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Bladder Carcinoma Treatment Challenges and Future Directions of Immunotherapy

Barnali Deb[1,2] and Prashant Kumar[1,2]*

[1]Institute of Bioinformatics, International Technology Park, Bangalore, India
[2]Manipal Academy of Higher Education, Madhav Nagar, Manipal, India

Editorial

Bladder carcinoma is one of the most common urological malignancies with a range of manifestations [1]. It accounts for approximately 90% of transitional cell carcinoma (TCC) [2]. TCC are histopathologically divided into non-muscle invasive bladder carcinoma (NMIBC) and muscle-invasive bladder carcinoma (MIBC). About 75% of the newly diagnosed bladder carcinoma is NMIBC [3]. These tumors are confined to the mucosal or sub-mucosal region of the bladder. Significant number of NMIBC progresses to MIBC, thus increasing the mortality rate. The recurrence of bladder carcinoma is relatively higher, ranging from 50 to 70% and out of which 15% have a higher chance of progressing to the MIBC [4]. Almost a quarter of the bladder carcinoma patients are diagnosed with the cancer already invading to the bladder muscle wall (i.e., MIBCs). The treatment advocated for bladder carcinoma basically involves the two approaches in which if the muscle layers are not involved then the bladder is spared with a few resection treatments. While in the adverse cases the removal of the bladder becomes essential. The treatment and therapeutic approaches for bladder carcinoma are as described in Figure 1.

Current Treatment Approaches and Challenges for Bladder Cancer Management

Transurethral resection of bladder tumors (TURBT) is the most common choice for bladder carcinoma treatment. It is usually intervened at the stage when there are visible masses of tumor in the bladder epithelium. It is done under the influence of regional or general anaesthesia and the removal of the tumor is accomplished through flexible cystoscopy and it also provides samples for the pathological examinations [5]. TURBT must be complete and correct to achieve a good prognosis [6]. Moreover, minor bleedings and irritation are also associated with TURBT. In case of incomplete resection, a second resection is considered when a high-grade or T1 tumors have been reported in the first resection [7]. The choice of therapy and treatment mostly depends on case-to-case basis of the patients and also the risk that can be undertaken by the patient as well as the urologist. Adjuvant therapy is often considered for the better prognosis of the patients. A chemotherapy instillation immediately after TURBT has been reported to reduce recurrence rate significantly [8]. For the patients with a higher risk of recurrence, an intermediate instillation is requisite due to the considerable risk of progression being involved. However, it has been reported that adjuvant chemotherapy with TURBT decreases the recurrence rate and not progression [9]. Cisplatin-based combination chemotherapy is the preferred initial regimen for patients with advanced bladder carcinoma. The cisplatin-based therapies have been shown to extend median survival to 12–15 months and 5-year survival of approximately 15% [10]. Standard first-line therapy remains gemcitabine plus cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin. However, the prognosis is generally poor for patients who relapse after first-line chemotherapy [11]. Radical cystectomy and bilateral pelvic lymphadenectomy is a standard treatment for high-grade, invasive bladder cancer. However, radical cystectomy is major abdominal surgery involving a high risk of post-operative complication and even longer post-operative recovery. Radiotherapy is also commonly advised in the case of patients with MIBCs.

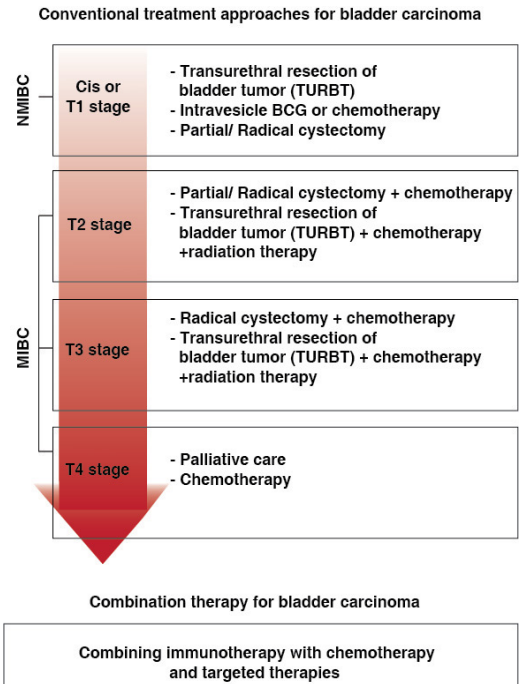

Figure 1: Bladder carcinoma treatment and therapy. Conventional treatment and combination therapy regimen for the treatment of bladder carcinoma.

Bladder Carcinoma and Targeted Therapies

Bladder carcinoma is highly heterogeneous with diverse clinical outcomes. Mutations, genomic deletions or amplifications that affect cell cycle are very common events in bladder carcinoma. Treatment of bladder carcinoma has not advanced beyond cisplatin-based combination therapy and surgery in the past three decades. Despite recent advances in technology and its application, targeted therapies has not emerged to be routinely used in the clinics. Currently, none of

***Corresponding author:** Prashant Kumar, Institute of Bioinformatics, International Technology Park, Bangalore, India; Tel: +918028416140; Fax: +918028416132; E-mail: prashant@ibioinformatics.org

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the targeted therapies have been approved for the treatment of bladder carcinoma. However, many novel targeted agents have been investigated in animal models in multiple independent studies. These studies have limitations of using cell lines with mutations in the downstream targets. Molecular studies have uncovered oncogenic roles of fibroblast growth factor receptor 1 and 3 (FGFR1 and FGFR3) in bladder carcinoma. MIBC show many chromosomal rearrangements, however, the only recurrent gene fusions reported is FGFR3-TACC3 [12,13]. The early clinical trials of FGFR3 are underway. This includes small molecular tyrosine kinase inhibitors (TKIs), and FGFR3 targeted antibodies and FGF ligand trap. Other studies revealed the MDM2 amplification is 6% of invasive bladder carcinoma and the therapeutic target of several drugs are in development [14]. The role of angiogenesis in the pathogenesis of bladder carcinoma has been described and employed for therapeutic interventions. Vascular endothelial growth factor (VEGF) has been reported to be the crucial inducer of angiogenesis in bladder cancer cell lines and its high expression have been noted in the bladder carcinoma urine samples [15]. Lately, it has also been reported that combination of angiogenesis-inhibitors and chemotherapeutic agents are able to attain objective responses greater than the other commonly used second-line therapies in bladder carcinoma [16]. Fibroblast growth factors (FGF) play a role in several oncogenic processes including angiogenesis, proliferation and wound-healing. Recurrent mutations in fibroblast growth factor receptor (FGFR) have been reported in bladder carcinoma [17]. Thus, FGFR signalling may have a pivotal role in urothelial carcinogenesis and accounts to be a promising target for personalized therapy. Several clinical trials have been planned and are ongoing using drug interventions such as B-701, LY3076226, BAY1163877, JNJ-42756493, BGJ398, FPA144 aiming to target FGFR in bladder carcinoma (www.clinical.trials.gov) [18]. Epidermal growth factor receptor (EGFR) are the family of receptors which are reported to be amplified in bladder carcinoma (9%) and overexpressed in 74% of the bladder carcinoma tissue sections [14,19,20]. EGFR mutations are targeted using Erlotinib and Afatinib, and currently undergoing clinical trials in bladder carcinoma [21]. Here we have summarized some of the pre-clinical and clinical trials on bladder carcinoma as described in Table 1 [22-32].

Immunotherapy for Bladder Carcinoma: The Future

The treatment of bladder cancer has encompassed recently beyond traditional modalities of chemotherapies and surgery, in particular the use of immunotherapy. The first immunotherapy was implicated in NMIBC was live, attenuated bacterial Bacillus Calmette-Guerin vaccine since 1990. However, BCG is only effective in 1/3 of patients [33]. Modern immunotherapy has focused on checkpoint proteins inhibitors that impede immune function. The T-cell function is inhibited through PD-L1 interaction with PD-1 leading to the decrease in T-cell clonal expansion and it results in a diminished antitumor immune response. Several checkpoint targets [programmed death ligand-1 (PD-L1)], and cytotoxic T-lymphocyte associated protein 4 (CTLA4) have received attention recently in the treatment of bladder cancer. The US Food and Drug Administration (FDA)'s approved Genentech's Tecentriq (atezolizumab) for the first time as an immunotherapy targeting programmed PD-L1. Simultaneously, the PD-L1 expression levels detection through immunohistochemistry was also approved by FDA owing to the fact that the patients with PD-L1 protein expression exhibited greater response to the therapy [34]. Five agents that target the PD-1 pathway have been FDA approved for the treatment of metastatic bladder carcinoma to be used post-platinum treatment and also for use in cisplatin-ineligible patients [35]. Also, immunosuppression in the tumor microenvironment is triggered through the differentiation of CD4+ /CD25 T lymphocytes into regulatory T cells [36-38].

Future Perspective

Despite the use of conventional cisplatin-based therapy, prognosis of bladder carcinoma is miserable. Thus there is an urgent need for the discoveries of more targets which will lead to personalized and

Target	Agent	Description	Study type	Reference
FGFR	R3Mab	An inhibitory monoclonal antibody targeting FGFR3.	pre-clinical study	[22]
	BGJ398	A potent and selective pan-FGFR antagonist	Phase I trial	[23]
	Vofatamab (B-701)	A highly specific human anti-FGFR3 monoclonal antibody	Phase I and II trial	NCT02401542, NCT03123055
EGFR	Gefitinib (ZD1839)	An orally active selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), inhibits the receptor and its related downstream process.	Phase II evaluation (study S0031)	[24]
	Erlotinib	A selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), used as a neo-adjuvant therapy.	Phase II trial	[25]
	Cetuximab	Anti-EGFR monoclonal antibody.	Phase II trial	[26]
VEGF	Bevacizumab (Avastin [A])	An inhibitor for the angiogenic VEGF.	Phase II trial	[27]
	Aflibercept	A unique fusion protein with the principal extracellular ligand-binding domains of human vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR receptor 2 (VEGFR2). It acts as a high-affinity soluble VEGF receptor and potent angiogenesis inhibitor.	Phase II trial	[28]
	Sunitinib malate	A multitargeted kinase inhibitor that inhibits vascular endothelial growth factor (VEGF) receptor (R)-1, 2 and 3, platelet-derived growth factor receptors (PDGFR)-alpha and beta, Flt3, RET, and Kit	Phase II trial	[29]
PD-L1	Atezolizumab	A class of immunotherapy drugs known as checkpoint inhibitors	Phase II trial	[30]
PD-1	Nivolumab (BMS-936558)	a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response	Phase II trial	[31]
CTLA-4	Ipilimumab	It is a monoclonal antibody that activates the immune system by targeting CTLA-4, a protein receptor that downregulates the immune system	Phase II trial	[32]
B7-H3*	MGA271	An monoclonal antibody against B7-H3 that mediates potent antibody-dependent cellular cytotoxicity against a broad range of tumor cell types.	Phase I trial	NCT01391143
Vaccines	Vesigenurtacel-L (DN24-02)	An autologous cellular immunotherapy product designed to stimulate an immune response against HER2/neu	Phase II trial	NCT02010203

Table 1: Targeted tyrosine kinase and immunotherapy trials in bladder carcinoma.

precision medicine in the treatment of bladder carcinoma. Recently considerable advancements have been made in this regard and many novel molecular-targeted agents inhibiting immune checkpoints, VEGF/R, FGF/R, or EGF/R are developed in clinical trials. The current ongoing trials evaluating immune checkpoint inhibitors, overcoming immune tolerance such as engineered T cell therapy, or novel antigens identification using next-generation sequencing would certainly lead to the development of effective personalized therapy in bladder cancer. In addition, combining immunotherapy with chemotherapy, and targeted therapies would revolutionize the future therapy. These combination therapies would be key strategy for the management of bladder cancer treatment.

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