Perioperative Systemic Treatment for MIBC

Subjects: Oncology

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Perioperative systemic treatment is important to improve MIBC prognosis. Current international guidelines recommend cisplatin-based neoadjuvant chemotherapy (NAC) followed by RC in patients with MIBC; adjuvant chemotherapy is also an option for select patients. Recently, owing to the success of immunotherapy in treating metastatic disease, a perioperative immunotherapy-based treatment strategy for MIBC is being extensively investigated.

Keywords: bladder cancer ; immunotherapy ; perioperative systemic treatment

1. Introduction

Currently, radical cystectomy (RC) with pelvic lymph node dissection is the primary treatment for MIBC; however, the disease tends to recur within two years in approximately 50% of patients [1]. Therefore, perioperative systemic treatment is important to improve MIBC prognosis. Recently, owing to the success of immunotherapy in treating metastatic disease, a perioperative immunotherapy-based treatment strategy for MIBC is being extensively investigated.

2. Perioperative Chemotherapy in MIBC

The National Comprehensive Cancer Network (NCCN) guidelines recommend cisplatin-based NAC as a category 1 treatment for patients with clinical T2–4a (cT2–4a) or N1 who are fit for cisplatin treatment [2]; the European Association of Urology (EAU) guidelines also strongly recommend cisplatin-based NAC for cT2–T4a disease [3]. The BA06 30894 trial was an international, multicenter study that compared local radical treatment alone with neoadjuvant cisplatin, methotrexate, and vinblastine (CMV), followed by local radical treatment. The primary endpoint was pathologic response (PaR), defined by pathologic downstaging to ≤pT1N0M0. The primary endpoint was pathologic complete response (pT0, pCR).

A total of 284 patients were randomly assigned (1:1) to either immediate AC (four cycles of GC, high dose MVAC, or conventional MVAC) or six cycles of deferred chemotherapy at relapse. The failure of this trial may be attributed to poor trial design and an inappropriate primary endpoint, and detailed information and the response of salvage treatment were not obtained. Other trials [4][5][6][7] were in favor of AC; the clinical impression of these trials is limited, as these trials either did not achieve the primary endpoint or did not have a significant clinical implication because of poor study design, incomplete patient accrual, or early termination. In 2013, an updated meta-analysis was performed including 945 patients in 9 randomized clinical trials [8].

3. Neoadjuvant Immunotherapy in MIBC

Recently, immune checkpoint inhibitor (CPI) therapy has become the standard treatment option for metastatic urothelial carcinoma (mUC) In 2016–2017, atezolizumab, avelumab durvalumab, nivolumab, and pembrolizumab were approved for use in mUC by the United States Food and Drug Administration (FDA). Owing to their clinical benefits in metastatic settings, several CPIs are being investigated in perioperative settings. Therefore, we have discussed the current evidence of perioperative CPIs, and have summarized the results from recent trials in this section (**Table 1**).

Table 1. Summary of current neoadjuvant trials for immunotherapy with or without other agents in MIBC.

Trial	Agent	Phase	Population	Cisplatin Eligibility	Upper-Tract Disease Included
Signle-Agent therapy					
NCT02662309 (ABACUS)	**Atezolizumab**	**2**	**cT2-T4N0**	**N**	**N**
NCT02451423	**Atezolizumab**	**2**	**cTa-T4N0**	**N**	**N**

Trial	Agent	Phase	Population	Cisplatin Eligibility	Upper-Tract Disease Included
NCT03577132	Atezolizumab	2	cT2-T4N0-1	Y	N
NCT03498196 (BL-AIR)	Avelumab	1/2	cT2-T4aN0	N	N
NCT03406650 (SAKK 06/17)	Durvalumab	2	cT2-T4N0-1	Y	Y
NCT02736266 (PURE-01)	Pembrolizumab	2	cT2-T4N0	Y	N
NCT03212651 (PANDORE)	Pembrolizumab	2	cT2-T4N0	N	N
NCT03319745	Pembrolizumab	2	cT2-T4N0	Y	N
CPI with other immunotherapy					
NCT02812420	Durvalumab + Tremelimumab	1	cT2-3aN0	Y	Y
NCT03472274 (DUTRENEO)	Durvalumab + Tremelimumab	2	cT2-T4N0-1	Y	N
NCT03234153 (NITIMIB)	Durvalumab + Tremelimumab	2	cTa-T4anyN	N	N
NCT02845323	Nivolumab + Urelumab	2	cTa-T4N0	N	N
NCT03387761 (NABUCCO)	Nivolumab + Ipilimumab	1b	cTa-T4anyN	Y	N
NCT03520491 (CA209-9DJ)	Nivolumab + Ipilimumab	2	cT2-4aN0	N	N
NCT03532451 (PrE0807)	Nivolumab + Lirilumab	1b	cT2-T4aN0-1	Y	N
NCT04209114 (CA045-009)	Nivolumab + Bempeg	3	cT2-T4N0	N	N
NCT03832673 (PECULIAR)	Pembrolizumab + Epacadostat	2	cT2-T3N0	Y	N
NCT04586244 (Optimus)	Retifanlimab + Epacadostat	2	cT2-T3bN0	N	N
NCT04430036	Zalifrelimab + Balstilimab	2	cT2-T4N0-1	Y	N
CPI with chemotherapy					
NCT02989584	Atezolizumab + GC	2	cT2-T4aN0	Y	N
NCT03674424 (AURA)	Avelumab + Chemotherapy	2	cT2-T4anyN	Y	N
NCT03732677 (NIAGARA)	Durvalumab + GC	3	cT2-T4aN0	Y	N
NCT03549715 (NEMIO)	Durvalumab + Tremelimumab + ddMVAC	1/2	cT2-T4N0-1	Y	N
NCT03912818	Durvalumab + Chemotherapy	2	cT2-T4N0-1	Y	N
NCT03661320 (ENERGIZE)	Nivolumab + BMS-986205 + GC	3	cT2-T4N0	Y	N
NCT03294304 (BLASST-1)	Nivolumab + GC	2	cT2-T4N0-1	Y	N
NCT03558087	Nivolumab + GC	2	cTa-T4N0	Y	N
NCT04506554	Nivolumab + aaMVAC	2	cT2-T3N0	Y	N
NCT04383743	Pembrolizumab + MVAC	2	cT2-T4N0-1	Y	N
NCT02690558	Pembrolizumab + GC	2	cT2-T4N0	Y	N
NCT02365766 (HCRN GU14-188)	Pembrolizumab + GC	2	cT2-T4N0	Y/N (two cohorts)	Y
NCT03924856 (KEYNOTE-866)	Pembrolizumab + GC	3	cT2-T4N0-1	Y	N
NCT04861584 (GZZJU-2021NB)	Teriprizumab + GC	2	cT2-T4N0-1	Y	N
NCT04730219	Tislelizumab + Nab-paclitaxel	2	cT2-T4aN0	Y	N

Trial	Agent	Phase	Population	Cisplatin Eligibility	Upper-Tract Disease Included
NCT04553939	Toripalimab + Gemcitabine	2	cT2-T4anyN	N	N
NCT04099589	Toripalimab + GC	2	cT2-T4aN0	Y	Y
CPI with other agents					
NCT04289779 (ABATE)	Atezolizumab + Cabozantinib	2	cT2-T4anyN	N	N
NCT03534492 (NEODURVARIB)	Durvalumab + Olaparib	2	cT2-T4aN0	Y	N
NCT03773666 (BLASST-2)	Durvalumab + Oleclumab	1	cT2-T4aN0	N	N
NCT04610671	Nivolumab + CG0070	1	cT2-T4aN0	N	N
NCT03518320	Nivolumab + TAR-200	1	cT2-T3N0-1	N	N
NCT04700124 (KEYNOTE-B15/EV-304)	Pembrolizumab + Enfortumab vedotin	3	cT2-T4N0-1	Y	N
NCT03924895 (KEYNOTE-905/EV-303)	Pembrolizumab + Enfortumab vedotin	3	cT2-T4N0-1	N	N
NCT03978624	Pembrolizumab + Entinostat	2	cT2-T4aN0	N	N
NA (SURE)	Pembrolizumab + Sacituzumab govitecan	2	cT2-T4N0	N	N
NCT04813107	Tislelizumab + APL-1202	1/2	cT2-T4aN0	N	N
CPI with radiation					
NCT04543110 (RADIANT)	Durvalumab + Radiation	2	cT2-T4aN0	N	N
NCT04779489 (CIRTiN-BC)	CPIs + Radiation	2	anyTN+	N	N
NCT03529890 (RACE IT)	Nivolumab + Radiation	2	cT3-T4anyN	N	N

There have been two pivotal trials of neoadjuvant CPI alone to date [9][10]: The PURE-01 trial (NCT02736266) [9] was an open-label, single-arm, phase 2 study that assessed the activity of pembrolizumab as neoadjuvant immunotherapy before RC in patients with MIBC with predominant UC histology and cT2-3bN0 stage. A total of 92% of patients were eligible for cisplatin. Recently, a study that evaluated the surgical safety of neoadjuvant pembrolizumab from the PURE-01 study population [11] indicated that high-grade complications (defined as Clavien –Dindo ≥ 3a) were observed in 34% of patients, and that there was no perioperative mortality at 90 days. Survival analysis from PURE-01 revealed that the pembrolizumab effect was maintained post-RC in most patients, with 1- and 2-year event-free survival (EFS) rates of 84.5% and 71.7%, respectively [12].

Cytotoxic T-lymphocyte antigen 4 (CTLA-4), another key immune checkpoint, is expressed by activated T cells and regulatory T cells. Blocking of the T-cell negative regulator CTLA-4 allows CD28 and B7 interactions, which result in T-cell activation, proliferation, tumor infiltration and, ultimately, cancer cell death [13]. CTLA-4 inhibits the early activation and differentiation of T cells (typically in the lymph nodes), whereas programmed cell death protein 1 (PD-1) modulates their effector functions (mostly within tumors), which can lead to T-cell exhaustion [14]. Furthermore, the combination of CTLA-4 and PD-1/PD-L1 inhibitors showed promising clinical activity in several clinical trials [15].

A total of 96% of patients underwent resection within 12 weeks, and grade 3–4 immune-related adverse events (AEs) occurred in 55% of patients. Furthermore, a total of 46% of patients showed pCR, and 58% had no remaining invasive disease (pCR or pTisN0/pTaN0). Cisplatin-eligible patients with cT2–T4aN0–1 were classified as immunologically “hot” or “cold” according to a tumor immune score devised by NanoString Technologies. In the “hot” arm, 36.4% of NAC and 34.8% of DU/TRE had a pCR, while 68.8% of patients in the NAC “cold” arm had a pCR.

Until recently, combination treatment with PD-1/PD-L1 and CTLA-4 inhibitors has been studied extensively; however, newer strategies are now being investigated in the neoadjuvant setting, such as combination treatment with epacadostat, BMS-986205 (IDO-1 inhibitor), or NKTR-214/BEMPEG (CD122-preferential IL-2 pathway agonist).

Neoadjuvant immunotherapy with cytotoxic chemotherapy is being extensively investigated. Conventional chemotherapy can stimulate tumor-specific immune responses either by inducing immunogenic cell death (ICD) of tumor cells or by engaging immune effector mechanisms [16]. ICD, with several mechanisms—including exposure of calreticulin to the outer cell surface; release of adenosine triphosphate, annexin-1, and high-mobility group box 1 protein; autophagy; inflammasome activation; induction of type 1 interferon signaling, and release of mitochondrial formyl peptides—induces premortem reticular stress and releases tissue-damage-denoting substances (alarmins) that alert the immune system [17]. Furthermore, conventional chemotherapy can promote the activation of immune effector cells, hamper the functions of immunosuppressive cells, or alter whole-body physiology through the promotion and/or activation of mechanisms that ultimately support immunological competence [18].

cohort 1 was cisplatin-eligible, and cohort 2 was cisplatin-ineligible. There was one death on post-RC day 9 due to mesenteric ischemia. Currently, there are three ongoing phase 3 trials of neoadjuvant immunotherapy combined with cisplatin-based chemotherapy (NIAGARA [NCT03732677], ENERGIZE [NCT03661320], and KEYNOTE-866 [NCT03924856]), but their results have yet to be reported. Meanwhile, several ongoing studies are investigating immunotherapy with non-cisplatin-based chemotherapy, including nab-paclitaxel and gemcitabine as neoadjuvant treatments.

ADCs are complex engineered therapeutics consisting of monoclonal antibodies directed toward tumor-associated antigens, to which highly potent cytotoxic agents are attached using chemical linkers [19]. Recently, several studies of ADCs in mUC have shown promising results.

EV-201 (NCT03219333) is a global, phase 2, single-arm study that administered 1.25 mg/kg enfortumab vedotin (intravenously on days 1, 8, and 15 of every 28-day cycle) to patients with locally advanced or metastatic UC who were previously treated with platinum chemotherapy and anti–PD-1/PD-L1 therapy [20]. Based on the results of EV-201, EV-301 (NCT03474107) was conducted; EV-301 is a global, open-label, phase 3 study that investigated enfortumab vedotin vs. chemotherapy in patients with locally advanced or metastatic UC who had previously received platinum-containing chemotherapy, and had disease progression during or after PD-1/PD-L1 inhibitor treatment [21]. Both ORR and disease control rate were significantly higher with enfortumab vedotin vs. chemotherapy (40.6% vs. 17.9% and 71.9% vs. 53.4%, respectively; one-sidedp The FDA granted accelerated approval to enfortumab vedotin to treat patients with locally advanced or metastatic UC who previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic settings.

Scott et al. performed a phase 1/2 basket study (NCT01631552) on patients with advanced solid tumors receiving intravenous sacituzumab govitecan administered on days 1 and 8 of 21-day cycles until progression or unacceptable toxicity, and reported the results of patients with mUC [22]. TROPHY-U-01 (NCT03547973) is a multicohort, global, open-label phase 2 study evaluating the clinical activity of sacituzumab govitecan in patients with unresectable, locally advanced or metastatic UC. The results of cohort 1—which includes patients progressing after platinum and CPI therapy with unlimited prior lines of therapy—were recently reported [23]. On 13 April, 2021, the FDA granted accelerated approval to sacituzumab govitecan for patients with locally advanced or metastatic UC who previously received platinum-containing chemotherapy and either a PD-1 or a PD-L1 inhibitor.

NEODURVARIB (NCT03534492) was a single-arm, phase 2 trial that assessed the impact of neoadjuvant durvalumab plus olaparib (a poly ADP-ribose polymerase inhibitor) in MIBC (cT2–T4aN0) One death related to postoperative complications was reported. Grade 3–4 AEs were detected in only 8.3% of patients. ABATE (NCT04289779) is an open-label, single-arm study to assess the efficacy and safety of cabozantinib (tyrosine kinase inhibitor whose targets include MET, AXL, and VEGFR2) with atezolizumab as neoadjuvant therapy for cT2–T4aN0/

In the metastatic setting, several studies assessed the clinical benefit of FGFR inhibitors. The confirmed response rate to erdafitinib therapy was 40% (3% with a CR and 37% with a partial response). Currently, there are no studies of neoadjuvant FGFR-targeted agents with immunotherapy combination in muscle-invasive disease. In the perioperative setting, only infigratinib (FGFR1–3-selective tyrosine kinase inhibitor) monotherapy is currently being investigated as neoadjuvant (NCT0422804) and adjuvant

Many efforts to find an appropriate partner for CPI therapy in the neoadjuvant setting are underway. There are several trials involving emerging agents—including CD73 inhibitor (NCT03773666), replication-competent oncolytic adenovirus (NCT04610671), and synthetic benzamide-derivative histone deacetylase inhibitor (NCT03978624). These studies are currently ongoing, and the results have not yet been reported.

Radiation can synergize with immunotherapy to improve oncological outcomes by causing ICD and increasing immune marker expression [24]. Based on this hypothesis, several trials of neoadjuvant immunotherapy with radiotherapy (RT) prior to cystectomy in MIBC are being conducted. RADIANT (NCT04543110) assesses the effect of sequential radiation and durvalumab immunotherapy given as treatment prior to surgery with RC for patients with bladder cancer who are unfit for or decline cisplatin. IT (NCT03529890, nivolumab + radiotherapy) and CIRTiN-BC (NCT04779489, several CPIs + radiotherapy) trials are also ongoing.

4. Adjuvant Immunotherapy in MIBC

There are three large-scale, randomized phase 3 trials for adjuvant immunotherapy (**Table 2**). The IMvigor 010 study (NCT02450331)—a multicenter, open-label, randomized phase 3 trial—evaluates atezolizumab for adjuvant therapy in patients with high-risk muscle-invasive UC (MIUC) [25]. Patients had ypT2–4a or ypN+ tumors following NAC or pT3–4a or pN+ tumors if no NAC was administered. A total of 807 patients were randomly assigned (1:1) to receive 1200 mg atezolizumab administered intravenously every 3 weeks for 16 cycles, up to one year, or to observation (whichever occurred first).

Table 2. Summary of phase 3 trials for adjuvant immunotherapy in muscle-invasive bladder cancer.

Trial	Phase	Agent	Control	N	Primary Endpoint	Upper Tract	Cisplatin-Based NAC
NCT03244384 [26] (AMBASSADOR)	3	Pembrolizumab	Observation	739	OS, DFS	Included	Included
NCT02632409 [27] (CheckMate 274)	3	Nivolumab	Placebo	700	DFS	Included	Included
NCT02450331 [25] (IMvigor010)	3	Atezolizumab	Observation	809	DFS	Included	Included

The CheckMate 274 trial (NCT02632409) is a recent randomized, double-blind, multicenter phase 3 trial of nivolumab vs. placebo in patients with high-risk MIUC after radical surgery, which reported positive results [27]. Patients had ypT2–4a or ypN+ tumors following NAC or pT3–4a or pN+ tumors if no NAC was administered. Patients were randomly (1:1) assigned to groups that received 240 mg nivolumab every 2 weeks or placebo for ≤1 year of adjuvant treatment. The primary endpoints were DFS in all randomized patients and patients with tumor PD-L1 expression ≥1%.

Although the IMvigor 010 (NCT02450331) and CheckMate 274 trials (NCT02632409) were similar in design, they showed conflicting results. These two trials had some differences in population and study design. Given that it is not appropriate to compare the two trials directly, these conflicting results should be interpreted cautiously. The AMBASSADOR (NCT03244384) trial—a multicenter, randomized phase 3 trial of adjuvant pembrolizumab vs. observation—is currently ongoing in patients with high-risk MIUC [26].

Currently, the use of adjuvant immunotherapy with other agents is not being actively investigated. Instead of the “adjuvant-only” setting, adjuvant immunotherapy with other agents is being researched in conjunction with the neoadjuvant approach. We have summarized the major phase 3 trials involving perioperative (sequential) immunotherapy with other agents in **Table 3**.

Table 3. Summary of phase 3 trials for perioperative sequential treatment.

Trial	Phase	Agent	Arm
NCT04209114 (CA045-009)	3	Nivolumab + Bempeg	Arm A: Neoadjuvant nivolumab + bempeg => RC => Adjuvant nivolumab + bempeg Arm B: Neoadjuvant nivolumab => RC => Adjuvant nivolumab Arm C: RC alone
NCT03732677 (NIAGARA)	3	Durvalumab + GC	Arm A: Neoadjuvant durvalumab + GC => RC => Adjuvant durvaluamb Arm B: Neoadjuvant GC => RC => No adjuvant therapy
NCT03661320 (ENERGIZE)	3	Nivolumab + BMS-986205 + GC	Arm A: Neoadjuvant GC => RC => No adjuvant therapy Arm B: Neoadjuvant nivolumab + placebo + GC => RC => Adjuvant nivolumab + placebo Arm C: Neoadjuvant nivolumab + BMS-986205 + GC => RC => Adjuvant nivolumab + BMS-986205

Trial	Phase	Agent	Arm
NCT03924856 (KEYNOTE-866)	3	Pembrolizumab + GC	Arm A: Neoadjuvant pembrolizumab + GC => RC => Adjuvant pembrolizumab Arm B: Neoadjuvant placebo + GC => RC => Adjuvant placebo
NCT04700124 (KEYNOTE-B15/EV-304)	3	Pembrolizumab + Enfortumab vedotin	Arm A: Neoadjuvant pembrolizumab + enfortumab vedotin => RC => Adjuvant pembrolizumab + enfortumab vedotin Arm B: Neoadjuvant GC => RC => No adjuvant therapy
NCT03924895 (KEYNOTE-905/EV-303)	3	Pembrolizumab + Enfortumab vedotin	Arm A: Neoadjuvant pembrolizumab + enfortumab vedotin => RC => Adjuvant pembrolizumab + enfortumab vedotin Arm B: Neoadjuvant pembrolizumab => RC => Adjuvant pembrolizumab Arm C: RC alone

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