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Review

The Future of Intravesical Drug Delivery for Non-Muscle Invasive Bladder Cancer

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Abstract. Despite being the fifth most common cancer in the United States, minimal progress has been made in the treatment of bladder cancer in over a decade. Intravesical instillation of Bacillus Calmette-Guerin (BCG) for the treatment of non-muscle invasive bladder cancer (NMIBC) has been in use for over 30 years and remains the standard treatment in cases of intermediate and high risk disease. Despite the relative success of intravesical BCG, unmet needs in the treatment of NMIBC persist. These challenges include disease recurrence and progression even with treatment with BCG, as well as issues regarding its availability and patient tolerability. The inherent properties of the bladder pose the biggest obstacle to developing effective intravesical treatments for NMIBC. Current research is now focusing on methods to improve the delivery of intravesical therapies. The objective of this review is to discuss novel intravesical drug delivery systems and how they are addressing these challenges in the treatment of NMIBC.

Keywords: Bladder cancer, intravesical therapy, drug delivery devices, nanocarriers, hydrogels

BACKGROUND

In the United States, approximately 76,960 new cases of bladder cancer and 16,390 bladder cancer related deaths are expected in 2016 [1]. Approximately 70% of new cases present as non-muscle invasive bladder cancer (NMIBC), of which 70% are pTa (confined to bladder epithelium), 20% are pT1 lesions (invasion of lamina propria), and 10% are carcinoma in situ (CIS). As many as 80% of patients with pTa disease will experience disease recurrence, and up to 45% of patients with pT1 or CIS will experience disease progression without treatment [2].

Intravesical Bacillus Calmette-Guerin (BCG) is recommended as adjuvant therapy to reduce the risk of tumor recurrence and possibly disease progression in intermediate risk (multiple or recurrent low-grade tumors) and high risk patients (T1, CIS, high-grade disease or multiple recurrent >3 cm low-grade Ta tumors) [3–10]. Mitomycin C (MMC) is an alternative intravesical therapy and is most often given as a single, immediate postoperative instillation after transurethral resection of bladder tumor (TURBT) to decrease the risk of recurrence [3–5, 11]. MMC is also recommended as adjuvant treatment because of its ability to reduce the risk of disease recurrence, however several studies have demonstrated superior prevention of tumor recurrence with BCG maintenance therapy as compared to MMC [7–8, 12].

Despite treatment with BCG up to 39% of pTa or pT1 disease will recur and 8% will progress to muscle invasive disease [6, 12]. BCG also has known side effects which impact patient acceptance. There has been a worldwide supply shortage since 2012. In addition, the intrinsic properties of the bladder pose unique challenges in developing effective intravesical therapies. Intravesical drugs are constantly diluted by urine and are regularly removed from the bladder by voiding. In this review we will discuss

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novel intravesical drug delivery systems and how they address these challenges in the treatment of NMIBC.

HISTORY OF INTRAVESICAL THERAPY

The first intravesical therapies can be traced to the 11th century. The Persian physician and philosopher Avicenna described transurethral injection of drugs into the bladder to treat bladder inflammation in his Canon of Medicine, which was completed in 1025 AD [13]. In the 1890 s bladder washings with iodoform and various acidic solutions were administered through a foley catheter or a glass nozzle inserted into the distal urethra to treat cystitis. Felix Guyon is often cited for his method of bladder instillation with a solution of bichloride mercury to treat cystitis [14]. Intravesical therapy for the treatment of bladder tumors was described in the medical literature in the 1950 s. Walton and Sinclair instilled radioactive solutions of sodium and bromine in 1952, and Ellis and Oliver instilled radioactive colloidal gold in 1955 [15, 16]. Jones et al. introduced Thiotepa [17], which was the first FDA approved intravesical agent for NMIBC. Thiotepa was found to have significant side effects, most notably bone marrow suppression [18]. In the 1970 s, intravesical BCG was first introduced in the treatment of bladder cancer when Morales demonstrated the success of BCG in treating carcinoma in situ [19].

ANATOMY AND PHYSIOLOGY, PHARMACODYNAMICS

The bladder is a muscular, hollow pelvic organ whose main functions include the storage and expulsion of urine. The bladder is relatively impermeable to prevent reabsorption of waste substances. This is accomplished by the bladder permeability barrier (BPB). The BPB includes the basal germinal cell layer (5–10 um), an intermediate layer (20 um), and the apical layer of umbrella cells (100–200 um). Umbrella cells are given their name for their hexagonal, umbrella shape and are able to change shape and surface area as the bladder fills and contracts. The umbrella cell apical surface consists of an asymmetrical unit membrane, which is composed of densely packed plaques made of uroplakins that cover 70–90% of the luminal surface and are surrounded by hinge membranes. Umbrella cells are then interconnected by tight junctions. These unique characteristics create a barrier between urine and plasma. In addition, a hydrophilic glycosaminoglycan (GAG) layer of mucin forms a thin aqueous layer on top of the umbrella cells that acts as an anti-adherent and prevents adhesion of foreign particles [20].

While the relative impermeability of the bladder minimizes the systemic absorption of the drug and the subsequent side effects, this also poses a challenge in achieving the desired effects of intravesical drugs. While urothelium is not completely impermeable and a small but finite passive permeability is present through transcellular and paracellular pathways, studies have shown that the permeability values of mammalian bladder epithelium are exceptionally low [21, 22].

More importantly, any drug instilled into the bladder is diluted as the bladder constantly receives urine from the kidneys and is quickly washed out during bladder emptying. This decreases both the concentration of the drug and the amount of time a drug is in contact with the targeted tissue. Au et al. studied the pharmacodynamics of Mitomycin C (MMC) in human bladder tumors and demonstrated that drug concentration and exposure time are paramount in determining tumor response to MMC. They determined that prolonging the exposure time leads to a proportional decrease in the drug concentration needed to achieve the same effect [23]. Consequently, research has focused on increasing the dwell time and absorption of intravesical drugs with the development of novel intravesical drug therapy systems.

NOVEL INTRAVESICAL DRUG DELIVERY SYSTEMS

Intravesical drug delivery devices

To increase the dwell time of intravesical drugs, researchers are developing intravesical drug delivery devices that are implanted in the bladder and left in place for an extended period of time. This increases the amount of time the bladder mucosa is exposed to the drug.

One such novel technology is the Taris Biomedical Lidocaine Releasing Intravesical System (LiRIS®) device. This device consists of a water permeable silicone double lumen tube. Drug tablets are placed into one lumen with an orifice that acts as an osmotic drug pump to release the drug over time. The gross structure of the device resembles a pretzel and was designed to resist structural collapse and promote retention of the device within the bladder with minimal irritation. This device is inserted transurethrally

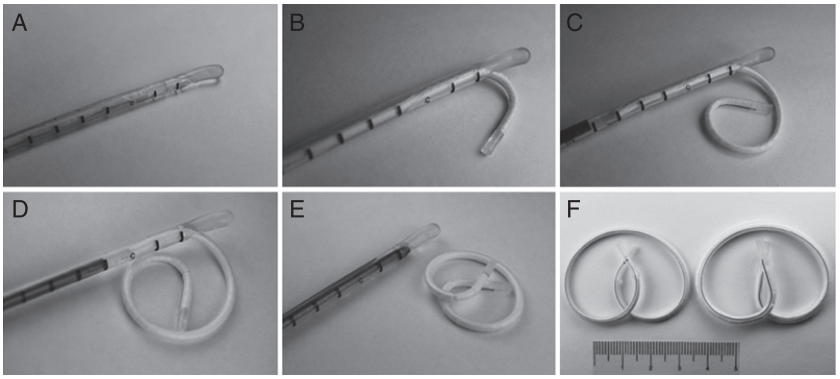

Fig. 1. Deployment of LiRIS® through a specialized catheter as demonstrated in (A) through (E). Two devices containing different doses of the same medication are shown in (F) with a 5 cm ruler for scale. Reproduced with permission [24].

Table 1
Current trials recruiting or soon to recruit to assess novel drug delivery systems (www.clinicaltrials.gov)

Trial	Drug Delivery System	Purpose
NCT01803295 (OPTIMA)	TC-3 hydrogel	Evaluate ablative effect and recurrence rate of MMC with TC-3 hydrogel compared to standard MMC on low risk NMIBC lesions
NCT02307487	TC-3 hydrogel	Evaluate the safety of escalating doses of MMC TC-3 hydrogel in high risk NMIBC prior to TURBT
NCT02720367	Gemcitabine Releasing Intravesical System (GemRIS)	Evaluate safety, tolerability and preliminary efficacy of GemRIS drug delivery system in patients with recurrent low or intermediate risk NMIBC prior to TURBT
NCT02202044	Electromotive Drug Administration (EMDA)	Evaluate recurrence free rate of sequential BCG and EMDA/MMC in high risk NMIBC after TURBT
NCT02471547	Thermo-chemotherapy	Evaluate recurrence rate of bladder wall thermo-chemotherapy with MMC in NMIBC prior to TURBT
NCT02009332	Albumin Bound Nanoparticles (ABI-009)	Evaluate safety, tolerability, and efficacy of Albumin Bound Rapamycin Nanoparticles (ABI-009) in BCG refractory or recurrent NMIBC

into the bladder through a foley catheter (Fig. 1) and is subsequently removed during office cystoscopy [24]. The original research for this device was performed at the Massachusetts Institute of Technology by Lee and Cima, where they demonstrated increased levels of lidocaine in the bladder tissue of rabbits after three days of exposure [25]. This device is currently in Phase 2 trials for the intravesical delivery of lidocaine in interstitial cystitis patients. Future research will explore its application in bladder cancer treatments. A Phase 1 trial is planned to study the safety and tolerability of their Gemcitabine Releasing Intravesical System (GemRIS) (Table 1).

As a corollary to intravesical drug delivery devices, the field of ophthalmology has had success in intravitreal delivery of drugs to the eye. There are currently multiple products on the market which utilize similar principles of osmotic diffusion that the LiRIS® device utilizes. These include the FDA approved Vitrasert® and Retisert® implants which utilize a polyvinyl alcohol membrane to control sustained release of medications into the vitreous of the eye for the treatment of CMV retinitis and non-infectious retinitis, respectively [26, 27]. Newer devices include the biodegradable reservoir Durasert™, which is currently in Phase II trials for the treatment of high intraocular pressure with intravitreal latanoprost and the refillable Capsule Drug Ring delivery device that delivers bevacizumab after cataract surgery into the peripheral lens capsule [28]. Utilizing similar concepts, the development of intravesical drug delivery devices may achieve similar success.

Nanotechnology

Nanocarriers can be used to optimize targeted drug delivery. Nanotechnology is a broad term comprising any structure on the nanometer scale. These

nanocarriers come in many forms including metals, proteins, lipids, and polymers. Many of these technologies have been studied in animal models with the hope to translate their potential to the treatment of human disease.

Magnetic nanocarriers are composed of a magnetic component typically made of iron and an activated carbon containing Doxorubicin. These nanocarriers are delivered into the bladder and an external magnet is placed over the skin to target specific areas of the bladder. Leakakos et al. studied the use of magnetic targeted carriers (MTC) with Doxorubicin in swine bladder and found MTCs in the bladder wall predominantly at targeted areas and also at greater depths in the bladder tissue with undetectable plasma doxorubicin levels [29]. The use of targeted local hyperthermia with magnetite nanoparticles and an alternating magnetic field is also being investigated in preclinical studies [30].

Nanoparticle albumin bound (NAB) particles increase the solubility of a drug to enhance transport across tumor epithelial cells by interacting with albumin receptors. McKiernan et al. completed Phase I and II trials with NAB Paclitaxel in patients with recurrent NMIBC who failed at least one prior BCG regimen. These investigators observed complete response in 10 out of 28 (36%) patients [31]. McKiernan et al. also demonstrated decreased tumorigenesis and prevention of progression to muscle invasive disease after intravesical treatment with rapamycin in a murine model [32]. Rapamycin is known to have antiproliferative effects by inhibiting the mammalian target of rapamycin (mTOR) pathway and is an otherwise water insoluble drug that becomes more soluble as an NAB. The use of NAB and Rapamycin (ABI-009) is currently undergoing recruitment for a combined Phase I and II study to establish its safety and efficacy in treating NMIBC (Table 1).

Liposome nanoparticles are spherical vesicles composed of phospholipid layers that surround an aqueous core. Liposomes are being studied for their ability to increase drug solubility and stability in urine, and a recent study confirmed that liposomes increase cellular uptake of drugs via endocytosis [33]. Frangos et al. studied the effectiveness of IFN-alpha incorporated into liposomes against a human urothelial cell carcinoma line and found that the liposome-IFN complex demonstrated increased antiproliferative activity compared to free IFN-alpha [34]. Liposomes are also being studied for their use in the treatment of interstitial cystitis with intravesical capsaicin [35], as well as the use of empty liposomes which do not carry a drug but demonstrate benefits on their own in a rat model [36].

Efforts have been made to develop better methods to administer Paclitaxel intravesically with the use of polymers. Paclitaxel is water insoluble and the traditional preparation utilizes ethanol and Cremophor to improve its solubility, which can have significant side effects and drug interactions. A new water-soluble amphiphilic polymer PMB30 W composed of 2-methacryloyloxyethyl phosphorylcholine (MPC) and n-butyl methacrylate was developed to deliver Paclitaxel to rat bladder tumors. They demonstrated a significant reduction in bladder wet weight as a marker of bladder tumor burden reduction, higher Paclitaxel concentration in bladder tumor tissue, as well as no cytotoxicity in comparison to the traditional Paclitaxel/Cremophor group [37]. Paclitaxel has also been studied with gelatin polymer nanoparticles and was found to maintain constant concentration in the urine regardless of urine volume. These investigators also demonstrated drug retention in bladder tissue up to 1 week, 360 times higher drug concentration in tumor tissue as compared to normal bladder tissue, and plasma Paclitaxel levels well below the threshold for systemic side toxicity [38].

Hydrogels

Reverse thermosensitive hydrogels are being investigated for their ability to increase the dwell time of intravesical drugs. These polymer hydrogels exist in the liquid state at cold temperatures and solidify into a gel at body temperature. Urogen Pharma has developed a reverse thermosensitive hydrogel for multiple urologic uses. VesiGel™ contains high dose MMC and is inserted into the bladder through a foley catheter. The hydrogel then coats and adheres to the bladder epithelium as a solidified gel reservoir. The drug is slowly released from the gel and can increase drug dwell times to 6–8 hours. The gel completely dissolves and is removed with voided urine. Preclinical results show an increased level of MMC in bladder tissue at the same dose of MMC alone, higher concentration of MMC in the bladder for a longer period of time, and low plasma MMC levels [39]. Clinical trials are currently ongoing, including the prospective Optimized Instillation of Mitomycin for Bladder Cancer (OPTIMA) study that will compare standard intravesical instillation of MMC versus instillation with VesiGel™ prior to TURBT in NMIBC (Table 1). Urogen Pharma has also developed MitoGel™, which utilizes a ureteral

catheter to deliver hydrogel with MMC in the treatment of upper tract urothelial cancer. Preclinical trials have established safety and feasibility [40]. Further clinical trials are underway, including the recruitment phase for the Optimized Delivery of Mitomycin for Primary Upper Tract Urothelial Carcinoma Study (OLYMPUS). They have also applied for the Investigational New Drug (IND) program for Vesimune™ for the treatment of carcinoma in situ (CIS). Vesimune utilizes a hydrogel with imiquimod, an immunotherapeutic toll-like receptor 7 (TLR7) agonist. Phase I studies demonstrated its safety for intravesical use for pTa and pT1 disease [41, 42]. Results from the Phase 2 pilot study for patients with CIS should be available soon. A separate group has also investigated the use of BackStop Gel®, a reverse thermosensitive hydrogel from Boston Scientific originally developed to prevent stone fragment retropulsion during ureteroscopy, in optimizing delivery of MMC to the upper tract of pigs [43]. MMC was instilled into the upper tract using ureteroscopy, and BackStop was applied as a plug to prevent premature drainage of MMC and was subsequently washed out after 60 minutes. They monitored intrarenal pressures and concluded reverse thermosensitive polymer can safely retain MMC in the upper urinary tract [44].

A rat cyclophosphomide-induced cystitis model showed that PEG-PLGA-PEG polymer Poly-(ethylene glycol)-Poly[lactic acid-co-glycolic acid]-Poly(ethylene glycol) delivered Misoprostol in a sustained fashion for up to 24 hours after instillation with significantly reduced urinary frequency [45]. Other thermosensitive hydrogels include OncoGel (PLGA-PEG-PLGA plus Pacitaxel), which has been studied in the treatment of esophageal cancer, brain cancer, and other solid tumors [46]. The commercially available hydrogel Pluronic F127 is being studied in other oncologic settings, including its use in combination with nanoparticles to deliver hydrophobic chemotherapeutics in depot fashion [47].

Mucoadhesives

Utilizing a similar concept, mucoadhesive carriers attach to the bladder epithelium to prolong dwell time. Chitosan is the main agent currently being investigated. Chitosan is a nontoxic, biodegradable, naturally occurring polysaccharide formed by cross-linking glucosamine and N-acetylglucosamine units by bi-functional glutaraldehyde. It has innate mucoadhesive properties and studies suggest the positively charged chitosan binds to negatively charged epithelial membrane and rearranges cellular junctions, thereby enhancing urothelial permeability [48].

Zaharoff et al. studied the effect of chitosan and Interleukin-12 on orthotopic bladder tumors in mice. They observed an 88–100% complete response (CR) rate in mice treated with chitosan/IL-12 compared to 30–68% CR rate in the IL-12 only group and 0% in the BCG group. Animals cured by chitosan/IL-12 administration were rechallenged with the same bladder tumor cell line and none developed new bladder tumors for at least one year. The chitosan/IL-12 group demonstrated increased immune response (increased urinary Th1 cytokines, increased T cell and macrophage infiltration of tumor) versus the IL-12 only and BCG groups, demonstrating the role of chitosan in enhancing the effects of IL-12 [49]. By rejecting bladder cancer cell lines inoculated both intravesically and subcutaneously in mice after instillation of intravesical chitosan and IL-12, the same group more recently demonstrated tumor specific, systemic immunity against a bladder cancer cell line. These mice also demonstrated durable response months after the initial treatment [50]. This therapy has the potential to decrease the number of intravesical treatments required and the downstream costs of frequent treatment and surveillance. This also demonstrates a novel intravesical to systemic transfer of immunity with the potential use for treatment of locally advanced or metastatic disease.

Zhang et al. studied the effect of a magnetic chitosan thermosensitive hydrogel in the delivery of BCG in rat bladders. Utilizing a combination of previously described concepts, they developed a chitosan and Beta-glycerophosphate based thermosensitive hydrogel and included Fe3O4 magnetic nanoparticles (Fig. 2). They demonstrated sustained release of BCG over 48 hours in the presence of a magnetic field. They also showed increased antitumor efficacy as demonstrated by smaller mean tumor volume and stronger Th1 immune response to BCG as demonstrated by increased urinary cytokines and T lymphocytes in the submucosal tissue [51]. Chitosan is also being studied with gemcitabine [52]. A recent study described the successful formulation of chitosan and thioglycolic acid nanoparticles that were loaded with gemcitabine and then suspended in chitosan gel or Polaxmer hydrogel. Results showed increased loss of the bioadhesive gelling ability of Polaxmer when diluted with artificial urine solution as compared to chitosan gel, which suggests chitosan gel as the superior system in delivery of chitosan-thioglycolic acid nanoparticles.

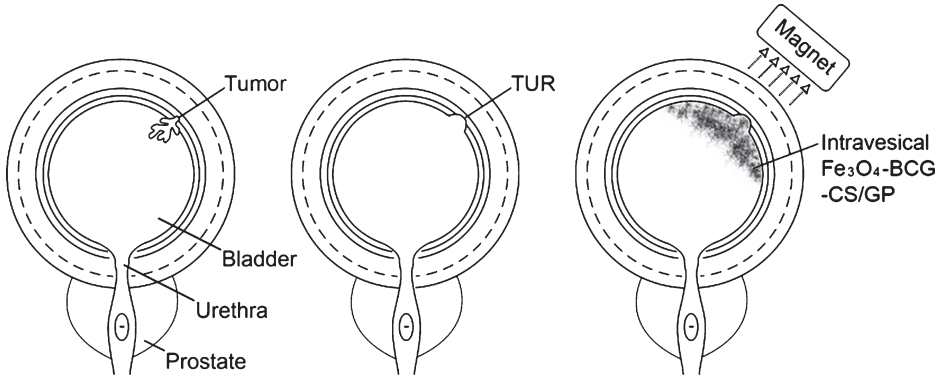

Fig. 2. An illustration demonstrating the use of magnetic nanoparticles in a chitosan (CS) and Beta-glycerophosphate (GP) hydrogel for targeted intravesical delivery of BCG. Reproduced with permission [51].

Chemohyperthermia and electromotive drug administration

Research in the early 2000 s investigated the use of chemohyperthermia (CHT) and electromotive drug administration (EMDA) to improve the delivery of intravesical therapies. CHT combines intravesical chemotherapy with hyperthermia. MMC is the most common chemotherapeutic agent used in CHT. Some studies have shown promising results with reported relative reduction in recurrence up to 59% when compared to MMC alone, however the same meta-analysis also concluded that definitive conclusions cannot be drawn because of the lack of randomized trials and heterogenous data [53].

EMDA utilizes the concepts of iontophoresis, electro-osmosis and electroporation to drive the movement of drugs across the urothelium with an electric current [54]. Di Stasi et al. have studied EMDA extensively. Their initial randomized controlled trial in 2003 demonstrated significantly higher response rates at 3 and 6 months for the EMDA-MMC group as compared to the passive diffusion group (53% vs. 38%, $p = 0.036$; 58% vs. 31%, $p = 0.012$ respectively), as well as significantly higher peak plasma concentration of MMC following EMDA as compared to passive diffusion [55]. More recently, combined BCG and EMDA with MMC have been studied. However, there are significant costs associated with EMDA and tolerability can be an issue.

Both CHT and EMDA are not widely used at this time. The European Association of Urology Guideline on NMIBC considers both CHT and EMDA as experimental based on limited evidence [3]. In addition, the American Urologic Association Guideline on NMIBC does not recommend their use based on lack of evidence but does note CHT may be effective with the need for further studies [5]. Neither CHT nor EMDA are approved for use in the United States. Ongoing trials hope to further evaluate the use of CHT and EMDA (Table 1).

CONCLUSION

Despite bladder cancer being the fifth most common cancer in the United States, there have been few advances in its treatment. Currently, the simple instillation of intravesical therapies is limited by the intrinsic properties of the bladder. This is changing in the face of our improved understanding of the pharmacodynamics of intravesical drug delivery with the development of novel intravesical drug delivery technologies. As our knowledge of the immunology of bladder cancer continues to progress, these technologies may also have the opportunity to converge with and exploit the parallel advances in systemic immunotherapy such as immune checkpoint inhibition.

CONFLICTS OF INTEREST

Coauthor Mark Schoenberg serves as an advisor to Urogen Pharma (Ra'anana, Israel).

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