Chapter 1

Intravesical Treatment Modalities in Bladder Cancer: Current and Future Perspectives

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Abstract

Non-muscle-invasive bladder cancers encompass the pathological stages of Ta, T1, and carcinoma in situ. To prevent recurrence, intravesical therapy, which is performed after complete transurethral resection, is the current standard therapy for non-muscle-invasive bladder cancers. In patients with low-risk non–muscle-invasive bladder cancer, post-transurethral resection (TUR) management is a single immediate intravesical instillation of chemotherapy alone. For an intermediate-risk patient, a 6-week course of induction intravesical chemotherapy or immunotherapy can be adapted. Bacillus Calmette-Guerin vaccine is still the gold standard of immunomodulating intravesical treatment used to reduce recurrence and progression. Nanotechnology is being developed for the diagnosis and treatment of non-muscle-invasive bladder cancer. The newly developed technology will be able to change intravesical therapy success in non-muscle-invasive bladder cancer.

Keywords: Bacillus Calmette-Guerin, bladder cancer, intravesical chemotherapy, intravesical immunotherapy, nanoparticle

1. Introduction

Bladder cancer (BC) is prevalent in the United States. It was estimated that the number of new bladder cancer cases would reach 76,960 in 2016 [1]. Non-muscle-invasive bladder cancers (NMIBCs) are among the most (75%) newly diagnosed cases [2]. NMIBC encompasses the pathological stages of Ta, T1, and carcinoma in situ (CIS). Patients with low-grade Ta disease have a very low risk of progression. Patients with T1 disease with concurrent CIS have a higher risk of progression and recurrence, approaching 50% [3]. To prevent recurrence, intravesical therapy, which is performed after complete transurethral resection, is the current standard

therapy for NMIBC. The risk categorization of the recurrence and progression of NMIBC is based on the European Organization for Research and Treatment of Cancer (EORTC) risk table developed from the data of 2596 patients from seven studies [3]. The scoring system is based on the six most essential clinical and pathologic factors, that is, the number of tumors, tumor size, prior recurrence rate, T category, presence of concurrent CIS, and tumor grade (WHO 1973). Another NMIBC scoring model is the Club Urológico Español de Tratamiento Oncológico (CUETO) model derived from 1062 patients from four trials [4]. As these two

	EAU [7]	**AUA [11]**
Low risk	Primary, solitary Ta, LG/G1, <3 cm, no CIS	Low-grade, solitary Ta _ 3 cm Papillary urothelial neoplasm of low malignant potential
Intermediate risk	All tumors not defined in the 2 adjacent categories (between the categories of low risk and high risk)	Recurrence within 1 year, low-grade Ta Solitary, low-grade Ta >3 cm Low-grade Ta, multifocal High-grade Ta, ≤3 cm Low-grade T1
High risk	Any of the following: T1 tumor HG/G3 tumor CIS Multiple, recurrent, and large (>3 cm) Ta G1G2 tumors (all conditions must be present at this point)	High-grade T1 Any recurrent, high-grade Ta High-grade Ta, >3 cm (or multifocal) Any CIS Any BCG failure in high-grade case Any variant histology Any LVI Any high-grade prostatic urethral involvement

Table 1. The risk stratifications of NMIBC.

	EAU (Update 2016)
Low risk	One immediate instillation of intravesical chemotherapy after TURB.
Intermediate risk	In patients with previous low recurrence rate (less than or equal to 1 recurrence per year) and expected EORTC recurrence score <5, 1 immediate instillation of intravesical chemotherapy after TURB. In all patients, either 1-year full-dose BCG treatment (induction plus weekly instillations for 3 weeks at 3, 6, and 12 months) or instillations of chemotherapy (the optimal schedule is not known) for a maximum of 1 year.
High risk Subgroup of highest-risk tumors • T1G3/HG associated with concurrent bladder CIS, multiple and/or large T1G3/HG and/or recurrent T1G3/HG, T1G3/HG with CIS in the prostatic urethra, unusual histology of urothelial carcinoma, LVI • BCG failures	Intravesical full-dose BCG instillations for 1–3 years or cystectomy. • RC should be considered. In those who refuse RC, intravesical full-dose BCG instillations for 1–3 years. • RC is recommended.

Table 2. Treatment recommendations of EAU guidelines for NMIBC.

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models were compared in an independent group of 4689 patients, an overestimated risk of disease progression and recurrence, especially in high-risk patients, was assessed [5]. A new EORTC nomogram, which was based on 1812 patients who underwent 1–3-year Bacillus Calmette-Guerin (BCG) vaccine maintenance, was recently published [6]. The European Association of Urology (EAU) and the American Urological Association (AUA) defined risk groups (**Table 1**). According to the individual risk classification of a patient, intravesical chemotherapy or immunotherapy is recommended according to EAU guidelines (**Table 2**) [7].

In this chapter, we describe the current state and future perspectives of intravesical therapy for NMIBC.

2. Intravesical therapy

2.1. Intravesical chemotherapy

Intravesical treatment is still accepted as the main treatment modality for NMIBC. Though the transurethral resection of bladder tumor (TURB) by itself can absolutely treat a TaT1 tumor, the recurrence of these tumors commonly occurs, and their progression to muscle-invasive BC (MIBC) can be observed. In patients with low-risk NMIBC, therapy is a single intravesical instillation of chemotherapy alone. Immediately, single instillation eradicates circulating tumor cells after TURB and residual tumor cells at the resection site. After TURB, tumor cell implantation should be started within the first few hours. Thus, tumor cells are implanted in the extracellular matrix [8]. To increase the efficacy of single instillation, chemotherapy should be given as soon as possible after TURB, preferably within the first 2 h. All patients in the low- and intermediate-risk groups should have immediate single intravesical chemotherapy if there is no suspicion of bladder perforation or significant bleeding, which requires bladder irrigation. Odden et al. noted that it can cause complications stemming from drug extravasation [9]. Moreover, in the meta-analysis of Sylvester et al., single instillation decreased the 5-year recurrence rate from 59 to 45%. The risk of recurrence was reduced by a single immediate instillation, but there appeared to be no cure in patients with prior recurrence rates of more than one recurrence per year or European Organization for Research and Treatment of Cancer recurrence scores ≥5. The use of mitomycin C (MMC), epirubicin and pirarubicin, for treatment was beneficial [10].

Although a single instillation of intravesical chemotherapy is used for low-risk BC patients, this treatment is inadequate for intermediate-risk disease, and an induction course 3–4 weeks following TURB is recommended according to the guidelines. For an intermediate-risk patient, a 6-week course of induction intravesical chemotherapy or immunotherapy can be adapted [11]. As a result of a meta-analysis of 3703 patients from 11 randomized trials, a highly significant 44% reduction in the odds of recurrence at 1 year in favor of chemotherapy over TURB alone was reported, but the effects on tumor progression have not been determined [12]. The length and frequency of chemotherapy instillations are still being argued. The guidelines do not support treatment >1 year [13]. Controlled urinary pH, reduced urinary excretion, and the balanced intravesical solution of MMC lowered the recurrence

rate [12]. A 1-h instillation of MMC was more beneficial than a 30-min instillation, but no efficient comparisons are attainable for 1- and 2-h instillations [14]. With patients from the high-risk group, using microwave-induced hyperthermia or electromotive drug administration (EMDA) can be efficient. Yet, the current evidence is restricted, and both treatment approaches are thought to be experimental [15, 16]. The study of Friedrich et al. included 495 patients with intermediate- and high-risk disease randomized to 6 weeks of MMC alone, 6 weeks of BCG, or 6 weeks of MMC with a 36-month maintenance regime. They reported that maintenance MMC was prevalent at reducing the risk of recurrence when compared to 6 weeks MMC and 6 weeks BCG ($p = 0.001$). They also showed that maintenance MMC was superior to induction BCG in reducing recurrence [17]. However, Hendricksen et al. suggested an immediate instillation with an intensive regime without a maintenance regime [18]. A randomized trial was conducted that compared radio frequency-induced hyperthermic MMC to BCG in 190 intermediate- to high-risk patients treated with 1 year of maintenance treatment. This study showed that 24-month recurrence-free survival (RFS) in patients was definitely better in the hyperthermic MMC arm in per-protocol analysis ($p = 0.008$) [19]. Still, a similarity was found in the complete response rates for CIS between the two groups. The results of this study were hopeful, and hyperthermic MMC can play a major role in the management of high-risk NMIBC in the future. However, no guidelines have advised that the use of device-assisted chemotherapy is not recommended until now. No changes have been made in treatment modalities for intravesical therapy for NMIBC over the past three decades. Gemcitabine and chemohyperthermia (CHT) are options for BCG therapy as adjuvant treatments for intermediate- and high-risk papillary NMIBC, but they are not yet considered standard.

2.2. Intravesical immunotherapy

Intravesical immunotherapy is well known, and its beneficial results for patients suffering from NMIBC are clear. BCG is still the gold standard of immunomodulating intravesical treatment used to reduce recurrence and progression, and its effect on the improvement of tumor-specific survival has been great. A meta-analysis has proved that BCG after TURB is superior to TURB alone or to TURB plus chemotherapy for negating the recurrence of NMIBC [20]. Morales et al. were the first to describe the BCG induction regime of once a week for 6 weeks in 1976. This is still supported today [21]. Many diverse maintenance schedules have been used. However, it is not possible to determine the most effective BCG maintenance schedule [22, 23]. To prevent recurrence or progression, a minimum of 1 year of maintenance BCG is needed to experience the superiority of BCG over MMC [24]. It is not possible to know the optimal number of induction instillations and the optimal frequency and duration of maintenance instillations. EORTC carried out a randomized controlled trial (RCT) of 1355 patients, which indicated that after BCG is given at full dose, 3 years of maintenance decreases the recurrence rate compared with 1 year in high-risk patients, but this is not seen in intermediate-risk patients [25]. In an RCT of 397 patients, CUETO recommended that in high-risk tumors, maintenance with only one instillation every 3 months for 3 years might not be sufficient [26]. In an RCT of 229 patients, a Finnbladder-6 study showed the efficiency of a monthly maintenance-BCG regimen and suggested that

it was more beneficial for preventing recurrence than a similar regimen of epirubicin and interferon-α2a [27]. To achieve a reduction in BCG toxicity, the instillation of a reduced dose was to be proposed. The EORTC found no difference in toxicity between one-third and full-dose BCG [28].

BCG instillations can be more beneficial for patients with NMIBC recurrence after a chemotherapy regimen. The continuity of BCG is not appropriate for patients with BCG failure because of a lack of response to therapy; in this case, radical cystectomy is more preferable. Several bladder preservation strategies may be classified as immunotherapy [29], chemotherapy, device-assisted therapy, and combination therapy [30, 31]. In one RCT, unified MMC and BCG reduced recurrences, yet the result of this combination was more toxic compared with that of BCG monotherapy [32]. In another RCT, for frequently recurrent cases of NMIBC, the use of weekly MMC followed by monthly BCG showed a significantly higher rate of efficacy in the reduction of the recurrence rate instead of BCG and interferon [33]. The incomplete BCG instillations due to intolerance prevent the appearance of the best treatment options for patients with high-risk tumors. Non-high-grade recurrence after BCG is not accepted as BCG failure. Treatment techniques should be decided according to tumor characteristics. For EAU, BCG failure is assessed as the development of MIBC, the recurrence of high-grade NMIBC, or pCIS during or after BCG treatment, and cystectomy is advised in these cases [7]. BCG is still considered a cornerstone treatment for high-grade NMIBC; however, the toxicity, limited efficacy in a subset of patients, and recurrence rates show the need for more effective treatment options. Recombinant BCG, monoclonal antibodies, vaccines, and adoptive immunotherapy are alternatives aimed at directing these deficiencies.

2.3. The future of intravesical therapy

To increase the dwell time of intravesical drugs, intravesical drug delivery devices implanted in the bladder are developed and abandoned in place for a length of time. This provides an increase in the drug's exposition period of time in the bladder mucosa.

The lidocaine-releasing intravesical system (LiRIS®) device was advanced as a result of experiments on rabbits. LiRIS has a double-lumen tube. While one of the lumens contains drug tablets, the other consists of lumen superelastic wire. This new technology includes a small flexible osmotic drug pump that provides the release of the drug within 2 weeks. The Massachusetts Institute of Technology by Lee and Cima carried out the research for this device, which demonstrated increased levels of lidocaine in the bladder tissue of rabbits after 3 days of exposure [34, 35]. The current use of this device is for the intravesical delivery of lidocaine in interstitial cystitis patients in phase 2 trials. Its application to bladder cancer treatments will be decided based on the results of future research studies.

A phase 1 trial is designed to deal with the safety and tolerability of the gemcitabine-releasing intravesical system (GemRIS). This system is based on the controlled release of gemcitabine during the 7-day indwelling time. As a consequence of intravesical drug delivery devices, the intravitreal delivery of drugs to the eye is seen as an achievement in the field of ophthalmology [36, 37]. Using similar concepts may bring about success in the development of intravesical drug delivery devices.

2.3.1 Nanotechnology

The treatment of NMIBC nanotechnology is a newly developed technology. Biological and cytotoxic agents for intravesical instillation are some of the therapeutic applications of nanotechnology in NMIBC. The intravesical instillation of live BCG bacteria requires standard care for high-grade NMIBC; however, this treatment has significant side effects, including BCG infections, sepsis, and even death. The harmful components of BCG bacteria have been explored to eradicate live bacteria without any risks. Nakamura et al. enclosed BCG-CWS within 166-nm liposomes, and this formulation showed efficacy in rat models against the development of bladder cancer [38]. The combination of chitosan and polysaccharide-based nanoparticles, chitosan and polylactic acid or chitosan and poly (ε-caprolactone) may be given with mitomycin C, and these nanoparticle drug delivery systems have demonstrated a similar efficacy to that of the release of the pure drugs. This delivery system indicated that the drug was slowly percolated out of the particles. As the polysaccharide structure might play the role of a bioadhesive, a rise in the exposure of the drug to the bladder surface may be observed, even after voiding [39].

The solubility of a drug is increased by nanoparticle albumin bound (NAB) particles to provide conveyance across tumor epithelial cells by interacting with albumin receptors. McKiernan et al. had phase I and II studies with NAB paclitaxel in patients with recurrent NMIBC who especially had failure with one prior BCG regimen. They observed great efficacy and response to this treatment technique in 10 out of 28 (36%) patients [40].

Paclitaxel has also been investigated with gelatin polymer nanoparticles. Lu et al. furthermore demonstrated drug retention in bladder tissue up to 1 week, which means a 360 times higher drug effect on tumor tissue than on normal bladder tissue [41]. The influence of reverse thermosensitive hydrogels has been explored to learn whether they increase the dwell time of intravesical drugs. These polymer hydrogels maintain their liquid character at cold temperatures and turn into gels at body temperature. To serve plenty of urologic uses, Urogen Pharma developed a reverse thermosensitive hydrogel. MMC is in VesiGel™ at a high dose, and this gel is released into the bladder with the help of a Foley catheter. Then, the coating of hydrogen comes out and turns into a solidified gel reservoir. The release of the drug from the gel can increase the dwell time to 6–8 h. The gel dissolves completely and is thrown out of the body via voided urine. According to preclinical results, there is an increased level of MMC in bladder tissue at the same dose of MMC alone, and there is a higher concentration of MMC in the bladder for a longer period of time [42]. Clinical trials are still going on. These also include the prospective optimized instillation of mitomycin for bladder cancer (OPTIMA) study, which will compare the standard intravesical instillation of MMC versus instillation with VesiGel™ prior to TURB in NMIBC. Urogen Pharma MitoGel™, which is developed by Urogen Pharma, uses a ureteral catheter to deliver hydrogel with MMC while treating upper-tract urothelial cancer. Safety and feasibility have been established via preclinical trials [43].

Imiquimod is an immunotherapeutic toll-like receptor 7 (TLR7) agonist. TMX-101 is a liquid formulation of imiquimod. A hydrogel with imiquimod and its safety for intravesical use for pTa and pT1 disease has been established via studies on phase I [44, 45]. A study for phase 2 patients with CIS should be completed soon.

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A separate group has conducted another investigation on the use of BackStop Gel®. This treatment consists of a reverse thermosensitive hydrogel from Boston Scientific, which is designed to prevent stone fragment retropulsion during ureteroscopy and to ensure the delivery of MMC to the upper tract of pigs [46]. In the study of Wang et al., MMC was given to the ureters via ureteroscopy, and by closing the system with a thermosensitive polymer plug, MMC was able to stay in the ureters at least 1 h. Then, they recorded the intrarenal pressure and histopathologic differences of the kidney. Finally, they published that the polymer plug was safe [47]. In the study of Tyagi et al., using thermosensitive hydrogel misoprostol on rats significantly reduced urinary frequency with the cyclophosphamide-induced cystitis model [48]. OncoGel (PLGA-PEG-PLGA plus Paclitaxel) was studied in the treatment of esophageal cancer, brain cancer, and other solid tumors [49]. Pluronic F127 is being investigated in other oncologic settings with regard to the effect of its use in combination with nanoparticles to deliver hydrophobic chemotherapeutics in depot fashion [50].

2.3.2. Mucoadhesives

Mucoadhesive carriers attach to the bladder epithelium to surrender the dwell time in this treatment technique. Mucoadhesive nanogels were recently analyzed in the porcine urinary bladder and can be a candidate for ensuring the intravesical delivery of hydrophobic drugs in BC therapy [51]. Chitosan, whose investigation is currently being completed, is the main agent. Chitosan enhances the permeability of the urinary bladder wall [52]. Zaharoff et al. evaluated the effect of chitosan/interleukin-12 on a mice bladder cancer model. A preclinical study showed that chitosan/IL-12 had high immune response [53]. Through this therapy, it is possible to decrease the number of intravesical treatments required and the costs of frequent treatment and surveillance. This also shows a novel intravesical for the systemic transfer of immunity with the potential to treat locally advanced or metastatic disease [54]. Through this therapy, it is possible to decrease the number of intravesical treatments required and the costs of frequent treatment and surveillance. In the trial of Zhang et al., the effect of a magnetic chitosan thermosensitive hydrogel in the delivery of BCG in rat bladders was investigated. Benefitting from previously described concepts, they developed a chitosan and Beta-glycerophosphate with a base of thermosensitive hydrogel; it comprised Fe_3O_4 magnetic nanoparticles. They indicated the ongoing release of BCG over 48 h in the presence of a magnetic field. They also showed an increase in the antitumor efficacy of BCG [55]. In addition, a study on chitosan with gemcitabine was conducted [56]. A recent study reported the successful formulation of chitosan and thioglycolic acid nanoparticles that were loaded with gemcitabine and then stayed in chitosan gel or polaxmer hydrogel. The results revealed a great number of losses in the bioadhesive gelling ability of polaxmer. This occurs because it is diluted with an artificial urine solution as compared to chitosan gel.

2.3.3. Chemohyperthermia, electromotive drug administration, and gemcitabine

The use of chemohyperthermia and electromotive drug administration was explored to improve the distribution of intravesical therapies in research carried out in 2000. CHT

established a connection between intravesical chemotherapy and hyperthermia. The most prevalent chemotherapeutic agent used in CHT is MMC. Some studies with promising results reported a relative reduction in recurrence up to 59% when compared to MMC alone. However, a meta-analysis determined that desperate conclusions could not be declared because of the deficiency of randomized trials and heterogeneous data [15]. EMDA uses the concepts of iontophoresis, electro-osmosis, and electroporation to carry the movement of drugs to the urothelium with an electric current [57]. Di Stasi et al. studied EMDA comprehensively. Their first RCT held in 2003 contained significantly higher response rates at 3 and 6 months for the EMDA-MMC group when compared to the passive diffusion group, as well as a significantly higher peak plasma concentration of MMC following EMDA when compared to passive diffusion [58]. More recently, the combination of BCG and EMDA with MMC was taken into account as a study. However, the significant costs associated with EMDA and its tolerability seem problematic. Therefore, the usage of both CHT and EMDA is not common at this time. According to the EAU guideline on NMIBC, both CHT and EMDA are experimental because of a lack of adequate evidence. Furthermore, the AUA guideline on NMIBC does not recommend their use for the same reason, yet it informs that CHT may be effective for further studies [11]. Neither CHT nor EMDA is accepted for use in the United States. There are ongoing trials to evaluate the use of CHT and EMDA.

Gemcitabine is a nonvesicant chemotherapeutic drug. Skinner et al. reported the results of a phase 3 trial in 2013. The study dealt with 47 patients with two previous BCG failures who each received 2 g of intravesical gemcitabine weekly for 6 weeks of induction, which was followed by monthly maintenance for 1 year. The RFS rate was 28% at 1 year and 21% at 2 years [59]. Until now, only a single study has been carried out that has compared the results of intravesical gemcitabine with those of another agent. In one RCT, Di Lorenzo et al. [60] studied a cohort of patients with a single prior BCG failure. The patients were randomized to receive either twice weekly intravesical gemcitabine for 6 weeks or weekly intravesical BCG for 6 weeks, followed by a 3-week mini-cycle maintenance therapy at 3, 6, and 12 months if disease free. A total of 40 high-risk patients were registered in each arm. After 2 years, the RFS rate in the gemcitabine arm was 19%, and in the BCG arm, it was 3%. Its optimistic tolerability, mild efficacy, and low rate of progression ensure that gemcitabine monotherapy be considered for salvage therapy in select patients.

2.3.4. Photodynamic therapy

Photodynamic therapy (PDT) includes a photo-sensitizing drug that is selectively taken up by malignant cells and followed by the irradiation of these cells with light of a specific wavelength. In 2014, Lee et al. [61] announced their results by using Radachlorin-based PDT for the treatment of high-grade NMIBC that had previously undergone BCG and showed intolerance to BCG or with refractory disease. Patients were checked via cystoscopy and cytology with or without bladder biopsies for the first 3 months and then at 3-month intervals thereafter. All patients were free of tumors at 3 months, and 91, 64.4, and 60.1% of them remained disease free at 12, 24, and 30 months, respectively. Recent reports on the efficacy of a Radachlorin-based protocol and mild side effects are really promising, but the need exists for replication and confirmation before further dissemination.

New clinical trials should be carried out on these nanoformulations and others, especially those covered with cancer-targeting ligand on the surface. These studies can possibly increase the response rate, alleviate recurrence, and decrease the need for cystectomy.

3. Conclusion

Intravesical therapy serves to alleviate the risk of bladder cancer recurrence and progression. Gemcitabine and chemohyperthermia are options for BCG therapy as adjuvant treatment for intermediate- and high-risk papillary NMIBC, but they are not yet considered standard. The newly developed technology will be able to change intravesical therapy success in non-muscle-invasive bladder cancer. New clinical trials should be carried out on nanoformulations, especially those covered with cancer-targeting ligand on the surface, and these studies can possibly increase the response rate, alleviate recurrence, and decrease the need for cystectomy.

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