Chapter 13
Intravesical Therapy for Non-muscle Invasive Urothelial Carcinoma

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Introduction

The majority of bladder cancer cases present as noninvasive disease [1]. Lower-grade disease tends to have a higher risk of recurrence, while higher-grade disease also carries the risk of disease progression (recurrence at a higher stage) [2]. The goal of intravesical therapy is to reduce the risks of recurrence and/or progression depending on the initial presenting pathological features.

Intravesical therapy is the administration of a medication directly into the bladder via the urethra through a urinary catheter. The goal of intravesical therapy is to maximize the exposure of malignant cells located within the bladder to therapeutic drugs while limiting a systemic response. The urothelium of the bladder is uniquely suited to limit a systemic response by minimizing absorption of the administered agent [3].

Intravesical agents are categorized into chemotherapeutic drugs and immunomodulators. These medications have different mechanisms of actions and side effects. The purpose of this chapter will be to outline the various available therapeutic options as well as their indications and methods of administration.

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Intravesical Chemotherapy

Intravesical chemotherapy is the installation of chemotherapeutic agents that inhibit or slow cancer cell production [4].

Mitomycin

Mitomycin C (MMC) is the most common chemotherapeutic agent used to treat non-muscle invasive bladder cancer (NMIBC) [5, 6]. It is an antibiotic that inhibits DNA synthesis and can be used in the perioperative setting to prevent tumor implantation or for induction and maintenance therapy [7, 8]. The typical dose of MMC is 40 mg in either 20 or 40 ml of saline. Side effects include cystitis and rarely bladder contraction (5%). Rash and desquamation may also occur if the drug comes in contact with skin. Increasing the concentration of MMC (40 mg/20 ml) [9] as well as urinary alkalinization has been shown to improve efficacy. Electromotive therapy has also been shown to improve the efficacy of MMC in some studies [10, 11].

Gemcitabine

Gemcitabine is a deoxycytidine analogue that inhibits DNA synthesis [12]. It has been recently shown to be useful in the perioperative setting. The typical dosage is 2 gm/100 ml of normal saline [13]. Side effects are uncommon and include dysuria and hematuria.

Doxorubicin

Doxorubicin is an antibiotic that inhibits protein synthesis by binding DNA pairs. It has been shown to reduce recurrences in the perioperative setting. The typical dose is 50 mg/50 ml of normal saline. Side effects include cystitis, fever, and rarely bladder contraction [14].

Epirubicin

Epirubicin is an anthracycline chemotherapeutic agent and a derivative of doxorubicin that exerts its antineoplastic effect by intercalating DNA strands, thereby inhibiting replication and RNA synthesis. The typical dose is 50 mg/50 ml of normal

saline. Side effects are similar to doxorubicin. It is also typically used in the perioperative setting but is not available in the United States [15].

Thiotepa

Thiotepa was one of the first agents used for intravesical chemotherapy. It is an alkylating agent that acts to cross-link nucleic acids. The typical dose is 30 mg/30 ml of normal saline. Due to its low molecular weight, however, a significant amount of the drug can be systemically absorbed which may cause myelosuppression in up to 30% of patients [14]. It is because of this that thiotepa is not commonly used in most institutions.

Valrubicin

Valrubicin is a semisynthetic analogue of doxorubicin and is the only therapy approved by the FDA for bacillus Calmette-Guerin (BCG) refractory carcinoma in situ (CIS) [12]. The dosage is 800 mg/75 ml of normal saline. Common side effects include cystitis and urinary frequency. Long-term disease-free survival rate remains poor, and it only has an 8% complete response rate at 30-month follow-up [16]. Its use therefore is rather limited.

Immunotherapy

Intravesical immunotherapy is the installation of agents that work by triggering the body's immune response to destroy malignant cells that may be present in the bladder after a transurethral resection [17].

BCG

Bacillus Calmette-Guerin (BCG) is a live strain of *Mycobacterium bovis* that was first used as a tuberculosis vaccine and later found to induce an immune response within the bladder [18]. BCG leads to the release of numerous cytokines that induces a Th1 immune response. BCG is supplied in various strains and is typically given as a vial diluted in 50 ml of normal saline. As it is a live attenuated bacterium, side effects can be more severe than intravesical chemotherapy and may include fever, irritative voiding symptoms, BCG sepsis, and rarely death [19].

Due to risks of systemic absorption, it is usually not given until 2–4 weeks after surgical resection to allow for bladder re-epithelialization. BCG should not be given in patients with a traumatic catheterization or hematuria. Caution should be used in immunosuppressed patients or patients with an active urinary tract infection (UTI) [20]. BCG has been shown to reduce the incidence of recurrence and progression of disease. BCG is typically given as an induction course of 6 weekly doses followed by a maintenance schedule. While maintenance schedules vary, the most effective schedule reported consists of a 6-week induction course followed by 3 weekly doses at 3, 6, 12, 18, 24, 30, and 36 months [21].

Interferon

Interferon is an immunotherapeutic agent that can be used as an individual therapy or in combination with BCG. The mechanism of action is lymphocyte activation and potentiates a T-helper type I immune response [22]. Although it does have some efficacy as a single agent in BCG failure, it has most thoroughly been evaluated in combination with BCG [12, 23].

Clinical Uses of Intravesical Therapy

Perioperative Intravesical Therapy

Tumor seeding at the time of transurethral resection of bladder tumor (TURBT) is postulated to be one of the causes of recurrence [24]. Intravesical chemotherapy immediately after TURBT (within 24 hours) reduces tumor recurrence by 11% in patients with low-risk disease [25]. MMC is commonly used in the United States, while epirubicin is used in Europe. Gemcitabine, however, has recently been shown to decrease recurrences by 47% and is currently the preferred drug of choice per NCCN guidelines [6, 13]. Either medication is instilled for 1 hour into the bladder after resection or ideally within 6 hours [26]. Instillation should be avoided in cases of bladder perforation at the time of resection due to the increased risk of toxicity.

Reducing Recurrence and Progression

Induction courses of 6 weekly doses of chemotherapy (MMC, doxorubicin, and epirubicin) have been shown to reduce the risk of recurrence in NMIBC by approximately 20–40% but have no appreciable effect on preventing disease progression [27]. They are typically used in low- to intermediate-risk disease and not

recommended for use in high-risk disease unless there is a contraindication to BCG therapy. The value of maintenance therapy with chemotherapy is controversial. If given, the maintenance schedule typically involves monthly doses for 1 year [6].

Induction courses of BCG reduce recurrences by 20–60%; however, the main clinical utility of BCG is to reduce the impact of disease progression [28]. The impact of reduced progression is only seen with maintenance protocols. BCG has been reported to reduce rates of progression by approximately 20–30% [29]. About 25% of patients who fail an initial induction course may be salvaged by a second 6-week induction course; however, further courses are not recommended as there is a much higher chance of disease progression (up to 50%). Those patients should proceed to cystectomy or other salvage therapy [19].

Refractory Disease

In general, patients with high-grade disease who fail intravesical therapy should proceed to cystectomy; however, salvage intravesical regimens may be attempted for patients who are not surgical candidates. Valrubicin is the only FDA-approved agent for BCG refractory disease. The complete response and disease-free survival rates are poor however (18% and 4%). Therefore, valrubicin is not commonly used [30].

Combination treatment with gemcitabine and docetaxel has been shown to have 49–54% complete response rate (CRR) after 1 year and 34% complete response rate after 2 years [31, 32]. Other therapies which have been shown to be safe and have achieved a complete response rate between 28% and 71% at 1 year include either gemcitabine as monotherapy [33] or in combination with mitomycin [34, 35] as well as nab-paclitaxel [36].

Complications of Intravesical Therapy

Intravesical therapy can cause local reactions to the urothelium that can cause some patients significant symptoms. The most common symptoms experienced are dysuria, bladder pain, gross hematuria, low-grade fever, and malaise. These usually occur 24–48 hours post-treatment.

These symptoms can be treated with analgesics–nonsteroidal anti-inflammatory drugs (NSAIDs), anticholinergic medications, and antispasmodics. If the symptoms persist, a urine culture should be obtained to rule out a bacterial infection. If the urine culture is positive, treatment should be withheld, and the infection should be treated with an appropriate antibiotic. A negative urine culture should be obtained before intravesical treatment is continued.

A decrease in the dose of intravesical treatment can be appropriate if side effects become more severe over time and the patient can no longer tolerate the full dose. In some patients, chemical cystitis and urinary tract infection can occur.

Cystoscopic Follow-Up

Cystoscopic follow-up is the standard tool for monitoring superficial bladder cancer. It is limited only to tumors that can be visualized, so therefore, urine cytology is used as an adjunct to detect high-grade disease [37]. Follow-up is imperative because of the high probability of tumor recurrence and the risk of progression. In general, the first cystoscopy should be 3 months after the initial transurethral resection. If the first cystoscopy is clear, follow-up was traditionally scheduled every 3 months for a period of 2 years, every 6 months until the end of the fifth year, and then yearly thereafter. However, this approach has been modified to individual risk using a scoring system (such as the EORTC) and risk tables for the prediction of short- and long-term risks of both recurrence and progression. The American Urological Association also recommends a more risk-adapted approach [37]. Fluorescent cystoscopy involves the intravenous injection of photoactive porphyrin precursors (commonly hexaminolevulinate) which preferentially accumulate in neoplastic tissue. Under blue light, they emit red fluorescence and aid in the diagnosis of subtle lesions. Blue light cystoscopy has been shown to reduce recurrences in multiple studies and should be considered if available [38, 39]. Narrow band imaging (NBI) utilizes two specific wavelengths (415 nm and 540 nm) that are specifically absorbed by hemoglobin and leads to improved visibility of blood vessels. Studies have been mixed, but the use of NBI may aid in the reduction of tumor recurrences [40, 41].

Key Points

Intravesical Administration

Intravesical chemotherapy has a clear impact on tumor recurrence when instilled immediately after TUR and as a maintenance protocol.

In general, side effects of chemotherapy tend to be less common and less severe than those with BCG.

Perform sterile catheterization using a sterile catheter kit and a 14F urethral catheter. Empty bladder completely.

Insert a catheter tip syringe or the primed tubing attached to the medication valve to the catheter and instill the agent per gravity flow or injection. Assess the patient for pain.

Remove syringe or medication vial with tubing intact using sterile gauze to help absorb any drops. If the patient has difficulty holding the solution, a Foley catheter may be used, and a catheter plug may be inserted onto the end of the catheter after

installation so the chemotherapeutic agent remains in the bladder for a specified amount of time, usually 1–2 hours. Depending on the patient's mobility, the catheter can be removed and the patient can void, or the catheter can be connected to a urinary drainage bag to drain the chemotherapeutic agent.

Once the catheter is removed, dispose of the equipment appropriately. Repeat inspection of the perineal area for leaks and reassess for pain. Cleanse area as indicated.

Instruct the patient to retain the treatment for 1–2 hours [20, 24].

Clinical Pearls

- BCG is the only agent shown to delay or reduce high-grade tumor progression.
- A 6-week induction course alone is insufficient to obtain an optimal response in many patients and that maintenance therapy is requisite.
- Ideally, maintenance should be given for 1 year for intermediate-risk and 3 years for high-risk NMIBC.
- BCG should not be started until 2 weeks after a TURBT. It should be held in the setting of traumatic catheterization, bacteriuria, persistent gross hematuria, persistent severe local symptoms, or systemic symptoms. BCG is contraindicated in immunosuppressed patients.
- Patients should be instructed to not void for 1–2 hours following intravesical installation. Bleach should be added to the toilet during the first 6 hours.
- Sexually active patients should use condoms during the duration of therapy.
- Dose reduction may be considered if there are substantial local symptoms during maintenance therapy.
- Quinolones may affect the efficacy of BCG and should be avoided for the duration of the treatment if possible.
- Patients may experience flu-like symptoms that can last 48–72 (low-grade fever below 38.5°C, fatigue, and joint achiness) hours. Local symptoms such as frequency, urgency, and dysuria are common. Anticholinergics, analgesics, and NSAIDS are helpful.
- Symptoms lasting more than 48 hours:
  - Urine culture, chest X-ray, and liver function tests.
  - Hold therapy or consider dose reduction.
- Consider therapy with isoniazid (300 mg/day) and rifampin (600 mg/day) until symptoms resolve.
- Severe symptoms such as hemodynamic instability should be treated with isoniazid (300 mg/day) and rifampin (600 mg/day) for 3–6 months. Ethambutol (15 mg/kg/day) should be added for solid organ involvement [6, 12, 20, 21, 42–48].

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