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Research Progress of Neoadjuvant Chemotherapy in Advanced Bladder Cancer

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Abstract

Systemic treatment, commonly referred to as chemotherapy, is a fundamental approach for treating muscle-invasive bladder cancer (MIBC) and metastatic bladder cancer. Neoadjuvant chemotherapy has recently become a standard treatment for MIBC, significantly reducing tumor recurrence rates and improving patient outcomes. Patients may receive adjuvant chemotherapy involving various drug combinations to improve prognosis following surgery. MIBC patients who are unwilling or unable to undergo radical cystectomy and instead opt for bladder-sparing surgery may benefit from systemic chemotherapy combined with radiotherapy, wherein chemotherapy proves more impactful than radiotherapy. Over the past 30 years, cisplatin-based chemotherapy has been the main approach for treating metastatic bladder cancer. Recent advancements in the molecular understanding of bladder cancer have led to the use of targeted therapies, which have shown promising results. Immunotherapy for MIBC has only recently emerged, with clinical trial results indicating that immunotherapy offers better efficacy and fewer side effects for metastatic bladder cancer. In recent years, basic research on bladder cancer has been burgeoning, and clinical treatment methods have been improving accordingly. This article reviews the development of systemic treatment for bladder cancer.

Key words bladder cancer, systemic treatment, neoadjuvant chemotherapy, muscle-invasive bladder cancer

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Introduction

Bladder cancer (BCa) ranks among the most common malignant tumors of the urinary system. In 2016, the United States reported approximately 74,000 new cases of bladder [1], with about 16,000 deaths. The incidence of bladder cancer in China, though lower than that in the United States [2], is exhibiting an annual increase in both incidence and mortality rates [3]. Such trends may be attributed to advancements in medical technology and heightened health awareness among the population. Bladder cancer can be classified into non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC) based on the depth of invasion into the bladder wall. At initial diagnosis, 80% of bladder tumors are NMIBC, with 10-20% progressing to MIBC [4, 5]. Approximately 30% of tumors are diagnosed as MIBC at the initial diagnosis. The natural history and prognosis of these two subtypes of bladder cancer differ significantly [6]; patients with muscle-invasive bladder cancer are prone to distant metastasis and death, with a 5-year survival rate of only 15% for metastatic bladder cancer. Therefore, treatment for such patients often involves a combination of surgery, chemotherapy, and radiotherapy [7]. Chemotherapy for bladder cancer is divided into intravesical chemotherapy and systemic chemotherapy. Intravesical chemotherapy, administered after transurethral resection, helps reduce NMIBC recurrence. Systemic chemotherapy is used as adjuvant treatment during the perioperative period for MIBC and remains a standard treatment for metastatic bladder cancer [8]. This article reviews the progress of systemic treatment for bladder cancer from the following three aspects: 1) perioperative chemotherapy for muscle-invasive bladder cancer; 2) the application of systemic chemotherapy in bladder-sparing surgery with trimodal therapy; 3) the use of chemotherapy in advanced or metastatic bladder cancer patients. Recent developments in molecular targeted therapy and immunotherapy for bladder cancer are also highlighted.

Neoadjuvant chemotherapy

According to the EAU guidelines, the standard treatment for invasive muscle layer bladder cancer is radical cystectomy combined with pelvic lymphadenectomy [9]. The MVAC regimen (Methotrexate, Vinblastine, Doxorubicin, and Cisplatin) has been used in neoadjuvant chemotherapy since 1996 [10]. Grossman and colleagues, in an 11-year follow-up study of 317 patients with locally advanced bladder cancer undergoing radical cystectomy, found that patients receiving neoadjuvant MVAC chemotherapy exhibit a median survival of 77 months, compared to 46 months for surgery alone treatment. Although the difference was not statistically significant (p=0.06), it is clinically significant as patients clearly benefit from neoadjuvant chemotherapy. Additionally, the patients lacking cancerous cells on bladder pathology specimens post radical resection, indicating downstaging to pT0, exhibited a better prognosis compared to others. The proportion of patients achieving pT0 in the neoadjuvant chemotherapy group was 38%, significantly higher than the 15% in the surgery-only group (p<0.001) [11]. Rosenblatt et al. [12] conducted a retrospective analysis on two Nordic Cystectomy Trials involving 449 patients and found that the proportion of patients achieving pathological downstaging was significantly higher in the neoadjuvant chemotherapy group compared to the surgery-only group. The likelihood of pathological downstaging was greatest for T3 tumors, with the proportion of complete pathological remission (pT0N0) being three times higher than in other subgroups. Patients who received neoadjuvant chemotherapy and achieved complete pathological remission had a 31.1% increase in 5-year overall survival compared to the control group. A retrospective analysis of SWOG8710 trial results revealed that patients achieving postoperative complete pathological remission (pT0) following neoadjuvant chemotherapy, coupled with negative surgical margins and the excision of at least ten lymph nodes, showed significantly improved overall survival [13]. Consequently, radical cystectomy combined with neoadjuvant chemotherapy has become the standard treatment for locally advanced bladder cancer. This approach reduces postoperative tumor staging and improves patient survival rates.

An early randomized controlled trial (RCT) found that among 976 patients with muscle-invasive bladder cancer scheduled for radical cystectomy or full-dose external radiotherapy, 491 patients received three cycles of neoadjuvant chemotherapy with Cisplatin, Methotrexate, and Vinblastine (CMV). After a median follow-up of 4 years, the 3-year survival rate for patients receiving CMV neoadjuvant chemotherapy was 55.5%, compared to 50.0% in the control group (P=0.075). The median survival in the neoadjuvant chemotherapy group was 44 months compared to 37.5 months in the control group, with a pathological complete response rate of 32.5% following neoadjuvant chemotherapy [14]. Long-term follow-up with a median duration of 8 years showed that the CMV neoadjuvant chemotherapy group exhibited a 16% higher overall survival rate (HR 0.84, 95% CI 0.72-0.99), with a 10-year survival rate of 36%, highlighting its critical role in improving the prognosis of patients with muscle-invasive bladder cancer (MIBC). A meta-analysis [15] encompassing 11 RCTs and a total of 3005 patients demonstrated a significant improvement in prognosis for patients receiving Cisplatin-based neoadjuvant chemotherapy (HR=0.86, 95% CI 0.77-0.95, p=0.003). The 5-year overall survival rate and the disease-free survival rate were notably better for these patients, highlighting the important role of neoadjuvant chemotherapy in bladder cancer treatment [16].

Cisplatin is the cornerstone of all bladder cancer chemotherapy regimens and is used in combination with other chemotherapeutic agents to enhance efficacy and mitigate side effects. Two prominent regimens include Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC) and Gemcitabine plus Cisplatin (GC). In a large Phase III RCT conducted by von der Maase et al., the efficacy and safety of the GC regimen were compared with the MVAC regimen in 405 patients with locally advanced or metastatic bladder cancer [17]. The findings revealed no significant differences between the two groups in terms of overall survival (HR 1.04, 95% CI 0.82-1.32, P=0.75), time to tumor progression (HR 1.05, 95% CI 0.85-1.30), time to treatment failure (HR 0.89, 95% CI 0.72-1.10), and response rate (GC 49% vs. MVAC 46%). However, the GC regimen exhibited a higher completion rate of all six chemotherapy cycles, fewer dose adjustments, and reduced drug-related mortality (1% vs. 3% in MVAC). The drug-related mortality rate was 1% in the GC group compared to 3% in the MVAC group. Although the GC group had a higher incidence of Grade 3-4 anemia (27% vs. 18%) and thrombocytopenia (57% vs. 21%), the rates of neutropenia (71% vs. 82%), febrile neutropenia (2% vs. 14%), sepsis (1% vs. 12%), mucositis (1% vs. 22%), and alopecia (11% vs. 55%) were significantly lower. Despite similar quality-of-life outcomes between the two groups, the GC regimen showed better results in terms of weight, performance status, and fatigue [15]. Long-term survival follow-up results indicated that there was no significant difference in overall survival between the GC and MVAC groups (HR 1.09, 95% CI 0.88-1.34, P=0.66). The median survival for the GC and MVAC groups was 14 months and 15.2 months, respectively, with 5-year overall survival rates of 13.0% and 15.3% (p=0.53). The progression-free survival was 7.7 months for the GC group and 8.3 months for the MVAC group (HR 1.09), and the 5-year progression-free survival rates were 9.8% and 11.3% (p=0.63). Given its comparable efficacy to the MVAC regimen and fewer side effects, the GC regimen has become the preferred

Table 1. Recommended systemic therapy drugs for advanced bladder cancer.

Therapy schedule	Chemotherapy drug 1	Chemotherapy drug 2	Chemotherapy drug 3	Immunotherapy drug	Recommendation level
First-line					
First-line 1	Fluorouracil	Xeloda	Oxaliplatin	Trastuzumab	IA
First-line 2	Fluorouracil	Xeloda	Cis-platinum	Palizumab	IB
Second-line					
Second-line 1	Fluorouracil	Docetaxel	Oxaliplatin	Nivolumab	IIA
Second-line 2	Xeloda	Cis-platinum	Oxaliplatin		iiA
Other					
Other 1	Fluorouracil	Irinotecan			iiB
Other 2	Paclitaxel	Cis-platinum			iiB

chemotherapy option for bladder cancer in clinical practice [16]. Dash et al. found no significant differences in the pathological response rates between the GC and MVAC regimens when used as neoadjuvant chemotherapy [18]. The similarity in efficacy coupled with the reduced toxicity profile of the GC regimen has led to its preference over MVAC in many treatment protocols. Notably, the GC regimen leads to fewer severe adverse effects like neutropenia and alopecia, offering a more manageable side effect profile that aligns with current clinical trends and guidelines. Galsky et al. [19] analyzed data from an international multicenter retrospective study, which reaffirmed these conclusions, showing a complete pathological response rate of 31% for the GC regimen, comparable to 29% for MVAC (OR 0.91, 95% CI 0.48-1.72, P=0.77). There was also no significant difference in survival rates between the two groups (HR 0.78, 95% CI 0.40-1.54, P=0.48). Additionally, research by Zargar et al. indicated that both the GC and MVAC regimens, when used as neoadjuvant chemotherapy, showed a lower rate of complete pathological response compared to previously reported figures. However, there was no significant difference between the two regimens (23.9% vs. 24.5%) [20]. Several reviews comparing the GC and MVAC regimens for neoadjuvant chemotherapy have corroborated these findings [21, 22], consistently showing that while both regimens yield similar pathological response rates and survival outcomes, the GC regimen's favorable toxicity profile often secures its preference in clinical settings. The consistent findings across multiple studies and reviews highlight the reliability of the GC regimen as a viable alternative to MVAC, reflecting its growing acceptance in contemporary treatment protocols for bladder cancer.

To shorten the interval between a definitive diagnosis and radical cystectomy, intensified chemotherapy can be considered as an option. In a preclinical trial involving 39 patients with muscle-invasive bladder cancer scheduled for radical cystectomy, MVAC chemotherapy was administered every two weeks for a total of four cycles. Postoperative results confirmed a pathological response rate (pT<2) of 49%, with 10% of patients experiencing grade 3-4 toxicities [23]. Another study by Plimack et al. found that patients receiving MVAC chemotherapy biweekly for three cycles resulted in a pathological downstaging rate to pT<2 of 53%, with 38% of patients achieving a pathological stage of pT0 after surgery [24]. Previous studies reported the patient with pelvic lymph node positivity (cN1). Choueiri et al. identified a rate of 43% for N1+ patients, while Plimack et al. reported 7% for N1+ patients. Choueiri et al. observed that 82% of patients preoperatively diagnosed with pelvic lymph node metastasis (cN1+) had pathological confirmation of negativity (pN0) after surgery, highlighting the significant therapeutic impact of preoperative systemic chemotherapy for lymph node-positive patients. However, due to severe cardiovascular adverse events in 7 out of 31 participants, the initial clinical trial using intensified GC regimen neoadjuvant chemotherapy was redesigned. The revised protocol found that increasing the chemotherapy density with the GC regimen resulted in a pathological response rate (< pT2) of 56.5%. Pouessel et al. also concluded that intensified chemotherapy did not significantly increase the rate of adverse effects [25]. These findings collectively suggest that intensified chemotherapy regimens, while potentially increasing the pathological response rates, can be managed with acceptable levels of toxicity, thus offering a promising approach to improve outcomes in muscle-invasive BCa patients. Systemic therapy drugs recommended for advanced bladder cancer are listed in **Table 1**.

Patients with muscle-invasive bladder cancer and non-suitable for cisplatin-based chemotherapy currently lack access to well-established chemotherapy regimens demonstrated to effectively reduce mortality. Therefore, these patients should either participate in clinical trials or proceed directly to radical cystectomy.

Adjuvant chemotherapy

Currently, a small fraction of patients with muscle-invasive bladder cancer (MIBC) receive neoadjuvant chemotherapy. Before 2003, only 1.2% of MIBC patients received neoadjuvant chemotherapy [26]. Although a gradual increase in its application, by 2010, the figure had risen to only 20.9% [27, 28]. Consequently, many patients still opted for radical cystectomy directly without receiving neoadjuvant chemotherapy.

There is no clear evidence from randomized controlled trials (RCTs) supporting the use of adjuvant chemotherapy [29]. However, some clinical observations and retrospective studies suggest that adjuvant chemotherapy might help prevent tumor recurrence and metastasis in patients who have undergone radical cystectomy without prior neoadjuvant chemotherapy [30]. Most

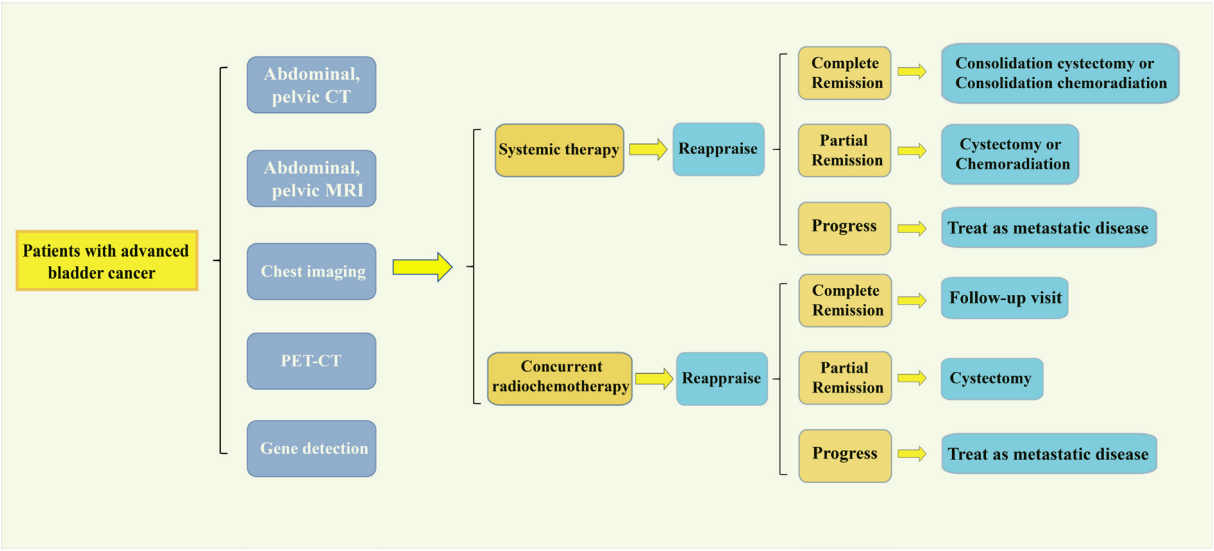

Figure 1. Possible mechanisms of obesity affecting prostate cancer.

clinical studies on adjuvant chemotherapy for MIBC are hampered by small sample sizes and often produce inconsistent findings [31-33]. A meta-analysis published in 2005 indicated that adjuvant chemotherapy could extend survival (HR 0.75, 95% CI 0.60-0.96), but this analysis included only 491 patients across 6 studies, which limits the robustness of the conclusion [34]. Subsequent large-scale randomized controlled trials have yielded conflicting results. An updated meta-analysis in 2014 pooled data from 9 clinical studies found that adjuvant chemotherapy could prolong survival (HR 0.77, 95% CI 0.59-0.99) [35]. Most of the patients were high-risk individuals, such as those with extravesical tumor invasion or positive lymph nodes. Evidence supporting the benefits of adjuvant chemotherapy exists, particularly for high-risk patients, yet the overall consensus is inconclusive due to the variability and limitations of the studies conducted.

The SOGUG 99/01 study enrolled 142 high-risk MIBC patients undergoing radical cystectomy. Following surgery, the patients were randomly divided into treatment and observation groups. The treatment group received four courses of adjuvant chemotherapy with paclitaxel, gemcitabine, and cisplatin (PGC regimen) after surgery. Subsequent follow-up revealed that the 5-year survival rate of patients receiving PGC adjuvant chemotherapy was significantly higher than that of the observation group (60% vs 31%, $p<0.0001$). The EORTC 30994 study represents the largest phase 3 clinical trial on adjuvant chemotherapy to date, originally targeting an enrollment of 660 patients, yet enrolled 284 patients, casting doubts on its reliability. High-risk MIBC patients with pT3-pT4 or lymph node-positive status undergoing radical cystectomy were randomly divided into two groups after surgery. The experimental group received four cycles of adjuvant chemotherapy after surgery, including GC, MVAC, or high-dose MVAC regimens. In contrast, the control group was followed up until tumor recurrence and then received delayed chemotherapy. The progression-free survival rate was significantly improved in the adjuvant chemotherapy group (HR 0.54, 95% CI 0.4-0.73, $p<0.0001$). The median progression-free survival time was 3.11 years (95% CI 1.84-7.77) in the adjuvant chemotherapy group, compared to 0.99 years (95% CI 0.63-1.49) in the delayed chemotherapy group. However, there was no significant difference in overall survival between the two groups (HR 0.78, 95% CI 0.56-1.08) [36]. Moreover, the study found that lymph node-negative patients benefited most from adjuvant chemotherapy, suggesting that four cycles of chemotherapy might be insufficient for lymph node-positive patients. Consequently, while adjuvant chemotherapy appears to enhance survival rates in high-risk MIBC patients, especially those who are lymph node-negative, the best chemotherapy regimen and duration are still unclear. Further research is needed to determine the most effective treatment strategies for these patients. Additionally, the low enrollment in the EORTC 30994 trial highlights the challenges of conducting large-scale clinical trials in this field and the need for continued efforts to improve patient recruitment and participation.

Galsky et al. presented an abstract at ASCO comparing the efficacy of adjuvant chemotherapy. They analyzed data from the NCDB database and compared two groups of patients with propensity score matching: those who received adjuvant chemotherapy after radical cystectomy versus those who underwent only radical cystectomy. The survival rate in the adjuvant chemotherapy group was significantly higher than that in the observation group (HR 0.72, 95% CI 0.71-0.86).

However, clinical randomized controlled trials on adjuvant chemotherapy may not be feasible in the foreseeable future. Given the risks and benefits of adjuvant chemotherapy, such as its side effects and the possibility of postoperative tumor recurrence, it is recommended that high-risk bladder cancer patients with pT3-pT4 or lymph node-positive status receive systemic chemotherapy prior to undergoing radical cystectomy. This recommendation takes into account the complex balance between potential therapeutic benefits and the risks associated with adjuvant chemotherapy. Addressing these factors before surgery might improve the overall treatment outcomes and potentially reduce the risk of disease recurrence, ultimately leading to better patient survival rates. Further research and clinical trials will be crucial in refining these recommendations and optimizing treatment strategies for high-risk bladder cancer patients.

Application of systemic chemotherapy in bladder-preserving treatment for MIBC patients

MIBC patients, unable or unwilling to undergo radical cystectomy, have a viable alternative of bladder-preserving treatment with trimodal therapy (TMT) [37]. This approach involves a combination of radiation therapy, chemotherapy,

and comprehensive transurethral resection of bladder tumors (TURBT) [38]. Initially, the chemotherapy regimens used in TMT included cisplatin with or without 5-fluorouracil, administered concurrently with radiation therapy [39-41]. However, initial studies showed no significant difference in overall survival rates. Subsequent research has confirmed that the 5-year survival rate for patients undergoing TMT ranges between 50% and 60%. Notably, a German study reported that the addition of 5-fluorouracil to cisplatin-based chemotherapy improved the overall response rate and 5-year survival rate. Moreover, the response rate was higher in the cisplatin and 5-fluorouracil group compared to the cisplatin and carboplatin group. Furthermore, incorporating paclitaxel with cisplatin has achieved 5-year overall survival rates of up to 56%. Current research continues to explore these combinations, with an ongoing Phase II clinical trial (NCT01495676) evaluating the efficacy of cisplatin combined with gemcitabine versus cisplatin alone in bladder preservation scenarios [42-44]. Additionally, within the trimodal approach, there appears to be no significant difference in outcomes between neoadjuvant chemotherapy administered before the TMT regimen and adjuvant chemotherapy given after the TMT. In summary, trimodal therapy offers a promising alternative for MIBC patients ineligible for radical cystectomy. Ongoing studies aim to further refine and enhance these treatment strategies to optimize patient outcomes. The treatment modalities for advanced bladder cancer are shown in **Figure 1**.

Targeted therapy for bladder cancer

Targeted therapy has transformed the treatment landscape for many cancers, yet its efficacy in bladder tumors remains elusive [45]. Research by TGCA on the molecular characteristics of 131 cases of MIBC found that 32 genes had significant mutations, and 69% of bladder tumors contain potential therapeutic targets [46].

Moreover, 44% of bladder cancers exhibit gene mutations in the receptor tyrosine kinase (RTK)/RAS signaling pathway, including 9% of tumors with epidermal growth factor receptor (EGFR) amplification [46]. However, the targeted agents, gefitinib, erlotinib, and cetuximab, have not demonstrated significant drug activity, even without selective enrollment based on EGFR status [47-51]. TCGA research found that 7% of bladder cancers have ERBB2 copy number variations [52]. Techniques like immunohistochemistry and fluorescence in situ hybridization (FISH) have been employed to detect HER2 overexpression in advanced bladder cancer [53, 54]. A regimen combining trastuzumab with gemcitabine, carboplatin, and paclitaxel yielded a promising overall response rate of 70% and a median overall survival of 14.1 months. Nonetheless, the absence of a randomized trial design precludes definitive conclusions regarding trastuzumab's effectiveness [52]. Although the immunohistochemistry results of most bladder tumors were positive, only a small portion tested positive with FISH, suggesting ongoing uncertainty about the optimal diagnostic method for confirming HER2 overexpression.

Fibroblast growth factor receptors (FGFRs) have mutations in 70% of non-muscle-invasive bladder cancers (NMIBC) and 15% of muscle-invasive bladder cancers [55, 56]. Some targeted drugs for FGFR signaling pathways are currently under investigation. Additionally, the vascular endothelial growth factor (VEGF) signaling pathway has been widely studied. Sunitinib has shown limited improvement in survival outcomes for advanced bladder cancer patients who underwent other treatments, with progression-free survival (PFS) of 2 months and median overall survival (OS) of 6-7 months [57]. As a first-line treatment for those unfit for cisplatin, sunitinib had a PFS of 4.8 months and an OS of 8.1 months [58]. The efficacy of sorafenib is correspondingly lowered [59, 60]. Necchi et al. found that pazopanib had an overall response rate of 17% in previously treated bladder cancer patients, but 5% of patients developed a bladder fistula during treatment [61]. Several novel targeted therapeutics are currently under development. Considering the high frequency of variations in the RB and CDK signaling pathways in bladder cancer, a phase II clinical trial (NCT02334527) is exploring the efficacy of palbociclib in the treatment of metastatic bladder cancer. Furthermore, ongoing research is evaluating additional cytotoxic chemotherapy drugs. Notably, at the 2015 ASCO Annual Meeting, eribulin demonstrated a 35% response rate and an overall survival of 9.5 months in a phase II clinical trial for metastatic bladder cancer, showing improvement compared to previous chemotherapy regimens.

Discussion

Advancements in high-throughput sequencing and molecular expression profiling technologies, along with the discovery of various biomarkers for predicting prognosis, have led to significant progress in the development of future anti-cancer drugs. This trend is particularly important in the field of tumor immunotherapy, where drug responses can be both stable and profound. However, only a small fraction of patients respond to these treatments, making it crucial to identify which patients are likely to benefit from therapy. Immunohistochemical analysis showing PD-L1 positivity suggests better responses to immune checkpoint inhibitors. Nonetheless, relying solely on PD-L1 status to predict drug efficacy is not entirely reliable. This limitation underscores the need for more comprehensive and accurate biomarkers to better identify patients who are likely to respond to immunotherapy and to enhance the overall effectiveness of these treatments. As research progresses, integrating various biomarkers and advanced technologies will be key to optimizing therapeutic strategies and improving patient outcomes in cancer treatment.

Tumor mutations can generate new antigens that are expressed on the surface of tumor cells and are specific to certain tumors, thereby inducing specific immune responses. In melanoma, early research suggests that a higher tumor mutation burden is associated with better responses to immune therapies targeting CTLA-4. Bladder cancer exhibits the highest tumor mutation burdens compared to normal tumors, underscoring the efficacy of immunotherapy in its treatment [62]. Recent studies have identified molecular subtypes of bladder cancer, classifying them into "basal" and "luminal" subtypes, similar to the classification of breast cancer. These subtypes exhibit distinctly different RNA expression profiles and prognoses. The basal subtype, in particular, is rich in immune infiltration, suggesting its enhanced responsiveness to immunotherapy [63]. This differential response underscores the potential for tailored immunotherapeutic approaches based on the specific molecular characteristics of bladder cancer subtypes, potentially leading to more effective treatment outcomes for patients [64, 65]. Further research into these subtypes and their interactions with immunotherapy will be crucial for optimizing treatment strategies and improving patient prognosis.

Recent advances in treatment for advanced bladder cancer have made significant progress. The use of neoadjuvant chemotherapy for muscle-invasive bladder cancer is increasingly attributed to its proven survival benefits. Adjuvant chemotherapy serves as a valuable supplement for patients not previously treated with neoadjuvant therapy. In bladder-preserving treatments, combining systemic therapy with radiation has been shown to improve patient outcomes. Advances in the molecular characterization of bladder cancer have propelled the development of targeted therapies. Clinical trials of immunotherapy have yielded promising results, and ongoing randomized controlled trials aim to further validate

their effectiveness. To optimize the selection of patients for targeted or immunotherapy, research into predictive biomarkers must progress alongside the development of these therapies. As the understanding of bladder cancer's molecular landscape deepens, targeted and immunotherapeutic strategies are expected to become increasingly effective. Identifying reliable biomarkers for predicting treatment response will be crucial for personalizing therapy and improving overall patient outcomes. Continued research and clinical trials will play a key role in advancing these treatments and refining therapeutic approaches for bladder cancer.

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None.

Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Haijun Hu and Xianghui Wu searched academic literature, wrote the draft manuscript, supervised the review writting progress and approved the final manuscript submission.

Competing interests

Authors report no conflict of interest.

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