BCG treatment of bladder cancer

Benjamin Ayres discusses the use of BCG in the management of non-muscle-invasive bladder cancer, emphasising the importance of controlling the inevitable side-effects of this toxic treatment.

Bacillus Calmette-Guérin (BCG) was first used in the treatment of non-muscle-invasive bladder cancer (NMIBC; Figure 1) in the 1970s by Morales. It was initially investigated as a cancer treatment because lower rates of cancer were found in people with tuberculosis at post mortem. Multiple studies since the 1970s have shown its efficacy in the management of intermediate- and high-risk NMIBC and level 1a evidence from meta-analyses shows that it reduces recurrence and possibly progression of disease in such patients.

As a result, it is currently recommended as an adjuvant intravesical treatment in patients with intermediate- and high-risk NMIBC in guidelines by the European Association of Urology (EAU), the American Urological Association and the British Association of Urological Surgeons. However, there is debate around the optimal dose and schedule, whether maintenance therapy is necessary and when other treatments, such as early radical cystectomy in high-risk NMIBC, should be used in its place. In addition, it is a fairly toxic treatment and understanding and managing side-effects is important for tolerability.

MECHANISM OF ACTION

BCG is an attenuated strain of Mycobacterium bovis. It was initially administered intravesically and intradermally, although the latter route was later deemed unnecessary. Several strains are used, such as Connaught and Tice strains; all are derived from the original strain developed at the Pasteur Institute.

Although the exact mechanism of action remains unknown, the anti-tumour effect of BCG is mediated through a local inflammatory response within the bladder and may involve adherence to the damaged urothelium through fibronectin (Figure 2).

Because of the necessary inflammatory reaction, it is expected that patients will experience side-effects such as bladder irritation, urgency, frequency, dysuria and haematuria and they need to understand this to improve tolerability. For severe side-effects, prophylactic antibiotics and reduced doses of BCG have been tried.

As BCG is an attenuated live bacterial strain, it is contraindicated in immunocompromised patients. In addition, systemic BCG infection...
is serious and potentially life-threatening, so BCG must not be given within two weeks of transurethral resection of bladder tumour (TURBT), or if there is ongoing haematuria, traumatic catheterisation or urinary tract infection.

INDICATIONS FOR BCG AND WHO SHOULD HAVE IMMEDIATE RADICAL CYSTECTOMY

Several meta-analyses have shown that adjuvant intravesical BCG is superior to TURBT alone or TURBT and adjuvant intravesical chemotherapy in reducing tumour recurrence, particularly in intermediate- and high-risk bladder cancer.3,4

Böhle et al.5 reviewed 11 trials involving 2749 patients with a median follow-up of 26 months. They found that 38.6 per cent of patients treated with intravesical BCG had tumour recurrence, compared with 46.4 per cent treated with mitomycin C (MMC; odds ratio [OR] 0.56, 95 per cent confidence interval [CI] 0.38–0.84). In particular, they found that only maintenance BCG showed a benefit over MMC (OR 0.42, 95 per cent CI 0.30–0.58). This benefit was for both intermediate- and high-risk groups, although individual patient data were not analysed.

A meta-analysis by the Cochrane group of six randomised trials of 1527 patients found considerable heterogeneity and no difference between BCG and MMC.1 However, a subset analysis of three trials that studied high-risk NMIBC only reported no heterogeneity and found BCG was more effective than MMC in reducing tumour recurrence by 31 per cent (p<0.001).

A meta-analysis of nine trials with 2820 patients published in 2009, using individual patient data, also showed a significant reduction, by 32 per cent, in the risk of recurrence with maintenance BCG compared to MMC.4 The time to first recurrence also increased. Median follow-up was 4.4 years, with a maximum of 17.7 years and almost three-quarters of the tumours were intermediate risk.

Intravesical BCG is also recommended for the treatment of bladder carcinoma in situ (CIS; Figure 3). However, few trials have assessed patients with CIS alone. A meta-analysis comparing BCG with chemotherapy for CIS demonstrated the superiority of maintenance BCG, with 46.7 per cent of patients disease-free after a median of 3.6 years, compared to 26.2 per cent in those who received chemotherapy.1 The risk of progression was reduced by 26 per cent with BCG, but this was not statistically significant.

An important consideration with all these trials is that they did not include many current practices, such as immediate postoperative MMC and restaging TURBT (which may have resulted in patients with muscle-invasive disease being recruited to trials as high-risk NMIBC). As a result, current recurrence and possibly progression rates are probably lower than those found in these studies, which may reduce the differences observed between efficacy of BCG and chemotherapy.

In spite of this, BCG remains the main treatment along with radical cystectomy for high-risk NMIBC and/or CIS because disease progression and death are real possibilities. BCG is often used in preference to immediate radical cystectomy because of the surgery’s morbidity and the risk of overtreatment. However, patients who require a cystectomy for disease progression following failure of BCG treatment have poorer cancer-specific and overall survival than those who have an immediate cystectomy. Patients who should be considered for an early radical cystectomy are those with T1G3 urothelial bladder cancer who also have two additional risk factors for disease progression/aggressiveness, which include either residual pT1 disease on re-resection, concurrent CIS, multifocality, tumours >3cm or tumours sited anteriorly/at the dome.6 Micropapillary NMIBC is also associated with a significantly poorer outcome and should therefore result in an early radical cystectomy.

In intermediate-risk NMIBC, reducing recurrence rather than disease progression is the main aim of treatment and both BCG and chemotherapy will achieve this. Although BCG is superior to chemotherapy in reducing recurrence, it causes more toxicity and the treatment decision should therefore be made on a patient-by-patient basis.

IS MAINTENANCE BCG NECESSARY?

The meta-analyses above all demonstrate superiority of maintenance BCG over MMC. In particular, individual patient data show that induction BCG alone is inferior to MMC and results in a 28 per cent higher risk of recurrence.4 However, individual studies comparing induction with maintenance BCG, rather than induction or maintenance BCG with MMC (as is the case with the meta-analyses above), have not always demonstrated a
benefit. As a result, some clinicians do not believe in maintenance BCG, although this is against current opinion and guidelines.

The reason that some studies have not shown a benefit of maintenance over induction may be because they were small and included all types of NMIBC, rather than just intermediate- and high-risk NMIBC. The largest study that compared induction with maintenance BCG is the seminal study by Lamm and the Southwest Oncology Group (SWOG). This did show a benefit of maintenance BCG. It randomised 384 patients and reported median recurrence-free survival of 76.8 months with maintenance BCG compared to 35.7 months with a six-week induction course of BCG (p<0.0001). It also found that maintenance BCG reduced the risk of disease progression to muscle invasion or change in treatment strategy (p=0.04).

**DOES BCG REDUCE PROGRESSION TO MUSCLE INVASION?**
The effect of intravesical BCG on the progression of NMIBC to muscle-invasive bladder cancer is difficult to assess, because although the risk is high (up to 45 per cent at five years using the European Organization for Research and Treatment of Cancer [EORTC] risk tables), many studies do not have sufficiently long follow-up or do not recruit enough high-risk patients – most trials group all NMIBC together.

An EORTC meta-analysis of 24 trials involving 4863 patients did report a benefit and found that after a median follow-up of 2.5 years (maximum 15 years), 9.8 per cent of patients on BCG progressed compared with 13.8 per cent in the control groups. On a subset analysis, again this benefit was found only with maintenance treatment. Being critical, though, this represents an absolute reduction of only 4 per cent, the control group was very heterogenous and there was a mixture of NMIBC risk groups. The definition of progression was treatment progression to radiotherapy or cystectomy, rather than progression to muscle invasion. However, a recent meta-analysis using individual patient data and longer median follow-up reported no significant difference in progression rates between BCG and MMC treatment groups. Seven trials with 1880 patients and a median follow-up of 4.8 years found that 10.9 per cent of BCG-treated patients and 13.3 per cent of MMC-treated patients progressed to muscle-invasive disease. About three-quarters of the patients in this meta-analysis had intermediate-risk tumours and therefore outcomes may be different in high-risk patients who have the highest risk of progression.

**TOXICITY, OPTIMAL DOSE AND SCHEDULE**
As intravesical BCG works by causing bladder inflammation, most patients experience bladder irritability, frequency, urgency, dysuria and haematuria. Systemic side-effects include fever and malaise. These are more concerning as they may reflect systemic BCG infection, which is serious and potentially life-threatening. In such situations, urgent treatment with antibiotic medication is required. This is rare and believed to occur in less than 1 per cent of cases. A recent EORTC study (30962), which was presented at the Annual EAU Congress in February 2012, reported that 8 per cent of patients stopped BCG treatment because of side-effects, with 6 per cent experiencing systemic toxicity. A further 50 per cent experienced side-effects but did not stop treatment.

The EAU guidelines state that the optimal frequency and duration of maintenance instillations remain unknown. They recommend at least one year of maintenance treatment. Many urologists follow the SWOG regimen.

To improve tolerability, reduced doses of intravesical BCG have been trialled. The Spanish Oncology Group (CUETO) compared a one-third dose of BCG (27mg Connaught strain) with the full dose (81mg) in 500 patients. They gave a six-weekly induction course followed by a further six doses (different from the SWOG regimen). In general, they found no difference in recurrence or progression rates, but the full dose was more effective in patients with multifocal tumours. Patients in the reduced dose group had fewer side-effects with fewer treatment delays and withdrawals, although systemic toxicity was similar in both groups.

In contrast, the EORTC 30962 study reported that one-third-dose BCG given for one year was inferior in terms of disease recurrence or progression (including metastasis and death) compared to full-dose BCG given for three years and that there was no significant difference in toxicity. This study followed the SWOG regimen, stopping at one year for those patients randomised to receive only one year of treatment. Patients were randomised to one of four treatment arms – full-dose BCG for three years, full-dose BCG for one year, one-third-dose BCG for three years and one-third-dose BCG for one year. However, only 36 per cent of patients randomised to receive three years of treatment actually received it. Patients with CIS were excluded. In total, results from 1355 patients were analysed. Disease-free rates at five years were 64.2 per cent (full dose for three years), 62.5 per cent (one-third dose for three years), 58.8 per cent (full dose for one year) and 54.5 per cent (one-third dose for one year). There was no difference in progression, survival or cessation of treatment because of side-effects among the four groups. Therefore, reducing dose and duration of maintenance treatment may not necessarily reduce treatment toxicity, but may affect outcome to some extent, although in reality only a minority of patients achieve three years of treatment.

Ofloxacin antibiotic prophylaxis has also been investigated to try to reduce the side-effects of BCG. In a randomised, double-blind study of 115 patients with NMIBC, ofloxacin 200mg or placebo was given at six and 18 hours
Intravesical bacillus Calmette-Guérin (BCG) is indicated in high-risk non-muscle-invasive bladder cancer (NMIBC) including bladder carcinoma in situ because of the high risk of disease recurrence and progression. Intravesical BCG should be considered as an option in the management of intermediate-risk NMIBC. Patients should receive maintenance BCG. BCG reduces the risk of disease recurrence in NMIBC. BCG may reduce the risk of progression in NMIBC. Systemic toxicity needs to be taken seriously and anti-tuberculous drugs may be required as it can be serious and potentially life-threatening. The optimal treatment regimen remains unknown, although dose reduction does not necessarily reduce side-effects and may impact on efficacy.

KEY POINTS

- Intravesical bacillus Calmette-Guérin (BCG) is indicated in high-risk non-muscle-invasive bladder cancer (NMIBC) including bladder carcinoma in situ because of the high risk of disease recurrence and progression.
- Intravesical BCG should be considered as an option in the management of intermediate-risk NMIBC.
- Patients should receive maintenance BCG.
- BCG reduces the risk of disease recurrence in NMIBC.
- BCG may reduce the risk of progression in NMIBC.
- Systemic toxicity needs to be taken seriously and anti-tuberculous drugs may be required as it can be serious and potentially life-threatening.
- The optimal treatment regimen remains unknown, although dose reduction does not necessarily reduce side-effects and may impact on efficacy.

Although reducing the dose and duration of maintenance BCG or giving prophylactic antibiotics to reduce BCG side-effects sounds appealing, the evidence is limited and contradictory. Therefore, it is not recommended on a general basis unless part of a clinical trial.

SUMMARY

Intravesical BCG reduces the risk of disease recurrence and possibly progression in intermediate- and high-risk NMIBC, including CIS. It remains the main treatment option for the majority of patients with high-risk NMIBC and/or CIS, although some may be better served by an early radical cystectomy. In intermediate-risk NMIBC it is an option, and although superior to intravesical chemotherapy in reducing disease recurrence, it causes more side-effects. Maintenance BCG is more effective than an induction course alone and although studies have looked at reducing doses or duration of treatment, full-dose treatment for three years appears optimal at present; although in reality few patients achieve this.

Declaration of interests

Benjamin Ayres has received an honorarium from Alliance Pharmaceuticals for a presentation at a nurse educational study day.

REFERENCES