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Review – Bladder Cancer

Intravesical Pharmacotherapy for Non–Muscle-Invasive Bladder Cancer: A Critical Analysis of Currently Available Drugs, Treatment Schedules, and Long-Term Results

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Abstract

Objectives: Review adjuvant intravesical pharmacotherapy for non-muscle-invasive bladder cancer (NMIBC), emphasising treatment schedules and long-term results.

Methods: Search of published literature on conventional treatment of NMIBC, emerging drugs, and device-assisted therapies.

Results: In low-risk NMIBC patients an immediate instillation with chemotherapy is sufficient. For patients with intermediate- or high-risk tumours, additional adjuvant instillations are needed. For intermediate-risk patients chemotherapeutic instillations, usually with mitomycin C or epirubicin, are safe and effective in reducing the risk of recurrence in the short term, but efficacy is only marginal in the long term. Newer drugs have promising results, but long term follow-up is limited or lacking. In these patients bacillus Calmette-Guérin (BCG) does not seem to be more effective, only more toxic. In high-risk NMIBC, or patients in whom chemotherapy fails, BCG is the best choice with lower rates of recurrence and progression. For BCG failures cystectomy is therapy of choice, although the combination of BCG and interferon- α can be considered, just as device-assisted therapies such as thermochemotherapy and electromotive drug administration.

Conclusions: Risk-adapted first-line adjuvant therapy for NMIBC after TURBT is well established but has its limitations because recurrences are still numerous. Some new drugs and second-line therapies are promising, but efficacy should be confirmed.

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1. Introduction

Bladder cancer is the fourth most common malignancy among men in the Western world, following prostate, lung, and colon cancers, but the high recurrence rates makes it probably the most prevalent malignancy of these four, and certainly the most expensive per patient treated [1]. More than 90% of bladder cancers are urothelial cell carcinoma (UCC), and on average 70% of bladder UCCs present as non-muscle-invasive bladder cancer (NMIBC). The initial treatment of NMIBC is transurethral resection of the bladder tumour (TURBT). After TURBT, patients receive adjuvant instillations of chemotherapy or immunotherapy to lower the (high) recurrence rate and to prevent or delay progression to muscle-invasive disease. As indicated, the progression rate and high recurrence rate are problems for the patient, the urologists, and the community. The probability of recurrence or progression can be calculated with risk tables as provided by the European Organization for Research and Treatment of Cancer (EORTC), based on six clinical and pathologic parameters [2]. Similar prognostic factors have been used by the European Association of Urology (EAU) to divide NMIBC into low-, intermediate-, and high-risk groups, with subsequent therapeutic advisories. Risks of recurrence at 5 yr vary from 31% in low-risk patients to 78% in high-risk patients, the risk of progression from <1% to 45%, respectively.

In this review, we discuss adjuvant intravesical treatment strategies for NMIBC, with emphasis on currently available drugs and long-term results of those drugs used for longer periods.

2. Chemotherapy

2.1. Single immediate instillation

An immediate instillation after TURBT is advised for all patients with NMIBC because it reduces the risk of recurrence by about 50% at 2 yr and $\geq 15\%$ at 5 yr [3-6]. Several surveys and personal communications, however, suggest that approximately half of the European urologists and a minority of the American urologists do, indeed, give an immediate instillation. Although an instillation within 6 h after TURBT seems to be most effective, Sylvester et al, in a meta-analysis of seven trials comparing TURBT alone to TURBT plus one immediate instillation, could not find significant differences in efficacy as long as the instillation is given within 24 h [6]. This meta-analysis also found that for one immediate

instillation all chemotherapeutic drugs studied appear to have similar efficacy. In two EORTC studies, 30 mg mitomycin C (MMC) or 50 mg doxorubicin was given and early (≤ 24 h) versus delayed (days 7-15) therapy regimens were compared [5]. For both agents early treatment with or without maintenance therapy was slightly superior to delayed therapy with maintenance. Although in general one immediate instillation is safe, as long as there is no evident bladder perforation, bladder complications have been reported anecdotally.

Data for one instillation with a new drug are very limited. An early single-instillation pharmacokinetic study has also been done with gemcitabine, a novel deoxycytidine analogue with a broad spectrum of antitumour activity, and considered standard in systemic therapy for advanced UCC of the bladder [7]. In nine patients, 2000 mg gemcitabine in 50 ml was instilled in the bladder during 1 h, immediately after TURBT. Grade 2 leukopenia and vomiting were seen, and the highest peak concentration of 4.26 $\mu\text{g/ml}$ was found after extended bladder resection. Although the authors concluded that this approach is feasible with acceptable toxicity, these results appear somewhat less favourable than the results we reported earlier [8], so very clearly more studies are needed.

In all, an immediate instillation can be considered sufficient for patients with low-risk tumours. For patients with intermediate- or high-risk tumours, additional adjuvant instillations are needed.

2.2. Multiple delayed instillations

A cycle of instillations with a chemotherapeutic drug is treatment of choice for patients with intermediate-risk NMIBC because it is able to reduce the short-term risk of recurrence. For this, the most used drugs are MMC and epirubicin. MMC is used in dosages of 20-60 mg and is administered once a week for 4-8 wk, eventually followed by some kind of maintenance schedule [9]. The same applies for epirubicin in dosages of 30-80 mg [10]. Both agents have relatively few side-effects. The results with intravesical chemotherapy, however, are relatively limited with long-term follow-up. In an analysis by Pawinski et al, the long-term efficacy of TURBT alone was compared to TURBT plus adjuvant treatment in 2535 patients with Ta-T1 NMIBC [11]. With a median follow-up of 4.6 yr for disease-free survival, 5.5 yr for muscle invasion, and 7.8 yr for survival, adjuvant treatment resulted in an only 6% decrease in the risk of recurrence (47%) as compared to the no treatment group (52.6%). Although there was a significantly favourable impact on the

disease-free interval, there was no difference in terms of time to muscle invasion or duration of survival or progression-free survival. In a study by Hendricksen et al, 1000 patients (the majority multiple Ta G1–2 UCC) were randomised among three different treatment schedules of epirubicin [12]. The results at 5-yr follow-up were even lower, as in the above-mentioned analysis; 44.0% of the patients were recurrence-free and 88.6% of the patients progression-free, with no significant differences among the three schedules. Obviously, the results with these drugs, although they have been studied extensively and are considered standard of care, have limitations. One of the possibilities to improve these somewhat disappointing results was reported by Au et al [13]. In the “optimized treatment arm” they instructed the patients to decrease urine output and used urine alkalinisation and a double dose of MMC. These changes led to an approximately 17-mo longer median time to recurrence and an approximately 15% higher recurrence-free rate at 5 yr. However, how much of this improvement is attributable to the double dose remains unclear.

Results with newer drugs are emerging, but long term follow-up data are still lacking, and as demonstrated above, long-term data are extremely important. One of these newer drugs, gemcitabine, appears to have minimal toxicity when used intravesically in doses up to 2000 mg/50 ml for 2 h [8,14]. Ablation of a marker lesion is seen in up to 56% [15–17]. Dalbagni et al even obtained a complete response in 15 of 30 patients (50%) refractory to bacillus Calmette-Guérin (BCG) refusing cystectomy, although with a 1-yr recurrence-free survival rate of only 21% [18]. A study with prophylactic intent reported a 1-yr recurrence rate of 25.9% (21 of 81 patients) with intermediate-risk tumours, of which again 6 of 24 patients (25%) patients were refractory to BCG therapy [19]. However, patients with high-risk tumours had a recurrence rate of 77.1% (27 of 35). Of even more recent date are the studies with apaziquone or EO9, a novel indole quinone derivative of MMC. Both drugs are inactive prodrugs that require activation by cellular reductase enzymes to become cytotoxic [20]. The enzyme that has a crucial role in the activation of EO9, deoxythymidine-diaphorase (DTD), has a high activity in about 40% of bladder tumours as compared to normal bladder tissue. This suggests that selective efficacy against tumour cells may be achieved [21]. In preclinical research the concentration of EO9 needed to achieve 50% cell kill at 37 °C was 6–78 times lower than that of MMC depending on the cancer cell line used [22]. In a marker lesion study on patients with low-intermediate risk NMIBC, 30 of 45

patients (67%) achieved a histologically proven complete response 2–4 wk after the last of six instillations of 4 mg/40 ml EO9 [23]. The side-effects of EO9 were comparable to other chemotherapeutic agents used against NMIBC.

Recently, also a phase 1 trial with intravesical docetaxel was reported in patients with recurring NMIBC [24]. In a dose-escalation study 18 patients were treated. No grade 3 or 4 dose-limiting toxicities nor systemic absorption of docetaxel were reported. Eight (44%) of 18 patients experienced grade 1 or 2 toxicities, predominantly dysuria. Ten (56%) of 18 patients had no evidence of disease at their posttreatment cystoscopy and biopsy; there was no progression in relapsing patients. Intravesical docetaxel appears safe, and further studies are needed.

In all, these studies show that chemotherapeutic instillations are safe and effective in reducing the risk of recurrence in the short term. Drugs that are currently used as standard are MMC and epirubicin. Unfortunately, there is only marginal long-term efficacy, which is not good for the patients, a burden for the urologic practice, and expensive for the community. Newer drugs are interesting and have promising results in the patient groups studied, but long-term follow-up is limited or completely lacking.

3. Immunotherapy

Because intravesical chemotherapy clearly has its limitation, intravesical immunotherapy becomes interesting. Intravesical immunotherapy is predominantly done with BCG, and comparisons clearly show that intravesical chemotherapy is less effective than intravesical BCG. Krega et al compared TURBT alone to TURBT plus adjuvant MMC or BCG in patients with Ta–T1, G1–3 NMIBC [25]. Patients receiving TURBT alone had a significant increase in risk of recurrence as compared to the adjuvant treatment groups, but there was no significant difference between the MMC or BCG groups. Witjes et al found similar results in a study comparing nine instillations with 30 mg MMC versus six instillations with either BCG-Tice or BCG-RIVM [26]. Recurrence rates, even in patients with carcinoma in situ (CIS), where numbers were low, were not significantly different.

In these older studies, however, predominantly low- and intermediate-risk patients were included, where a difference in efficacy is more difficult to prove. Moreover, in both studies no maintenance BCG was used. Only recently was the superior

efficacy of BCG over chemotherapy clearly proven by several large meta-analyses. Sylvester et al performed a meta-analysis of 24 clinical trials with 4863 patients comparing TURBT plus intravesical BCG to either resection alone or resection plus another treatment than BCG [27]. They found that adjuvant BCG is superior to TURBT alone and more effective than adjuvant chemotherapeutic drugs with regard to progression-free survival; after a median follow-up of 2.5 yr, progression was seen in 9.8% in the BCG-treated group versus 13.8% in the non-BCG group (odds ratio [OR] = 0.73, $p = 0.001$). This difference was even larger when only maintenance trials were used: OR 0.63, $p = 0.00004$. However, the follow-up is relatively short, resulting in a low absolute number of patients with progression: 6.4% in patients with papillary tumours and 13.9% in patients with CIS. Moreover, several small trials were included and finally no difference in tumour-related survival was found.

Boehle et al came to similar conclusions after their meta-analysis, comparing nine trials with 1328 NMIBC patients treated with adjuvant MMC, to 1421 patients treated with BCG [28]. Without a clear separation of results for patients with intermediate- or high-risk NMIBC, the overall recurrence rate was 46.4% for MMC and 38.6% for BCG, after a mean follow-up of 26 mo. BCG also had a statistically significant superiority in reducing the risk of progression; after a median follow-up of 26 mo the rate of progression using all trials was 7.7% for BCG-treated patients versus 9.4% for MMC-treated patients (OR = 0.77, $p = 0.08$). Including only the five trials that used BCG maintenance increased the OR to 0.66 ($p = 0.02$). Also in this meta-analysis follow-up was limited. Whether with longer follow-up the difference between BCG and MMC increases or decreases remains a question. One of the very few long-term studies comparing BCG and MMC was recently published. Gardmark et al reported the 10-yr follow-up of a randomised study comparing 2 yr of maintenance BCG (Danish strain) or MMC (40 mg) in 261 patients with intermediate- and high-risk NMIBC [29]. After a median follow-up for survivors of 123 mo, disease progression was found in 58 of the 250 evaluable patients, 34 in the MMC group and 24 in the BCG group ($p = 0.26$). Overall survival was also similar (log-rank $p = 0.98$), with 32% dying due to bladder cancer. Whether the use of this specific BCG strain explains this lack of difference or the use of this maintenance MMC schedule remains unclear. Arguments in favour of an extensive MMC schedule can also be found in a recent German study [30]. They studied 495 intermediate- and high-risk NMIBC patients. Patients

received 6 weekly instillations with BCG-RIVM 2×10^8 (8) colony-forming units (CFUs) or 20 mg MMC, or 20 mg MMC for 6 wk followed by monthly instillations for 3 yr. They found that 3 yr of MMC significantly increased the recurrence-free rates compared to BCG or 6 wk of MMC (86.1% vs. 65.5% vs. 68.6%, log-rank test, $p = 0.00$), without increasing the toxicity in the maintenance MMC group.

Clearly the reduction in the risk of progression is only achieved with maintenance BCG, which, in turn, leads to more frequent and more severe local and systemic side-effects than with intravesical chemotherapy. Lamm et al also showed significantly improved recurrence-free survival time in high-risk NMIBC with BCG maintenance therapy [31], but also found increased side-effects; 5% of patients had to stop during induction therapy and 20% of patients during maintenance therapy [32]. In an attempt to control these side-effects the EORTC randomised 957 patients with intermediate- and high-risk NMIBC for adjuvant treatment with BCG, BCG and isoniazid, or epirubicin [33]. The superiority of BCG was again proven; at 3 yr, 49% of patients receiving epirubicin were recurrence free and about 65% of patients treated with BCG (with or without isoniazid). Progression to muscle-invasive disease was infrequent (5%) and similar in the three groups. As also expected, in the epirubicin group drug-induced cystitis was less and there were no systemic side-effects. Isoniazid, unfortunately, did not reduce BCG toxicity, nor, by the way, did it influence BCG efficacy.

Surprisingly, a recent study in 115 BCG-naïve patients, treated with BCG and 200 mg ofloxacin or placebo, showed that prophylactic ofloxacin decreased the incidence of moderate to severe side-effects and improved compliance to BCG therapy [34].

Obviously, another way of trying to overcome BCG toxicity is lowering the BCG dose. Ojea et al recently reported a trial comparing MMC (30 mg) to a one-third (27 mg) and one-sixth (13.5 mg) dose of BCG in 430 intermediate-risk patients [35]. Instillations were weekly during 6 wk and once every 2 wk during again 6 wk. The 27-mg BCG dose had the lowest recurrence rate, but only significantly better than MMC. Toxicity was similar in both BCG groups, but less in the MMC group. This study suggests that the optimal BCG dose lies around one third of the full dose.

BCG is apparently also more cost effective than intravesical chemotherapy. Uchida et al recently calculated costs of BCG therapy during an 86-mo observation period in 138 tumours [36]. Because BCG was the most significant factor preventing

recurrence, improving the 5-yr recurrence-free survival rate from 28% to 78%, the cost-effectiveness ratio of BCG therapy was approximately \$3900/5-yr recurrence-free period.

In all, for patients with intermediate-risk NMIBC, BCG does not seem to be superior to chemotherapy and has significantly more side-effects. However, in studies with more high-risk NMIBC patients included, the superiority of BCG is evident with regard to the reduction in recurrence rate, progression, and costs. BCG should, therefore, be reserved for intermediate-risk patients in whom intravesical chemotherapy fails, but it is the treatment of first choice for patients with high-risk NMIBC.

Patients in whom adequate BCG treatment fails, especially high-risk patients, are confronted with the threat of radical therapy, such as radical cystectomy as treatment of choice [37]. Alternative intravesical therapy is an option, but imposes an oncologic risk. Tumour-specific survival in case of cystectomy for BCG failures is between 80% and 90% in 5 yr, approaching the tumour-specific survival of 88–90% of the whole group of patients with NMIBC [38,39]. In comparison, a small study conducted by Schrier et al showed a 5-yr tumour-specific survival of 55% for patients with primary muscle-invasive tumour, and only 28% 5-yr tumour-specific survival for patients with progressive invasive tumour [40]. Still, patients may refuse or be unfit for major surgery.

The combination of interferon- α (IFN- α) and BCG for BCG failures has been the subject of a large multicentre phase 2 trial [41]. In all, 467 patients in whom BCG failed were treated with low-dose BCG plus IFN- α . Twenty-seven percent of these patients had isolated or concomitant CIS. With a median follow-up of 24 mo 45% remained tumour free compared to 59% in the BCG-naïve group ($n = 536$). The authors concluded that this combination could be effective for BCG-failing patients but also stress that certain characteristics influence durable response. So again, also this approach needs confirmation.

4. Device-assisted therapy

Other possibilities are new conservative approaches such as device-assisted therapies. Of course, one should realise that currently available device-assisted therapies are not used on a large scale (yet), and mainly in small groups of high-risk patients or as second-line therapy. This means that these results also clearly have to be interpreted with caution.

4.1. Thermochemotherapy

The Synergo[®] system induces bladder wall hyperthermia around 42–43 °C with a special catheter, also equipped with internal thermocouples to monitor the temperature. It is currently used in combination with intravesical MMC (thermochemotherapy), and several trials have shown its superiority over MMC alone [42,43]. It has significantly more side-effects, although these are moderate and transient. Van der Heijden et al reported the use of thermochemotherapy with prophylactic intent in 90 patients with intermediate- and high-risk NMIBC [44]. After 1 yr and 2 yr follow-up, respectively, 14.3% and 24.6% of all patients experienced a recurrence. In 41 patients in whom BCG failed the recurrence rates, respectively, were 23% and 41%. Witjes et al recently presented a multicentre study in which 57 patients (40 BCG failures, 29 with concomitant papillary tumours) with CIS were treated with 6–8 weekly and 4–6 monthly sessions of thermochemotherapy [45]. Forty-five of 48 patients (94%) evaluable for response, had a biopsy- and cytology-proven complete response. Despite promising initial results, obviously long-term follow-up is awaited.

4.2. Electromotive drug administration

Electromotive drug administration (EMDA) is based on the concept of temporarily enhancing penetration of drugs through the urothelial barrier of the bladder with an electrical gradient between the bladder wall and the bladder contents. Colombo et al compared four weekly ablative sessions prior to TURBT in low-intermediate risk patients undergoing either thermochemotherapy ($n = 29$), or EMDA ($n = 15$), or MMC only ($n = 36$), obtaining complete responses in, respectively, 66%, 40%, and 27.7% [46]. Di Stasi et al compared MMC only, MMC combined with EMDA, and BCG in 108 high-risk patients and obtained complete responses in, respectively, 31%, 58%, and 64%, after 6 mo of follow-up [47]. Side-effects with EMDA were more than with MMC alone, but still significantly less than with BCG. In a study by the same authors, 212 patients with stage T1 UCC were randomised for BCG alone versus sequential BCG and MMC/EMDA, with maintenance therapy in both arms [48]. With a mean follow-up of 88 mo, sequential BCG and MMC/EMDA had a higher disease-free interval of 69 mo versus 21 mo for BCG only, a lower recurrence rate of 41.9% versus 57.9%, a lower progression rate of 9.3% versus 21.9%, and a lower disease-specific mortality rate of 5.6% versus 16.2%. Even if this is only one smaller study,

especially the significant difference in the progression rate after sequential use of MMC/EMDA is remarkable.

4.3. Photodynamic therapy

Photodynamic therapy (PDT) is just emerging as a potential new treatment option. It combines photosensitizers that selectively bind to tumour and a powerful intravesical light source to destroy the complex of tumour cell and photosensitizer. The first studies on PDT were performed after oral administration of 5-aminolevulinic acid (5-ALA), causing hemodynamic side-effects (hypotension, tachycardia) in the majority of patients [49]. These could be avoided by the use of intravesical 5-ALA [50]. Berger et al showed that 16 of 31 PDT-treated NMIBC patients were recurrence free after a median follow-up of 23.7 mo (4 of 10 BCG failures). Local side-effects were minimal and included including dysuria and haematuria. PDT was proposed as a second-line treatment for patients with multiple comorbidities, who are not surgical candidates. With the newer generation of photosensitizers, which at least have improved diagnostic potential, these results might even be better. Clinical data, however, are not available as yet.

5. Conclusions

An immediate intravesical instillation after TURBT with a chemotherapeutic drug is considered first-line therapy for all patients with NMIBC and is sufficient for patients with low-risk tumours. For intermediate-risk patients an additional course of chemotherapy is indicated because BCG offers little advantage in this group and is more toxic. Still, with long-term follow-up the effect is limited, and the risk of progression is not reduced at all. New drugs are under investigation, but follow-up is limited. Patients in whom chemotherapy fails and those with high-risk NMIBC should be treated with maintenance BCG. BCG is superior in reducing recurrences in these patients, and additionally it reduces the risk of progression although BCG has more and more severe side-effects.

For patients in whom BCG therapy fails, cystectomy should be considered. If patients are unwilling or unfit, BCG plus IFN- α offers some potential, as does novel device-assisted therapies such as thermochemotherapy and EMDA. Results are promising but should be confirmed.

Conflicts of interest

The authors have nothing to disclose.

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