



“Immunotherapy For Bladder Cancer: A Review Of Current Landscape”

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ABSTRACT: Bladder cancer, a common malignancy with high recurrence and progression rates, presents significant treatment challenges despite advancements in traditional therapies like surgery, chemotherapy, and radiation. Immunotherapy has emerged as a revolutionary approach, harnessing the immune system to combat cancer. This review highlights the current landscape of bladder cancer immunotherapy, emphasizing mechanisms, approved therapies, and future directions. Checkpoint inhibitors, such as pembrolizumab and atezolizumab, target immune evasion pathways like PD-1/PD-L1, reactivating T-cell-mediated tumor responses. The Bacillus Calmette-Guérin (BCG) vaccine remains a cornerstone for non-muscle-invasive bladder cancer, stimulating local immune responses. Emerging therapies, including adoptive T-cell therapies and neoantigen-based vaccines, show potential in enhancing efficacy. Combination therapies, integrating immunotherapy with chemotherapy, radiation, or targeted agents like FGFR inhibitors, offer synergistic benefits and improved outcomes. Advanced techniques like blue-light cystoscopy aid in precise tumor detection, while gene therapies such as nadofaragene firadenovec are expanding therapeutic horizons. Despite these advancements, challenges persist, including resistance mechanisms, patient selection, and immunotherapy-associated toxicities. Current research focuses on biomarkers, such as tumor mutational burden and PD-L1 expression, to stratify patients and optimize treatment. Immunotherapy has redefined bladder cancer treatment, offering durable responses and improved survival rates for many patients. However, continued research and personalized strategies are essential to address unmet needs, maximize benefits, and broaden the applicability of these transformative therapies. This review provides insights into ongoing advancements and future prospects in bladder cancer immunotherapy.

INDEX TERMS - Bladder cancer, immunotherapy, checkpoint inhibitor, gene therapy, adoptive T-cell therapy.

1. INTRODUCTION:

Immunotherapy, too known as biologic treatment or biotherapy, could be a sort of cancer treatment that tackles the control of the immune system to battle cancer. Bladder cancer could be a common harm in ladies and is the fourth most common danger in men. Bladder cancer ranges from unaggressive and as a rule non-invasive tumor that repeat and commit patients to long-term obtrusive observation, to forceful and obtrusive tumours with tall disease-specific mortality [1]. It is coming up to 40 a long time since the primary report of the utilize of Bacillus Calmette— Guerin (BCG) as an immunotherapy for the treatment of bladder cancer. Since at that point, various ponders have set out to clarify how BCG applies its impact on urothelial tumor cells. Assist, a few clinical trials have endeavored to address the clinical questions relating to BCG immunotherapy, with specific consideration paid to dosing regimens, acceptance and support treatment, comparison with the cytotoxic chemotherapeutic operators, and combination treatment, for illustration, utilizing intergalactic (IFN) α . Resistant checkpoint inhibitors (ICI) have illustrated the next advantage in overwhelming CD8

resistant cell penetrated tumors and in tumors with tall tumor mutational burden (TMB), such as the case of bladder cancer [2].

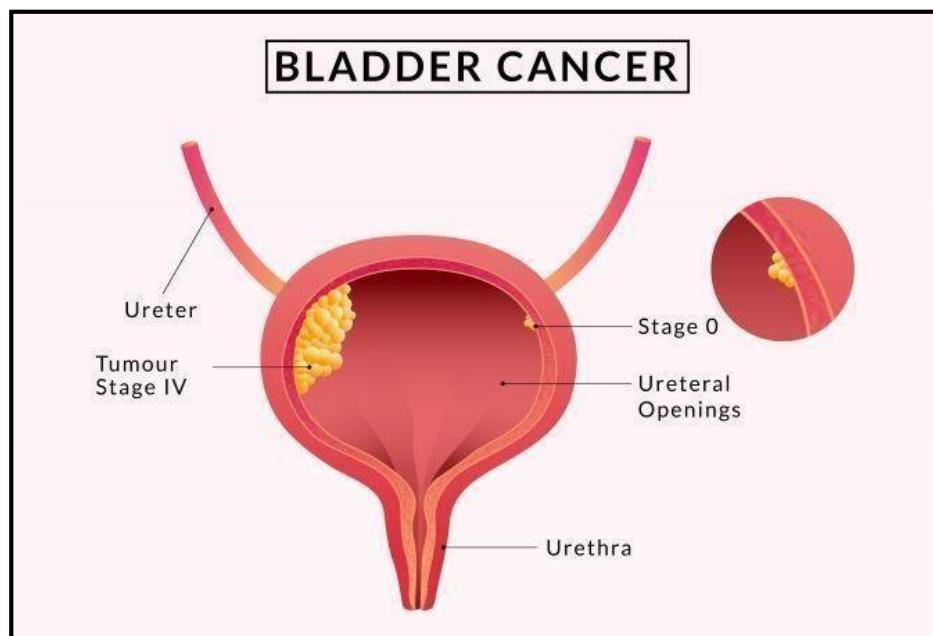


Fig.1. Bladder cancer

2. MECHANISM OF ACTION OF IMMUNOTHERAPY ON BLADDER CANCER:

Step 1: Bladder Cancer

The process starts with bladder cancer cells in the body, which the immune system should ideally recognize and attack.

Step 2: PD-1/PD-L1 Pathway Activation

Bladder cancer cells express the PD-L1 protein on their surface. T cells, part of the immune system, have PD-1 receptors. When PD-1 on T cells binds to PD-L1 on cancer cells, it sends an inhibitory signal, which dampens the immune response and allows cancer cells to evade the immune system.

Step 3: Immune Checkpoint

Inhibition Immunotherapy drugs, such as Pembrolizumab and Atezolizumab, block the interaction between PD-1 and PD-L1. These drugs are known as immune checkpoint inhibitors. By blocking the PD-1/PD-L1 interaction, the immune system is no longer inhibited, and T cells can remain active.

Step 4: T cell Activation

The PD-1/PD-L1 blockade in place, T cells are activated. These activated T cells can now recognize bladder cancer cells as harmful and proceed to attack and destroy them.

Step 5: Tumour Cell Death

Activated T cells release toxic substances that kill the bladder cancer cells.

Step 6: Immune Memory

In some cases, immunotherapy can lead to the generation of immune memory. This means the immune system "remembers" the cancer antigens and can respond more effectively if the cancer tries to recur [4].

2.1 Mechanism of action for BCG

BCG impacts the immune system by stimulating various immunology molecule and cells enhancing tumour cell recognition and elimination. Its effects are multifaceted, involving both nonspecific and specific pathways contributing to its anticancer activity.[5]

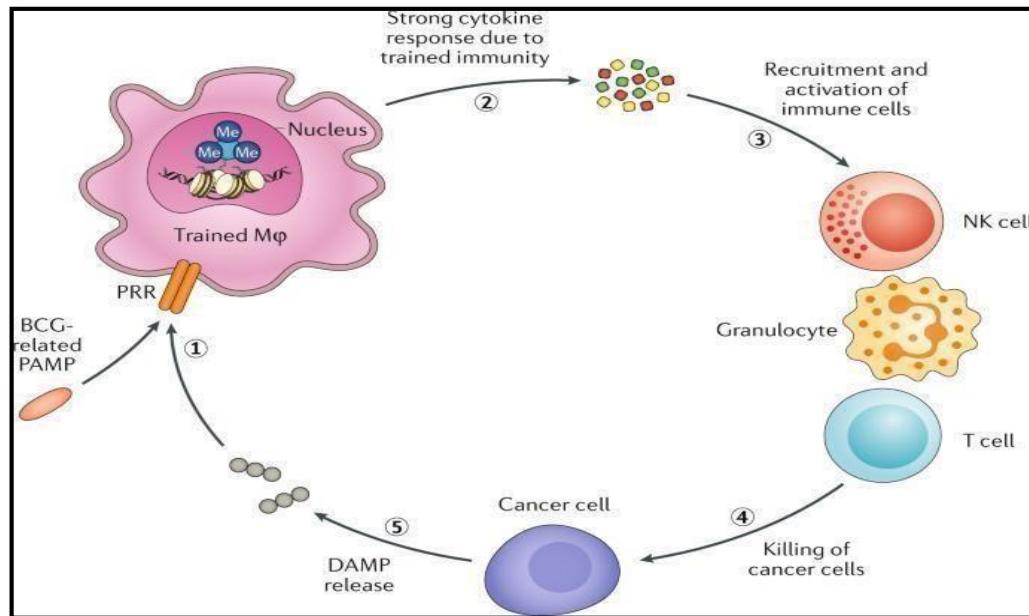


Fig. 2. Mechanism of Action of Bladder Cancer

3. TYPES OF BLADDER CANCER:

1. Urothelial Carcinoma

Urothelial carcinoma it is additionally called transitional cell carcinoma is cancer that starts within the urothelial cells, which line the urethra, bladder, ureters, renal pelvis, and a few other organs. Nearly all bladder cancers are urothelial carcinomas.

2. Squamous Cell Carcinoma

It is cancer that starts in squamous cells (thin, level cells lining the interior of the bladder). This sort of cancer may frame after long-term aggravation or disease with a tropical parasite called schistosomiasis, which is common in Africa and the Center East but uncommon within the Joined together States. When unremitting bothering happens, transitional cells that line the bladder can slowly alter to squamous cells.

3. Adenocarcinoma

It is cancer that starts in glandular cells that are found within the lining of the bladder. Glandular cells within the bladder make bodily fluid and other substances.

4. Little Cell Carcinoma

It is cancer that starts in neuroendocrine cells (nerve-like cells that discharge hormones into the blood in reaction to a flag from the apprehensive framework) [6].

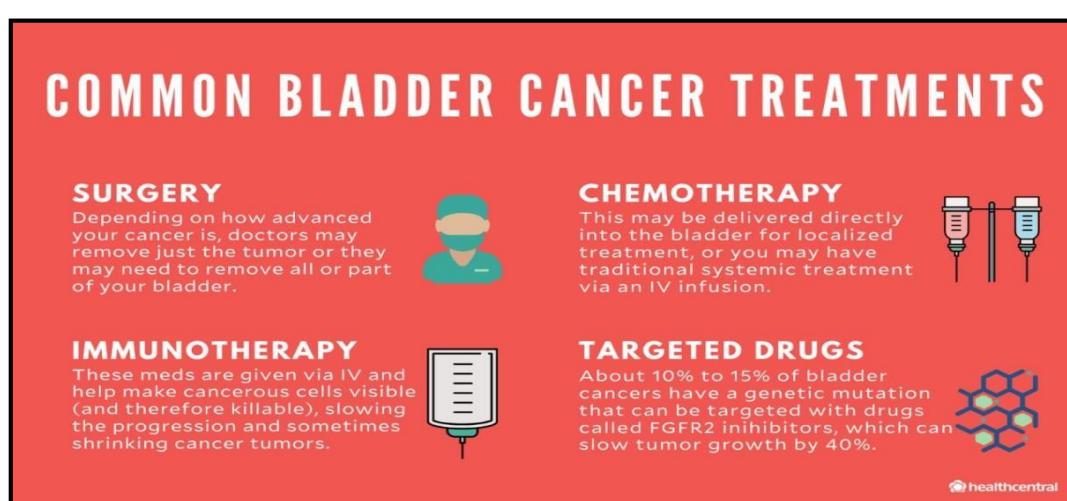


Fig. 3 Treatment of Bladder Cancer

4. TREATMENT OF BLADDER CANCER:

1. Immunotherapy

Immunotherapy is treatment that makes a difference the body's safe framework battle cancer more viably. Certain immunotherapy drugs, called resistant checkpoint inhibitors, are affirmed to treat a few patients with locally progressed or metastatic bladder cancer.

2. Focused on Treatment

Focused on treatment treats cancer by focusing on proteins that control how cancer cells develop, partition, and spread. In 2019, erdafitinib (Balversa) got to be the primary focused on treatment to be affirmed by FDA to treat patients with locally progressed or metastatic urothelial carcinoma.

3. Quality Treatment

In 2022, the FDA affirmed a sort of quality treatment called nadofaragene firadenovec-vncg (Adstiladrin) for a few grown-ups with a certain sort of high-risk, non-muscle-invasive bladder cancer. By making a difference the resistant framework recognize and murder cancer cells, this treatment can advantage patients whose tumors do not react to the commonly utilized BCG treatment [7].

4. Endorsed treatments

- Checkpoint inhibitors (e.g., pembrolizumab, atezolizumab, Nivolumab)
- Cancer immunizations (e.g., BCG)
- Assenting T-cell treatment

5. CAUSES OF BALDDER CANCER:

1. Smoking

Cigarette smoking increments the chances of creating bladder cancer. Smoking channels and cigars, as well as being uncovered to second-hand smoke, are the major causes of bladder cancer.

2. Introduction to radiation treatment and chemotherapy

Cancer radiation treatment may increment the chance of creating bladder cancer. The utilize of certain chem chemotherapy drugs may increment the chances of bladder cancer.

3. Presentation to a few chemicals

Agreeing to considers, there may be the next hazard for individuals who work with particular chemicals found in colors, elastic, calfskin, paint, a few textures, and hair care items.

4. Visit event of bladder contamination

The chance of squamous cell carcinoma may be higher in individuals who as often as possible encounter bladder contaminations, bladder stones, or other urinary tract diseases.

6. SYMPTOMS OF BALDDER CANCER

- Blood within the pee
- Visit urination
- Agonizing or burning urination (dysuria)
- Changes to criticalness and urine flow
- Attending to the washroom a few times within the night (nocturia)
- Having inconvenience peeing
- Determined bladder contaminations [8].

7. DIAGNOSIS OF BLADDER CANCER:

1. Photodynamic Diagnosis/Blue-light Cystoscopy

Photodynamic diagnosis (PDD) improves the detection of hard-to-spot bladder cancer. A dye, is used in the bladder. Cancerous tissue absorbs this dye and glows red under blue light, while normal tissue looks blue [9].

2. Narrow-Band Imaging

Narrow-band imaging (NBI) cystoscopy highlights details of the bladder surface without using dyes, allowing for deeper visibility with special light. Unlike blue-light cystoscopy (BLC), NBI doesn't require extra procedures like inserting dye into the bladder [10].

3. Urinary Markers

Urinary cytology is a common, non-invasive test for detecting bladder cancer, especially high-grade tumours, but it's less reliable for low-grade tumours and results take time. Some urine-based markers, like FISH (Fluorescence in situ Hybridization) and NMP22, have been developed to help with diagnosis [11].

8. SIDE EFFECTS OF IMMUNOTHERAPY ON BLADDER CANCER

- Gentle torment or burning in your bladder
- Feeling the ought to urinate regularly
- Torment once you urinate
- Wicked pee, or indeed blood clots in your pee

Table no.1: List of serious complications and preventions methods for bladder cancer.

Complications	Brief Prevention Methods
Infusion reaction	Strictly regulate infusion operation, closely observe patient infusion.
Sepsis	Timely targeted treatment, avoid cross infection.
Colitis	Avoid raw and cold diet, avoid repeated infections, and control with medication if necessary.
Pancreatitis and peptic ulcer	Pay attention to dietary hygiene, inhibit gastric acid secretion, and protect gastric mucosa. Improve resistance, avoid repeated infections.

9. CURRENT ADVANCES IN BLADDER CANCER :

Bladder cancer treatment has seen several advancements recently, particularly in immunotherapy and targeted therapies.

1. For non-muscle-invasive bladder cancer (NMIBC)

The FDA approved the combination of N-803 (Anktiva) with Bacillus Calmette Guerin (BCG) in April 2024. This treatment is for patients whose cancer has become unresponsive to BCG alone. In a clinical trial, this combination therapy significantly improved patient outcomes, preventing bladder removal surgery (cystectomy) in over 90% of cases. The combination activates natural killer cells and T cells, enhancing the immune system's ability to fight cancer more effectively [12].

2. For metastatic urothelial carcinoma (advanced bladder cancer)

In 2023, enfortumab vedotin (Padcev) combined with pembrolizumab (Keytruda) was approved as a first-line treatment. This combination showed impressive results, with tumours shrinking in two-thirds of patients and complete remission in about 12%. This is particularly significant for patients who cannot receive cis-platin-based chemotherapy, which is the standard but often unsuitable due to toxicity [13].

10. FUTURE PROSPECTIVE :

Bladder cancer (BC) treatment can be complicated because not all patients respond the same way to therapies like immunotherapy. This could be due to the unique way each person's genes signal their cells to act. Bladder cancer is often genetically unstable, meaning it changes a lot, and so treatments need to be tailored to each patient. One promising approach involves targeting the epidermal growth factor receptor (EGFR), a protein that plays a role in cancer growth and resistance to chemotherapy. EGFR normally helps regulate the growth of tissues, but when things go wrong, it can help tumours grow. About 25% of people with aggressive bladder cancer show over activity in the genes related to EGFR [14].

11. CONCLUSION :

Immunotherapy has become a promising treatment option for bladder cancer, particularly for patients with advanced or metastatic disease. By harnessing the body's immune system, immunotherapies such as immune checkpoint inhibitors (like PD-1 and PD-L1 inhibitors) have demonstrated significant efficacy in improving survival and response rates for some patients. This has led to their approval as second-line treatments for bladder cancer after chemotherapy or as frontline therapies in cases where chemotherapy is not suitable. However, not all patients respond equally to immunotherapy, and there are still challenges related to patient selection, resistance, and potential side effects. Future research aims to better understand the mechanisms of action and resistance, refine patient stratification, and explore combination therapies with chemotherapy or targeted treatments to enhance outcomes. Overall, immunotherapy represents a key advancement in bladder cancer treatment, offering hope for improved survival, though continued research is necessary to optimize its use and broaden its effectiveness across a wider range of patients.

12. REFERENCES:

- [1] Lenis, A.T., Lec, P.M. and Chamie, K., 2020. Title. *Journal of the American Medical Association*, 324(19), pp.1980-1991.
- [2] Fuge O, Vasdev N, Allchorne P, Green JS. Immunotherapy for bladder cancer. *Research and reports in urology*. 2015 May 4:65-79.
- [3] Gupta RG, Li F, Roszik J, Lizée G. Exploiting tumor neoantigens to target cancer evolution: current challenges and promising therapeutic approaches. *Cancer discovery*. 2021 May 1;11(5):1024-39.
- [4] van Dorp J, van der Heijden MS. The bladder cancer immune micro-environment in the context of response to immune checkpoint inhibition. *Frontiers in immunology*. 2023 Aug 31;14:1235884.
- [5] Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer—a current perspective. *Nature reviews urology*. 2014 Mar;11(3):153-62.
- [6] Primo WQ. National Cancer Institute and the 2023-2025 Estimate—Cancer Incidence in Brazil. *Revista Brasileira de Ginecologia e Obstetrícia*. 2023 Jan;45(1):01-2.
- [7] Ahmed R, Sheu M, Wei W, Ornstein MC, Gilligan TD, Dima D, Campbell S, Lee BH, Weight C, Wee CE, Mian OY. Prognostic factors and clinical outcomes in patients with upper tract urothelial carcinoma undergoing surgery: The Cleveland Clinic experience.
- [8] Hede K. Increase in oral cancer drugs raises thorny issues for oncology practices.
- [9] Cheung G, Sahai A, Billia M, Dasgupta P, Khan MS. Recent advances in the diagnosis and treatment of bladder cancer. *BMC medicine*. 2013 Jan 17;11(1):13.
- [10] Witjes JA, Redorta JP, Jacqmin D, Sofras F, Malmström PU, Riedl C, Jocham D, Conti G, Montorsi F, Arentsen HC, Zaak D. Hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: review of the evidence and recommendations. *European urology*. 2010 Apr 1;57(4):607-14.
- [11] Naselli A, Introini C, Timossi L, Spina B, Fontana V, Pezzi R, Germinale F, Bertolotto F, Puppo P. A randomized prospective trial to assess the impact of transurethral resection in narrow band imaging modality on non-muscle-invasive bladder cancer recurrence. *European urology*. 2012 May 1;61(5):908-13.
- [12] Eyre H, Blount L. American Cancer Society. *Journal of oncology practice*. 2006 Mar;2(2):99.
- [13] Heady, D. (2024, April 23). The FDA approves immunotherapy drug combo for non-muscle invasive bladder cancer after UCLA-led research shows improved outcomes for patients.
- [14] Hussain M, Daignault S, Agarwal N, Grivas PD, Siefker-Radtke AO, Puzanov I, MacVicar GR, Levine EG, Srinivas S, Twardowski P, Eisenberger MA. A randomized phase 2 trial of gemcitabine/cisplatin with or without cetuximab in patients with advanced urothelial carcinoma. *Cancer*. 2014 Sep 1;120(17):2684-93.