



Organ-Preserving Approach in Bladder Cancer: Assessment of the Current Situation

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Abstract

Intravesical bacillus Calmette-Guérin (BCG) therapy is the gold standard treatment option in high-risk non-invasive bladder cancer. However, BCG is a very toxic agent. A significant proportion of patients have BCG intolerance after beginning intravesical treatment. Radical cystectomy is the recommended approach for patients with either BCG failure or BCG intolerance. Alternative intravesical salvage treatments are needed for patients who cannot tolerate radical cystectomy due to comorbidities or who refuse surgery.

In this review, current intravesical treatment alternatives to radical cystectomy in intravesical BCG failure are discussed with oncologic outcomes.

Keywords: Bladder cancer, bacillus Calmette-Guérin failure, intravesical salvage therapy

Introduction

Bladder cancer is the seventh most common type of cancer among males and eleventh among both genders combined (1). In 2016 alone, 76,960 new cases were diagnosed and 16,390 cancer-related deaths were reported in the United States of America (2). Cancer staging and treatment planning can be achieved with a successful endoscopic resection and when necessary, metastatic evaluation. Although 70% of cases are non-muscle invasive superficial cancers (NMIBC) at the time of diagnosis, about 20% of these are grade Ta and T1 tumors including carcinoma *in situ* (CIS), which form a special group associated with high risk of cancer progression and relapse (3). Intravesical bacillus Calmette-Guérin (BCG) therapy is the primary treatment method for these high-risk NMIBCs (4). For non-metastatic muscle-invasive bladder cancer, radical cystectomy is considered the gold standard treatment option that provides the longest survival. With a goal of complete tumor elimination, grade 3-4 complication rate of 13% and mortality rate of 2.5-5.2% are considered acceptable (5).

Although NMIBC patients can be successfully treated with intravesical BCG, they exhibit relapse and progression rates of 80% and 40% respectively at 5-year follow-up. As described in a 2000 study by the Southwestern Oncological Group (SWOG), the intravesical BCG regimen is administered as a 6-week induction course followed by 3 years of maintenance therapy if there are no signs of tumor in follow-up endoscopic examinations (6). However, in the presence of persistent or recurrent NMIBC, a substantial proportion of patients may benefit from an additional 6-week induction course with or without interferon (IFN) alpha (3). Findings indicating BCG resistance during therapy include high-grade NMIBC in the first cystoscopic examination, CIS in the first or second cystoscopic examination, and high-grade cancer in follow-up cystoscopic examinations during or after completing the intravesical BCG protocol (7). The occurrence of adverse effects that prevent continuation of treatment is referred to as BCG intolerance (7,8). NMIBC patients exhibiting BCG resistance or intolerance are candidates for radical cystectomy (9). However, the various comorbidities in elderly patients and the reluctance of younger patients to risk undergoing such a

procedure have led to a search for local therapeutic alternatives to radical cystectomy (5).

Mitomycin C

Thiotepa, adriamycin, and mitomycin C (MMC) were initially the preferred first-line agents for patients who were sensitive to BCG but could not undergo BCG therapy (9). Today, only MMC still holds this position (10). MMC has an important place among chemotherapeutic agents. It is an alkylating agent that disrupts DNA synthesis (4). It is used perioperatively in NMIBC treatment due to its ability to block tumor seeding in particular (4). However, maintenance therapy does not yield satisfactory outcomes when BCG fails (10). To that end, it seems that advances in intravesical drug administration techniques are starting to provide favorable outcomes. Chemohyperthermia (CHT) and electromotive drug administration (EMDA) are two methods developed to achieve this aim. In CHT, a specialized urethral catheter is used to deliver radiofrequency waves inside the bladder, thus raising the temperature. This increases cell permeability to MMC and promotes apoptosis by inducing stress in tumor cells (11). After using this technique in 111 patients with failed BCG, Nativ et al. (12) reported recurrence-free rates of 85% at 1 year and 56% at 2 years. In another study including 51 patients with failed BCG from 15 centers in Europe, Witjes et al. (13) reported complete response rates of 92% initially and 50% after 2 years. Although CHT is recognized by many authorities, it is still in the Food and Drug Administration (FDA) review process. EMDA aims to create an electromagnetic field to increase bladder surface epithelial cell permeability to MMC (14). Like CHT, EMDA was designed to increase the efficacy of MMC in moderate and high-risk NMIBC, but was unable to provide satisfactory results when applied after resistance to BCG. Sockett et al. (15) reported 31% relapse at 15 months in 13 patients with failed BCG who were given MMC by EMDA.

Gemcitabine

Gemcitabine (GC) is a nucleotide antimetabolite that disrupts DNA synthesis in tumor cells by inhibiting ribonucleotide reductase and cystine diaminase (4). In a randomized controlled study, Addeo et al. (16) determined that GC was more effective and less toxic than MMC. In their phase 2 trial, Skinner et al. (17) reported a recurrence-free rate of 28% after 1 year of treatment with intravesical GC. Prasanna et al. (18) also reported in their study that intravesical GC provided a similar disease-free survival to intravesical BCG and caused less toxicity. Although intravesical BCG is currently the gold standard treatment for high-risk NMIBC, GC may be recommended as an alternative first-line intravesical therapy for BCG-resistant patients not suitable for cystectomy and patients who cannot tolerate the toxicity of BCG (18).

Valrubicin

Valrubicin is a synthetic anthracycline analogue that exerts a toxic effect by penetrating nucleic acid sequences and arresting the cell cycle (19). Steinberg et al. (19), who comprise the valrubicin study group, reported a complete response

rate of 21% and disease-free rate of 8% at the end of 18 months follow-up in 90 patients with BCG-refractory CIS. As a result of this study, intravesical valrubicin therapy is the only chemotherapeutic agent approved by the FDA for BCG-refractory CIS (20).

Taxanes (Docetaxel and Paclitaxel)

Agents in the taxane group act by disrupting microtubule function and halting cell division at M-phase (21). Preclinical studies have shown that taxane chemotherapeutics are highly effective on bladder cancer cells (22). Laudano et al. (22) conducted a phase 1 trial in which intravesical docetaxel (DTX) was administered to 18 patients who did not respond to intravesical BCG, and reported a complete response rate of 22%, partial response rate of 17%, and non-response rate of 61% during a mean follow-up of 48 months (22). In another study by Barlow et al. (23) 54 non-responders to BCG were administered intravesical DTX, and recurrence-free rates at 1 and 3 years were 40% and 25%, respectively.

Intravesical agents must remain in the bladder for 2 hours to achieve maximum efficacy (24). However, due to reasons such as bladder irritability or low bladder capacity, this waiting period is often unachievable (24). Since paclitaxel (PTX) was first introduced in 1967, many carrier agents have been investigated to increase the efficacy of taxanes due to their lipophilic properties and low cell penetration (4). In the phase 1 study by McKiernan et al. (25) using PTX bound to intravesical nanoparticle albumin (NPA), the complete response rate at 6 weeks was 28% and only grade 1 toxicity occurred in 10 of the 18 patients. In a subsequent phase 2 study, the complete response rate was 35.7% and toxicity rate was 32.1% at 1 year (26). Robins et al. (27) recently reported a disease-free rate of 18% and a cancer-specific survival rate of 9% at the end of 41 months follow-up in patients treated with NPA-bound PTX after BCG failure.

Interferon

IFN is a cytokine with immunomodulatory, antiproliferative, and antiviral properties (28). Earlier research established that IFN monotherapy had no utility in the treatment of NMIBC (28). The first of these studies was a 1990 prospective randomized study by Glashan (29) including 87 patients who were treated with either low-dose (10 million U) or high-dose (100 million U) intravesical IFN monotherapy and followed for 12 months. After 1 year, complete response rate was 43% in the high-dose arm and 5% in the low-dose arm (29). The most common side effects were influenza-like symptoms, which occurred in 17% of patients in the high-dose arm and 8% of those in the low-dose arm (29). However, in 1995, Hudson and Ratliff (30) conducted a prospective study with 12 patients who were treated with intravesical IFN (100 million U) after non-response to previous BCG treatment, and they reported a complete response rate of 8% at the end of 24 months. In a multi-center randomized phase 2 trial of intravesical BCG and IFN combined therapy conducted by Joudi et al. (31) a cancer-free survival rate of 13% was reported at the end of 24 months follow-up. In another prospective study including 50 patients treated

with a combination of BCG and IFN, Bazarbashi et al. (32) reported that 62% of the patients were recurrence-free after a median follow-up of 55.8 months. Eighteen percent of the patients developed grade 3 dysuria and 14% developed grade 3 frequency (32).

Mycobacterial Cell Wall Extracts

Intravesical BCG, currently the gold standard treatment for high-risk NMIBC, seems to stimulate an inflammatory response in target cells (33). Research on mycobacteria first started in 1970 with animal studies, and the first study regarding its successful intravesical use in humans was published by Morales et al. (34) in 1976. Although treatment with BCG obtained from live attenuated mycobacteria is undeniably effective, it also gives rise to local and systemic adverse effects (33). This has led to a search for more effective and less toxic agents (33). *Mycobacterium phlei* cell wall and mycobacterial cell wall-nucleic acid complex (MCNA) were tested in the treatment of NMIBC in 1996 and 1997, respectively (35,36). Morales et al. (37,38) first published initial results with the purportedly immunomodulatory and cytotoxic MCNA in 2001, and in a recent phase 3 trial of MCNA for BCG-resistant patients published in 2015, they reported complete response rates of 22% and 19% at 1 year and 2 years, respectively (36). However, MCNA failed to gain FDA approval in 2016 (39).

Targeted Therapies

Bladder cancer is one of the most immunogenic cancers, with high rates of somatic mutation (40). One of the unique features of the bladder is that it forms a defense against microorganisms without eliciting an immune response (41). This makes it rather difficult to generate an anti-tumor response against bladder tumors (41). Bladder tumor cells evade the immune system using immune checkpoints that block T-lymphocyte defense. Programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 are the most extensively studied checkpoints (42). Research has been based on the premise that immune checkpoint blockade would shrink the tumor cells. The search for less toxic second-line agents for metastatic bladder cancer patients who cannot be treated with cisplatin (MDP)-based chemotherapeutic agents resulted in the discovery of targeted agents, some of which have been approved by the FDA (43). Current research is focusing on targeted agents to be used in NMIBC when BCG fails (43). Phase 2 studies of anti-PD-1/PD-L1 seem promising for patients with intravesical BCG-refractory NMIBC (44,45). Intravesical use of targeted agents to reduce systemic side effects is an important and necessary area of research (46). VB4-845 is an immunomodulatory recombinant protein bound to *Pseudomonas* exotoxin that can be administered intravesically (9). This agent causes apoptosis of tumor cells, but a complete response rate of only 16% at 12 months was reported in a phase 2 trial (9).

Oncoviral Agents

The use of viral agents for tumor control is an area of intensive study in current medical practice. Inducing tumor cell lysis

(oncolysis) via oncolytic viral agents can be achieved by direct stimulation of infected cells, by indirect stimulation of non-infected cells, or by stimulation of the immune system (47). In a phase 1 trial by Burke et al. (48) evaluating intravesical administration of CG0070 (adenoviral agents expressing granulocyte-macrophage colony-stimulating factor ([GM-CSF]) in 3 sessions over 28 days or in 6 weekly sessions, the response rate was 48.6% and the complete response rate was 61.5% at even the lowest doses. A single-arm, multi-center phase 3 trial evaluating the safety and efficacy of GC0070 in NMIBC patients who have previous BCG failure and refuse cystectomy is still in progress (47).

Photodynamic Treatment Approaches

Photodynamic therapy (PDT) is a method in which photosensitized agents are activated by specific wavelengths of light to cause apoptosis and necrosis of tumor cells (49). Dating back to the early 20th century, PDT has been used for tumor treatment in many fields (49). In 1976, Kelly and Snell (50) reported the first data on the use of PDT in bladder cancer. However, the degree of systemic toxicity necessitated the development of new agents. The first data on the use of 5-aminolevulinic acid (5-ALA) were reported by Kriegmair et al. (51) in 1996. Intravenous administration of 5-ALA in PDT resulted in a complete response rate of 31% at 1 year, and 19% of the patients experienced bladder spasms as an adverse effect (49). In a study by Lee et al. (52) including 34 patients, tumor-free survival rate was 90% at 12 months and 60% at 30 months. Berger et al. (53) reported a complete response rate of 40% at 1 year in patients treated with intravesical 5-ALA. When hexaminolevulinic acid was used for the same purpose, the complete response rate at 1 year was 12% (54). Although low response rates prevent the widespread use of PDT, it may become relevant as an alternative therapy in the future.

Combined Therapies

Because different chemotherapeutic agents have different mechanisms of action, combined therapies are utilized to create synergistic effects for cancer treatment (4). This known property of chemotherapeutics in cancer treatment has been investigated in salvage intravesical applications in patients with failed BCG (4).

In a study evaluating intravesical administration of an adriamycin and MMC combination, Fukui et al. (55) reported that 13 of 30 CIS patients were completely tumor-free at the end of 23 months follow-up, but the high rate of local toxicity (70%) compelled the researchers to seek new combinations.

In a retrospective study by Cockerill et al. (56) including 27 patients, 37% were recurrence-free at 22 months follow-up while recurrence was detected at a mean of 15 months in the other 63%, and 1 patient (3.7%) showed progression during treatment. In another retrospective multi-center study in which 47 patients with failed BCG received intravesical combined GC/MMC, Lightfoot et al. (57) reported a recurrence-free rate of 48% at 1 year and 38% at 2 years. The first known data on treatment with intravesical GC/DTX in patients with failed BCG were published by Steinberg et al. (58) who reported a

recurrence-free rate of 54% at 1 year and 34% at 2 years, and a complete response rate of 66%. Milbar et al. (59) retrospectively analyzed the data of 33 patients who received intravesical GC/DTX therapy and reported recurrence-free rates of 56% and 42% at 1 and 2 years, respectively. Only 2 (3%) patients could not tolerate the treatment (59).

Chen et al. (60) compared the success rates of BCG with those of an intravesical MMC, doxorubicin, and MDP protocol, and reported comparable recurrence rates at 5 years (37.9% vs 33.9%). With a 5.8% major adverse event profile, intravesical MDP seems superior to intravesical BCG, which had a 15% major adverse event profile (60). Despite these data, further research is needed on intravesical MDP therapy in patients resistant to intravesical BCG.

In a study of 54 patients with BCG failure, Steinberg et al. (61) added intravesical interleukin-2 and subcutaneous GM-CSF to intravesical BCG and IFN therapy, and reported success rates of 55% and 53% at 1 and 2 years, respectively. Treatment intolerance was observed in 6% of the patients (61).

Conclusion

Intravesical BCG has been used in high-risk NMIBC for nearly half a century (9). Nevertheless, radical cystectomy is still recommended in patients with resistance to or intolerance of intravesical BCG therapy. However, the FDA has also acknowledged the need for intravesical salvage therapy for patients who are ineligible for or refuse a complicated surgery like cystectomy, and research is being supported to accelerate the discovery of new agents for this patient group (3). All of the treatments described above appear to offer some degree of success, but most of the studies are focused on small and heterogeneous patient groups with short follow-up periods.

Consequently, therapies that are potentially useful for high-risk NMIBC patients with limited options should be reevaluated with appropriate endpoints.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.A.M., R.G. Design: N.A.M., Data Collection or Processing: R.G., Analysis or Interpretation: N.A.M., R.G., Literature Search: R.G., Writing: R.G.

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