**1. Introduction**

Bladder cancer is a heterogeneous disease with a variable natural history. On average, 70% of bladder tumours present as non-muscle-invasive bladder cancer (NMIBC), and the remainder as muscle-invasive bladder cancer [1]. Among NMIBCs, approximately 70% present as Ta lesions, 20% as T1 lesions, and 10% as carcinoma in situ (CIS). At one end of the spectrum, low-grade Ta tumours have a low progression rate and require initial endoscopic treatment and surveillance, but rarely present a threat to the patient. At the other extreme, high-grade tumours have a high malignant potential associated with significant progression and cancer death rates. The European Organisation for...
Research and Treatment of Cancer (EORTC) has provided risk tables that allow calculation of a NMIBC patient’s risk of recurrence and progression after transurethral resection of the bladder tumour (TURBT) [2]. On the basis of six clinical (number of tumours, tumour size, prior recurrence rate) and pathological (T category, CIS, grade) factors, the calculated probability of recurrence ranged from 15% to 61% at 1 yr and 31% to 78% at 5 yr. For progression the calculated probability ranged from <1% to 17% and <1% to 45%, respectively. The risk tables provide a good starting point for discussion of the pros and cons of the therapeutic options, but one must consider that more factors contribute to the risk of recurrence and progression. Current clinical practice has changed over the last decade, and may have led to lower recurrence and progression rates as calculated because the studies included predate the Bacille Calmette-Guérin (BCG) maintenance era and the standard second TURBT in high-risk patients. In addition, approximately 20% of the patients did not receive any additional intravesical treatment, and <10% received an immediate instillation.

Intravesical instillations of chemotherapy or immunotherapy are given after TURBT to reduce the recurrence and progression rate of NMIBC. Oosterlinck et al [3] used prognostic factors for recurrence and progression to divide NMIBC into risk groups. In this review we use this risk classification to discuss adjuvant treatment options for low, intermediate-, and high-risk NMIBC, with emphasis on intermediate-risk tumours.

2. Low-risk tumours

After TURBT one immediate instillation with a chemotherapeutic agent should be encouraged in all patients with NMIBC because it can reduce the risk of recurrence by about 50% at 2 yr and ≥15% at 5 yr [4–7]. Low-risk tumours, classified as single TaG1 tumours ≤3 cm in diameter [3], have a probability of recurrence at 1 yr and 5 yr, respectively, of 15–24% and 31–46%, and a probability of progression, respectively of ≤1% and ≤1–6% [2]. For patients with these low-risk tumours, one immediate instillation is considered sufficient [3]. Gofrit et al [8] determined the outcome of a watchful waiting policy in patients suffering from small (<10 mm), papillary, asymptomatic tumour, with negative urine cytology and previously resected TaG1–2 tumour(s). The authors concluded that, for this kind of patient, a watchful waiting approach is reasonable, with minimal risk for tumour progression.

Tolley et al [5] performed a multicentre randomised trial of 502 patients with newly diagnosed stage Ta or T1 urothelial cell carcinoma (UCC), and approximately two thirds were at low risk for recurrence. Those who received intravesical 40 mg mitomycin-C (MMC) in 40 mL water within 24 h of TURBT had a statistically significant decreased risk of tumour recurrence compared with those who received placebo.

Oosterlinck et al performed a multicentre randomised trial of 431 patients with NMIBC (Ta–T1), comparing a single adjuvant dose of 80 mg epirubicin in 50 mL saline with sterile water as placebo, within 6 h of TURBT [6]. After a mean follow-up of 2 yr, the overall recurrence rate for those who received epirubicin was 17%, significantly lower than 32% in the placebo group. In all subgroups the recurrence rate was decreased by nearly half.

Bouffioux et al [7] performed two multicentre, randomised trials comparing the efficacy of either early (<24 h) versus delayed (days 7–15) 30 mg MMC in 50 mL saline, or 50 mg doxorubicin in 50 mL saline, as adjuvant intravesical therapy for patients with Ta or T1 NMIBC. Analyses demonstrated for both agents that early intravesical therapy, with or without maintenance therapy, was slightly superior to delayed therapy with maintenance. If early treatment was given, further maintenance therapy was not beneficial. A meta-analysis of seven trials by Sylvester et al [4] confirmed that one immediate intravesical instillation of chemotherapy significantly decreased the risk of recurrence after TURBT, not only in patients with low-risk NMIBC but also in patients with stage Ta–T1 single and multiple bladder cancers.

BCG immunotherapy is not indicated in low-risk patients because of the good prognosis of patients in this group and the potential toxicity of BCG. It should not be given immediately postoperatively because the mycobacteria can induce systemic BCG infection.

It is recommended to administer the chemotherapy within 24 h after TURBT, unless there has been perforation or extensive/deep resection [9]. Some authors prefer to administer ≤6 h after TURBT, but the real impact of timing is still unknown. Studies that compared early versus late instillations always chose 6 or 24 h post-TURBT as the time of early instillation compared with the first instillation from day 7 on for late instillations [7,10]. In a study comparing three schedules of epirubicin, an immediate instillation within 48 h of TURBT in addition to the standard instillation scheme was as equally effective as the standard instillation scheme alone [11].
In summary, a single adjuvant instillation of various chemotherapeutic drugs is sufficient to treat patients with low-risk NMIBC. The drugs are well tolerated, and toxicity is only mild and transient, involving mostly chemical cystitis and, in case of MMC, possible skin allergy.

3. High-risk tumours

The high-risk group contains T1G3, multifocal or highly recurrent (≥3 in 24 mo) tumours, and CIS [3]. On the basis of the EORTC risk tables and prognostic factors for this risk group, the probability of recurrence at 1 yr and 5 yr, respectively, is 24–61% and 46–78%, and the probability of progression, respectively, is 1–17% and 6–45% [2]. Series have shown that, when a second TURBT is performed, the risk of upstaging is ≥30%, but the risk of residual tumour also is significant [12,13]. Therefore, a second TURBT for patients with high-risk NMIBC is highly recommended to prevent understaging and possible progression to metastatic disease [14].

Conservative treatment of high-risk NMIBC primarily consists of intravesical instillations with BCG. Before the use of BCG immunotherapy, the incidence of progression of T1G3 UCC, and thereby muscle-invasive disease, ranged from 27% to 65% with 26–84 mo follow-up [9]. With the use of intravesical BCG in T1 disease, overall progression was in the range of 12%, varying from 0–35%, with follow-up time of 22–78 mo. Sylvester et al [15] performed a meta-analysis of clinical trials comparing TURBT plus intravesical BCG with either resection alone or resection plus a treatment other than BCG. These trials show that adjuvant BCG is superior to TURBT alone with regards to recurrence-free survival time, but it is also more effective than adjuvant chemotherapeutic drugs. Bohle et al [16] performed a meta-analysis, comparing the efficacy of adjuvant intravesical BCG versus MMC in, respectively, 1421 and 1328 patients with intermediate- and high-risk NMIBC. BCG had a statistically significant superiority over MMC in reducing tumour recurrence, especially when BCG maintenance was given. With a mean follow-up of 26 mo, 38.6% of BCG-treated patients and 46.4% of MMC-treated patients had tumour recurrence. However, BCG-associated cystitis was significantly more frequent than for the MMC group. In an EORTC study [17], 957 patients with intermediate- and high-risk NMIBC were randomised for adjuvant treatment with BCG, BCG and isoniazid, or epirubicin, showing that the time to first occurrence was significantly longer for both BCG regimens. At 3 yr, 49% of patients on epirubicin were recurrence-free versus around 65% of patients treated with BCG (+isoniazid). However, drug-induced cystitis was less for the epirubicin group, without systemic side-effects, in contrast to the BCG regimens. Gemcitabine has promising features for patients with intermediate- and high-risk NMIBC, but to date there are no published comparative phase 3 studies (gemcitabine is discussed in paragraph 4.2).

With regards to progression, the meta-analysis by Sylvester et al [15] showed that progression for patients treated with BCG was low, 6.4% in patients with only papillary tumour and 13.9% in patients with CIS, provided that some form of BCG maintenance was used. Lamm et al [18] showed a significantly longer recurrence-free survival time for patients with CIS, and Ta–T1 NMIBC when BCG maintenance therapy was used in addition to BCG induction therapy. BCG instillations are generally well tolerated, but local and systemic side-effects are more severe and more frequent compared with intravesical chemotherapy, causing 5% of patients to stop during induction therapy and 20% of patients during maintenance therapy [19].

Patients who fail on BCG (refractory, resistance, relapsing, or intolerance) in the most general sense are presented with the option of alternative intravesical therapy or radical cystectomy [20]. The latter would mean the safest option with regards to tumour progression and metastasis. Tumour-specific survival is between 80% to 90% in 5 yr, approaching the tumour-specific survival of 88–90% of the whole group of patients with NMIBC [21,22]. In comparison, a small study conducted by Schrier et al [23] 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. But patients may be reluctant to undergo major surgery for a condition that does not pose an immediate threat to their lives, or they may be unsuitable for surgery because of comorbidity.

The combination of interferon-α and BCG as second-line immunotherapy after BCG failures has been the subject of a multicentre phase 2 trial [24]. Forty-five percent of 467 patients were disease-free after 24 mo follow-up. Progression to muscle-invasive disease occurred in 4.3%, whereas metastasis occurred in 2.6% [25]. Although these results are promising, the authors concluded correctly that certain patient and tumour characteristics that influence durable response should be considered before starting salvage therapy. Intravesical chemotherapy is not a standard treatment option for BCG failures, with only a few attempts known in
literature. We will discuss the conventional and new chemotherapeutic options in the next paragraph, which deals with intermediate-risk tumours.

It is becoming more and more common practice to perform a second TURBT in high-risk tumours to prevent understaging and to rule out residual tumour. BCG is superior to any other adjuvant intravesical drug in the prevention of recurrence of NMIBC, and it is considered to prevent or delay progression of NMIBC. However, significantly more cases of BCG-associated cystitis are reported compared with intravesical chemotherapy, and BCG has systemic side-effects. When patients fail on BCG, radical cystectomy is the safest option. Adjuvant intravesical treatment remains an option, but for this indication experience is limited and it is not without risks.

4. Intermediate-risk tumours

4.1. Conventional treatment

This risk group contains all other tumours between the low- and high-risk groups, namely Ta–1, G1–2, multifocal, >3 cm in diameter [3]. On the basis of the EORTC risk tables, the calculated probabilities of recurrence at 1 yr and 5 yr, respectively, are 24–38% and 46–62%, and the probabilities of progression, respectively, are ≤1–5% and ≤1–17% [2]. The meta-analysis by Sylvester et al [4] and the Bouffioux et al [7] studies showed that one immediate intravesical instillation of chemotherapy significantly decreased the risk of recurrence after TURBT in patients with stage Ta–T1 single and multiple bladder cancers. Patients with single or multiple tumours had a risk of recurrence of 65.2% or 35.8%, respectively, which also showed that one instillation alone is insufficient treatment for patients with multiple tumours [4]. These patients should be treated with an additional 4- to 8-wk course of bladder instillations [3].

Among the chemotherapeutic agents, MMC and epirubicin are mostly used. Numerous trials evaluated the prophylactic use of MMC, with 20–60 mg MMC administered once a week for 4–8 wk, with or without maintenance once every 2 wk–3 mo for 6 mo–2 yr [26]. In the meta-analysis by Bohle et al [16], 1328 NMIBC patients were treated with adjuvant MMC. Without a clear separation of results for patients with intermediate- or high-risk NMIBC, the overall recurrence rate was 46.4% after a mean follow-up of 26 mo.

Most trials reporting on prophylaxis with epirubicin contain 50–250 evaluable patients, with the largest published trial [17] discussed in the previous paragraph. Generally, 30–80 mg epirubicin was administered once a week for 4–8 wk, with or without maintenance once every 1–4 mo for 10 mo–2 yr [27]. One study from 24 participating centres in the Netherlands (including ours) reports on a randomised trial comparing three different treatment schedules of epirubicin as adjuvant treatment for 1000 patients with intermediate- and high-risk NMIBC [11]. The majority of patients had multiple TaG1–2 lesions and the mean follow-up was 2.1 yr. Without a significant difference between the treatment groups, the mean recurrence-free survival was 3.2 yr; 44% and 88.6% of the patients, respectively, were recurrence-free and progression-free at 5-yr follow-up. These percentages are comparable to the probabilities of recurrence and progression as calculated by Sylvester et al [2].

Pawinski et al [28] analysed six EORTC and Medical Research Council trials (five intravesical chemotherapy trials) that compared adjuvant treatment after TURBT to TURBT alone in patients with Ta–T1 NMIBC. The 1629 patients were randomised to adjuvant prophylactic treatment, with median follow-up of 4.6 yr for disease-free survival, 5.5 yr for muscle invasion, and 7.8 yr for survival. In the long term, adjuvant prophylactic treatment had a 6% decrease in the risk of recurrence compared with the no-treatment group (47% vs. 52.6%), and had a statistically significant favourable impact on the disease-free interval. However, in the long term, there was no difference in terms of time to muscle invasion, duration of survival, or progression-free survival.

In all, intravesical instillations with a chemotherapeutic drug can clearly reduce the risk of recurrence for patients with intermediate-risk NMIBC in the short term. However, in the long term, it has only a modest effect on the risk of recurrence, without reduction in the risk of progression. When a recurrence presents as intermediate-risk NMIBC, the initial instillation schedule can be restarted depending on its previous efficacy, or an alternative chemotherapeutic drug can be chosen. In case of highly recurrent NMIBC or multiple recurrences, it is advocated to change to BCG therapy.

4.2. Gemcitabine

2’,2’-Difluorodeoxycytidine or Gemzar (Eli Lilly and Co, Indianapolis, IN, USA) is a novel deoxycytidine analogue with a broad spectrum of antitumour activity. It is considered standard in systemic therapy for advanced UCC of the bladder and is studied for its potential in the intravesical use.
Several phase 1 and phase 2 studies have shown that intravesical gemcitabine is well tolerated, with minimal toxicity up to 2000 mg/50 mL for 2 h [29,30]. The ablative effect of gemcitabine varies, with a highest complete response rate of 56% [31]. In a phase 1 study, Dalbagni et al [32] treated 18 BCG-refractory patients, who refused cystectomy, with two courses of 500–2000 mg gemcitabine for 3 wk twice a week, obtaining a complete response in 7 of 18 (39%) patients after 8 wk. In a comparable phase 2 study, 15 of 30 (50%) BCG-refractory patients obtained a complete response with a 1-yr recurrence-free survival rate of 21% [33]. Gemcitabine as a single post-TURBT instillation was tested in two studies [34,35], but not yet with prophylactic intent.

In a phase 2 study by Bartoletti et al [36], 116 patients with histologically confirmed stage Ta–T1 UCC or CIS of the bladder were enrolled and treated weekly for 6 wk with 2000 mg/mL for 1 h. The recurrence rate for the first year was promising for intermediate-risk tumours, 21 of 81 (25.9%), of which 6 of 24 (25%) were BCG-refractory. Patients with high-risk tumours had a recurrence rate of 27 of 35 (77.1%).

In all, gemcitabine has a good safety profile with promising features for the use against intermediate-risk tumours. It can be a potential chemotherapeutic drug for patients with high-risk and BCG-refractory NMIBC.

4.3. Apaziquone

Eoquin or EO9 (Spectrum Pharmaceuticals Inc, Irvine, CA, USA) is a novel indolequinone derivative of MMC. Both drugs are bioreductive (ie, inactive prodrugs) that require activation by cellular reductase enzymes to become cytotoxic [37]. The enzyme deoxythymidine-diaphorase (DTD) has a central role in activating EO9, and about 40% of bladder tumours have high DTD activity compared with normal bladder tissue, suggesting that selective toxicity against tumour cells may be achieved [38]. 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 [39]. Van der Heijden et al [40] performed a phase 2 marker lesion study on 46 patients with Ta–T1 G1–G2 NMIBC undergoing TURBT, with the exception of one lesion of 0.5–1 cm. Six weekly intravesical EO9 instillations of 4 mg/40 mL were administered. The side-effects of EO9 in this study were comparable to that of other chemotherapeutic agents used against NMIBC, and the histologically proven complete response 2–4 wk after the last instillation was 67% (30 of 45 patients). These results are very promising and warrant further study. Currently there are two studies recruiting patients: one study on a single immediate post-TURBT instillation of EO9 for patients with Ta–T1 G1–G2 NMIBC, and one study on a course of adjuvant EO9 for patients with high-risk and BCG-refractory NMIBC.

4.4. Device-assisted therapies

The currently available device-assisted therapies for bladder cancer are designed to enhance adjuvant intravesical chemotherapy with an energy source, or to activate photosensitisers that selectively bind to tumours, with a powerful intravesical light source.

First, the Synergo®-system (Medical Enterprises Europe BV, Amsterdam, The Netherlands) induces bladder wall hyperthermia via an energy-delivering unit in the tip of a special catheter, equipped with internal thermocouples to monitor the temperatures to be around 42–43 °C. The Synergy-system is currently used in combination with intravesical instillations of MMC (thermochemotherapy), and several randomised trials have shown its superiority over MMC alone. In a marker lesion study Colombo et al [41] randomised patients with Ta–1 G1–3 NMIBC for either MMC 40 mg/50 mL alone or MMC combined with hyperthermia, and obtained a complete response in, respectively, 5 of 23 (22%) patients and 19 of 29 patients (66%). In a comparable study with prophylactic intent and 2-yr follow-up, recurrences were seen in 6 of 35 (17.1%) patients treated with thermochemotherapy, significantly less than 23 of 40 (57.5%) patients treated with MMC alone [42]. However, for the thermochemotherapy group, subjective intolerance and clinical complications were significantly higher, although moderate and transient. Gofrit et al [43] reported a beneficial prophylactic effect of thermochemotherapy in patients with G3 tumours; 15 of 24 (62.5%) patients were recurrence-free after a mean follow-up of 35.3 mo. In addition, ablation of high-grade tumours was achieved in 21 of 28 (75%) patients, of whom 81% remained tumour-free after a mean follow-up of 20 mo. Van der Heijden et al [44] reported the use of thermochemotherapy with prophylactic intent in 90 patients with intermediate- and high-risk NMIBC. After 1-yr and 2-yr follow-up, respectively, 14.3% and 24.6% of all patients experienced a recurrence. In 41 patients previously failing on BCG, the recurrence rates, respectively, were 23% and 41%.

So far, the combination of intravesical chemotherapy and hyperthermia is promising for patients with intermediate- and high-risk tumours,
including those who previously failed on BCG. However, this strategy of treatment needs long-term follow-up. A comparative phase 3 study is currently recruiting patients with high-risk NMIBC, who are randomised for either adjuvant thermochemotherapy or BCG.

Second, electromotive drug administration (EMDA) is based on the concept of temporarily breaching the urothelial barrier of the bladder and enhancing penetration of drugs in a controllable manner. EMDA is combined with intravesical MMC. All forms of EMDA apparatus basically comprise an electrical source, an active electrode containing the drug solution that is supplied to the bladder, and a dispersive (ground) electrode on the skin. In the first ablative phase 2 study [45], MMC alone was compared with MMC/EMDA in intermediate-risk NMIBC patients. Both arms had an equally complete response rate around 40%, but the recurrence rate was higher for patients treated with MMC only (60% vs. 33%) and the disease-free interval was shorter (10.5 mo vs. 14.5 mo).

Colombo et al [46] compared four weekly ablative sessions prior to TURBT in patients undergoing either thermochemotherapy (29), or EMDA (15), or MMC only, obtaining complete responses of 66%, 40%, and 27.7%, respectively. Di Stasi et al [47] included 108 high-risk NMIBC patients to prospectively compare MMC only, MMC combined with EMDA, and BCG as a third arm [47]. All groups were treated with one or two 6-wk courses. The 6-mo complete response rates were 31% for MMC only, 58% for MMC combined with EMDA, and 64% for BCG. Side-effects with EMDA were more than with MMC alone, but still significantly less than with BCG. Plasma MMC concentrations were also higher after EMDA.

Recently, Di Stasi et al [48] performed another randomised controlled trial in 212 patients with stage T1 NMIBC, comparing 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 significantly higher disease-free interval of 69 mo versus 21 mo for BCG only, a significantly lower recurrence rate of 41.9% versus 57.9%, a significantly lower progression rate of 9.3% versus 21.9%, and a significantly lower disease-specific mortality of 5.6% versus 16.2%. The significant difference in the progression rate after sequential use of MMC/EMDA is especially remarkable. The authors interpreted this finding as a possible increase of the permeability of the bladder mucosa by BCG-induced inflammation, such that MMC can reach the target tissue more easily and exert its anticancer effect.

Finally, photodynamic therapy (PDT) combines photosensitisers that selectively bind to tumours and a powerful intravesical light source to destroy tumours. The first studies on PDT were performed after oral administration of 5-aminolevulinic acid (5-ALA). Waidelich et al [49] used PDT with orally administered 5-ALA, and found 3 of 5 patients with CIS and 4 of 19 patients with papillary tumour to be recurrence-free after a median follow-up of 36 mo. Haemodynamic side-effects like hypotension and tachycardia occurred in the majority of patients. Berger et al [50] reported that these systemic side-effects could be avoided by using intravesical 5-ALA. Thirty-one patients with NMIBC (10 BCG failures) were treated with a mean laser light dose of 3.9 W for a mean time of 21 min; 16 of 31 patients were recurrence-free after a median follow-up of 23.7 mo, including 4 of 10 who failed BCG. Local side-effects were minimal, including dysuria and haematuria. PDT was proposed as second-line treatment for patients with multiple comorbidities, who are not surgical candidates. With the newer generation of photosensitisers, which at least have improved diagnostic potential, these results might be even better.

5. Conclusions

Patients with NMIBC can be divided into low-, intermediate- or high-risk groups, which are correlated with the risk of having recurrence and progression of NMIBC, and are indicative of the kind of adjuvant treatment to start post-TURBT. Patients with a low-risk tumour are generally well covered with a single immediate instillation of a chemotherapeutic drug, with minor risk of progression. Patients with intermediate- and high-risk tumours benefit form a single immediate instillation, but need additional courses of chemotherapy or immunotherapy. For intermediate-risk NMIBC, it is advised to start with chemotherapy because various agents have fewer side-effects than immunotherapy (i.e., BCG) and the surplus value of BCG is not as outspoken in this risk group. However, in the long term, chemotherapy has only a modest effect on the risk of recurrence, without reduction in the risk of progression. A recurrence rate of about 50% and an increased risk of progression clearly point out the need for novel adjuvant treatment options with higher efficacy and lower toxicity in this risk group.

High-risk NMIBC is the greatest challenge for the urologist because patients have high recurrence rates and a considerable risk of progression to...
muscle-invasive disease, corresponding with a significantly decreased disease-specific survival. BCG with maintenance therapy is the treatment of first choice for this group, with the ability to slightly decrease the risk of progression. When patients fail on BCG, the safest option is to perform cystectomy, but not all patients are willing to undergo this procedure or are unsuitable for surgery. For these patients there is a clear need for novel alternative agents or optimisation of existing therapies. Gemcitabine has shown efficacy in patients who failed on BCG, and apaziquone is emerging. Data on thermochemotherapy are promising, and even EMDA has shown its efficacy in reducing the progression rate when used in combination with BCG.

Conflicts of interest

The authors have nothing to disclose.

References


