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.

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-
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 dominance 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 caesipitosus, 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].

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

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Low risk</td>
<td>Early chemotherapy</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>Early chemotherapy, Chemotherapy, Immunotherapy, Chemotherapy + immunotherapy, Chemotherapy + hyperthermia, Chemotherapy + EMDA, Cystectomy</td>
</tr>
<tr>
<td>High risk</td>
<td>Immunotherapy, Chemotherapy + immunotherapy, Chemotherapy + hyperthermia, Chemotherapy + EMDA, Cystectomy</td>
</tr>
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</table>

EMDA, electromotive drug administration.
of recurrence and progression of Ta and T1 bladder tumours and carcinoma in situ (CIS) compared with TURB alone [1].

Unfortunately, all of the above adjuvant treatments have limitations in terms of disease recurrence or progression and morbidity. There is increasing interest in alternative first-line drugs (eg, gemcitabine and apaziquone [EO9]) [19,20], although the results are not yet mature, and in second-line therapies (eg, intravesical microwave hyperthermia in combination with intravesical chemotherapy or electromotive drug administration [EMDA; 21,22]). The combination of intravesical mitomycin and the application of hyperthermia (42 °C, delivered using a microwave applicator) has been shown to reduce recurrence [21]. Furthermore, there is evidence of a decrease in disease recurrence and even in disease progression with the sequential combination of BCG and electromotive mitomycin, which increases the penetration of the drug into the bladder wall [23].

3. Results

A meta-analysis of the results of randomised clinical trials comparing TURB alone with TURB plus one immediate instillation of chemotherapy (epirubicin, MMC, thiotepa, or pirarubicin) has shown that a single, immediate chemotherapy instillation significantly decreases the risk of bCA recurrence in patients with stage-Ta/T1 single and multiple bladder tumours, and the authors recommend this strategy as the treatment of choice for patients with one low-risk papillary tumour [6]. Further intravesical treatment is needed for patients with intermediate-risk and high-risk tumours, although patients who have received an early post-TURB instillation do not seem to require long-term maintenance—6 mo of intravesical chemotherapy produces good results [24].

In a Cochrane meta-analysis, Shelley et al conclude that post-TURB instillation of BCG provides significantly better prophylaxis of tumour recurrence in Ta and T1 urothelial bCA compared with TURB alone [25]. Two meta-analyses have also demonstrated delayed disease progression in patients treated with BCG [26,27].

3.1. BCG versus chemotherapy

Various studies have shown that intravesical BCG produces better results than chemotherapy [28–31]. For example, in one multicentre study of patients with Ta and T1 tumours and without CIS, the estimated probability of being disease free at 5 yr was 17% after doxorubicin, compared with 37% after BCG immunotherapy (p = 0.015) [11].

However, there have also been several studies showing few differences between chemotherapy and immunotherapy in intermediate-risk bCA, so both types of treatment are accepted as standard in this patient group [1]. One randomised, multicentre phase 4 clinical trial of short-term and long-term MMC versus short-term BCG after TURB for non-muscle-invasive bCA suggests that patients with Ta/G1 tumours are significantly less likely to experience recurrence after long-term MMC (3 yr) than after short-term BCG (6 wk) or short-term MMC (6 wk), and without enhanced toxicity [31]. Patients treated with short-term BCG instillations had a 25.1% recurrence rate at 1 yr, compared with 25.7% in the short-term MMC group and 10.4% in those receiving long-term MMC. Recurrence-free rates in the second and third year were, respectively, 70.5% and 68.6% for short-term MMC, 68.5% and 65.5% for short-term BCG, and 88.3% and 86.1% for long-term MMC. Sekine et al have compared the efficacy of intravesical therapy with MMC plus doxorubicin versus BCG in 42 patients with CIS and conclude that both strategies are equally effective as initial therapy and that a combination of both would be the most efficient treatment for CIS [32]. In 2007, the Greek Bladder Cancer Study Group presented the results of a prospective, randomised, comparative study of high-dose (80 mg) intravesical epirubicin and BCG as prophylaxis for cancer recurrence in 234 patients with intermediate-risk superficial TCC [33]. The treatments were given 2 wk after TURB, then weekly for 6 wk, followed by 3 weekly instillations at 3, 6, 12, 18, 24, 30, and 36 mo. The results in 212 patients appropriate for assessment were a disease-free survival of 23.24 ± 10.3 mo for the epirubicin group and 23.26 ± 10.2 mo for those treated with BCG (p = 0.0778). The authors conclude that a high dose of intravesical epirubicin in an extended treatment schedule is well tolerated and as effective as BCG in the prevention of recurrence after TURB in patients with intermediate-risk superficial bladder tumours.

3.2. Sequential BCG and chemotherapy

Intravesical chemotherapy and BCG have different mechanisms of action and may thus have a potentiating anti-tumour effect. For example, intravesical chemotherapy causes a chemical cystitis, which has a positive effect on the adherence of BCG particles to the bladder wall—a necessary step in the BCG mechanism [34,35]. Several studies have shown that the efficacy of immunotherapy is increased by prior chemotherapy [35].

Di Stasi et al have investigated the effect of sequential BCG and MMC, but starting with BCG to provoke inflammation of the mucosa and facilitate penetration of MMC into the bladder wall. They also
used EMDA to further enhance the penetration of MMC. They found that BCG plus MMC produced lower cancer recurrence and progression rates than BCG used alone [23]. However, the Nordic Urothelial Cancer Group found that 1 yr of BCG monotherapy was more effective than alternating MMC and BCG at reducing disease recurrence in a study of 304 patients with CIS [36].

A combination of a chemotherapeutic drug and BCG can also have an impact on treatment toxicity [35]. In a prospective, randomised, multicentre study of 188 patients, the efficacy of alternating MMC and BCG was equal to MMC monotherapy, and there was less toxicity in the alternating treatment group compared with earlier BCG monotherapy results [37].

4. Discussion

There is controversy over the optimal schedule for BCG maintenance. Many different maintenance schedules have been used, although the instillations are classically given according to the empirical six-weekly induction schedule introduced by Morales in 1976 [38]. The US Southwest Oncology Group has shown that maintenance treatment reduces disease recurrence and progression compared with induction therapy alone [39], but only 16% of patients in the maintenance group finished the scheduled instillations. It has been suggested, based on published evidence for different BCG schedules, that at least 1 yr of maintenance treatment is necessary [1], but this assertion is still to be confirmed.

In a bid to reduce the toxicity of BCG, some authors have proposed cutting the instilled dose to one-third or one-quarter of the normal level. For example, a Spanish group has published the findings of a multicentre, randomised, prospective trial comparing a standard 81-mg dose of intravesical BCG with a 27-mg dose in the treatment of superficial bCA, showing no overall difference in efficacy [40]. Nevertheless, there was a suggestion that a full dose of BCG might be more effective in multifocal disease. Another study compared low-dose BCG (27 mg), very low-dose BCG (13.5 mg) and MMC [41]. The authors conclude that 27 mg (one-third of the standard dose) appears to be the minimum effective dose for adjuvant treatment of intermediate-risk superficial bladder tumours. The incidence of toxicity was similar in the low-dose and the very low-dose groups. The European Organisation for Research and Treatment of Cancer is now running a trial of the one-third dose; it will be interesting to see whether the results confirm the earlier findings.

5. Conclusion

For intermediate-risk patients, a cycle of chemotherapeutic instillations—usually with MMC or epirubicin—is safe and effective in reducing the short-term risk of recurrence, but the usefulness of maintenance treatment is open to debate. BCG it is also effective in intermediate-risk patients [42] and is accepted as an alternative to chemotherapy. BCG has become the treatment of choice for high-risk non-muscle-invasive bCA and for patients in whom chemotherapy fails. It is superior to intravesical chemotherapy in terms of both disease recurrence and progression to muscle-invasive disease [16,27,39]. Future studies will determine whether lower doses of BCG are enough to maintain the same oncological results with reduced morbidity.

Conflicts of interest

Juan Palou acts as a company consultant for Sanofi Pasteur, Eli Lilly and Company, and Amgen and has been involved in trials funded by Eli Lilly and Company and Zambon Group.

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References


