short review

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Next generation drugs in urothelial cancer: adenoviruses in the treatment of BCG-unresponsive nonmuscle invasive bladder cancer

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Summary Treatment options for nonmuscle invasive urothelial carcinoma of the bladder (NMIBC) unresponsive to Bacillus Calmette-Guérin (BCG) instillations are currently limited and often total resection of the bladder is the only therapeutic option for these patients. Thus, novel treatment options that are safe and effective are needed to avoid the substantial treatment morbidity, impact on the quality of life and the significant surgical risk associated with radical cystectomies. Besides intravesical cytotoxic therapies, immune checkpoint inhibitors, cytokines or cancer vaccines, different approaches of intravesical application of adenoviruses are being evaluated in BCG-unresponsive NMIBC. Recently, intravesical nonreplicating adenovirus vector-based gene therapy with nadofaragene firadenovec, which induces intravesical interferon expression, was approved for the treatment of BCG-unresponsive NMIBC by the US Food and Drug Administration after a recently published phase III trial. In this short review, different adenoviruses that are currently being investigated in BCG-unresponsive NMIBC are discussed and the therapeutic potential of nadofaragene firadenovec is highlighted.

Keywords Nonmuscle invasive bladder cancer · Therapy · Interferon · Bacillus Calmette-Guerin unresponsive · Nadofaragene firadenovec · Adstiladrin

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Introduction

Bladder cancer is the 10th most common cancer worldwide overall, but incidence and mortality rates are up to four times higher in men compared to women. Geographically incidence rates are higher in western and developed countries and are strongly correlated with smoking habits and tobacco use [1]. According to the GLOBOCAN database, there were an estimated 573,278 new cases worldwide in 2020, while mortality was high with 212,536 bladder cancer-related deaths [1]. While roughly a quarter of patients are diagnosed with either localized or even metastatic muscle-invasive urothelial cancer, 75% of patients initially present with nonmuscle invasive disease stages and sole infiltration of the mucosae (Ta and carcinoma in situ (CIS)) or submucosa (T1) [2, 3]. As the prognosis of muscle-invasive urothelial bladder cancer (MIBC) is generally considered poor with 5-year cancer-specific survival (CSS) rates ranging between 85% and 35% in localized or locally advanced stages and 7% at stage IV, CSS of non-muscle invasive bladder cancer (NMIBC) is substantially more favorable with >90% of patients alive after 5 years [4].

Today, transurethral resection of the primary tumor followed by Bacillus Calmette-Guérin (BCG) or chemotherapy instillations is the standard of care for the treatment of NMIBC [5], but up to 50% of patients do not respond to BCG instillations or develop recurrent disease [6]. In this case, total bladder resection with high morbidity, a substantial impact on the quality of life and a significant surgical risk is recommended [2]. Thus, there is an urgent need for the establishment of reliable and effective second-line options in the treatment of localized BCG-unresponsive

NMIBC in order to treat patients who are too frail or who decline radical cystectomy [5].

In the setting of BCG-unresponsive NMIBC, several clinical trials investigating intravesical cytotoxic therapies, such as docetaxel and gemcitabine [7, 8], immune checkpoint inhibitor therapy [9, 10], cytokines [11] or cancer vaccines [5] are currently underway. Yet another approach is the use of modified adenoviruses which are currently being tested and are nearly on the doorstep of clinical routine.

Adenoviruses as potential treatment for BCG-unresponsive NMIBC

CG0070—cretostimogene grenadenorepvec

CG0070 is a conditionally replicating oncolytic serotype 5 adenovirus which replicates under the control of the tumor-selective E2F-1 promotor. In tumors with deficiency of the well-known tumor suppressor retinoblastoma gene (Rb), which frequently occurs across various cancers, E2F-1 is highly active. This leads to the amplification of the virus proteins of CG0070 as well as of GM-CSF, whereby the gene is embedded in the virus DNA, thereby inducing further systemic anti-tumor immunity in addition to its direct cytotoxic effect [12, 13]. The interim analysis of an ongoing phase II trial including 45 patients with carcinoma in situ, or high-grade Ta or T1 tumors reported a 6-month complete response rate of 47% in the overall study population and a tolerable safety profile with the occurrence of mainly bladder-related adverse events [14].

Nadofaragene firadenovec

Another approach is to use adenoviruses as vectors for gene therapy in NMIBC. Early research suggested that recombinant human interferon-α (INFα) inhibits angiogenesis and induces cell death via TNF-related apoptosis-inducing ligand (TRAIL) in a STAT-1/RIF-1 dependent manner in vitro [15]. As such, the intravesical application of INFα-2b was subsequently tested in several clinical trials. However, results were disappointing since the efficacy of intravesical INFα-2b instillation remained behind the expectations gained from in vitro and in vivo experiments [16]. For instance, in 2002, Jajala et al. [17] compared the efficacy of a single posttransurethral resection instillation of either INFα-2b or epirubicin in 200 patients with Ta or T1 bladder cancer. While epirubicin showed a clear benefit in the prevention of intravesical tumor recurrence with a more than 2-fold relative risk reduction and only 46% of patients experiencing disease recurrence, 68% of patients receiving INFα-2b relapsed within 3 years [17]. Moreover, addition of INFα to BCG treatment showed no additional benefit over BCG alone [18].

The discrepancy between in vitro and in vivo experiments and results from clinical trials investigating intravesical INFα instillations in NMIBC was mainly attributed to the rather short exposure time of the urothelial cells to INFα (not more than 2 h), which may not be enough to provoke a strong and durable immune response [16].

This resulted in the development of a nonreplicating adenovirus vector-based gene therapy using the novel excipient Syn3, aiming to directly deliver human INFα-2b gene sequences to urothelial cells, thus inducing INFα-2b production directly at the tumor site and achieving longer exposure times [16]. This concept showed promising results both in vitro and in in vivo murine bladder cancer models with the achievement of high urinary INFα-2b levels and tumor responses [19, 20]. Mechanistically, the previously mentioned inhibition of angiogenesis by INFα, TRAIL-mediated cell death and soluble bystander factors were identified as the modes of action of INFα-2b-based gene therapy [15, 16, 21–23].

Ultimately, intravesical application of nadofaragene firadenovec, a nonreplicating recombinant adenovirus vector containing the human INFα-2b gene, was tested in both phase I and phase II trials, which reported a tolerable safety profile and efficacy for the prevention of high-grade recurrence after 12 months (35% without recurrence) in patients with BCG-unresponsive NMIBC [24, 25].

The results of a recently performed single-arm phase III trial of repeated intravesical nadofaragene firadenovec gene therapy in 157 BCG-unresponsive patients with NMIBC finally led to the approval by the Food and Drug Administration (FDA) in the USA in December 2022 [26, 27]. In the study, unresponsiveness to BCG treatment was defined as persisting carcinoma in situ and high-grade Ta or T1 tumors after 6 months of adequate BCG treatment as well as recurrence of Ta or T1 or carcinoma in situ after 6 or 12 months of BCG treatment. Patients underwent transurethral resection of visible bladder tumors at study enrollment and were subsequentially intravesically instilled with 75 mL nadofaragene firadenovec (3×10^{11} viral particles per mL). If no recurrence was evident at the follow-up visits, patients received further doses of nadofaragene firadenovec after 3, 6, and 9 months, respectively. Patients were monitored for recurrence by urine cytology and cystoscopy every 3 months and had additional bladder biopsies after 12 months [27]. Overall, the rate of complete response after 3 months, i.e., after one application nadofaragene firadenovec, was 60% with a median duration of response or high-grade recurrence-free survival of 7.3 months. Of patients with carcinoma in situ, 53.4% showed complete response after 3 months of treatment with a median duration of complete response of 9.7 months. The impressive efficacy of nadofaragene firadenovec treatment was also evident in the high-grade Ta or T1 cohort, where response rates were as

high as 72.9% with a median recurrence-free survival of 12.4 months. After 12 months, 44% of patients in this group were still without signs of recurrence [27]. Treatment was well tolerated with 66% of patients experiencing grade 1 or grade 2 adverse events, and only 4% documented grade 3 adverse events. The most common relevant adverse events in the study were fatigue (20%), bladder spasm (15%), micturition urgency (14%), chills (12%), dysuria (11%), and pyrexia (10%) [27].

Considering that besides radical cystectomy not many other options may be offered to patients who do not respond to BCG, the results of the study are encouraging and treatment with nadofaragene firadenovec may spare patients the substantial treatment morbidity, impact on the quality of life, and the significant surgical risk of cystectomy. Since half of the patients included in the study were older than 71 years and may not even be considered fit for surgery, nadofaragene firadenovec may be an important therapeutic option with a favorable safety profile in patients who would otherwise be difficult to treat.

Conclusion

Given the promising results of the discussed phase III trial and the recent FDA approval of nadofaragene firadenovec, gene therapy using adenovirus vectors is on the doorstep of clinical routine in the treatment of BCG-unresponsive NMIBC and may be of particular interest as a novel therapeutic option for elderly and frail patients.

Take home message

Gene therapy with nadofaragene firadenovec in BCG-unresponsive nonmuscle invasive bladder cancer is on the doorstep of clinical routine and may particularly represent a novel therapeutic option for elderly and frail patients.

Conflict of interest D.A. Barth and M. Pichler declare that they have no competing interests.

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