Novel Therapeutic Approaches for Recurrent Nonmuscle Invasive Bladder Cancer

Brock E. Boehm, DO, Robert S. Svatek, MD, MSCI*

KEYWORDS

• Bladder • Cancer • Novel • Therapeutics

KEY POINTS

- Pharmacokinetics of intravesical chemotherapy delivery demonstrates that treatment of bladder cancer cells located deep to the superficial cell layer is inadequate.
- BCG vaccine's clinical activity is thought to depend in part on eliciting a Th1 immune responses characterized by increases in pro-inflammatory cytokines such as interleukin (IL)-2 and interferon (INF-γ).
- Checkpoint inhibitors, including programmed death-1 (PD-1) and programmed death ligand 1 inhibitors, have demonstrated impressive and durable antitumor response in advanced, metastatic bladder cancer, and this has prompted considerations for testing in nonmuscle invasive bladder cancer.

INTRODUCTION

Urothelial cell carcinoma of the bladder is the fourth most common malignancy in men, and most present with nonmuscle invasive bladder cancer (NMIBC). It is currently estimated there will be 74,690 new cases of bladder cancer in the United States, with 15,580 estimated deaths in 2014.[1] Standard therapy for NMIBC is complete transurethral resection of the bladder tumor (TURBT). In some cases, perioperative or adjuvant intravesical therapy is indicated. Bacillus Calmette-Guérin (BCG) immunotherapy is indicated for high-grade disease, and this has been the stable of standard care since it received US Food and Drug Administration (FDA) approval for the treatment and prophylaxis of NMIBC. Despite the success of BCG therapy, however, recurrence rates remain high, and progression is still possible.[2] Patients who fail BCG therapy have limited options, and most will succumb to bladder removal. Thus, there is strong impetus to find alternative treatment options in NMIBC.

This article aims to provide a summary of novel strategies currently being investigated in patients with NMIBC. It focuses on approaches that have initiated studies in patients, including phase 1 through 3 trials and pilot studies. Considerable progress has been made toward improving the delivery method of the available intravesical agents. Presently, intravesical therapy is limited by the finite amount of time that the agent remains in contact with the bladder. Bladder cancer is widely considered to be responsive to immune therapy, as BCG immunotherapy has been the mainstay of treatment for decades. Thus, many novel approaches are immune-based therapies and include cancer vaccines, use of BCG subcomponents, and checkpoint inhibitors. Finally, access to bladder mucosa via direct catheterization into

Disclosures: There are no financial disclosures.
Adult Cancer Program, Department of Urology, Cancer Therapy and Research Center, The University of Texas Health Science Center San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78023, USA
* Corresponding author.
E-mail address: svatek@uthscsa.edu

Urol Clin N Am 42 (2015) 159–168
http://dx.doi.org/10.1016/j.ucl.2015.02.001
0094-0143/15/$ – see front matter

the bladder via the urethra has enabled unique strategies for delivery of cancer therapy including viral- or plasmid-based gene therapy. These and other miscellaneous approaches currently being developed for testing in patients with NMIBC will be reviewed. Current therapeutic trials in nonmuscle invasive bladder cancer accessed in clinicaltrials.gov are represented in (**Table 1**).

Delivery Methods

The structure of the urothelium and function of the bladder serve as a restrictive barrier that creates unique challenges when considering delivery of intravesical therapy. The bladder is constantly receiving urine, and as such, will begin to dilute the agent in question as urine is drained from the kidneys. It will also rapidly wash out the agent during the bladder's voiding stage.

The urothelium itself is composed of 3 distinct cell layers: superficial umbrella cells that measure 100 to 200 μm; intermediate cells (20 μm), and a basal cell layer (5–10 μm), which makes up a layer that functions as precursor stem cells and lies immediately superficial to the basement membrane.[3] On the apical surface of the umbrella cells lie several different glycosaminoglycans that act as a barrier to potential toxic substances that may be in the urine.[3] These hydrophilic molecules extend far above the cell surface and function to create an aqueous layer that serves as a barrier between the bladder lumen and urothelium.

Electromotive drug administration

Studies analyzing the pharmacokinetics of intravesical chemotherapy delivery noted that treatment of bladder cancer cells located deep to the superficial cell layer was inadequate.[4] This was thought to be secondary to decreased drug concentrations beyond the urothelium, and electromotive therapy was proposed as a means to improve drug penetration. When exposed to a conductive current such as NaCl and an electrical field, mitomycin (MMC) delivery across the urothelium increases as a result of current-induced convective flow of water. Thus, water will bring the nonionized MMC particle with it across the urothelium as it travels down its electrical gradient. Results indicated that mean concentration of MMC in the bladder wall delivered by electromotive drug administration vastly exceeded MMC concentration achieved through passive delivery by a factor of almost 7.[5]

In a randomized controlled trial of adjuvant treatment following complete transurethral resection, patients with T1 bladder cancer assigned sequential BCG and electromotive MMC had a longer disease-free interval than did those assigned BCG alone.[6] However, because patients in the control group did not receive standard maintenance BCG therapy, the benefit of this therapy over standard BCG remains to be tested. More recently, benefit of electromotive therapy was also observed in the perioperative setting. In a phase 3 study enrolling patients with NMIBC, the efficacy of TURBT alone was compared with that of immediate post-TURBT passive diffusion MMC or immediate pre-TURBT electromotive MMC. With a median follow-up of over 7 years, disease-free rates were: 36%, 41%, and 62% of patients treated with TURBT alone, post-TURBT passive diffusion of MMC, and pre-TURBT electromotive administration of MMC, respectively. This represents a 21% absolute improvement in disease-free rate over passive diffusion.[7] Electromotive MMC is not currently approved by the FDA.

Nanoparticle-based therapy

Small molecule platform nanoparticles can be engineered to increase the drug contact time with the urothelium by functioning as controlled drug release systems. They are specifically created to have multiple functional groups (eg, albumin, amine, carboxyl, or sulfhydryl) that can interact with the urothelium in order to increase adhesion rates. Nanoparticle albumin-bound (NAB) agents are currently under clinical investigation. The addition of albumin is proposed to increase solubility and facilitate drug delivery to tumor cells through biological interactions with albumin receptors that facilitate drug transport across epithelial cells.[8] Intravesical administration of NAB linked with paclitaxel demonstrated safety and tolerability in a phase 1 trial including 18 patients with BCG-refractory high-grade Ta, T1, or carcinoma-in-situ (CIS).[9] Results of the phase 2 data were recently reported.[10] A complete response was observed in 10 (35.7%) of 28 patients treated with NAB-paclitaxel with recurrent NMIBC who had failed at least 1 prior BCG regimen.[10]

In murine models, the mTOR inhibitor rapamycin was found to potentiate the induction of BCG-mediated immune responses in mice.[11] In addition, rapamycin demonstrated antitumor activity in preclinical models of bladder cancer.[12] Albumin-bound rapamycin (ABI-009) could facilitate uptake of rapamycin, which is normally water-insoluble. This novel agent is currently being tested in early clinical trials for patients with BCG-refractory or recurrent NMIBC (NCT02009332).

Hydrogel formulations

One potential means to improve contact duration of intravesical therapy, including BCG, is through the use of a hydrogel delivery system. Thermosensitive hydrogels are able to exist as a