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Immunotherapy and urinary bladder cancer

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Abstract

Bladder cancer is a type of cancer, which arises from the epithelial lining (urothelium) of the urinary bladder due to the uncontrolled growth of abnormal cells in the bladder. Transitional cell carcinoma (TCC) is the most common type of cancer, involving urinary bladder. It is one of the leading causes of death, worldwide. As per statistical analysis, it is the 7th leading cancer in men worldwide and 17th leading cancer in women worldwide. The bladder cancer represents 4.5% of all the new cancer cases in U.S. The bladder cancer is mainly of three types: Transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma. The molecular instabilities and abnormal metabolic pathways play a key role in the development of urinary bladder cancer and its progression. Intravesical immunotherapy has been approved by FDA for the treatment of urinary bladder cancer and some other drugs, vaccines, and therapies are in clinical trials for FDA approval. Everolimus, sorfenib, and suitinib are highly potential agents for the treatment of urinary bladder cancer and are under clinical trials. Researchers are still challenged in exploring innate and adaptive immune systems.

Abbreviations

ASR: Age standardized incidence rate; BER: Base excision repair; BCG: Bacillus calmette-guerin; DSB: Double-strand break; MABs: Monoclonal antibodies; NER: Nucleotide excision repair; TCC: Transitional cell carcinoma; TUR: Transurethral resection

Introduction and Epidemiology

Bladder cancer is a type of cancer, which arises from the epithelial lining (urothelium) of the urinary bladder. Transitional cell carcinoma (TCC) is the most common type of cancer, involving urinary bladder. However, squamous cell carcinoma, neuroendocrine tumors as well as sarcoma and lymphoma may be present in the bladder, less frequently [1].

Urinary bladder cancer is one of the leading causes of death, worldwide. As per American Cancer Society in United States in 2014, around 74,690 new cases were diagnosed (about 56,390 in men and 18,300 in women), and in the same year around 15,580 cases of death were reported due to bladder cancer (about 11,170 in men and 4,410 in women) [2]. As per statistical analysis, it is the 7th leading cancer in men worldwide and 17th leading cancer in women worldwide [3]. Egypt, Spain, Italy, Zambia and Netherland have high incidence rates as compared to rest of the world. Cancer is caused primarily due to uncontrolled growth of abnormal cells in the urinary bladder [4]. The bladder cancer represents 4.5% of all the new cancer cases in U.S. [5].

The age standardized incidence is 10.1 per 100,000 for men and 2.5 per 100,000 for women worldwide. The worldwide age standardized incidence rate (ASR) is 10.1 per 100,000 for males and 2.5 per 100,000 for females [6]. It includes different type of the histopathologic and genetic characteristics. Generally, bladder cancer occurs in the old age people, and around 9 out of 10 people, over the age of 55, are diagnosed with this cancer. The chances of bladder cancer throughout the life are about 1 in 26 in men and 1 in 90 in women [2].

Etiology and predisposing factors

Bladder cancer is a type of cancer, which arises from the epithelial lining (urothelium) of the urinary bladder due to the uncontrolled growth of abnormal cells in the bladder. The bladder cancer is mainly of three types: Transitional cell carcinoma, squamous cell carcinoma, and adenocarcinoma [6]. The most common symptom of bladder cancer is painless hematuria, however, in advanced cases, pain in lower abdomen resulting from pelvic wall extension, and bone pain due to metastatic involvement might be clinically present [7]. Etiological factors, which contribute to the progression of disease include smoking, age, gender, chronic bladder irritation and infections, personal history of bladder or other epithelial cancer, congenital abnormalities or defects of bladder wall, genetics and family history, chemotherapy and radiation therapy, arsenic in drinking water, and low fluid consumption [2].

Pathophysiology and molecular basis

The molecular instabilities and abnormal metabolic pathways play a key role in the development of urinary bladder cancer and its progression. They include1) altered metabolism/detoxification of carcinogens, and 2) inherent or acquired genetic abnormalities, which may encourage tumor growth, impair DNA repair, or inhibit tumor cell proliferation (tumor suppressor genes) [8,9]. The pathways involved in the altered chemical metabolism of exogenous carcinogens, include N-acetyltransferase genetic and metabolic derangements, glutathione-s-transferase abnormalities, and aberrant cytochrome P450 metabolism (associated genetic defects) pathways [10-13].

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Key words: *epithelial lining (urothelium), transitional cell carcinoma (TCC), squamous cell carcinoma, and adenocarcinoma, altered metabolism/detoxification of carcinogens, inherent or acquired genetic abnormalities, tumor suppressor genes (TSG), intravesical immunotherapy, bacillus calmette-guerin (BCG), transurethral resection (TUR)*

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The DNA abnormalities may be acquired or inherent, secondary to carcinogenic exposure. Genetic instability may result in the abnormal activity of oncogenes, such as RAS and MYC families, resulting in resistance to apoptosis, cellular proliferation, and aberrant protein expression, such as GDP/GTP binding proteins [13,14]. The tumor suppressor gene abnormalities related with urinary bladder cancer have also been well studied and comprise Rb (retinoblastoma), p16, p21, and p53 tumor suppressor genes, which may be inactivated or mutated. Some defects may thereby, predispose to cell cycle dysregulation and the progression and development of tumor cells [15-18]. Alterations in DNA repair, such as double-strand break (DSB) repair genes, Base excision repair (BER) genes, and Nucleotide excision repair (NER) genes have similarly been related with polymorphisms, which may result in urinary bladder cancer [13,19,20]. Other potential acquired and inherent pathways have also been recognized and may also be involved, including telomere dysfunction, cellular inflammation, and apoptosis [21,22].

Immunotherapy

Monoclonal antibodies (MABs)

Non-FDA approved drugs: (Table 1)

Checkpoint inhibitors

Non-FDA approved drugs: (Table 2)

Vaccine based immunotherapy

Non-FDA approved vaccines: (Table 3)

Kinase inhibitors

Non-FDA approved drugs: (Table 4)

Growth factor receptor inhibitors

Non-FDA approved drugs: (Table 5)

mTOR inhibitors

Non-FDA approved drugs: (Table 6)

Intravesical immunotherapy

Bacillus Calmette-Guerin therapy [44]

Bacillus Calmette-Guerin (BCG) is the most efficient intravesical immunotherapy, which is used for the treatment of early stage bladder cancer. BCG is a bacterium, which is associated with the germ and causes tuberculosis, but it does not generally cause serious type of disease [2].

Indications and usage

BCG is indicated for the prophylaxis and treatment of carcinoma *in situ* of urinary bladder cancer, and used for the prophylaxis of primary stage Ta or T1 papillary tumors, following transurethral resection (TUR). BCG is not suggested for the stage TaG1 papillary tumors, if they are concluded to be at high risk of tumor repetition.

Contraindication

- BCG should not be used in immunosuppressed patients or

Table 1. Non-FDA approved monoclonal antibodies [23-25].

MABs	Clinical trial identifier number	Phase	Study design	Target
Panitumumab	NCT01916109	Phase II	Safety/Efficacy Study, Open Label	EGF stimulation
GSK2849330	NCT01966445	Phase I	Non-Randomized, Safety Study, Open Label	HER3
SAR408701	NCT02187848	Phase I/II	Non-Randomized, Open Label, Safety/Efficacy Study	CEACAM5

Table 2. Non-FDA approved checkpoint inhibitors [26-28].

Checkpoint Inhibitors	Clinical trial identifier number	Phase	Study design	Target
MPDL3280A	NCT02302807	Phase III	Randomized, Open label, Safety/Efficacy study	PDL1
Pembrolizumab	NCT02256436	Phase III	Randomized, Open label, Efficacy study	PDL1
Ipilimumab	NCT01928394	Phase II	Randomized, Efficacy Study, Open Label	CTLA-4
Nivolumab	NCT01928394	Phase I	Randomized, Efficacy Study, Open Label	CTLA-4

Table 3. Non-FDA approved vaccines [29].

Vaccine	Clinical trial identifier number	Phase	Study design	Target
DEC-205-NY-ESO-1	NCT01522820	Phase I	Non-Randomized, Safety Study, Open Label	Bladder cancer cells

Table 4. Non-FDA approved kinase inhibitors [30-40].

Kinase inhibitors	Clinical trial identifier number	Phase	Study design	Target
Sorafenib	NCT00772694	Phase II	Efficacy Study, Open Label	RAF/VEGF
Sunitinib	NCT00526656	Phase II	Single Group Assignment, Open Label	VEGF
Pazopanib	NCT01108055	Phase II	Non-Randomized, Safety/Efficacy Study, Open Label	VEGFR, PDGFR
Cabozantinib	NCT01688999	Phase II	Open Label, Efficacy Study	RTKs
Neratinib	NCT01953926	Phase II	Non-Randomized, Safety/Efficacy Study, Open Label	EGFR
Afatinib	NCT02122172	Phase II	Open Label, Efficacy Study	EGFR
Erlotinib	NCT02169284	Phase II	Randomized, Dpuble Blind, Efficacy Study	EGFR
BBI503	NCT02232646	Phase II	Safety/Efficacy Study, Open Label	CSC
Vemurafenib	NCT02304809	Phase II	Safety/Efficacy Study, Open Label	BRAF
Palbociclib	NCT02334527	Phase II	Open Label, Efficacy Study	CDK4 and 6
Alisertib	NCT02109328	Phase I/II	Randomized, Single Blind, Efficacy Study	Aurora A kinase

patients with acquired or congenital immune deficiencies, whether due to immunosuppressive therapy, cancer therapy or concurrent disease such as AIDS.

- Treatment should be delayed until declaration of a concurrent gross hematuria, urinary tract infection, or febrile illness.

- BCG should not be administered to patients with active tuberculosis.

Warning

- BCG LIVE is not a vaccine, which is used for the prevention of cancer. BCG vaccine, U.S.P., not BCG LIVE, must be used for the prevention of tuberculosis.

- Instillation of BCG with actively bleeding mucosa may promote systemic BCG infection. Therefore, the treatment must be delayed for at least one week following TUR, traumatic catheterization, biopsy, or gross hematuria.

- The use of BCG may cause the tuberculin sensitivity. Since, this is a valuable aid in the diagnosis of tuberculosis, it is advisable to determine the tuberculin reactivity by PPD skin testing before the treatment.

- Small bladder capacity has been associated with increased risk of severe local reactions and should be considered in deciding to use BCG therapy.

Adverse effects

Hematuria, flu-like syndrome, urinary frequency, dysuria, malaise/fatigue, fever, nausea/vomiting, rigors, cramps/pain, nocturia, urgency, and cystitis are the most common adverse effects of BCG.

Mechanism of Action

The mechanism of action of bacillus Calmette-Guérin (BCG) therapy is partly understood. Some early studies proposed that an immune response against the BCG surface antigens cross-reacted with bladder cancer antigens, and this was projected as the mechanism of action for the different therapeutic effect of BCG; though, multiple following studies disprove this claim.

The live organism enters macrophages in the urinary bladder, where they induce the same type of immunologic and histologic reaction, as established in the patients with tuberculosis. BCG vaccine also has been shown to have a predilection for entering bladder cancer cells, where the proteins are broken down and other fragments are combined with histocompatibility antigens and monitored on the cell surface. This induces cytokines and direct cell-to-cell cytotoxity response, which targets these cells for destruction.

Heat shock protein inhibitors

Non-FDA approved drugs: (Table 7)

Cytokine therapy

Non-FDA approved drugs: (Table 8)

Cancer cell stemness inhibitor

Non-FDA approved drugs: (Table 9)

Proteasome inhibitor:

Ixazomib citrate

This drug along with Gemcitabine Hydrochloride and Doxorubicin Hydrochloride in Treating Patients with Urothelial Cancer That is

Table 5. Non-FDA approved growth factor receptor inhibitors [41].

Growth factor inhibitors	Clinical trial identifier number	Phase	Study design	Target
JNJ-42756493	NCT02365597	Phase II	Randomized, Safety/Efficacy Study, Open Label	FGFR

Table 6. Non-FDA approved tyrosine kinase inhibitor [42,43].

mTOR Inhibitor	Clinical trial identifier number	Phase	Study design	Target
Everolimus	NCT01466231	Phase II	Efficacy Study, Open Label	mTOR
Sirolimus	NCT01938573	Phase I/II	Safety/Efficacy Study, Open Label	mTOR

Table 7. Non-FDA approved heat shock protein inhibitors [45].

HSP inhibitors	Clinical trial identifier number	Phase	Study design	Target
SNX-5422	NCT01848756	Phase I/II	Open Label, Safety/Efficacy Study	Hsp90

Table 8. Non-FDA approved cytokine therapy [46].

Cytokine	Clinical trial identifier number	Phase	Study design	Target
ALT-801	NCT01326871	Phase I/II	Non-Randomized, Open Label, Safety/Efficacy Study	Bladder cancer cells

Table 9. Non-FDA approved cancer cell stemness inhibitor [47].

CCS Inhibitors	Clinical trial identifier number	Phase	Study design	Target
BBI608	NCT01325441	Phase I/II	Non-Randomized, Open Label, Safety/Efficacy Study	CSC

Table 10. Proteosome inhibitor.

Drug	Clinical trial identifier number	Phase	Study design	Target
Ixazomib Citrate	NCT02420847	Phase I/II	A Phase I Two-Dimensional Dose-Finding Study Followed by a Phase II Extension to Assess the Efficacy	PI3K/AKT Pathway

Table 11. Oncolytic virus therapy.

Oncolytic virus	Clinical trial identifier number	Phase	Study design	Target
CG0070	NCT02365818	Phase III	Open label, single arm,multicenter study of the safety and efficacy	GMCSF

Metastatic or Cannot Be Removed by Surgery (Table 10).

Oncolytic virus treatment

The oncolytic virus therapy that is under clinical trial phase I-III is given in Table-11 below. The purpose of the study was to evaluate the safety and efficacy of CG0070, an oncolytic virus expression GMCSF in high grade non-muscle invasive bladder cancer patients who failed BCG therapy and refused cystectomy (Table 11).

Conclusion

There has been a promising development in the immunotherapy in the past few years. Intravesical immunotherapy has been approved by FDA for the treatment of urinary bladder cancer and some other drugs, vaccines, and therapies are in clinical trials for FDA approval. Everolimus, sorfenib, and suitinib are highly potential agents for the treatment of urinary bladder cancer and are under clinical trials. Our success in treating urinary bladder cancer is increasing and advancing with the knowledge of the function of the immune system. Researchers are still challenged in exploring innate and adaptive immune systems.

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