcinoma (95). Another meta-analysis revealed that neoadjuvant and AC administered during the perioperative period significantly improved OS rate (HR: 0.84) and DSS rate (HR: 0.56) (96).

2022 ASCO reported the latest progress of SAKK 06/17 trial, including 61 operable muscle-invasive urothelial carcinoma (MIUC) patients with cT2-T4aN0-1M0 pathologic stage who received four cycles durvalumab combined with GC neoadjuvant therapy and ten cycles durvalumab maintenance treatment after operation. Fifty-eight patients were included in the full analysis set (FAS), with 95% of MIBC patients. Fifty-three of them accepted RC, 32 patients reached < ypT2N0 (representing 60% of RC patients and 55% of FAS), and 18 out of 53 patients reached ypT0. Two-year RFS rate of 83.5% (95% CI: 69.6–91.4%) and OS rate of 87.3% (95% CI: 73.8–94.1%) were reached in FAS population 2 years after resection. Overall, 26% of AEs above grade 3 were caused by durvalumab during treatment (97). The most recent progress about EV103 cohort L was disclosed in the 2023 European Society for Medical Oncology (ESMO) meeting abstract. Patients with cisplatin-ineligible cT2-4aN0M0 or cT1-4aN1M0 urothelial carcinoma were given three cycles of EV neoadjuvant therapy followed by RC and six cycles of EV adjuvant therapy. For pathologic outcomes, the pCR was 34% and pDS occurred in 42% of patients. The majority of EV-related AEs were grade 2 or lower (98). This study applied ADC drugs to the continuous treatment of MIUC during the perioperative period, providing reference for the population of MIUC with or without lymphatic metastasis who were cisplatin intolerant. In another typical study of continuous and combined perioperative treatment models is EV303, which is designed to provide perioperative management for MIBC patients who are cisplatin-intolerance, 836 MIBC patients are going to be enrolled and divided into three arms: arm A (three cycles of pembrolizumab neoadjuvant therapy followed by 14 cycles of pembrolizumab adjuvant therapy); arm B (RC alone); and arm C (three cycles of pembrolizumab combined with EV neoadjuvant therapy following by six cycles of pembrolizumab combined with EV adjuvant therapy). This research is about to be completed in September 2027.

In HCRN 16-257, a bladder-sparing trial with GC plus nivolumab after transurethral resection of bladder tumor (TURBT) in MIBC patients, 76 patients participated and received four cycles of GC combined with nivolumab treatment, followed by eight cycles of nivolumab maintenance therapy. Thirty-three patients (43%) achieved a clinical complete response (cCR). Interestingly, this study showed that higher tumor mutational burden (TMB) was associated with treatment benefit (99), which is a great novelty since it examines the connections between genomic features, imaging features, and immunological features with therapeutic benefits. In another multicenter bladder preservation study in which MIBC subjects received one cycle of pembrolizumab followed by maximal TURBT and then whole bladder radiation therapy twice weekly and maintenance treatment with three cycles of pembrolizumab, 2-year bladder-intact DFS (2-year BI-DFS) were able to go up to 71% (95% CI: 56–82%). Grade ≥3 irAEs occurred in two subjects with colitis, one subject with polyneuropathy and one subject with grade 5 colonic perforation (100).

The continuous and combination treatment of MIBC in the perioperative phase appears promising based on currently available study findings, and more research is actively being conducted currently (*Table 3*). The majority of current research on continuous and combination therapy approaches is single arm trials, with more exploratory research. In the future, we plan to conduct a large-scale phase 3 RCT, similar to CheckMate 274, to validate the practicality and rationality of this model, as well as to investigate the ideal medication cycle before and after surgery, making this treatment model more comprehensive.

Conclusions

Immunotherapy is becoming an indispensable part of MIBC perioperative period care with the advent of the immunization era. Nevertheless, it is still inconclusive whether perioperative immunotherapy can replace perioperative chemotherapy or should just be used as an alternative for patients with cisplatin intolerance at present. Currently, the trials of continuous neoadjuvant therapy and adjuvant therapy combined with multiple drug regimens are being carried out. An early and full-course standardized management of perioperative period will be the future trend. We anticipate more new biomarkers that can

Table 3 Ongoing continuous and combine trials

Regimen of medication combination	NCT	Including population	Sample size	Study regimen	Primary outcome	Study completion date
Chemotherapy combined with immunotherapy	NCT02621151	cT2-4aN0M0	60	Pembro + Gem + RT	cCR	Dec. 2025
	NCT03558087	cT2-4aN0M0	76	GC + Nivo	cCR	Aug. 2024
	NCT05401279	cT2-3N0M0	20	GC + Tisle	BI-DFS	May. 2025
	NCT04506554	cT2-3N0M0	71	AMVAC + Nivo	MFS	Nov. 2028
	NCT05200988	cT2-4aN0-2M0	50	Nivo + Ipili	BI-EFS	Dec. 2027
Radiotherapy combined with immunotherapy	NCT04216290	cT2-4aN0M0	95	GC + RT + Durva	cCR	Jun. 2026
	NCT05445648	cT2-4aN0M0	65	Tisle + TURBT + RT	cCR	Feb. 2026
	NCT03697850	pT2-3NxMx	79	Atezo + CRT	DFS	Feb. 2029
Novel combined immunization regimen	NCT04876313	cT2-4aN0M0	29	Nivo+ Nab	pCR	Jun. 2025
	NCT05979740	cT2-4N0-2M0	6	Toripa + RC48 + RT	AE	Feb. 2024
	NCT05328336	cT2-4aNxM0	74	Tisle+ Nab	pCR	Nov. 2025
	NCT05239624	cT2-4NxM0	23	Pembro + EV	pCR	Jun. 2024

NCT, National Clinical Trial; Pembro, pembrolizumab; Gem, gemcitabine; RT, radiation therapy; GC, gemcitabine and cisplatin; Nivo, nivolumab; Tisle, tislelizumab; AMVAC, accelerated methotrexate/vinblastine/adriamycin/cisplatin; Ipili, ipilimumab; Durva, durvalumab; TURBT, transurethral resection of bladder tumor; Atezo, atezolizumab; CRT, chemo-radiotherapy; Nab, nab-paclitaxel; Toripa, toripalimab; RC48, disitamab vedotin; EV, enfortumab vedotin; cCR, clinical complete response; BI-DFS, bladder-intact disease-free survival; MFS, metastasis-free survival; BI-EFS, bladder-intact event-free survival; DFS, disease-free survival; pCR, pathological complete response; AE, adverse event.

accurately predict the curative effect to guide perioperative treatment, whether in the selection of drug treatment or the decision to use continuous or combined management. Recently, ADC drugs have gradually entered the field of tumor treatment and achieved favorable results. How to apply ADC drugs in MIBC perioperative treatment may be a focus in the future.

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