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REVIEW ARTICLE

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A Review of Emerging Neoadjuvant Intravesical Strategies to Enhance Systemic Immune Checkpoint Blockade in Patients With Cisplatin-Ineligible Muscle-Invasive Bladder Cancer Through the Induction of Immunogenic Cell Death and Activation of Tertiary Lymphoid Structure formation

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Patients diagnosed with muscle-invasive bladder cancer (MIBC) frequently exhibit a high incidence of micrometastatic disease. The current standard of care for localized MIBC involves cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy. Novel treatment alternatives in the neoadjuvant setting are urgently needed because more than 50% of the patients are ineligible for standard cisplatin-based neoadjuvant chemotherapy. Neoadjuvant approaches for patients with cisplatin-ineligible MIBC are rapidly evolving, with significant advancements transforming the treatment landscape for MIBC. Recently, systemic immune checkpoint inhibitors (ICIs) have substantially improved neoadjuvant outcomes in this patient population. However, ICIs as standalone therapies provide durable effects in only a small subset of patients, with many ultimately developing drug resistance over time, adversely affecting the overall efficacy of ICI therapy. Combination strategies integrating various treatment modalities to modulate the highly immunosuppressive tumor microenvironment and enhancing the efficacy of ICI-mediated anticancer immunity are thus crucial to overcome resistance and improve the clinical applicability of ICIs. Incorporation of systemic ICIs into combination regimens with advanced intravesical therapies, such as TAR-200 and the oncolytic adenovirus CG0070, may offer safe and clinically effective treatment alternatives with the potential to transform the current standard of care for patients with cisplatin-ineligible MIBC. Several prospective studies that have investigated the combination of systemic ICIs with intravesical therapies, including innovative mechanisms of action, such as TAR-200 and oncolytic viruses, have provided preliminary data regarding their efficacy and safety. This review aims to summarize the mechanistic rationale and ongoing clinical trials involving novel neoadjuvant strategies combining intravesical TAR-200 or CG0070 with systemic ICIs for patients with cisplatin-ineligible MIBC, particularly focusing on the induction of immunogenic cell death and the development of tertiary lymphoid structures.

Key Words: Muscle-invasive bladder cancer, Immune checkpoint inhibitors, Intravesical therapy, Tertiary lymphoid structures, Immunogenic cell death

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INTRODUCTION

Bladder cancer (BC) ranks 13th in terms of mortality among all cancer types, with its incidence increasing with age [1-3]. Approximately 25% of newly diagnosed patients present with muscle-invasive BC (MIBC) [4,5], a rate that has remained relatively stable over the past decade [6]. Although radical cystectomy (RC) combined with pelvic lymph node dissection is the current primary treatment for nonmetastatic MIBC, up to 50% of patients develop distant metastases and ultimately succumb to their disease because of the presence of occult micrometastatic disease at the time of RC [7-9]. Furthermore, the decrease in long-term survival outcomes after RC correlated with the pathological stage and nodal involvement indicates a high risk of early systemic dissemination in localized MIBC [7,9-13]. A systematic review of 57 studies evaluating long-term survival outcomes of patients after RC reported a 10-year disease-specific survival rate of 78.9% for patients with T2 disease, compared with 43.1% for those with T3–4 disease [10]. In patients who undergo RC, systemic recurrence rates vary by stage, ranging from 20%–30% for pathologic stage pT2, 40% for pT3, >50% for pT4, and approximately 70% for node-positive disease [11-13]. In the context of MIBC, the implementation of effective neoadjuvant systemic therapy is essential for downstaging the primary tumor prior to RC and eradicating clinically undetectable micrometastases at the time of RC [8,9,14-16].

The chemosensitivity observed in MIBC underpins the rationale for administering neoadjuvant cisplatin-based combination chemotherapy prior to RC, which is considered the standard treatment for patients with clinically nonmetastatic MIBC [9,14-20]. This approach provides an absolute 5-year overall survival (OS) benefit of 5%–8% compared with that with RC alone [17,18]. Currently, the most frequently employed treatment regimens consist of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin supplemented with granulocyte-stimulating factor support, in addition to gemcitabine combined with cisplatin, in which cisplatin is administered at a dose of 70 mg/m^2 per cycle for a maximum of 4 cycles [8,19-26]. The clinical efficacy of these treatment regimens is comparable, with pathological complete response (pCR) rates ranging from 30%–40% and pathological partial response (PR) rates of 40%–60%, both of which correlate with improved OS [8,19-24].

Unfortunately, cisplatin-based neoadjuvant strategies are underutilized in patients with MIBC owing to a confluence of factors, including advanced age, inherent frailty, poor performance status, multiple comorbidities, and renal dysfunction [27-32]. Cisplatin ineligibility is explicitly delineated by the Galsky criteria, which encompass a World Health Organization or Eastern Cooperative Oncology Group performance status of 2, a Karnofsky performance status ranging from 60%–70%, presence of peripheral neuropathy classified as ≥grade 2 according to the Common Terminology Criteria for Adverse Events version 4, audiometric hearing loss also classified as ≥grade 2 per Common Terminology Criteria for Adverse Events version 4, New York Heart Association Class III heart failure, and creatinine clearance <60 mL/min [27]. Various clinical factors, such as renal dysfunction, suboptimal performance status, peripheral neuropathy, hearing impairment, and cardiovascular dysfunction, contribute to the ineligibility of nearly 50% of patients with MIBC for cisplatin-based neoadjuvant chemotherapy [27-32]. This ineligibility is predominantly attributed to compromised renal function. As cisplatin is primarily excreted by the kidneys through glomerular filtration and renal tubular secretion, DNA crosslinks and adducts formed by cisplatin accumulate in the renal proximal tubules, resulting in cisplatin-induced nephrotoxicity via tubulointerstitial damage and decreased blood flow in the renal vasculature [33,34]. Furthermore, renal function may be impaired by obstructive uropathy caused by tumor invasion, a condition frequently observed at the time of presentation because of the aggressive nature of MIBC [35]. With no alternative options currently available, patients with MIBC who are ineligible for cisplatin represent a population with significantly unmet needs for the development of effective neoadjuvant therapies [32,36].

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LIMITED CLINICAL EFFICACY OF NEOADJUVANT SYSTEMIC IMMUNE CHECKPOINT BLOCKADE AS MONOTHERAPY FOR CISPLATIN-INELIGIBLE MIBC

BC demonstrates considerable immunogenicity, activating both the innate and adaptive components of the immune system [37-49]. The first line of defense against BC comprises innate immune effectors, including macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells. These innate immune cells coordinate with antigen-specific B and T lymphocytes to eliminate tumors and confer long-term immunity. However, to evade immune surveillance, tumors secrete or promote the release of immunosuppressive and anti-apoptotic factors such as transforming growth factor-β, prostaglandin E2, interleukin-10, and interleukin-6. Consequently, there is an influx of various immunosuppressive effectors from the bloodstream, including neutrophils, $FoxP3^+$ regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs). A highly immunosuppressive tumor microenvironment (TME) significantly contributes to BC progression by facilitating the expansion and activation of M2-like tumor-associated macrophages (TAMs), Tregs, and MDSCs, while also restricting neoantigen expression and upregulating immune checkpoints. These processes collectively diminish T-cell functionality, inhibit antitumor immune responses, and facilitate evasion of immune surveillance by cancer cells through multiple mechanisms, such as limiting T-cell effector functions by engaging immune checkpoints. Programmed cell death protein 1 (PD-1) is a membrane receptor found on the surface of several immune cell types, including mature T lymphocytes, NK cells, B lymphocytes, and macrophages. Upon activation, PD-1 interacts with its ligands, programmed cell death ligand 1 and 2 (PD-L1/PD-L2), which are expressed on the surface of antigen-presenting cells (APCs) as well as certain tumor cells. Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), predominantly expressed on T lymphocytes, negatively regulates T-cell activation by demonstrating greater affinity for CD80 and CD86 on APCs than for CD28.

T lymphocytes, particularly their ability to mediate antigen-specific cytotoxicity, have emerged as a pivotal focus for harnessing the adaptive immune system in the battle against cancer [37,44-46,48-51]. A diverse array of T-cell subtypes has been identified, including proinflammatory cytotoxic $CD8^+$ T cells (CTLs), anti-inflammatory Tregs, and $CD4^+$ helper T cells (Th), particularly those of the Th1 subtype, revealing notable T-cell heterogeneity in BC. Tumor-derived DNA and other damage-associated molecular patterns (DAMPs) facilitate DC activation and the subsequent production of type I interferons and interferon-gamma (IFN-γ). Th1 cells primed by DCs in the lymph nodes are subsequently recruited to the TME, where secreting IFN-γ can stimulate the antigen presentation of DCs and CTL function, as well as polarize macrophages to the M1 proinflammatory phenotype. However, BC cells release a range of immunosuppressive and antiapoptotic factors, such as transforming growth factor-β, prostaglandin E2, C-C motif ligand 2, interleukin-10, and interleukin-6 [37,43,45,47]. This secretion establishes a highly tolerogenic TME, closely associated with the accumulation of various types of immunosuppressive cells, including MDSCs, tolerogenic DCs, TAMs, and Tregs. High infiltration of TAMs, MDSCs, and Tregs within the TME reduces tumor immune surveillance and correlates negatively with the stage, grade, and prognosis of BC [49,52,53]. A recent single-cell RNA sequencing study analyzing dynamic TME alterations during BC progression also revealed several key findings [39]. The study identified upregulation of glycolysis, increase in PD-L1 levels, and downregulation of chemokines and major histocompatibility complex (MHC)-II molecules, which contribute to a reduction in immune cell recruitment and facilitate the mechanisms of immune evasion. Metabolic reprogramming in tumor cells during the progression to MIBC, particularly through glycolysis, enhances the exhaustion of $CD8^+$ T cells and promotes the remodeling of immune cells towards immunosuppressive phenotypes, contributing to the establishment of an immunosuppressive TME.

Immune checkpoint inhibitors (ICIs) targeting CTLA-4 and the PD-1/PD-L1 axis function by obstructing interactions between immune checkpoints and their corresponding ligands [37,40,45-47]. This blockade enhances the ability of T lymphocytes and NK cells to effectively eliminate cancer cells,

reprogram the functionality of immunosuppressive immune cells, and foster a robust and sustained antitumor response. Over the past few years, alternative systemic neoadjuvant options for patients with cisplatin-ineligible MIBC have rapidly evolved with the advent of ICIs to provide greater efficacy and improved tolerability [36,38,54-61]. Clinical trials investigating neoadjuvant ICI monotherapy before RC in patients ineligible for cisplatin have provided evidence supporting the use of ICIs as a viable neoadjuvant treatment option for clinically localized MIBC [36,54-60]. These trials have reported pathological response rates of less than pT2 at 54%–66%, with pCR observed in 18%–46% of participants. For example, findings from the PURE-01 trial, a single-arm phase II study utilizing the PD-1 inhibitor pembrolizumab, indicated a pCR rate of 42% and a downstaging rate to <pT2 in 54% of patients [54]. In an update of the PURE-01 study, the 36-month event-free survival and OS rates were reported to be 74% and 84%, respectively, with a recurrence-free survival (RFS) rate of 96% among patients who achieved pCR [56].

Despite significant advancements associated with the implementation of ICI therapy in the neoadjuvant treatment of MIBC, only a limited proportion of patients derive therapeutic benefits from single-agent ICI treatments [54-60]. For instance, both the PURE-01 and ABACUS studies revealed significant disparity in pCR rates based on pretreatment PD-L1 expression levels [54,55]. Specifically, 37.1%–54.3% of patients with high PD-L1 expression achieved pCR at RC, in contrast to only 13.3%–24.5% of those with low PD-L1 expression who achieved pCR. The phenomenon of low response rates associated with low PD-L1 expression can be mainly attributed to the emergence of resistance to ICIs. Major intrinsic and extrinsic factors contributing to ICI resistance include, but are not limited to, the following [46,62-65]:

(1) First, there is an upregulation of various immune checkpoints on T cells, including CTLA-4, PD-L2, lymphocyte-activation gene 3, T-cell immunoglobulin and mucin-domain containing-3, and T-cell immunoglobulin and ITIM domain, among others [66-69].

(2) The second mechanism pertains to the downregulation or loss of MHC molecules in tumor cells, which enables these cells to evade recognition by T cells. This modification results in a reduced ability to present tumor neoantigens to T cells [70-72].

(3) The third mechanism relates to the insufficient activation of signaling pathways in T cells and tumor cells, particularly the IFN-γ receptor-Jak1/Jak2-STAT1 pathway [73].

(4) The fourth mechanism pertains to either a complete absence of tumor-infiltrating effector lymphocytes or the presence of immune infiltrates that are solely restricted to the periphery of the tumor cell mass [38].

(5) Finally, the presence of immunosuppressive cells within the TME, including TAMs, MDSCs, and Tregs, significantly contributes to the highly immunosuppressive TME and the subsequent suppression of anticancer T-cell immune responses [74-76].

These mechanisms of resistance to ICIs as monotherapy not only elucidate the rationale for developing more effective combination treatment strategies but also contribute to the clinical success of immunomodulatory neoadjuvant interventions for patients with cisplatin-ineligible MIBC interventions [37,38,41,42,45,46,62,77,78]. For example, targeting TAMs, MDSCs, and Tregs, or restoring MHC molecule expression could enhance ICI-mediated anticancer immunity [62]. Implementing combination therapies that incorporate innovative treatment modalities is crucial for modulating the adverse TME and augmenting antitumor immunity through ICIs. This review aims to delineate the current landscape and available clinical evidence regarding the combination of intravesical TAR-200 or oncolytic viruses (OV) with systemic ICIs in the neoadjuvant setting for patients with cisplatin-ineligible MIBC, highlighting the biological rationale underlying their synergistic anticancer effects, particularly focusing on the induction of immunogenic cell death (ICD) and activation of tertiary lymphoid structure (TLS) formation.

POTENTIAL SYNERGY BETWEEN ICD INDUCERS AND ICIs

In recent years, ICD has emerged as a novel and significant pharmacological strategy for enhancing ICI effectiveness [38,62,78-81]. ICD is a specific form of stress-induced regulated cell death characterized by activation of the endoplasmic reticulum (ER) and cellular stress [79,82,83].

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This process is accompanied by alterations in cell surface composition and the release of soluble mediators, occurring in a defined spatiotemporal sequence [78-80,84-87]. The release of tumor-associated antigens (TAAs) and DAMPs from injured or necrotic tumor cells, such as high-mobility group box 1, calreticulin, and heat shock proteins (HSP70/HSP90) is crucial for ICD to elicit anticancer effects. Following their release, DAMPs and TAAs are both recognized by cell surface pattern recognition receptors expressed on innate and adaptive components of the immune system, resulting in the establishment of immunological memory against tumors. TAAs function as neoantigenic epitopes derived from dying tumor cells, eliciting a robust adaptive immune response, whereas DAMPs serve as adjuvants that enhance the presentation of TAAs, promote the extracellular release of immunostimulatory factors, facilitate APC maturation, support the phagocytic uptake of dying cells, and recruit immune cells to the TME [80,84,87,88]. This process generates tumor-specific CTLs, subsequently leading to tumor cell destruction.

Consequently, ICD has been recognized as a crucial factor in modulating the immunosuppressive TME and affecting the clinical outcomes of systemic immune checkpoint blockade (ICB) strategies by adjusting tumor immunity [38,62,78-81,89-91]. ICD can transform an immunosuppressive TME with immunosuppressive M2-like TAMs and Tregs into an inflamed TME characterized by substantial infiltration of DCs, CTLs, and NK cells. For example, ICD-inducing regimens enhance antigen uptake and promote tumor-resident DC migration to tumor-draining lymph nodes, facilitating the priming and expansion of CTLs, subsequently leading to their increased infiltration into the TME. Systemic ICB therapy, which targets immune checkpoints expressed by infiltrating CTLs, can enhance ICD efficacy, thereby providing a compelling rationale for developing combinatorial clinical strategies with improved clinical outcomes. Consequently, ICD inducers, including chemotherapy and OV therapy, have garnered significant attention as potential combinatorial ICI partners for treating various tumors, particularly challenging-to-treat cancers, with minimal risk of overlapping toxicities among individual drugs [78-80,90,91].

POTENTIAL SYNERGY BETWEEN TLS INDUCERS AND ICIs

TLSs are clusters of immune cells that resemble and function similarly to secondary lymphoid organs, representing well-organized clusters of tumor-infiltrating lymphocytes (TILs) that provoke delayed immune responses [46,77,92-94]. TLSs contain an inner zone of $CD20^+$ B cell follicles juxtaposed with a $CD3^+$ T-cell-rich zone and are commonly recognized as lymphocyte niches at the tumor site. TLSs in close proximity to malignant lesions enhance the trafficking and presentation of adjacent tumor antigens via DCs. This process activates T and B cells, leading to the generation of Th cells, CTLs, memory B cells, and antibody-producing plasma cells, contributing to effective generation of antitumor immune responses. TLSs occur more frequently in MIBCs than in non–muscle-invasive BC [95,96]. The TME in MIBC demonstrates an increased prevalence of $CD8^+$ T cells, Tregs, NK cells, DCs, and plasma cells, suggesting a notable degree of immune activation and a more vigorous antitumor immune response [96,97]. Additionally, the presence of mature and/or high-density TLSs correlate with favorable clinical outcomes and immunotherapeutic responses in patients with MIBC, aligning with the robust antitumor immune responses observed in the TLS region [94,96-99]. T cells in TLS-positive MIBC are more likely to differentiate into $CXCL13^+$ $CD8^+$ T cells, which are associated with a better prognosis [97]. CXCL13, secreted by $CXCL13^+$ T cells, facilitates the clustering of NR4A2 B cells, thereby fostering TLS development. Interestingly, the *in situ* activation of germinal center B cells within TLSs for differentiation and antibody production further underscores the significance of B cells in the cancer immune cycle [94]. In patients with MIBC enriched with $CD19^+$ B cells, these cells can act as APCs to activate $CD4^+$ TILs within the TME [99]. As B cells are predominantly localized within TLSs, the presence of TLSs serves as a practical clinical marker for quantifying B cell levels in MIBC [97,99].

Consequently, therapeutic interventions that stimulate TLS neogenesis may augment adaptive immune responses and enhance the efficacy of ICIs in MIBC [92,97]. Importantly, intratumoral TLSs have emerged as promising biomarkers for predicting and potentially improving the efficacy of ICB

therapy [61,77,92,94,96-98,100]. TLS signatures are correlated with enhanced survival rates and improved responses to ICIs in MIBC [96,100]. CXCL13 expression by follicular helper cells within the TLS may serve as a significant predictive biomarker for response to ICI in patients with MIBC, as well as a biomarker for TLS in this patient population [61,98].

COMBINATIONS OF INTRAVESICAL DELIVERY OF ICD AND TLS INDUCERS WITH SYSTEMIC ICB AS NEOADJUVANT THERAPY FOR CISPLATIN-INELIGIBLE MIBC

Unlike cancers of other visceral organs, the bladder is uniquely accessible through direct catheterization of the urethra, enabling intravesical administration of anticancer agents while avoiding drug sequestration and off-target toxicity [36,38]. The immunogenic and antitumor effects of intravesical treatments can extend to distant sites [38]. The Pandore clinical trial demonstrated that both cellular and humoral immune responses to uropathogenic *Escherichia coli* correlated with improved efficacy of pembrolizumab in the neoadjuvant context [61], reinforcing the link between mucosal immunity and responsiveness to systemic ICB in BC [36]. Therefore, a combination of therapies that elicit a robust yet tolerable local response within the bladder, followed by systemic enhancement of tumor-specific abscopal effects, represents a promising option warranting further clinical investigation. These innovative combinatorial therapeutic strategies have the potential to transform the existing standard of care for patients with cisplatin-ineligible MIBC in the neoadjuvant setting for 3 primary reasons: (1) they may enhance the rate of pCR by integrating local and systemic treatment modalities; (2) they can prime bladder mucosal immunity while augmenting the diversity and amplitude of tumor-specific CTL clones; and (3) they can mitigate toxicity and off-target effects [36]. Modulation of mucosal immunity within the bladder via the intravesical administration of immunostimulatory agents intended to elicit ICD and TLS responses, may produce a synergistic effect when combined with systemic ICB [101]. This approach merits further investigation regarding potential advantages in clinical trials as a viable and safe neoadjuvant therapeutic strategy for cisplatin-ineligible patients with MIBC.

CURRENT EVIDENCE PERTAINING TO CLINICAL COMBINATION TRIALS OF TAR-200 AND SYSTEMIC ICIs FOR CISPLATIN-INELIGIBLE MIBC

Chemotherapy directly targets cancer cells by disrupting DNA synthesis and cell division as well as by inducing apoptosis; further, it has the potential to enhance the immune TME and reduce resistance pathways that are known to mitigate the antitumor effects of ICIs [77,101,102]. The administration of chemotherapy before ICIs administration may facilitate the release of tumor antigens through ICD, which can enhance antigenic stimulation and consequently promote a more targeted immune response. Chemotherapy also activates elements of the innate immune system by recruiting effector NK cells, DCs, and CTLs to the tumor site. This process enhances the differentiation of tumor-specific CTLs through proinflammatory cytokine production while reducing immunosuppressive cells, such as MDSCs and Tregs [101,102]. Moreover, the concurrent administration of chemotherapy and ICIs demonstrate a synergistic effect, facilitating enhanced TLS neogenesis and maturation, which substantially increases antitumor immunity and the incidence of pCR [92]. Finally, the efficacy of ICIs is augmented by tumor reduction achieved through chemotherapy, which concurrently diminishes the likelihood that drug-resistant clones will emerge [92,102]. The findings presented herein offer novel insights into the biological mechanisms underlying the clinical benefits of combining chemotherapy with ICIs. Intravesical gemcitabine instillations are effective and safe for treating non-muscle-invasive BC and systemic gemcitabine serve as a standard component of chemotherapy in combination with cisplatin for managing MIBC [103]. Gemcitabine exerts direct cytotoxic effects on tumor cells by inhibiting DNA synthesis and enhances the immunogenicity of tumor cells by releasing immunogenic substances [104-108]. Considerable evidence indicates that gemcitabine also modifies the immunosuppressive TME by facilitating CTL infiltration into the tumor, augmenting CTL cytotoxicity, inhibiting Th2-type immune responses while promoting Th1-type immune responses, and depleting TAMs and

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MDSCs [106,107,109-114].

The administration of a sustained, therapeutically effective dose of chemotherapy directly into the bladder effectively mitigates the drug dilution by continuous urine production and enhances drug exposure [103]. An intravesical drug delivery system specifically designed to prolong the duration of drug-urothelial contact can enhance absorption of the administered drug across the urothelium into tumor cells residing in the deeper layers of the bladder. TAR-200 is a single-compartment system comprising a silicone dual-lumen tube, wherein gemcitabine is located in the larger lumen, thereby creating a solid drug core [115,116]. TAR-200 is also designed to resist structural collapse and promote retention within the bladder owing to its intrinsic mobility and compressibility. Within the bladder, osmotic pressure regulates gemcitabine release from the internal reservoir of TAR-200, thereby ensuring a sustained therapeutic concentration of gemcitabine in the urine over an extended duration. This formulation improves the targeted treatment of urothelial carcinoma within the bladder for an indwelling duration of up to 21 days, while simultaneously minimizing both the local and systemic adverse effects associated with gemcitabine.

Two phase I studies (TAR-200-101 and TAR-200-103) have assessed the safety and preliminary antitumor efficacy of TAR-200 monotherapy in MIBC [115,117]. The TAR-200-101 trial assessed the efficacy of two 7-day cycles of neoadjuvant TAR-200 in patients diagnosed with MIBC undergoing RC, including those with a residual tumor >3 cm after transurethral resection of the bladder tumor and those who had undergone maximal transurethral resection of the bladder tumor (residual tumor <3 cm) [115]. Among 20 patients who underwent RC, 10 (50%) exhibited a pathological response, 4 (20%) achieved a pCR, and 6 (30%) demonstrated a PR. TAR-200-103 investigated 4 consecutive 21-day cycles of TAR-200 in patients with MIBC who were assessed by investigators as unfit for RC or who either refused or were ineligible for curative-intent therapy [117]. Among 35 patients, 11 achieved a pCR and 3 demonstrated a pathologic PR, resulting in an overall response rate of 40%. Across these studies, TAR-200 demonstrated a favorable tolerance profile, with the majority of adverse events classified as grade 1 to 2, including dysuria, urinary frequency, micturition urgency, urinary incontinence, pollakiuria, and urethral syndrome [115,117].

TAR-200 is administered at one-tenth of the usual intravesical gemcitabine dose (225 mg compared with 2,000 mg) [115,117-119]. In particular, low-dose gemcitabine can selectively eliminate Tregs, while concurrently inducing ICD [87,120,121]. A recent study including 61 patients with advanced solid tumors demonstrated that low-dose gemcitabine, when administered in conjunction with PD-1 inhibitors, promotes the secretion of interferons that facilitate DC maturation [121]. This combination therapy increases the efficiency of antigen cross-presentation and enhances the antitumor immunity mediated by $CD8^+$ T and NK cells through the depletion of MDSCs and Tregs. The data offer a compelling justification for implementing a treatment regimen that combines low-dose intravesical gemcitabine administered through TAR-200 with inhibitors of the PD-1 pathway to patients with cisplatin-ineligible MIBC. The SunRISe-4 study (NCT04919512) is an open-label, multicenter, randomized phase II clinical trial designed to assess the efficacy and safety of TAR-200 in conjunction with cetrelimab, an anti-PD-1 monoclonal antibody, in comparison with cetrelimab monotherapy in patients with confirmed cT2-T4aN0M0 MIBC scheduled for RC who are ineligible for or refuse neoadjuvant platinum-based chemotherapy [119]. The patients (n=160) are randomized to receive TAR-200 plus cetrelimab (cohort 1; C1) or cetrelimab alone (cohort 2; C2). TAR-200 was placed intravesically at the initial visit, removed, and replaced over a 12-week period. The primary outcome measure was the pCR rate at the time of RC, accompanied by several secondary outcomes, including safety, tolerability, and RFS. Additional exploratory outcomes included patient-reported cancer-related quality of life and pathologic overall response rate at RC, in addition to the OS and time to symptomatic progression, pharmacokinetics, biomarker analysis, and immunogenicity. The prespecified interim analysis for the SunRISe-4 study was presented following completion of the RC by the first 80 participants [122]. As of a date cut off of May 31, 2024, 120 patients (median age, 73 years; 85% male; 81% cT2; 18% residual disease) were treated (C1, n=79; C2, n=41). In the efficacy evaluation set, the centrally confirmed pCR and pathological OR rates were 42% and 60% in C1 and

23% and 35% in C2, respectively. Only 5 patients in the entire cohort progressed (1.3% in C1 and 9.5% in C2). In terms of safety, 72% of patients in C1 and 44% of patients in C2 experienced treatment-related adverse events (TRAEs), with the majority of these events classified as grade 1 or 2. The results of the SunRISe-4 trial, when contextualized alongside other neoadjuvant combination trials, indicated that the combination of TAR-200 and cetrelimab demonstrated a more favorable safety profile, while maintaining comparable efficacy outcomes [122], supporting further investigation of TAR-200 in conjunction with cetrelimab in patients with cisplatin-ineligible MIBC.

CURRENT EVIDENCE PERTAINING TO THE CLINICAL COMBINATION TRIALS OF INTRAVESICAL OVS AND SYSTEMIC ICIS FOR CISPLATIN-INELIGIBLE MIBC

OVs represent a novel and promising immunotherapeutic anticancer strategy based on various mechanisms including oncolysis, enhancement of antitumor immunity, transgene expression, and induction of vascular collapse [38,84,123,124]. OVs are distinguished by their non-pathogenic nature, selective targeting, destruction of cancer cells, and ability to be genetically engineered to produce agents lethal to tumors. Malignant cells demonstrate increased vulnerability to OV infection, which can be attributed to tumor-driver mutations inherent in cancer cells as well as specific cytokines secreted by these cells. Upon replication within cancer cells, OVs induce cell lysis, subsequently facilitating their spread to adjacent tumor tissues, thereby initiating a new cycle of infection. This process stimulates strong antitumor immune responses and leads to a sustained increase in viral load, thereby enhancing the destructive efficacy against tumors. Simultaneously, OVs induce changes in cellular function, ultimately resulting in the death and lysis of cancer cells owing to the damage inflicted on organelles by proteins synthesized during viral replication within tumor cells [123,124]. Furthermore, OVs can effectively inhibit tumor-induced angiogenesis and disrupt the supply of nutrients and oxygen to tumor cells through the direct lysis of vascular endothelial cells and microthrombosis [38,124].

A robust mechanistic rationale supports the use of a combination of OVs and ICIs. OVs facilitate the emergence of novel TAAs, recruit new antigen-specific CTLs, and enhance the immunogenicity of tumors, thereby establishing a foundation for ICI therapy [84,124,125]. OVs facilitate the establishment of an effective and long-lasting antitumor immune memory, which plays a crucial role in preventing tumor recurrence and metastasis [38,123,126-128]. This is accomplished by releasing the complete spectrum of TAAs into an inflammatory environment through tumor lysis and ICD induction while simultaneously disrupting the immunosuppressive TME. A significant accumulation of misfolded viral proteins within the ER lumen induces ER stress and subsequently triggers ICD [38,127]. The cumulative downstream effects of OV-induced ICD disrupt the immunosuppressive TME and induce the immunological eradication of primary, metastatic, or recurrent tumor cells [38,124,126,128]. The advantages of OVs over other ICD inducers are primarily ascribed to their capacity to selectively target and eradicate tumor cells while sparing non-malignant cells [84]. Consequently, the most substantial therapeutic benefits may be achieved by integrating the complementary immunogenic effects of OVs and ICIs. The therapeutic efficacy of the combination is substantial in the short term, and can modify the TME as well as improve tumor immunity over the long term. The application of OVs as incendiary agents to induce ICD and disrupt the immunosuppressive TME before ICI administration is supported by substantial scientific rationale and preclinical evidence [38,84,124,129]. Furthermore, no dose-limiting toxicities were observed during safety testing, suggesting that OVs are promising candidates that may synergize with ICIs to enhance the efficacy of ICB [124,129].

BC is one of the most immunogenic tumor types, owing to its high mutational burden and neoantigen load, making it a suitable candidate for OV [38,123,130]. OV therapy presents innovative strategies for MIBC treatment with numerous benefits, such as precise targeting of cancer cells, a lower incidence of adverse effects, reduced likelihood of drug resistance, and high efficacy of tumor cell eradication [84,123,124]. The direct intratumoral infusion of OVs not only safeguards the OV from the systemic antiviral humoral response but also promotes site-specific tumor lysis and viral replication, thereby reducing systemic viral dissemination

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and associated toxicity [38,84]. The urinary bladder serves as an appropriate target organ for OV therapy for several reasons, particularly to minimize systemic side effects. The bladder is a distinct organ characterized by an asymmetric multilayered unit membrane that limits systemic exposure to various agents [131]. The anatomical features of the bladder also enhance the delivery of intravesical OV therapy, allowing OVs to specifically target BC cells via membrane receptors [38,124,131,132]. The direct administration of OVs into the bladder through the urethra enhances the exposure of the tumor to elevated viral titers. Furthermore, recent evidence indicates that OV infections may facilitate CXCR5-dependent recruitment of B cells, which initiates the development of TLSs containing functional germinal centers, subsequently enhancing the humoral response against tumor-specific antigens [38]. These findings prompt an inquiry into whether intravesical administration of OVs prior to the commencement of PD-1/PD-L1 axis inhibition may augment the effectiveness of systemic ICB in MIBC, particularly in patients whose tumors exhibit low PD-L1 expression, immune exclusion, or immune desert phenotypes [38,133]. In theory, integration of intravesical OVs with systemic ICB in a neoadjuvant context is anticipated to achieve local control through direct oncolysis and facilitate the eradication of disseminated micrometastatic disease through the establishment of adaptive immune memory in patients with MIBC by reducing the systemic toxicity linked with viral dissemination [38]. However, the distinctive urothelial architecture, along with the presence of a negatively charged glycosaminoglycan layer, presents challenges for intravesical drug delivery and may limit the effectiveness of OVs in establishing infection [38,132]. Pretreatment with intravesical agents such as dodecyl maltoside may be necessary to either remove or diminish the functionality of the glycosaminoglycan layer, thereby facilitating OV infection in the urothelium without impairing their efficacy [38].

Adenoviruses can be produced with relative ease at high titers and purity, which makes them one of the most frequently utilized viral vectors for cancer therapy [123,134]. CG0070 (Cretostimogene grenadenorepvec), a conditionally replicating double-stranded DNA-based oncolytic serotype 5 adenovirus, represents the most advanced oncolytic virus currently under development for treating BC [38,135,136]. CG0070 has been genetically engineered so that its essential *E1a* gene is regulated by the human E2F1 promoter, specifically designed to replicate selectively in cancer cells that exhibit defects in the retinoblastoma (*Rb*) gene pathway. The Rb pathway is disrupted in approximately 90% of BC cases [135]. In addition to tumor-specific replication, CG0070 selectively expresses granulocyte-macrophage colony-stimulating factor, a potent inducer of specific, long-lasting antitumor immunity [135,136]. Intravesical administration of CG0070 may enhance ICI efficacy through several mechanisms: (1) direct tumor lysis achieved by selective replication within tumor cells defective in the Rb pathway, (2) reduction of the immunosuppressive TME owing to a decrease in tumor burden, (3) immune-mediated cytotoxicity resulting from the induction of ICD and TLS, and (4) promotion of a more favorable inflammatory environment for tumor-reactive T cells because of antiviral immune responses [123,135,137].

Accordingly, a phase 1b study (NCT04610671) was initiated to assess the efficacy of the combination of intravesical CG0070 and systemic nivolumab (an anti-PD-1 inhibitor) in a neoadjuvant setting for cisplatin-ineligible patients with cT2-4aN0-1M0 MIBC [135]. The primary objective of this study was to evaluate safety, and the secondary objective was to assess antitumor efficacy, as indicated by the rate of pCR and 1-year RFS. The exploratory objectives encompassed the correlation between pharmacological treatment and the following baseline factors: (1) E2F1 expression, (2) immune infiltration, (3) PD-L1 expression, and (4) TLS expression. No instances of dose-limiting toxicity were observed in 21 patients who were enrolled and treated. The most commonly reported TRAEs associated with CG0070 included grade 1/2 catheter leakage, bladder spasms, and dysuria [135]. In contrast, TRAEs attributed to nivolumab primarily include grade 1/2 fatigue and maculopapular rash [135]. Grade 3 or higher TRAEs, most due to complications of RC, occurred in 57% of patients. In total, 17 of 20 patients who successfully completed neoadjuvant treatment subsequently underwent RC, with a median interval of 82 days from the initation of neoadjuvant therapy to RC. Of all evaluable patients, the pCR rate was 42.1% and higher in patients with PD-L1 expression. Overall, the median follow-up was 27.3 months,

and the 1-year RFS rate was 70.4%. Indeed, the 1-year RFS rate was much higher in patients with pCR (87.5%). Interestingly, the clinical response correlated with the baseline tumor mutational burden, increased tumor-reactive $CD8^+$ T cells, and systemic neoantigen-specific immune response unleashed during the course of treatment. In particular, *de novo* formation of TLSs and the enlargement and maturation of pre-existing TLSs within bladder wall after intravesical CG0070 were found to be more abundant in responders than in nonresponders. The collective findings underscore the potential of this combination regimen to improve therapeutic efficacy in cisplatin-ineligible patients with MIBC, warranting phase 2/3 studies to evaluate similar combinations as neoadjuvant therapeutic options.

CONCLUSION AND PERSPECTIVES

A significant and clinically urgent need exists for novel neoadjuvant treatment options against MIBC, particularly for patients ineligible for first-line cisplatin-based chemotherapy. An enhanced understanding of how TAR-200, GC0070, and systemic ICIs modulate anticancer responses is expected to yield more effective neoadjuvant therapeutic options for this patient population. The combination of innovative intravesical strategies, including TAR-200 and CG0070, with systemic ICIs exerts anticancer effects by inducing ICD in tumor cells and promoting TLS formation within the TME. This process further stimulates specific coordinated cellular and humoral antitumor immune responses, which have been associated with pCR in the neoadjuvant setting for patients with cisplatin-ineligible MIBC. Moreover, these immunotherapy regimens are generally well-tolerated and do not delay or hinder potentially curative RC. Collectively, these findings underscore the potential of innovative intravesical strategies, such as TAR-200 or CG0070, in conjunction with systemic ICIs, to enhance therapeutic outcomes in patients with MIBC, offering new hope for those unable to receive cisplatin-based treatments.

These innovative combinations of immunomodulatory agents, while promising, remain in the early stages of clinical development and exhibit several limitations at this point in time. First, all current studies are in preclinical and early-stage clinical trials with limited sample size and controls. Although the preliminary results are encouraging and suggest potential hypotheses, more randomized controlled phase II or III clinical trials involving larger cohorts are warranted to validate the feasibility and efficacy of these combination neoadjuvant strategies. Second, the majority of endpoints reported in these clinical studies have primarily concentrated on short-term pathological responses and have involved brief follow-up periods. The impact of the pCR rate on long-term prognosis remains ambiguous, highlighting the need for an assessment of long-term clinical benefits and survival outcomes through extended follow-up. Third, the safety and tolerability are essential factors contributing to the success of neoadjuvant regimens, particularly for elderly patients with MIBC who present with multiple comorbidities. A major concern of intravesical TAR-200 or CG0070/systemic ICB combination is the occurrence of potential overlapping toxicities. It is a challenge to distinguish whether TAR-200-related TEAEs were attributable to either the drug or the device constituent, as they are integral. Although OVs are generally designed to be less infectious and virulence compared to their parent strains, the potential for *de novo* mutations during extensive replication, as well as the risks associated with transmission to untreated individuals, remain significant challenges in clinical applications. A comprehensive assessment of safety and quality of life, along with the implementation of overlapping toxicity management guidelines, should be undertaken. Fourth, additional research into the identification of the best regimens and their associated schedules is crucial for achieving an appropriate balance between the risks and benefits of these combination strategies. Finally, further elucidations are necessary to facilitate the selection of biomarkers that can effectively identify the population most likely to benefit from these combination therapies. Neoadjuvant strategies are powerful research tools for understanding MIBC biology, treatment resistance, and therapeutic responses. For example, developing efficient imaging techniques to analyze ICD and TLS within the TME represents a promising research direction for enhancing the use of novel biomarkers for patient selection. Additionally, BC urine-derived cells more accurately reflect the immune TME than blood and shared tumor signatures related to metabolic perturbation, immune suppression, and tissue

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residency [138]. This suggests potential clinical or research applications for profiling BC urine-derived cells through single-cell RNA sequencing to assess the pretreatment TME, predict sensitivity and resistance to immunotherapy, and monitor treatment response in BC.

Collectively, this review provides a fresh perspective on the biological mechanisms that underlie the clinical benefits associated with the integration of intravesical chemotherapy or OV therapy with systemic ICB based on the theoretical framework of inducing ICD and promoting TLS neogenesis and maturation. Despite several existing challenges, continued technological advancements and more comprehensive clinical investigations provide an optimistic outlook for these approaches.

NOTES

- **Author Contribution:**

  Conceptualization: HWL, HHS. Data curation: HWL, HHS. Formal analysis: HWL. Methodology: HWL, HHS. Project administration: HWL, HHS. Writing - original draft: HWL. Writing - review & editing: HWL, HHS.

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