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Intravesical Chemotherapy and BCG for the Treatment of Bladder Cancer: Evidence and Opinion

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Abstract

Objectives: Review the chemotherapeutic and immunotherapeutic options for post-resection intravesical treatment of low-risk, intermediate-risk, and high-risk non-muscle-invasive bladder cancer (bCA).
Design, Setting, and Participants: The authors conducted a review of the literature on chemotherapy and immunotherapy regimens used to reduce the risk of cancer recurrence and progression after transurethral resection of the bladder (TURB).
Results and Limitations: The choice of post-TURB regimen for intravesical treatment of non-muscle-invasive bCA depends on the risk category of the tumour: Chemotherapy is the treatment of choice for low-risk superficial bladder carcinoma; intermediate-risk disease can be treated with either chemotherapy or immunotherapy with bacillus Calmette-Guérin (BCG); and BCG is now the treatment of choice for high-risk tumours. In all cases, the overall aim of treatment is to prevent recurrence and delay disease progression. There is debate over the optimal treatment regimens, and the options may include sequential treatment with chemotherapy and BCG.
Conclusions: Intravesical chemotherapy and BCG are both effective post-TURB treatments for non-muscle-invasive bCA, and the choice of regimen depends on the risk category of the tumour. There may also be a role for sequential instillations of chemotherapy and BCG.

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1. Introduction

Transurethral resection of the bladder (TURB) is well established as the standard initial intervention for non-muscle-invasive bladder cancer (bCA) and the first step toward a correct diagnosis and subsequent intravesical adjuvant treatment with chemotherapy or immunotherapy. The goals of intravesical therapy are to (1) avoid post-TURB implantation of tumour cells, (2) eradicate residual disease, (3) prevent tumour recurrence, and (4) delay or reduce tumour progression. This article considers the mechanisms of action of the various agents used post-TURB for the intravesical treatment of non-

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Table 1 – Classification of risk groups according to the 2006 European guidelines [1]

Low risk	Intermediate risk	High risk
G1–2Ta	Multifocal G2Ta, G1T1, solitary G2T1	Multifocal G2T1, G3Ta–T1, CIS

muscle-invasive bCA and the evidence for the efficacy and safety of these treatments according to the three main risk groups (Table 1) [1].

2. Methods

2.1. *Bacillus Calmette-Guérin*

Bacillus Calmette-Guérin (BCG) acts by means of an immunological reaction strongly associated with cell apoptosis. Furthermore, the findings of several studies suggest that the immune response cascade in local areas of the bladder is involved in the anti-tumour mechanism of BCG. However, the detailed mechanism remains to be clarified [2,3].

According to de Boer and colleagues, there is a correlation between the level of interleukin 8 (IL-8) produced at the initial BCG instillation and the patient's immune responsiveness [4]. Shintani et al also report that the clinical efficacy of BCG can be predicted from the IL-8 level within 6 h of intravesical BCG instillation [5]. They measured urinary cytokine levels 4 h after the sixth instillation of intravesical BCG therapy and found infiltration of granulocytes into the bladder wall and dominancy of $CD4^+$ cells.

2.2. *Chemotherapy*

The effect of early chemotherapy instillations may be explained by their destruction of circulating tumour cells that could otherwise implant themselves at the site of the resection or by their ability to eradicate any small tumour that remains following incomplete resection. To obtain the best results from early instillation, chemotherapy must be administered soon after TURB [6,7]. The duration of the effect (ie, time to first recurrence) varies in different studies. Solsona et al suggest that a single, early instillation of chemotherapy remains effective for 2 yr post-TURB [8].

The main anti-tumour mechanism of mitomycin C (MMC), an alkylating agent isolated from *Streptomyces caespitosus*, is not known, but its union with DNA is believed to inhibit DNA synthesis and cause double string rupture. Another theory is that use of MMC leads to production of superoxide free radicals that affect the integrity of DNA and cause cell necrosis [9].

Alkalinisation of urine and low patient water intake may improve the results of MMC treatment [10]. The clinical efficacy of multiple intravesical instillations of MMC is difficult to determine from the literature, because the reported series varies in patient populations, doses, instillation volumes, and indwelling times.

Doxorubicin, an anthracycline antibiotic, has limited efficacy in bCA treatment [11]. Epirubicin, a derivative of doxorubicin, can be effective in patients at intermediate risk [12]. Thiotepa acts as an alkylating agent. Its efficacy for tumour prophylaxis has been demonstrated in several trials, but it has haematological side effects resulting from systemic absorption [13]. Gemcitabine, a deoxycytidine analogue used in chemotherapy against several tumours, including systemic therapy for advanced bCA, inhibits growth activity, mediates apoptosis, and has been shown to be effective and well tolerated. It appears to be one of the most active systemic therapies against transitional cell carcinoma (TCC), with significantly better activity than intravesical thiotepa, doxorubicin, epirubicin, or MMC, but further studies are needed to establish its usefulness as an intravesical treatment [14,15].

2.3. *Treatment options*

TURB followed by early intravesical chemotherapy instillation (for example, with MMC) is the treatment of choice for low-risk superficial bladder carcinoma (Table 2). This strategy has been shown to reduce the risk of recurrence and possibly prevent the implantation process [6].

The treatment of choice for intermediate-risk non-muscle-invasive bCA is either chemotherapy or immunotherapy, according to the 2006 guidelines from the European Association of Urology (EAU) [1]. A meta-analysis of 11 randomised controlled trials comparing various intravesical chemotherapies with TURB alone has shown that intravesical chemotherapy is associated with a 44% reduction in tumour recurrence at 1 yr, with an odds ratio of 0.56 (95% CI, 0.48–0.65; $p < 0.00001$) [16]. The analysis also showed that short-term, 1-yr and 2-yr schedules of intravesical therapy are associated with—respectively—a 32%, 31%, and 73% reduction in tumour recurrence compared with TURB alone. This suggests that longer schedules may be more beneficial than shorter schedules. In two meta-analyses focusing on the intermediate-risk group, there seemed to be no difference in recurrence between intravesical chemotherapy and immunotherapy [17,18].

For high-risk tumours, post-TURB treatment with BCG has become one of the most successful and low-cost immunotherapies available. It is highly effective for the prevention

Table 2 – Treatment options by risk group

Risk group	Treatment
Low risk	Early chemotherapy
Intermediate risk	Early chemotherapy Chemotherapy Immunotherapy
High risk	Immunotherapy Chemotherapy + immunotherapy Chemotherapy + hyperthermia Chemotherapy + EMDA Cystectomy

EMDA, electromotive drug administration.