Editorial

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Nadofaragene: a new era of precision medicine for bladder cancer

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Introduction

With an anticipated 573 278 new cases and 212 536 fatalities in 2020[1], bladder cancer ranked as the 10th most frequent cancer globally. Additionally, it is the sixth most prevalent cancer among men and the 17th among women[2]. Despite recent major improvements in the treatment of bladder cancer, the prognosis for individuals with advanced illness is still dismal[3].

Bladder cancer is classified as either nonmuscle-invasive (NMIBC) or muscle-invasive bladder cancer (MIBC)[4]. Noninvasive cancer reflects the inner lining of the bladder being affected excluding the deep muscle layer. NMIBC involves subgroups that are linked to an increased risk of cancer development. It includes the following, (I) 70% of patients have Ta disease, with polyps extending into the lining of the bladder; (II) 20% of patients have T1 disease, with tumors below the superficial lining but not involving the muscular layer of the bladder wall; and (III) 10% of patients have carcinoma in situ (CIS) with flat, superficial growth[5]. Bladder cancer presents itself as malignant with few treatment choices that back in date mainly revolved around chemotherapy, surgery, and radiation tailored to the cancer's complexity. Transurethral resection and intravesical therapy are now the recommended courses of treatment for NMIBC. The most effective intravesical medication now available is Bacillus Calmette-Guérin (BCG), which is recommended for high-risk individuals[4]. Unfortunately, most patients eventually develop BCG-unresponsive illness, a condition with few treatment options that save severe cystectomy due to its intrinsic resistance. Nevertheless, incorporating Nadofaragene firadenovec accounts for the first gene therapy in combating genitourinary malignancies. The component of Nadofaragene Firadenovec (rAd-IFN/Syn3) that delivers a copy of the human interferon alfa-2b gene to urothelial cells is rAd-IFN, a nonreplicating recombinant adenovirus vector-based gene therapy[6]. Transfected urothelial cells produce IFN-2b, which has anticancer properties including immunostimulatory, antiangiogenic, and apoptotic actions[7]. This gene therapy is the first one to be approved for the treatment of unresponsive BCG NMIBC by the FDA in December 2022[4]. High response rates and controllable adverse effects in clinical studies have produced encouraging findings. Improvements in patient selection, the discovery of biomarkers for response prediction, the investigation of alternative vectors for improved transfection efficiency, and the creation of combination tactics aimed against resistance mechanisms are the main areas of the current studies. Future advances have the potential to significantly improve the efficacy and impact of gene therapy for bladder cancer, and the approval of Nadofaragene firadenovec is an important milestone in that regard. Precision medicine is a method of treating patients that considers the genetic, environmental, and behavioral variability of each patient. Instead of using a one-size-fits-all strategy, precision medicine aims to provide therapies that are customized to each patient. For bladder cancer, Nadofaragene is a good illustration of precision therapy[8]. The development of nadofaragene and other targeted therapies is a significant step forward in the treatment of bladder cancer. These therapies offer patients with advanced bladder cancer new hope for a better future.

Understanding Bladder Cancer

Globally, the highest incidence of bladder cancer is presently observed in the majority of developed communities. Bladder cancer mostly affects the elderly population, with around one in every five individuals worldwide developing the illness before reaching 75 years of age, the average age at which individuals get a diagnosis of bladder cancer is 73 years[9,10]. However, the susceptibility to bladder cancer in an individual is based on several factors. Depending upon the invasion of the bladder wall, urinary bladder cancer can be divided into invasive and noninvasive types. Most cases, accounting for 70–80% are of nonmuscle invasive tumors[11]. Bladder cancer treatment options vary by patient's age, general health, and the extent of their cancer. Transurethral resection of bladder tumor (TURBT) followed by intravesical chemotherapy is the standard treatment for patients with nonmuscle-invasive bladder cancer. Radical cystectomy is the gold standard therapy for cancer that has spread to the muscle layer. Chemotherapy followed by radical cystectomy is the conventional treatment for locally advanced bladder cancer (T3) that has not migrated to other parts of the body. Advanced patients with distant metastases are often treated first with chemotherapy. Bladder cancers have a high recurrence rate, and if this recurrence persists, cystectomy may be required[10].

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However, there are significant limitations in the therapy of bladder cancer attributed to the aberrant growth and invasive nature of tumor cells. Over the course of treatment, many cancer cells may become resistant to chemotherapy and targeted treatments, which can ultimately result in the ineffectiveness of chemotherapy[12]. In the contemporary period, several types of cancer continue to exhibit limited efficacy in terms of accessible treatment choices, hence posing challenges in their management. Moreover, available cancer treatments often include notable adverse effects that may significantly impact the overall health and well-being of patients. Other factors that limit treatment include a late cancer diagnosis and the significant costs associated with treatment.

Precision Medicine in Bladder Cancer

Precision medicine is an innovative approach to the management and prevention of diseases, which takes into account the unique variances in an individual's genetic makeup, environmental circumstances, and lifestyle choices. This approach aims to customize treatments and interventions in a more targeted manner[13]. Precision medicine is a novel approach to treating cancer that is gaining traction in the area of oncology. It takes into consideration the unique qualities of each patient as well as the tumor's and immune system's contexts while developing a therapy plan. This not only enhances patient care but also helps patients in other ways, such as assisting with the management of cancer-related pain, especially near the end of life when no further antitumor therapies are possible[14]. By customizing therapies to an individual's genetic makeup, precision medicine can indeed substantially enhance treatment outcomes and decrease mortality rates for bladder cancer. A significant achievement in the field of precision medicine for bladder cancer involves the precise targeting of specific genetic alterations. For instance, drugs such as Erdafitinib have demonstrated efficacy in selectively targeting genetic mutations, such as FGFR2/3 mutations, the administration of Erdafitinib has been observed to effectively impede or even arrest the proliferation of cancer cells exhibiting FGFR2/3 alterations. Ongoing research is focused on exploring additional indicators to enhance the precision of treatment strategies related to modifications in DDR genes, amplifications of FGFR genes, changes in ErbB receptor kinase genes, and mutations in PIK3CA genes[15]. The use of circulating tumor DNA (ctDNA) exhibits potential in the prediction of patient response and prognosis. By monitoring changes in ctDNA levels over the course of therapy, healthcare personnel can evaluate treatment response. Immunotherapies, such as immune checkpoint inhibitors, are successful in treating some individuals with bladder cancer whose tumors express PD-L1, the selection of patients for first-line immunotherapy has been improved because of the use of this marker. Immunomodulatory agents, such as inhibitors targeting the Mammalian Target of Rapamycin (mTOR) and Protein kinase B (AKT), exhibit potential as therapeutic interventions due to their ability to modulate the immune response[15]. However, the application of precision medicine in bladder cancer is currently limited, and additional work and research are required in this field for the advancement of bladder cancer care.

Nadofaragene: Mechanism and Development

Nadofaragene firadenovec (nadofaragene) is a nonreplicating adenoviral vector-based gene therapy developed by Ferring Pharmaceuticals that delivers a copy of the human interferon-α2b (IFN- α2b) gene to the bladder urothelium[16]. IFN-α 2b is a powerful cytokine with anticancer and immunomodulatory properties[17]. The adenoviral vector penetrates urothelial cells when nadofaragene is injected into the bladder and releases the IFN- α2b gene. IFN- α2b is then generated through the transcription and translation of the IFN- α2b gene[6]. Depending on the type of cells that are being treated with IFN- α2b, various biological effects that might be either direct or indirect can be caused. First, IFN-α2b has a direct effect on cancerous cells, causing cell cycle arrest, apoptosis, and angiogenesis suppression, which has a significant effect on the development and growth of tumors. Second, immune cells like dendritic cells (DCs), macrophages (M), and natural killer (NK) cells proliferate, mature, and present antigens with increased frequency in the tumor microenvironment when IFN-α2b is stimulated. This enhances both innate and adaptive immunity to pathogens and cancer[18,19], Third, the lysis of cancerous cells and the release of exposed tumor antigen might result from direct and indirect effects, strengthening the antigen presentation and indirect effects. Fourth, these immune cells that have been stimulated by indirect effects may release additional IFN-α to amplify the direct effects. Therefore, under ideal circumstances, both actions may show synergy against malignant tumors[17]. The effectiveness of nadofaragene in the treatment of bladder cancer is thought to be influenced by the anticancer and immunomodulatory properties of IFN-α2b.

The development of nadofaragene was based on the encouraging findings of preclinical investigations, which showed that nadofaragene was efficient in inducing tumor shrinkage and prolonging survival in animal models of bladder cancer. A single-arm phase 2 trial in patients with high-risk, BCG-unresponsive NMIBC was one of the clinical trials that Nadofaragene underwent after that. According to the trial's findings, 44% of patients experienced complete responses (CRs) after using nadofaragene. The average CR lasted 14.3 months[6]. Nadofaragene represents a substantial development in the treatment of bladder cancer. The well-tolerated treatment of nadofaragene has a controllable safety profile. Nadofaragene is an exciting novel gene therapy for bladder cancer treatment. Its unique mode of action combines immunomodulatory and direct anticancer actions. Both muscle-invasive and nonmuscle-invasive bladder cancer have shown effectiveness with nadofaragene. The creation of nadofaragene represents a substantial advancement in the treatment of this illness.

Nadofaragene's Impact on Precision Medicine

In treating bladder cancer, Nadofaragene is a shining example of precision medicine. It is a targeted treatment created to selectively target bladder tumor cells. Nadofaragene is also being studied for its potential use in other cancers, including MIBC and urothelial carcinoma of the upper urinary tract. A significant step towards the development of precision medicine for bladder cancer has been reached with the approval of nadofaragene. It has the potential to greatly improve the outcomes for patients with high-risk, BCG-unresponsive NMIBC because it is the first gene therapy to be licensed for the treatment of this condition[7].

Nadofaragene is a personalized treatment that is created specifically for each patient's tumor. This is because of nadofaragene's focus on the precise genetic abnormalities that the patient's tumor has. It is a minimally invasive treatment, which means that a catheter is used to deliver the medication straight into the bladder. This makes it a more practical and safer alternative to conventional treatments like surgery and chemotherapy[6]. More studies are required to completely evaluate the long-term effectiveness and safety of nadofaragene because it is a relatively new medication. Nadofaragene; however, has the potential to become a standard of care treatment for patients with high-risk, BCG-unresponsive NMIBC since the early clinical results are so encouraging.

Challenges and Future Directions

Despite the advantages it offers, there are also certain challenges related to the use of nadofaragene for the treatment of bladder cancer. Nadofaragene firadenovec is a contemporary therapeutic option for noninvasive bladder cancer, which is consistently being evaluated in clinical studies to optimize patient outcomes and ensure smooth treatment progression. The task of determining the optimal treatment for individuals diagnosed with nonmuscle invasive bladder cancer (NMIBC) is a considerable challenge, mostly because of the diverse mechanisms of action and varying degrees of efficacy shown by the range of therapeutic drugs now available[20]. The major adverse effects associated with Nadofaragene mostly include hematuria, bladder spasms, micturition urgency, weariness, and urinary tract infection. In a few instances, it has also resulted in significant unfavorable consequences such as bladder contracture, urinary fistula, and bladder perforation. Also, the administration of nadofaragene firadenovec to immunocompromised individuals is contraindicated due to its potential to cause disseminated adenovirus infection[21]. Additionally, Nadofaragene firadenovec is less cost-effective than other combination therapies, primarily pembrolizumab[22]. The traditional strategy for treating NMIBC is being changed by the incorporation of immunotherapies and combination treatments, such as pembrolizumab and gemcitabine/docetaxel, these treatments utilize the immune system and multiple medications to improve outcomes. Intravesical nadofaragene firadenovec therapy features a convenient dosage regimen (one intravesical treatment every 3 months) that is simple for both the patient and the doctor to follow. Future studies should conduct analysis to help identify patients who react to therapy quickly and to shed light on the probable causes of treatment resistance. Continuous efforts and testing in healthcare provide hope for improvement for professionals and patients[21]. INFα gene therapy can be refined by targeting patient selection by locating patient traits or biomarkers indicating sensitivity or resistance timely. This results in an increase in response rate since choosing treatment candidates who are likely to react. Finding alternative vectors that increase transfection efficiency and deliver more long-lasting therapeutic results is another area for exploration. The creation of creative combination tactics that target resistance pathways offers another chance to enhance IFN gene therapy. Several therapeutically actionable targets, such as PD-L1 and the EGFR, were discovered in the trials testing LV-IFN gene therapy and demand more research when combined with interferon gene therapy[4].

Conclusion

The first gene therapy to be authorized for the treatment of bladder cancer is nadofaragene firadenovec. It is a targeted treatment created to selectively target the bladder tumor cells. Patients with high-risk, BCG-unresponsive NMIBC have proven that Nadofaragene is very effective. Overall, nadofaragene is an exciting novel gene therapy with the potential to completely change the way bladder cancer is treated. In clinical studies, this personalized, minimally invasive treatment has proven to be quite successful. For patients with high-risk, BCG-unresponsive NMIBC, nadofaragene has the potential to become the standard of care treatment. However, further study is required to fully understand its long-term effectiveness and safety. It is still too early to determine for sure if nadofaragene is ushering in a new era in bladder cancer precision treatment. Early clinical findings; however, show great promise.

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References

[1] GLOBOCAN 2020: Bladder cancer 10th most commonly diagnosed worldwide - World Bladder Cancer Patient Coalition. Accessed 3 October 2023. https://worldbladdercancer.org/news_events/globocan-2020-bladder-cancer-10th-most-commonly-diagnosed-worldwide/

[2] Bladder cancer statistics | World Cancer Research Fund International. Accessed 3 October 2023. https://www.wcrf.org/cancer-trends/bladder-cancer-statistics/
[3] Dietrich B, Siefker-Radtke AO, Srinivas S, *et al*. Systemic therapy for advanced urothelial carcinoma: current standards and treatment considerations. Am Soc Clin Oncol Educ Book 2018;38:342–53.
[4] Martini A, Tholomier C, Mokkapati S, *et al*. Interferon gene therapy with nadofaragene firadenovec for bladder cancer: from bench to approval. Front Immunol 2023;14:1260498.
[5] Beinfeld M, Atlas SJ, Touchette D, *et al*. The effectiveness and value of nadofaragene firadenovec, oportuzumab monatox, and pembrolizumab for BCG-unresponsive non-muscle-invasive bladder cancer: a summary from the institute for clinical and economic review's midwest comparative effectiveness public advisory council. J Manag Care Spec Pharm 2021;27:797–804.
[6] Boorjian SA, Alemozaffar M, Konety BR, *et al*. Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. Lancet Oncol 2021;22:107–7.
[7] Lee A. Nadofaragene firadenovec: first approval. Drugs. 2023;83:353.
[8] The Promise of Precision Medicine | National Institutes of Health (NIH). Accessed 4 October 2023. https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/promise-precision-medicine
[9] Richters A, Aben KKH, Kiemeney LALM. The global burden of urinary bladder cancer: an update. World J Urol 2020;38:1895–904.
[10] Treatment of Bladder Cancer, by Stage | American Cancer Society. Accessed 4 October 2023. https://www.cancer.org/cancer/types/bladder-cancer/treating/by-stage.html
[11] DeGeorge KC, Holt HR, Hodges SC, *et al*. Bladder cancer: diagnosis and treatment. Am Fam Physician 2017;96:507–14.
[12] Ashrafizadeh M, Zarrabi A, Karimi-Maleh H, *et al*. (Nano)platforms in bladder cancer therapy: challenges and opportunities. Bioeng Transl Med 2023;8:e10353.
[13] What is precision medicine?: MedlinePlus Genetics. Accessed 4 October 2023. Online. https://medlineplus.gov/genetics/understanding/precisionmedicine/definition/
[14] Hoeben A, Joosten EAJ, van den Beuken-Van Everdingen MHJ. Personalized medicine: recent progress in cancer therapy. Cancers (Basel) 2021;13:1–3.
[15] Guercio BJ, Iyer G, Rosenberg JE. Developing precision medicine for bladder cancer. Hematol Oncol Clin North Am 2021;35:633–53.
[16] FDA Approves First Gene Therapy for the Treatment of High-Risk, Non-Muscle-Invasive Bladder Cancer | FDA. Accessed 5 October 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-high-risk-non-muscle-invasive-bladder-cancer
[17] Xiong F, Wang Q, hua Wu G, *et al*. Direct and indirect effects of IFN-α2b in malignancy treatment: not only an archer but also an arrow. Biomark Res 2022;10:1.
[18] Blaauboer A, Sideras K, van Eijck CHJ, *et al*. Type I interferons in pancreatic cancer and development of new therapeutic approaches. Crit Rev Oncol Hematol 2021;159:103204.
[19] Lukhele S, Boukhaled GM, Brooks DG. Type I interferon signaling, regulation and gene stimulation in chronic virus infection. Semin Immunol 2019;43:101277.
[20] Valenza C, *et al*. Emerging treatment landscape of non-muscle invasive bladder cancer. Expert Opin Biol Ther 2022;22:717–34.
[21] Nadeem A, Qamar K, Bilal W, *et al*. Nadofaragene firadenovec: a breakthrough in the field of bladder oncology. Frontiers in Urology 2023;3:1206398.
[22] Joshi M, Atlas SJ, Beinfeld M, *et al*. Cost-effectiveness of nadofaragene firadenovec and pembrolizumab in Bacillus Calmette-Guérin immunotherapy unresponsive non-muscle invasive bladder cancer. Value Health 2023;26:823–32.