Oncolytic Viruses for the Treatment of Bladder Cancer

Subjects: Surgery

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Bladder cancer is one of the most prevalent cancers. Despite advancements in bladder cancer therapy, new strategies are still required for improving patient outcomes, particularly for those who experienced Bacille Calmette–Guerin failure and those with locally advanced or metastatic bladder cancer. Oncolytic viruses are either naturally occurring or purposefully engineered viruses that have the ability to selectively infect and lyse tumor cells while avoiding harming healthy cells. In light of this, oncolytic viruses serve as a novel and promising immunotherapeutic strategy for bladder cancer. A wide diversity of viruses, including adenoviruses, herpes simplex virus, coxsackievirus, Newcastle disease virus, vesicular stomatitis virus, alphavirus, and vaccinia virus, have been studied in many preclinical and clinical studies for their potential as oncolytic agents for bladder cancer.

Keywords: bladder cancer ; oncolytic virus ; oncolytic viral therapy

1. Introduction

Bladder cancer (BC) is one of the most prevalent malignancies, with approximately 550,000 new cases every year [1][2]. The transurethral resection of bladder tumor (TURBT) and subsequent intravesical therapy (IVT) are the standard treatments for nonmuscle invasive bladder cancer (NMIBC) [3], while for patients with T2-T4a muscle-invasive bladder cancer (MIBC), radical cystectomy is recommended [4]. In addition, systematic chemotherapy is the first-line therapeutic method for metastatistic cancer [5]. While these therapeutic approaches may provide successful curative options, more treatment methods are still required to further improve the outcomes of BC patients, especially those who suffered Bacille Calmette–Guerin (BCG) failure and those with locally advanced or metastatistic BC.

Over the past ten years, immunotherapeutic approaches for the treatment of BC have gained popularity in both preclinical research and clinical practice [6]. One of the immunotherapy drugs is immune checkpoint inhibitors (ICIs). ICIs have gained great success in the treatment of BC, from patients who are unresponsive to BCG to MIBC patients who require systemic neoadjuvant or adjuvant immunotherapy. In addition, oncolytic viruses (OVs) represent another cutting-edge and promising immunotherapeutic strategy for cancer.

2. OVs and Their Antitumor Mechanisms in BC

The use of viruses as potential treatments for many diseases has gained more and more attention [7]. OVs are either naturally occurring or purposefully engineered viruses that have the ability to selectively infect and lyse tumor cells while avoiding causing excessive damage to healthy cells [8][9]. Nonpathogenicity, selectively targeting and killing cancer cells, and the ability to be engineered to express tumor-killing substances are common characteristics of OVs [10]. BC is a good candidate for oncolytic immunotherapy. These are the causes: (1) Intravesical therapy for BC using BCG or other drugs is well established in clinical practice; (2) through intravesical instillation, the BC can be exposed to high virus titers; and (3) the surface area for topical application is increased by the papillary structure of BC [11][12].

2.1. Direct Oncolysis

Malignant cells are particularly vulnerable to OVs infection due to tumor-driver mutations in cancer cells and particular cytokines that these cells produce [13]. For example, numerous tumor cells sustained preferential virus multiplication, which was likely brought on by a deficit in type I interferon's antiviral signaling [14][15]. In addition, some OVs are molecularly engineered to infect cancer cells specifically [9]. Once infection takes hold, OVs will take control of the tumor cell's production line for nucleic acids and proteins, preventing the cancer cells from producing enough nucleic acids and proteins to meet their growth requirements and destroying their normal physiological processes [16]. The viruses cause alterations in cell function and ultimately kill and lyse the cancer cells by damaging organelles [17][18][19][20]. Then more OVs are released and spread to nearby cancer cells. OVs may infect healthy cells, but they are unable to proliferate there because these cells have normal antiviral capability and response [9].

2.2. Promoting Antitumor Immunity

The tumor microenvironment (TME) of advanced malignancies is “cold” as lacking anti-tumor immune activity [21]. OVs can directly lyse malignant cells and lead to the release of cell-derived damage-associated molecular patterns (DAMPs), viral pathogen-associated molecular patterns (PAMPs), and soluble tumor-associated antigens (TAAs). These molecules recruit and activate antigen-presenting cells such as dendritic cells (DCs), natural killer (NK) cells, and other immune cells to the infection site. DCs take up soluble tumor antigens and then activate adaptive T cell responses against the tumor at regional lymph nodes. Additionally, enhanced antigen processing and presentation factors and tumor-specific CD8+ T lymphocytes recruitment are brought about by the viral-mediated production of chemokines and type I interferons. These cytotoxic T lymphocytes can recognize and kill both primary and metastatic tumor cells. Interferons’ counterregulatory effects can also increase the production of immunological checkpoint molecules by tumor cells, such as galectin 9 and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), as well as programmed cell death 1 ligand 1 (PD-L1) [22]. The immune suppressive TME is finally broken down by OVs to produce an immunologically “hot” TME that promotes the eradication of primary, metastatic, or recurrent tumor cells [23][24][25].

2.3. Inhibition of Intratumor Angiogenesis

Angiogenesis assumes a significant part in tumor growth and development [26]. By directly lysing the vascular endothelial cells, causing microthrombosis and producing anti-angiogenesis viral proteins, some OVs can successfully suppress intratumor angiogenesis and reduce the supply of nutrients and oxygen to cancer cells, thus preventing the proliferation of tumor cells [27][28][29].

3. OVs for BC

Initially, wild-type viruses were used in oncolytic virotherapy (OVT). To improve the effectiveness of treatment, second-generation OVs were built on genetically engineered viruses. Third-generation OVs are “armed viruses” that have been cloned with immune stimulatory or toxic genes such as granulocyte macrophage colony-stimulating factor (GM-CSF) and interleukin-2 to accelerate resistant antitumor immunity and increase tumor destruction [30][31]. A wide diversity of viruses have been investigated for their potential to act as oncolytic agents for BC, including adenoviruses, herpes simplex virus (HSV), Coxsackievirus, alphavirus, vaccinia virus, Newcastle disease virus (NDV), and vesicular stomatitis virus (VSV), et al. [32][33][34][35][36][37][38][39][40][41][42][43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64].

3.1. Adenovirus

Adenovirus is the most explored and studied OVs in BC. As a double-stranded DNA virus, it has an icosahedral capsid and infects the cell through Coxsackie and adenovirus receptors [63]. To increase antitumor effectiveness and cancer cell selectivity, many genetically modified adenoviruses have been created. In 2002, Zhang et al. published their pioneering work in this area [58]. They engineered Uroplakin II (UPII) promoter into adenovirus type 5 to create an attenuated replication-competent adenovirus variant termed CG8840. In contrast to normal cells, CG8840 was highly selective (10,000:1) and capable of efficiently replicating in and eliminating BC cells. Additionally, the injection of CG8840 intravenously and intratumorally to RT4 human BC xenografts significantly slowed the growth of the tumors [58]. Then, Ramesh et al. constructed CG0070, a serotype 5 adenovirus that contains the cDNA for human GM-CSF [49]. GM-CSF is well known for being a strong inducer of specific and persistent anticancer immunity. Several BC models were used in in vitro and in vivo experiments and confirmed the GM-CSF production, cytotoxicity, selective replication, and antitumor effectiveness of CG0070 [49]. Results from preclinical studies led researchers to assess the safety, pharmacokinetics, and anticancer activity of CG0070 in 35 patients with NMIBC. According to the phase I trial, intravesical therapy is safe and generated considerable anticancer activity [65]. Additionally, the overall CR rate for BCG-unresponsive NMIBC patients is 47% according to the phase II study’s 6-month interim results. The CR rate for patients with pure CIS was 58%, and it was 50% in BC patients whose tumors incorporating CIS [66]. In an orthotopic model, Wang et al. discovered that the direct intravesical instillation of AxdAdB-3, a oncolytic adenovirus with the deletion of E1B-55KD and mutant E1A, dramatically slowed the growth of the bladder tumor [56]. Lichtenegger et al. demonstrated that the intratumoral delivery of XVir-N-31, a YB-1-selective adenovirus, significantly inhibited tumor development and caused higher immunogenic cell death (ICD) in BC cells than wild-type adenovirus [42]. Furthermore, Lu and his colleagues evaluated the teratogenic toxicity of BC-specific adenovirus Ad-PSCAE-UPII- E1A-AR on mice and determined that it was safe in pregnant mice and had no discernible effects on the development of F1 mice [45]. There are numerous other OVs that have been studied preclinically in BC, for example, Ad-MK-E1a [53], Ad.9OC [57], Ad5F35/MKp-E1 [34], Ad/PSCAE/UPII/E1A [60][61][67], RGD-hTERT-TRAIL [62], AdLCY [44]. Most of the results are encouraging.

3.2. Herpesvirus

HSV is a double-stranded DNA virus with enclosed virions that has the ability to remain latent in host cell neurons [68][69]. HSV-1 is quite prevalent; about 67% of people worldwide have ever been exposed to it [70]. Many different oncolytic HSVs (T-VEC, G207, HSV1716, NV1020, HF10, et al.) have been designed and developed to treat a variety of malignant tumors, including BC [69][71][72]. However, the main issue with applying HSV-1 in clinical practice is that it is neurotropic, which could increase the risk of neurovirulent side effects when used in clinical settings. To decrease this risk, recombinant HSV-1s were developed by deleting the neurovirulent genes such as the diploid 134.5 genes and thymidine kinase (TK). G207 is a genetically engineered OV based on wild-type HSV-1. The deletion of γ134.5, which results in greatly decreased neurovirulence, is one of G207's distinguishing characteristics [73]. NV1020 is another HSV-1 mutant with a loss of 700-bp in the TK gene [72][73]. All four human BC cell lines and MBT-2 cells were susceptible to infection, internal replication, and lysing by both viruses. In vivo research showed that these viruses were efficient at reducing tumor burden in syngeneic C3h/Hej mice with a single intravesical instillation and even more effective with multiple instillations [72]. In 2005, the effectiveness of a HSV-1 mutant HF10 for regulating the proliferation of human and mouse BC cells was examined by Kohno et al. in vitro and in vivo [40]. They discovered that HF10 replicated effectively in MBT-2 and T24 BC cells and caused significant cell lysis. In mice with disseminated peritoneal and BC models, the treatment of HF10 markedly increased survival rates and lengthened survival durations [40]. There are also some similar HSV-1 mutants such as NV1066. According to Mullerad et al., NV1066 synergistically increased MMC's cytotoxicity for BC cell lines (KU19-19 and SKUB) [46]. However, these deletions unavoidably diminish the oncolytic effectiveness and replication efficiency of HSV-1 [74]. Therefore, Zhang et al. designed a recombinant virus and tried to regulate the expression of genes essential for replication with endogenous microR143 and microR124. They found that the miR143/124-regulated HSV-1 could restrict viral replication in neurons and normal bladder cells while killing BC cells with high potency. Thus, it is possible to maintain the full viral genome for the greatest oncolytic potency while maintaining the highest level of safety by translationally regulating the expression of essential viral genes [63].

Pseudorabies virus (PrV), a neurotropic herpesvirus, infects a variety of hosts but is nonpathogenic for humans [75][76]. Shiau et al. generated YP2 virus, a Glycoprotein E/TK-defective PrV mutant carrying both Glycoproteins D and HSV-1 TK genes under the transcriptional control of the HER-2/neu promoter [52]. In MIBC, there has been evidence of HER-2/neu overexpression, which is associated with worse clinical outcomes and increased metastases [77][78]. It enhances cancer cell survival, invasion, and angiogenesis, leading to increased cancer metastases and resistance to various cancer therapies [78]. Researchers found that YP2 selectively lysed HER-2/neu-overexpressing mouse and human BC cells. In addition, YP2 significantly inhibited the growth of the MBT-2 bladder tumor in mice [52].

Recently, Joo et al. constructed an oncolytic virus from HSV-2 termed FusOn-H2 that targets cancer cells selectively by activating the signaling pathway of Ras [38]. In an orthotopic murine BC mode, they assessed the anticancer activity of FusOn-H2. They found that in the majority of the animals, two moderately dosed intravesical instillations of the virus completely eliminated the tumors. Additionally, FusOn-H2 triggered a potent systemic immune response to the native tumor antigens created by tumor cells. They also compared FusOn-H2 with an oncolytic HSV-1 (Baco-1) and discovered that FusOn-H2 had considerably higher anticancer efficacy [38]. According to their findings, FusOn-H2 may act as an effective oncolytic drug for orthotopic BC.

3.3. Coxsackievirus

A naturally occurring common cold RNA virus known as Coxsackievirus A21 (CVA21) has demonstrated specific oncolytic activity in many tumors [79]. In a panel of human BC cell lines, Pandha et al. studied CVA21-induced cytotoxicity and discovered a variety of sensitivities that were largely correlated with the expression of the viral receptor ICAM-1 [32]. They also discovered the expression of the ICD determinant calreticulin and the release of HMGB-1 in CVA21-treated BC cell lines, which indicated that CVA21 could induce immunogenic apoptosis [32].

Based on these findings, a phase I/II trial (CANON, NCT02316171) was conducted to investigate the therapeutic potential of CVA21 (CAVATAK) for NMIBC. This trial included 15 NMIBC patients who were candidates for TURBT and evaluated the feasibility, safety, and biological effects of escalating intravesical doses of CAVATAK, either alone or combined with MMC. The production of tumor inflammation and bleeding after intravesical installations of CAVATAK served as clinical evidence of the drug's activity. CAVATAK induced significant inflammatory alterations within NMIBC tissue whether it was used alone or in combination with MMC. One patient had a complete resolution of the tumor. Regardless of whether a patient was getting viral or combination therapy, no severe toxicities were reported [80].

3.4. Vesicular Stomatitis Virus

VSV, a negative-sense RNA virus with an envelope, can selectively replicate in IFN-resistant cancer cells [14][81]. IFN resistance favors tumor growth over normal cells but impairs the cancer's ability to fight viruses [82][83]. This vulnerability of tumor cells is present in many malignancies [84]. A study assessed 57 cancer cell lines and found that 47 of them were sensitive to VSV oncolysis [85].

Hadaschik et al. treated four human BC cell lines (KU-7, UM-UC3, MGH-U3, and RT4) with either a mutant d51M variant (AV3) or wild-type VSV [35]. They discovered that the IFN-nonresponsive and more aggressive BC cell lines UM-UC3 and KU-7 were more frequently destroyed by AV3 and wild-type VSV, whereas IFN-responsive RT4 and MGH-U3 BC cells were less vulnerable. Intravesically administering type VSV and AV3 both dramatically reduced the growth of the KU-7 tumor in mice by 98% (wild-type) and 90% (AV3). These discoveries provide preliminary evidence supporting the intravesical use of VSV in NMIBC patients, particularly those with IFN resistance [33]. Furthermore, they found that type I interferon receptor down-regulation made BC cells more susceptible to VSV-induced cell death [64].

Recently, Rangsitratkul et al. armed VSVd51 with GM-CSF [50], treated human and mouse BC cells or spheroids with VSVd51-m/hGM-CSF, and observed the enhanced release of immunogenic factors and anger signals. Additionally, the intravenous administration of the OV increased survival and decreased tumor volume in MB49 BC-bearing C57Bl/6 mice and promoted the activation of bladder-infiltrating and peripheral effector immune cells [50]. These results suggest that the engineered VSVd51-hGM-CSF may be a promising OV for BC.

3.5. Alphavirus

Oncolytic alphaviruses have seen investigated to treat different types of malignancies such as brain cancers, leukemia, melanomas, lymphomas, and BC [86]. A Getah-like alphavirus strain with positive single-strand RNA called M1 was discovered in China's Hainan Province [87]. The M1 virus has the ability to specifically reproduce in cancer cells, which allows it to eliminate them without seriously affecting healthy organs [88]. The zinc-finger antiviral protein (ZAP) gene regulates M1's replication, which has a powerful and selective anticancer effect. According to a study of cancer tissue banks, 61% of BC tissue has low levels of ZAP, which suggests that M1 has a wide range of potential applications [17]. M1 caused endoplasmic reticulum stress, which led to apoptosis [17] Additionally, M1 can make cancer cells more sensitive to them when the cyclic adenosine monophosphate pathway is activated [89].

Orthotopic MIBC mice given M1 treatment had significantly slower tumor growth and longer survival times [37]. M1 has more potent antitumor effects than the first-line chemotherapeutic drug cisplatin. Decreased Ki-67 signals and enhanced cleaved-caspase-3 signal, which are indicators of cell proliferation and death, respectively, were seen in treated tumors [37]. This indicates that M1 is a novel oncolytic agent for MIBC. The M1 virus is susceptible to the antiviral effects of coiled-coil-domain-containing 6. And knocking down it increased M1's oncolytic effects through endoplasmic reticulum stress-mediated apoptosis [43].

3.6. Newcastle Disease Virus

The NDV genome is a nonsegmented, single-stranded, negative-sense RNA, and it is a pleomorphic enveloped virus with a diameter of 200–300 nm [90]. Despite the possibility of modest transient flu-like symptoms or conjunctivitis, NDV is typically not harmful to people [30]. Numerous human cancers with pathogenic (Ulster, PV701, and MTH-68/H) and nonpathogenic (73-T, LaSota, HUJ, and Hitchner-B1) viral strains have shown that NDV has oncolytic potential [30]. As early as 1992, the cytolytic activity 73-T was determined on six human tumor cell lines including BC cells (HCV29T). The researchers found that the intratumoral injection of 73-T caused full tumor regression in mice and that the drug selectively and effectively lysed BC cells [51]. Infected human and mouse cells with NDV cause ICD, the activation of innate immune pathways, and the elevation of major histocompatibility complex and PD-L1, according to a recent discovery by Anton Oseledchyk [47]. Intratumoral therapy with NDV enhanced immune infiltration and effected a change from an inhibitory to an effector T cell phenotype in both treated and untreated BC tumors [47]. Improvements in local and distant tumor control and overall survival have been seen when intratumoral NDV was combined with systemic programmed cell death protein 1 (PD-1) or CTLA-4 inhibition [47]. These results support more clinical studies combining intratumoral NDV treatment with systemic immunomodulatory drugs.

3.7. Reovirus

Reovirus is a nonenveloped, double-stranded (ds) RNA virus with 2 concentric icosahedral protein capsids, measuring around 85 nm in diameter [91]. Although reovirus can be found in the human respiratory and gastrointestinal tracts, it is not

known to be harmful. Reovirus's oncolytic abilities seem to be somewhat reliant on Ras signaling. Ras transformation also influences many phases of the viral life cycle, which helps to increase reovirus oncolysis [92]. Reovirus was shown to have the ability to destroy rat AY-27 BC cell lines and human BC cell lines (RT-112 and MGH-U3) in a preclinical investigation by Kilani et al. [39]. Using an orthotopic bladder tumor model, Hanel et al. reported the first intravesical oncolytic reovirus for the treatment of NMIBC [36]. When compared with the BCG group, the reovirus group's side effects were fewer. Reovirus treatment significantly increased tumor-free survival compared with BCG or standard saline treatment in animals [36].

3.8. Vaccinia Virus

The double-stranded DNA virus vaccinia virus (VV), which has a genomic length of roughly 190 kb, offers a number of features that make it a promising OVT agent [93][94][95]: (1) VV has been crucial to the effectiveness of the smallpox vaccine. VV has a long history of usage in people with success, which implies that it is a secure oncolytic drug. (2) VV has a vast genome; a significant amount of foreign DNA can be inserted without affecting the virus's ability to reproduce. VV stays in the cell cytoplasm throughout the infectious cycle, in contrast to other groups of DNA viruses [94][95]. VV has been studied in a variety of human malignancies including BC [94][95][96]. The F4L gene, which codes for the virus's homolog of the ribonucleotide reductase's cell-cycle-regulated small subunit, is a crucial part of VV virulence, and viral strains lacking the F4L gene exhibit in vivo attenuation [48]. By muting F4L, Potts et al. created a new oncolytic VV that selectively replicates in BCG-resistant BC cells (AY-27) and xenografted human RT112-luc orthotopic BC mice, significantly inhibiting tumor growth without producing any apparent side effects [48]. Their research offers patients with BC who are resistant to BCG a potentially effective treatment.

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