Chapter 32
Intravesical Therapy for Bladder Cancer

Benjamin L. Jackson, T.R. Leyshon Griffiths, and J. Kilian Mellon

Introduction

Transurethral resection (TUR) of bladder tumours was first described by Gibson in 1935, but by the 1960's there was a growing realisation that TUR alone for superficial bladder cancer was associated with an unacceptable rate of recurrence of approximately 50 % [1]. Following the introduction of intravesical thiotepa in 1961 by Jones and Swinney [2], a number of different agents have been investigated both as an ablative treatment (chemoresection) and as an adjuvant treatment where the primary intention is to prevent recurrence. Intravesical immunotherapy became an alternative treatment option following the introduction by Morales et al. [3] of intravesical Bacille Calmette-Guerin (BCG) in 1976. Over the last 50 years, there has been an extensive body of research devoted to establishing which tumours should be treated with which type of intravesical therapy (if any), and how that therapy should be administered. Despite this, there remains significant controversy in certain areas of the field, and our knowledge continues to evolve with the publication of new data.

B.L. Jackson, MB, ChB (Hons), FRCS (Urol) • T.R.L. Griffiths, BSc, MD, FRCS (Urol)
J.K. Mellon, MD, FRCS (Urol) (✉)
Department of Urology, University Hospitals Leicester, Leicester, UK
e-mail: jkm7@le.ac.uk; jkm7@leicester.ac.uk

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Intravesical Chemotherapy

Thiotepa (**Triethylenethiophosphoramide**) was the first intravesical agent used for bladder cancer, and remains the only agent specifically approved for that purpose by the United States Food and Drug Administration (US FDA). It is an alkylating agent that acts throughout the cell cycle. To date, 6 of 11 randomised controlled trials of thiotepa have demonstrated a reduction in tumour recurrence in comparison with TUR alone, with a mean absolute risk reduction of 17 % [4]. Its use has been limited however, as its low molecular weight leads to significant absorption, which may result in myelosuppression.

Doxorubicin (**Adriamycin**) is an anthracycline antibiotic that acts by binding DNA base pairs, inhibiting topoisomerase II, and interfering with protein synthesis. Its higher molecular weight compared to thiotepa results in a reduction in systemic absorption. Importantly, this allows it, along with epirubicin and mitomycin C, to be used safely immediately after TUR as a single instillation. A combined analysis of randomised trials using doxorubicin demonstrated a mean reduction in recurrence rate of 16 % in comparison to TUR alone [4].

Epirubicin is a derivative of doxorubicin and demonstrates a mean reduction in recurrence rate of 12 % compared to TUR alone [4]. It can be used either as a course of instillations or as a single post-operative instillation.

Mitomycin C (**MMC**) is an anti-tumour antibiotic derived from the *Streptococcus caespitosus* bacterium. It has been successfully used both as a course of weekly instillations (usually for 6–8 weeks) and as a single post-operative instillation. Complete response rates in stage Ta and T1 TCC average 36 % and a mean reduction in recurrence rate of 12 % has been demonstrated in randomised trials [4].

Which Chemotherapeutic Agent Is Most Effective?

A combined analysis of the early randomised trials evaluating the various chemotherapeutic agents above, suggested fairly modest reductions in recurrence rate with all, and no significant differences between the various agents [4]. However, a subsequent meta-analysis of 8 randomised trials of intravesical chemotherapy, using more stringent inclusion criteria, suggested that in fact the benefit of intravesical chemotherapy might be greater than initially appreciated, with a 38 % reduction in recurrence over the first year of follow-up and up to 70 % reduction in recurrence over 3 years [5]. This study suggested that doxorubicin may be inferior to the other agents. A subsequent meta-analysis by the same author pooled eight randomised trials comparing intravesical chemotherapy to BCG treatment, and suggested that MMC may be more effective than the other chemotherapeutic agents studied [6]. Furthermore, when intravesical chemotherapy is compared to intravesical BCG for the treatment of primary carcinoma in-situ, whilst BCG is clearly superior in this setting, the additional benefit is less notable when compared to MMC than to other

chemotherapy agents [7]. As a result of these data, MMC is emerging as the preferred chemotherapeutic agent.

Optimising Administration

Intravesical chemotherapy is usually administered via a urethral catheter. In the case of immediate post-operative instillation, an irrigating catheter is typically placed at the end of the TUR procedure, and the irrigation channel spigotted. This allows continuous bladder irrigation to be commenced if required after drainage of the chemotherapy agent if bleeding is present. After catheter placement the drug is instilled after appropriate dilution, and the catheter occluded by means of a flip-flow valve. Ideally, the instillation should be performed by the surgeon immediately after completing the operation. However, instillation can be performed up to 6 h later when the patient is in the ward or recovery room. After a dwell time of 1 h the valve is opened to release the agent into a catheter bag, which is disposed off as cytotoxic waste.

For patients undergoing regular instillations of chemotherapy, the instillation may be performed using a temporary Nelaton catheter, which can then be withdrawn and the patient allowed to void the solution into the toilet after 1 h. Men should void sitting down to minimise the risk of splashing.

Mechanistic studies in cultured tumour cells, animal models and human bladder tissue have suggested several approaches to enhance MMC concentration in tumour cells which may translate into improved clinical outcomes. Only one small randomised trial has compared "optimised" MMC with standard MMC administration [8]. In the "optimised" arm, the urine was alkalinised by use of sodium bicarbonate, the dose volume was reduced from the conventional 40 to 20 ml, patients were voluntarily dehydrated by fluid restriction, the volume of residual urine at the time of treatment was minimised and the MMC dose was 40 mg (i.e. standard dose). In the control arm, these optimisation measures were not performed and the dose administered was only 20 mg, a dose now considered by most to be suboptimal. With this caveat, "optimised" MMC was superior to standard MMC with respect to disease-free survival at 5 years (41 % vs 25 %). Drug concentration appears to be more important than dwell time [9]. Some have advocated asking patients to turn prone during dwell time to assist delivery to the anterior bladder wall/dome but there is no evidence to support this.

Single Instillation Chemotherapy

A single instillation of post-operative chemotherapy has been demonstrated to reduce the likelihood of tumour recurrence following TUR. This was first demonstrated in a randomised trial by Oosterlinck et al. comparing a single instillation of

epirubicin to water following TUR of solitary bladder tumours [10]. The benefit was subsequently confirmed for multiple tumours in a further randomised trial using MMC [11]. The effect can be explained by the destruction of detached tumour cells immediately after TUR, or as an ablative (chemoresection) effect of residual tumour cells at the resection site.

Sylvester et al. conducted a meta-analysis of randomised trials of single instillation chemotherapy and concluded that over a median follow-up of 3.4 years there was a reduction in tumour recurrence from 48.4 to 36.7 %. The benefit was greater in those with multiple tumours and in those at higher risk of recurrence as defined by the EORTC risk tables [12] (see Chap. 31). As a result of this the European Association of Urology (EAU) now recommends single instillation chemotherapy following TUR of all new bladder tumours [13]. An exception to this is when there is confirmed or suspected bladder perforation, where there is a risk of local complications due to extravasation of the drug, or when post-operative bleeding necessitates that continuous bladder irrigation be maintained. There is also little point in administering chemotherapy where the tumour is clearly determined to be muscle invasive based on cystoscopic or bimanual examination findings.

The timing of the instillation appears to be important. Kaasinen and co-workers found in a retrospective analysis that the recurrence rate doubled if the instillation was given more than 24 h following TUR [14]. The EAU recommends that the instillation be performed within 6 h [13]. There are a number of potential advantages to administering the drug in theatre immediately, in that the surgeon can take responsibility for administration, there is a controlled environment, the bladder can be fully emptied prior to administration, the patient will be drowsy for most of the dwell time, and there will be close monitoring following administration as the patient will be in the recovery room.

Single instillation chemotherapy has not, despite the above evidence, become uniform practice amongst urologists. Objections include doubt about whether there is benefit in those with intermediate- or high-risk tumours in whom further intravesical treatment may be required anyway. Gudjonsson et al. found no evidence of benefit to early single instillation chemotherapy for intermediate and high risk tumours [15]. However, this conclusion from this study has been criticised, as the trial was underpowered for reliable sub-group analysis [16]. Cai and coworkers also found no benefit to single instillation chemotherapy in patients who subsequently underwent BCG treatment for high risk disease, although again this study was underpowered [17]. A further objection is that in solitary, low-grade tumours the risk of recurrence is small, consequently the number needed to treat to prevent a recurrence is high (8.5) and single instillation chemotherapy may only prevent small recurrences that can be fulgurated in the office setting via flexible cystoscopy [18]. However, 50 % of patients in that study who recurred required an inpatient TUR procedure, and many would argue that the number needed-to-treat is acceptable for a treatment with good tolerability. It should be noted that whilst there is ample evidence of a reduction in recurrence rate with single-instillation chemotherapy it does not reduce the risk of progression to muscle invasive disease.

Recent publication of the results of a Phase III trial has led to the establishment of a new indication for single instillation chemotherapy, following nephroureterectomy for upper tract urothelial cancer. Up to 40 % of patients treated for upper tract tumours will subsequently develop a bladder tumour during follow-up. The ODMIT-C trial in the UK demonstrated that a single instillation of MMC at the time of catheter removal following nephroureterectomy can reduce the likelihood of developing a bladder tumour by 11 % in absolute terms; the number needed-to-treat was 9 [19].

Courses of Intravesical Chemotherapy

It has been estimated from the combined data of several randomised trials that the effect of a single instillation of intravesical chemotherapy lasts for approximately 500 days [20]. For low risk tumours a single instillation alone is considered to be sufficient adjuvant treatment. For intermediate and high-risk tumours however the risk of recurrence despite single instillation chemotherapy remains significant, and further instillations of chemotherapy are a treatment option, although for high-risk tumours intravesical BCG is preferred.

Huncharek et al. in a meta-analysis of eleven randomised trials including 3,703 patients demonstrated a 44 % reduction in the 1-year recurrence rate for patients with solitary tumours treated with adjuvant intravesical chemotherapy in comparison with TUR alone [21]. This study demonstrated significant heterogeneity in treatment effect, with greater benefit in those undergoing longer courses of chemotherapy up to 3 years in duration. A subsequent meta-analysis confirmed the efficacy of adjuvant chemotherapy in prevention of recurrence in patients with multiple tumours [1]. Intravesical chemotherapy has not been shown to reduce the risk of tumour progression [22].

The ideal duration and schedule of intravesical therapy remains uncertain [23]. At present the EAU does not recommend maintenance schedules lasting longer than 1 year [13], although individual studies have shown benefit with regimes lasting as long as 3 years [24]. A 6-week course of weekly instillations is typical in UK practice.

Toxicity

In general, intravesical chemotherapy is well tolerated [25]. Transient lower urinary tract symptoms due to chemical cystitis occur in up to 30 % of patients. Allergic skin rashes may occur in up to 12 %. Systemic complications such as myelosuppression are rare. Extravasation and consequent local tissue reaction have been reported following post-operative instillation, but these represent isolated case reports only [26–28]. The incidence of adverse events following immediate instillation has, in general, been reported to be low.

Intravesical Immunotherapy (BCG)

Mechanism of Action

The precise mechanism of BCG anti-tumour activity is unknown. The mycobacteria are thought to bind to the bladder wall via the interaction between the bacterial antigen 85 complex and fibronectin. The subsequent reaction is certainly immunologically mediated, as athymic mice are unable to mount an anti-tumour response [29], and T-cell deplete mice respond poorly [30]. BCG behaves as a non-specific immune stimulant and activates a variety of immune cells. It is likely that exposure to BCG acts as a danger signal, leading to local dendritic cell activation and enhanced antigen presentation [31]. The activated dendritic cells may then migrate to local lymph nodes where peptides of BCG and TCC origin are presented to T lymphocytes. Activated T lymphocytes then migrate to the urothelium and lyse TCC cells, either directly through the CD8-positive population or indirectly by activating natural killer cells or macrophages.

The precise underlying immune mechanisms behind BCG response are not fully elucidated, but an array of cytokines are demonstrable in the urine of patients treated with BCG, as well as in immunocompetent cell cultures [32]. High expression of Th1 cytokines (Il-2, Il-12 and IFN-γ(gamma)) has been noted in BCG-responsive patients, and hence proper induction of the Th1 pathway may be an important factor in determining efficacy. It has been demonstrated that activation of the Th1 pathway facilitates induction of BCG-induced macrophage cytotoxicity [32]. Upregulation of the Th1 pathway at the expense of the Th2 pathway occurs in patients who are co-administered interferon-α(alpha), which may explain the potential of this agent to induce tumour response in those unresponsive to induction BCG [33] (see later).

Administration and Dosing

Induction BCG

The use of intravesical BCG as a treatment for superficial bladder cancer began in 1976 with the work of Morales et al. [3, 5]. Their initial protocol of six instillations given on a weekly basis over 6 weeks has persisted to the present day, and now represents the standard induction course. Morales initially combined intravesical BCG with percutaneous injection of the same, but intravesical instillation alone has proven to be sufficient [34]. Commonly used strains include Tice, RIVM, and Connaught. The live attenuated vaccine is combined with 50 ml of normal saline and instilled via a temporary urethral catheter. If catheterisation is traumatic or haematuria is encountered then the dose should be withheld. The dose is retained in the bladder for 1 h, following which the patient voids sitting down.

Following an induction course of six instillations, initial response is assessed via a cystoscopy with or without bladder biopsies, usually undertaken a further 6 weeks after the final instillation. If residual or recurrent disease is present then various options may be considered including radical cystectomy, further BCG treatment, or newer intravesical treatments (see BCG Failure). If there is no persistent or recurrent tumour present, then a maintenance schedule of treatment may be instituted, or further cystoscopic follow-up scheduled.

The effectiveness of intravesical BCG was initially demonstrated in a randomised trial by Lamm et al. [24, 35] who demonstrated a reduction in recurrence rate from 42 % in those receiving TURBT alone to 22 % with TUR followed by BCG treatment. The ability of BCG treatment following TUR to reduce recurrence in comparison with TUR alone was confirmed in a meta-analysis by Shelley and co-workers who analysed six randomised trials of BCG treatment for Ta/T1 bladder cancer and demonstrated a 56 % hazard reduction for recurrence in the BCG treated group [36].

Maintenance BCG

The concept of giving further instillations of BCG at intervals after the initial induction course, in order to sustain an immune response within the urothelium, is known as maintenance treatment. Lamm and co-workers [37] in a Southwest Oncology Group (SWOG) trial compared a maintenance BCG regime with induction BCG alone in a randomised trial of patients with carcinoma *in situ* (CIS) or those at high risk of recurrence (defined as two tumour episodes in the last year, or three within 6 months). They demonstrated an improvement in median recurrence-free survival with maintenance BCG (76.8 months *vs.* 35.7 months in the induction-only group). There was also an improvement in worsening–free survival (defined as development of muscle invasive disease, or need for cystectomy, radiotherapy, or systemic chemotherapy). Since that landmark study, there have been a number of meta-analyses that have confirmed the importance of maintenance therapy, particularly in terms of reduction in tumour progression. Sylvester et al. reviewed data from 24 randomised trials, 20 of which included some form of maintenance therapy, and concluded that BCG treatment reduced the overall risk of progression to muscle invasive disease from 13.8 to 9.8 % over a median follow-up of 2.5 years, but only where maintenance therapy of at least 12 months duration was used [38].

Whilst it remains likely that maintenance therapy is required to achieve optimal outcomes with BCG treatment, this conclusion has been thrown into doubt by a recent study by Herr et al. [39] who reviewed the outcomes of 1,021 patients with high-risk non-muscle invasive bladder cancer treated with induction BCG only following initial TUR and re-resection. They demonstrated similar progression and recurrence rates to those seen in other studies where maintenance BCG was used. However, these results need to be interpreted with caution. The study in question was non-randomised and a further caveat is the lack of patients with CIS.

The ideal maintenance schedule is not known. The SWOG regimen used by Lamm involves three instillations given over a 3 week period at 3, 6, 12, 18, 24, 30, and 36 months following induction. Various other regimens have been proposed, but none has proven superiority over the SWOG protocol. A minimum of 12 months treatment appears to be required for superiority over MMC in terms of recurrence and progression [40, 41].

The principal drawback of maintenance therapy is toxicity. Only 16 % of patients enrolled in the aforementioned SWOG study [37] completed the full maintenance course due to the side-effects of treatment. However, the majority of patients in the SWOG trial were able to tolerate at least one instillation every 6 months. Furthermore, Van der Meijden found in a large cohort of patients receiving the SWOG regime, that whilst cessation of treatment increased from induction to 6 months it remained stable or decreased thereafter. They concluded that local and systemic side-effects tended to remain stable or even decrease after the first 6 months on maintenance BCG [42].

Reduced Dose BCG

The toxicity of BCG maintenance regimes have led to attempts to reduce the administered dose in order to minimise side effects. The Club Urológico Español de Tratamiento Oncológico (CUETO) group from Spain compared one-third dose to standard dose BCG and found no difference in recurrence or progression rates overall, however there were higher recurrence and progression rates in multifocal tumours [43]. The same group compared one-sixth dose to one-third dose BCG in intermediate risk tumours and found a significant reduction in efficacy with the lower dose, indicating that one-third dose may be the maximum feasible dose reduction [44]. The European Organisation for Research and Treatment of Cancer (EORTC) 30962 study is soon to be reported comparing one-third to full dose BCG in 1 and 3 year maintenance regimes, and may give further information as to the ideal treatment dose and duration. The study protocol does not include multifocal high-grade T1 tumours or those with CIS however, so its conclusions will not be applicable to most patients with high-risk disease.

Sequential or Alternating Intravesical Chemotherapy and BCG

Several investigators have tested the hypothesis that alternating or sequential chemotherapy and immunotherapy is more effective and less toxic than chemotherapy or BCG alone. A phase III trial compared the efficacy of sequential MMC and BCG (MMC weekly for 4 weeks followed by BCG weekly for 10 weeks) with MMC monotherapy (weekly instillation for 10 weeks) in patients with intermediate and

high-risk superficial bladder cancer including CIS [45]. The sequential schedule was comparable with MMC alone in terms of recurrence, progression and toxicity. Another randomised trial compared alternating MMC and BCG instillations (MMC weekly for 6 weeks followed by alternating monthly instillations of BCG and MMC for 1 year) with BCG monotherapy (weekly for 6 weeks followed by monthly for 1 year) in the treatment of CIS [46]. Alternating therapy was shown to be less effective for reducing recurrence but better tolerated than BCG monotherapy. Sequential BCG and epirubicin (alternating weekly BCG and epirubicin for 6 weeks followed by alternating monthly instillations for 1 year) has been compared with BCG monotherapy following the same schedule, and shown to be similar with regard to efficacy and superior in terms of toxicity [47].

Choice of Intravesical Therapy According to Risk Stratification

The EORTC risk tables [12] may be used to quantify the risk of recurrence and progression in patients with superficial bladder cancer, and thus may be used to stratify them into low-, intermediate-, and high-risk groups (see Chap. 31). This is useful as a basis for determining which adjuvant intravesical treatment is required. It should be noted however that various approaches have been taken in different trials in order to stratify risk of recurrence and progression, and hence the definitions of low, intermediate and high-risk are somewhat heterogeneous amongst the available evidence.

Low-Risk Disease

Patients with solitary, low-grade, non-invasive tumours have a low risk of recurrence (24–37 % at 5 years) and a very low risk of progression (0–1.7 % at 5 years) [12]. Consequently, the EAU recommend that a single post-operative instillation of chemotherapy is adequate treatment [13], and no further intravesical therapy should be considered unless there is recurrence.

Intermediate-Risk Disease

Intermediate-risk bladder cancer represents a broad spectrum, and within this risk group there will be a variable risk of recurrence and progression depending on tumour characteristics. It is difficult, therefore, to recommend a single intravesical treatment option. The EAU recommend that either a course of intravesical

chemotherapy (the duration and intensity of which is not specified) be given or intravesical BCG depending on whether prevention of simply recurrence, or recurrence and progression is required.

A recent meta-analysis by Malmstrom et al. [48] has helped to clarify the relative efficacy of intravesical BCG and intravesical chemotherapy with regard to prevention of recurrence in intermediate-risk patients. Some [41, 49], but not all [25], of the previous meta-analyses had demonstrated a lower recurrence rate for BCG-treated intermediate-risk patients in comparison to those treated with intravesical chemotherapy. However, it had been suggested that this might partly be due to pre-treatment with chemotherapy biasing the results of these studies in favour of BCG [50]. Malmstrom et al. conducted a meta-analysis using the individual data from 2,820 patients in nine randomised controlled trials comparing MMC with BCG. Three quarters of the patients had intermediate-risk disease. They demonstrated a 32 % lower recurrence rate in the group receiving maintenance BCG. The additional benefit was seen regardless of whether previous chemotherapy had been given.

It seems likely, therefore, that maintenance BCG offers greater prophylaxis against recurrence than intravesical chemotherapy in intermediate-risk patients. However, as discussed previously, this comes at the cost of more side-effects [25]. For patients at the low end of the intermediate risk spectrum, therefore, it seems difficult to justify. Furthermore, it must be remembered that the EORTC risk tables may overestimate the risk of recurrence in some patients [51], as the data they are compiled from is from an era when single-instillation chemotherapy was not in routine use.

In practice, the management of this group of patients varies according to individual tumour characteristics, patient choice, and local protocol, with some receiving singe-instillation chemotherapy only, others a course of chemotherapy, others a BCG schedule, and still others a single post-operative instillation of chemotherapy following TUR or biopsy of a recurrence. Whether an induction course of chemotherapy should be followed by maintenance therapy is uncertain, but as mentioned previously, it is thought that maintenance should not be given for longer than 1 year [23]. The role of single-dose postoperative intravesical chemotherapy following TUR/biopsy for recurrence has not been specifically evaluated in a randomised trial.

High-Risk Disease

Patients with high-risk disease have an increased risk of both recurrence and progression and consequently BCG treatment is recommended by the EAU in all such patients, other than where early radical cystectomy is undertaken [13]. The EAU guidelines recommend the use of a maintenance schedule, although as mentioned previously this has recently been challenged in a non-randomised study [39].

A number of studies have demonstrated the superiority of BCG over MMC and other forms of intravesical chemotherapy in terms of recurrence in patients with high-risk disease. Bohle et al. in a meta-analysis including 11 trials and 2,749 patients with superficial bladder cancer demonstrated a significant reduction in recurrence rate with BCG treatment compared with MMC (38.6 % vs 46.4 %) [41]. In this study, benefit was seen in both high and intermediate risk patients, but mainly limited to those undergoing BCG maintenance therapy as opposed to induction alone. Shelley and co-workers performed a further meta-analysis comparing BCG with MMC, which demonstrated a reduction in recurrence of 31 % but only in high-risk patients. Again, the benefit was limited to those undergoing maintenance therapy [25]. Since the publication of these meta-analyses, there have been several further randomised trials including high-risk patients demonstrating the superiority of BCG in terms of recurrence compared with MMC [52], epirubicin and interferon in combination [53], and epirubicin alone [54].

The question of whether BCG treatment is capable of reducing the risk of progression of high-risk superficial bladder cancer to muscle invasive disease is more controversial. The majority of individual studies comparing BCG with chemotherapy are insufficiently powered to detect a difference in progression, as few patients progress within the follow-up period. The EORTC 30911 trial comparing BCG, BCG and isoniazid, and epirubicin, whilst not demonstrating a difference in progression to muscle invasion, did demonstrate a reduction in metastases and improvements in disease-specific and overall survival in the BCG groups (isoniazid offered no additional value) [54]. However, this may be a reflection of the lack of efficacy of epirubicin. To date, two meta-analyses have demonstrated a reduction in tumour progression in high-risk patients. The analysis by Sylvester et al. for the EORTC mentioned earlier demonstrated a reduction in tumour progression in comparison with patients receiving varying types of intravesical chemotherapy, but only with maintenance BCG [38]. Bohle and colleagues confirmed similar findings in an analysis of BCG compared with MMC specifically, with maintenance treatment again being required for benefit [40].

The ability of BCG treatment to reduce tumour progression is, however, not beyond question. The EORTC meta-analysis [38] has some weaknesses in that the control group received varying types of chemotherapy, some of which may be less effective than MMC [6], and that a heterogeneous definition of progression was used in the component trials. The meta-analysis by Bohle and colleagues [40] has also been criticised for including non-randomised studies. Furthermore, the recent individual patient data meta-analysis by Malmstrom et al. demonstrated no difference in progression between patients receiving BCG and MMC over 4.4 years follow-up [48].

Regardless of the debate about tumour progression, BCG treatment has demonstrated clear superiority over chemotherapy in terms of recurrence prevention in the setting of high-risk disease, and the balance of evidence suggests that maintenance BCG is the optimum treatment in high-risk patients, excepting those that opt for early radical cystectomy (Chap. 31).

CIS

CIS may either be primary (present in isolation), or seen in association with papillary (stage Ta or T1) or muscle invasive tumours. When present with papillary disease it confers an increased risk of progression and these tumours are in the high-risk group by definition. CIS is unlikely to be eradicated by endoscopic treatment alone so either adjuvant intravesical treatment or cystectomy is required.

Sylvester et al. [7] looked specifically at a subgroup of 700 patients from the aforementioned EORTC meta-analysis of BCG *vs.* intravesical chemotherapy that had CIS, either in isolation or in association with papillary disease. They demonstrated a higher complete response rate with BCG treatment in comparison with chemotherapy (68.1 % *vs.* 51.5 %) and a greater disease-free rate at a median follow-up of 3.6 years (46.7 % *vs.* 26.2 %). MMC performed better than other forms of chemotherapy, with a disease-free rate of 32.9 %. Superiority of BCG over MMC was only confirmed when maintenance BCG was used. As a consequence of these data, there is a consensus that maintenance BCG is the optimum treatment for patients with CIS, with or without papillary disease where radical cystectomy is not performed.

BCG Toxicity and Management of Adverse Events

Whilst BCG treatment possesses advantages in terms of efficacy over intravesical chemotherapy, this comes at the cost of increased side effects. A meta-analysis comparing BCG treatment (both maintenance and non-maintenance) to MMC demonstrated a greater incidence of local and systemic side-effects with BCG (44 % *vs.* 30 % and 19 % *vs.* 12 % respectively) [25].

Preventive measures to minimise adverse events include allowing at least 2 weeks after TUR before initiating treatment and deferring an instillation if haematuria is present or catheterisation is traumatic. A randomised trial has shown a reduction in BCG adverse events with prophylactic ofloxacin administration with each dose, although whether this affects the efficacy of BCG in an adequately powered study is unknown [55]. Isoniazid did not reduce BCG toxicity in a randomised study [54].

Common local side effects of BCG treatment include irritative urinary symptoms and haematuria due to cystitis. If these occur then urinary tract infection should be sought and treated if present. Further treatment options include anticholinergic medication or non-steroidal anti-inflammatory drugs. If symptoms persist then dose reduction or cessation of treatment may be required.

Granulomatous prostatitis is common histologically in patients undergoing BCG treatment but gives rise to symptoms in less than 5 % of cases [56]. Initial treatment is usually with a 6-week course of a fluoroquinolone antibiotic, often combined with prednisolone. If this fails, anti-tuberculous chemotherapy may be required.

Less common local complications include bladder contracture, which may give rise to intractable urinary frequency. Cystoscopic hydrodistention may be tried, but if this fails then a cystectomy may ultimately be required if symptoms are severe. Ureteric obstruction occurs occasionally and may require nephrostomy insertion or stenting, although it usually resolves spontaneously.

Allergic reactions including skin rashes and arthropathy may occur with BCG treatment. BCG-associated reactive arthritis is seen in patients with the HLA – B27 genotype. Allergic reactions are treated with cessation of treatment and corticosteroids. This is of particular importance in those with arthropathy as permanent joint damage may occur.

Sepsis during BCG treatment is most commonly due to uropathogens, and therefore the initial management of the febrile patient undergoing BCG treatment is urine culture and treatment with intravenous antibiotics. If a fever of greater than 38.5 °C persists for more than 48 h, then systemic BCG infection ("BCGosis") must be suspected and triple therapy with isoniazid, rifampicin and ethambutol for 6 months is required. Pyrazinamide, whilst commonly used to treat tuberculosis, is ineffective against *Mycobacterium bovis* and is therefore not used. Cessation of BCG treatment is mandatory.

Failure of Intravesical BCG

BCG failure can be subdivided into BCG refractory, resistant, and relapsing cases. BCG refractory disease refers to cases in which there is inadequate initial response to an induction course of BCG. If muscle invasive disease is present at the initial check cystoscopy at 3 months, then BCG-refractory disease is confirmed and radical treatment is required. If high-risk superficial disease is present at the initial check cystoscopy (either high-grade Ta/T1 tumour or CIS), then a second course of six instillations of BCG may be given, with complete response achieved in up to 50 % [57]. In the SWOG 8507 study, one-third of patients with persistent CIS after six instillations of BCG achieved a complete response after a further three BCG instillations [37]. However, failure to achieve an initial complete response to BCG, particularly if T1 TCC persists, is associated with an increased risk of subsequent progression, and hence consideration should be given to opting for radical cystectomy at this stage [58]. If high-risk superficial disease remains at the second check cystoscopy at 6 months then BCG-refractory disease is confirmed and radical cystectomy is suggested as the preferred treatment modality. Patients with persistent high-risk superficial disease who are not fit for radical cystectomy, or who decline the procedure, may be eligible for the alternative intravesical therapies described in the following section.

BCG-resistant disease refers to a situation where there is persistent superficial tumour at the 3 and 6 months check cystoscopies, but where the disease is low- or intermediate-risk by the time of the second check cystoscopy. The management of this group of patients is more controversial. Radical cystectomy may represent

overtreatment for low-grade superficial recurrent disease. These patients may be managed with endoscopic resection of recurrences alone, a trial of intravesical chemotherapy (if not given previously), or one of the alternative treatment modalities in the following section.

BCG-relapsing disease refers to patients who achieve an initial complete response (disease-free state), but who subsequently develop further disease. If the recurrent disease is muscle invasive then neoadjuvant systemic chemotherapy and radical cystectomy or radical radiotherapy is required. In those with recurrent superficial disease, especially if low- or intermediate-risk, management is more controversial. There is evidence that a longer disease-free interval prior to recurrence portends a better prognosis [59], and it has been suggested that more conservative strategies might be adopted in these patients.

In summary, radical cystectomy remains the mainstay of treatment for failure of intravesical BCG, however there are a number of further intravesical options for patients in whom this is not feasible or is declined. These are summarised in the following section.

Intravesical Therapy After BCG Failure

Post-BCG Immunotherapy

BCG Combined with Interferon

One-third dose intravesical BCG combined with interferon-α(alpha) at a dose of 50–100 million units has been utilised in patients with BCG-refractory disease. The principle is that the immunomodulatory activity of interferon-α(alpha) in terms of stimulation of natural killer cells and enhancing antibody responsiveness will enhance the activity of BCG. A randomised phase II trial enrolled 1,007 patients, some of whom were BCG-naïve and received interferon-α(alpha) in combination with full dose BCG, whilst the group who had failed BCG therapy received one-third dose BCG in combination with interferon [60]. The disease-free rate in the BCG-refractory group at 24-month follow-up was 45 %, with an improved response rate in those who failed BCG treatment more than 12 months after their induction course [59].

Keyhole-Limpet Hemocyanin (KLH)

KLH was first used clinically for intravesical treatment of bladder cancer by Olsson et al. in 1974 [61]. It is a non-specific immune response modifier, isolated from the sea mollusc *Megathura crenulata*. In BCG-refractory patients, the overall complete response rate is only 26 %, however those with BCG-refractory CIS without papillary disease fared better with a complete-response rate of 50 % [62].

Other Novel Immunotherapeutic Agents

The immunotoxin VB4-845 has demonstrated safety in a Phase I study, and the potential for efficacy with a complete-response rate of 39 % in 64 patients evaluated [63]. Urocidin[tm] (Bioniche Life Sciences) is a mycobacterial cell wall–DNA complex currently undergoing phase III trials in BCG refractory patients.

Post-BCG Chemotherapy

Mitomycin-C (MMC)

There are few reliable data analysing the use of MMC in BCG-refractory patients. In one study comparing BCG and MMC, patients were allowed to cross-over after treatment failure. Of 21 patients who underwent MMC treatment after BCG, only 4 remained disease free after 64 months of follow-up [64].

Gemcitabine (Intravesical)

Gemcitabine, a nucleoside analogue that inhibits DNA replication, is used as part of standard chemotherapy regimes for invasive urothelial cancer in the neo-adjuvant and palliative settings, and hence it was hypothesised that it may be effective as intravesical treatment. Phase II studies have shown its potential to achieve recurrence-free survival in BCG refractory patients, with one group reporting a 1-year recurrence-free survival rate of 21 % [65]. Another group reported a lower recurrence rate after 1-year in those with BCG-refractory intermediate-risk disease (25 %) in comparison with BCG-refractory high-risk disease (56 %) [66]. A further phase II study randomised 80 patients with persistent high-risk superficial bladder cancer after induction BCG to receive either intravesical gemcitabine twice-weekly for 6 weeks followed by a maintenance schedule, or further BCG treatment. The group treated with gemcitabine demonstrated an improvement in 2-year recurrence-free survival (19 % *vs.* 3 %) [67].

The apparently promising results of these small studies are tempered somewhat by data demonstrating that gemcitabine is significantly less efficacious than BCG in the primary treatment of high-risk superficial disease [68], and that it is no better than placebo when given as single-instillation treatment following TUR [69]. Its current role in BCG-refractory cases is therefore unclear.

Docetaxel

Docetaxel, a member of the taxane group of chemotherapy agents, is a microtubule inhibitor. Laudano and coworkers reported their experience of 33 BCG-refractory patients treated with intravesical docetaxel with a median follow-up of 29 months

[70]. 61 % of patients achieved a complete response, with 32 % remaining disease free at 2 years. These are promising early results, but further large scale studies are needed.

Device-Assisted Therapies

Chemohyperthermia (c-HT) describes the combination of intravesical chemotherapy and hyperthermia (HT). Although the term thermochemotherapy has been used, there is a need to distinguish treatments, which not only heat the chemotherapy but also the bladder wall to supraphysiological temperatures of between 44 and 45 °C. The most common form of c-HT uses the Synergo HT system in which local HT is administered via direct microwave irradiation of the urothelium by means of a 915 MHz intravescial microwave applicator. Over the last 15 years, c-HT has been tested in a variety of clinical settings including several phase II randomised trials in the BCG-naïve setting [71]. Hyperthermia increases cell membrane permeability, alters intracellular drug trafficking, and enhances the effects of cytostatic chemotherapy on inhibition of DNA synthesis and DNA damage [72].

Data supporting the role of c-HT in BCG-refractory disease has come from several proof-of-concept studies. The Synergo working party evaluated 51 patients with CIS, 34 of whom had failed BCG treatment. They demonstrated a complete-response rate of 92 %, with 50 % remaining disease-free at 2-year follow-up [73]. In the largest series to date, Nativ and coworkers used maintenance HT-MMC in 111 patients with superficial bladder cancer in whom BCG therapy had failed, including 77 % with high-risk disease. They reported recurrence-free rates of 85 and 56 % at 1 and 2 years; 3 % of the patients progressed to muscle invasion and 5 % withdrew from treatment due to adverse events [74].

The use of c-HT is being further evaluated in BCG-refractory patients who are not candidates for cystectomy in the UK-based HYMN trial. This study includes patients with persistent grade 2/grade 3 papillary disease or CIS after induction BCG who are randomised to c-HT or a second course induction course of BCG. Patients who have relapsed on maintenance BCG may also be enrolled, and are randomised to c-HT or their institution's standard treatment.

Electromotive Drug Administration of MMC (**EMDA-MMC**) is an alternative way of enhancing MMC absorption, by using an electrical gradient generated across the bladder wall by means of electrodes placed within the catheter and on the patient's lower abdominal wall. EMDA-MMC has been demonstrated to be superior to standard MMC in the treatment of high-risk superficial bladder cancer, but did not demonstrate superiority to BCG [75]. The same group then evaluated a regimen alternating BCG doses with EMDA-MMC in a sequential fashion. This study randomised 212 BCG-naïve patients with high-risk disease to receive either the sequential regime or BCG alone. After a median follow-up of 88 months, there were significant reductions in recurrence (42 % *vs.* 58 %), progression (9.3 % *vs.* 22 %), disease-specific mortality (5.6 % *vs.* 16.2 %), and overall mortality (21.5 % *vs.*

32.4 %). These results are promising, but it is worth noting that the mortality in the BCG-treated group in this trial is unusually high (50 %).

A recent study again from Di Stasi et al. has evaluated the use of a single treatment with EMDA-MMC immediately prior to TUR (n = 124) in comparison to patients undergoing TUR alone (n = 124) or TUR followed by standard post-operative MMC (n = 126) [76]. They demonstrated a greater median disease free interval with pre-operative EMDA-MMC (52 months) compared with TUR and standard MMC (16 months) or TUR alone (12 months). It should be noted however that patients who were found to have CIS were excluded from the analysis.

To date, no studies have specifically evaluated EMDA-MMC in patients who are BCG-refractory, although the study by Di Stasi et al. allowed crossover of patients to EMDA-MMC if they did not respond to primary BCG treatment [75]. The efficacy of EMDA-MMC in the BCG-refractory setting is therefore experimental at present.

Photodynamic Therapy (**PDT**) relies on the selective uptake of photo-sensitising compounds by tumour cells, which allows their subsequent destruction via excitation with a specific light wavelength. 5-aminolevulinic acid (5-ALA) has been used as the photo-sensitiser, and can be administered intravesically. Berger and colleagues evaluated this technique in a cohort of 31 patients 10 of whom were BCG-refractory [77]. At a mean follow-up of 23.7 months, 16 patients were free of recurrence, and the remaining 15 had recurred after a mean of 8.3 months. Four of ten BCG-refractory patients were free of recurrence at the end of the study.

Summary

Newer intravesical chemotherapy agents such as gemcitabine and docetaxel, novel immunotherapies, and device-assisted treatments have all shown promise in the treatment of patients who have failed BCG treatment and are not candidates for radical cystectomy. To date, however, much of their potential benefit is based on non-randomised proof-of-concept studies or small phase II trials, and no single treatment can be recommended as the preferred choice based on the current evidence. At best, currently available bladder-sparing treatments for those with BCG-refractory TCC are associated with 2-year disease-free survival rates of approximately 50 %. Treatments with the most promising developmental data such as c-HT are now being evaluated in phase III trials.

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