BCG immunotherapy for superficial bladder cancer

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Bladder cancer is the fourth most common tumour in men and the eighth most common in women. The initial treatment is usually a transurethral resection, which allows histological grading of the tumour (degree of anaplasia) and staging according to the depth of invasion through the bladder wall; superficial bladder cancer involves the bladder wall no deeper than the subepithelial tissue—i.e. it does not reach the detrusor muscle layer. This initial resection is usually successful, but unfortunately these tumours have a great propensity to recur. Around 70% will recur[1] and this means these patients require regular cystoscopies, with resections where necessary. If the tumours continue to be superficial then they are not life-threatening, but they are a considerable nuisance to both the patient and the health service. In addition, tumour progression or the potential to progress needs to be recognized early. The risk factors for progression include high grade, stage T1, multifocality at presentation, the presence of *carcinoma-in-situ*, and size of initial tumour[1,2].

Intravesical BCG (bacille Calmette–Guérin) immunotherapy is used in superficial transitional cell bladder cancer for three reasons—to treat *carcinoma-in-situ* (or occasionally residual papillary tumours); to reduce the number and frequency of recurrent tumours; and to prevent disease progression. This use of BCG is not well known outside urology—which is regrettable, first, because this treatment is quite successful and, second, because the side-effects can present to other areas of medicine.

HISTORY

The notion that tuberculosis might have an anti-tumour effect emerged early in the twentieth century; and in a necropsy series published in 1929 Pearl[3] reported that patients with tuberculosis had a lower than expected prevalence of cancer. The use of BCG for cancer therapy was proposed in the 1930s, but little was done until the 1950s and 1960s, when leukaemia, colorectal cancer, lung cancer and melanoma were all considered. The results were unimpressive, with the exception of a promising paper from Mathé[4] on the treatment of lymphoblastoid leukaemia in 1969 which others were unable to confirm. The advent of successful chemotherapeutic agents and new forms of radiotherapy reduced enthusiasm for BCG. However, Coe and Feldman[5] had meanwhile shown a strong delayed hypersensitivity reaction to BCG in the guinea-pig bladder, and Morales *et al.*[6] were to exploit this immune response when they successfully used intravesical BCG for superficial transitional cell bladder cancer in 1976. The treatment became popular in 1980 when a controlled study by Lamm *et al.*[7] showed unequivocal benefits in terms of decreased recurrence rate and increased time to recurrence when BCG was used as prophylaxis.

TREATMENT REGIMEN

Most centres still use the initial six-week 'induction' course employed by Morales, consisting of six instillations of BCG mixed in 50 mL normal saline. The catheterization must be atraumatic to avoid severe side effects (see later) and the patient retains the fluid in the bladder for about one hour. The BCG is live attenuated and therefore a theoretical risk of infection exists. At our institution the administering nursing staff wear masks, goggles, gloves and gowns and the patients are advised to use bleach in the toilet after urinating for the remainder of the day after each treatment.

Previous immunization against tuberculosis is not necessary: there is no evidence that previous or simultaneous immunization with intradermal BCG affects the outcome of intravesical BCG treatment. Some centres give more treatments (called maintenance) every 3–6 months for up to three years in an attempt to improve efficacy.

3 months after starting the 6-week induction course of BCG the patient has a cystoscopy. If the bladder is free of tumour recurrence then the patient simply needs to have regular cystoscopies (and maintenance therapy if deemed necessary). If tumour does recur then the patient can have further courses of BCG. A second 6-week course of BCG increases the number of patients free of tumour by 20–30%[8,9]; however, Catalona reported that after more than two unsuccessful courses, the chance of rendering a patient tumour-free is only 20% and the future risk of metastatic bladder cancer is 50%[9].

MECHANISM OF ACTION

The mechanism of action of intravesical BCG is not completely understood. A prerequisite is an intact immune

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system, as demonstrated by Ratliff who found that athymic mice were unable to mount an antitumour response[10]. The first step is to establish contact between BCG and the bladder endothelium. Fibronectin is important in binding BCG to both normal and tumour cells[11] and the BCG is then, probably, endocytosed[12]. This leads on to an inflammatory reaction in which the cellular infiltrate is typically heavy with T-cells, both CD4 and CD8, and macrophages. Ratliff[13] showed that depletion of either CD4 or CD8 reduces the BCG-mediated response in mice. There is also an increase in production of cytokines, which are chemotactic for the cellular infiltrate and activate the lymphocytes. These in turn produce more cytokines. Many of these cytokines can be detected in urine[14] and the levels increase with each instillation of BCG. The peak levels are achieved after the last two or three cycles of the six-week induction. Interleukin 2 and gamma-interferon are produced by activated T-cells.

There is a debate as to whether the antitumour activity is specific or non-specific, mediated by inflammation. The fact that inflammation of the bladder caused by radiotherapy or a urinary tract infection does not have the same effect suggests specificity, though a non-specific 'bystander' effect is also likely to be important in the anti-tumour process.

Jackson[15] proposes that there must be both an immune response and a tumour response. The immune response consists of the inflammatory infiltrate and the secretion of cytokines. The CD8 T-cells kill via induction of necrosis or apoptosis, possibly after recognizing intercellular adhesion molecule (ICAM) and/or major histocompatibility complex type two (MCH II) molecules in target cells. CD4 T-cells contribute by secretion of cytokines which cause maturation of cytotoxic T-cells or possibly more specific BCG-activated killer cells (BAK). BAK are capable of differentiating between normal and tumour cells. Their exact origin is unknown and they may not be a single entity, but they can be produced *in vitro* by incubation of live BCG with peripheral blood mononuclear cells. This explains why BCG must be live for successful intravesical therapy.

The tumour response relates mainly to a change of phenotype (also seen in normal epithelial cells) secondary to cytokine activity, especially gamma interferon. This results in an increased expression of ICAM-1 and MHC II. Activated leukocytes are dependent on the expression of ICAM-1 to conjugate with target cells before delivering a lethal hit. MHC II is involved in antigen presentation, and tumour cells might present BCG-derived antigens to CD4 T-cells[16].

There is also some evidence that BCG directly reduces the rate of growth in bladder tumour cell lines. Therefore both the immune and tumour systems must respond if the full anti-tumour effect of BCG therapy is to be gained. If the tumour system does not respond then the immune response may be ineffective.

Table 1 **Summary of results for carcinoma-*in-situ* (CIS) and papillary tumours treated primarily with intravesical bacille Calmette–Guérin (BCG))**

Disease	*Author*	*No. of patients*	*Initial response rate (%)*	*Follow-up (mo)*
CIS	Akaza (Ref 17)	32	84.4	20
	Harland (Ref 18)	53	53	32
	Merz (Ref 19)	25	88 (primary)	44
			78 (secondary)	40
Papillary	Akaza (Ref 17)	125	66.4	42

EFFICACY

The success of BCG depends on what it is being used for.

Carcinoma-in-situ

BCG is first-line therapy for *carcinoma-in-situ* (CIS). Akaza[17] showed a complete response of 84% for 32 cases of CIS; Harland[18], using a lower dose, achieved only 53%. Merz[19] reported an 88% complete response for primary CIS and 78% for secondary CIS (i.e. found with papillary tumours) with a median disease follow-up of 40 months for 115 patients. Harland's patients remained in remission for a median of 32 months. Akaza gave half the patients prophylactic BCG maintenance and half no further treatment. 74% of the latter were disease free at 3 years compared with 78% of those on prophylaxis—not a statistically significant difference.

Papillary tumours

This is a less common indication for BCG therapy and has generally been reserved for patients in whom endoscopic control is not possible, either because disease volume makes complete resection difficult or because an operative procedure will not be tolerated. Akaza[17] achieved 66% complete response with BCG as primary treatment in 125 cases of Ta or T1 tumour. They recorded a partial response for a further 21%. These results are summarized in Table 1.

Recurrence prophylaxis

Most patients will have recurrences of their bladder cancer. Reduction of the number of tumours or a longer interval between recurrences will be beneficial to both the patient and the healthcare system. Intravesical agents, including

BCG, have been assessed in many trials but comparisons are made difficult by the differing drug doses and administration regimens. Reviewing the long-term results of intravesical therapy, Lamm[2] noted that four out of five prospective controlled comparisons of BCG immunotherapy with surgery alone showed significantly lower tumour recurrence rates with BCG—overall, 75% versus 31%. He also reviewed twenty controlled chemotherapy studies and only eleven of them achieved significantly lower recurrence rates—average 41% for intravesical chemotherapy versus 58% for surgery alone. The advantage of BCG seems to persist. With chemotherapy the incidence of recurrence at 5 years was the same as that in the surgery-alone group, whereas the incidence in the BCG group remained lower. Several groups have compared BCG with intravesical chemotherapy. Lundholm[21] randomized 261 patients to receive either BCG or mitomycin C (MMC). After a median follow-up of 39 months 49% of those given BCG and 34% of those given MMC were disease-free. In patients who did have recurrences the number of recurrences was lower and the time to recurrence was longer if they had had BCG. BCG and MMC were also compared in the Southwest Oncology Group study[22], which was terminated early when recurrence rates in the BCG group were clearly much lower. Time to recurrence was also extended from 20 months to 36 months. Results of these trials are summarized in Table 2.

Not all studies have favoured BCG. Rubben *et al.*[23] found that MMC and BCG had only a 7% advantage over their controls; however, the controls had a low recurrence rate of 42%, which may explain the lack of difference between the treatments. Vegt[24] found no difference between the RIVM strain of BCG and MMC, and MMC was superior to the Tice strain of BCG. However the MMC treatment lasted 6 months compared with BCG's 6 weeks and large numbers of the patients had low-grade Ta lesions, a preponderance that might hide any benefit for the high-risk patients.

Progression

If intravesical therapy is to improve patient survival then it must reduce the incidence of tumour progression. Herr[25] compared transurethral resection (TUR) and BCG with TUR alone and showed 35% progression for the controls and 28% for those treated with BCG. The rate of cystectomy in the control group (42%) was higher than in the BCG group (26%) and the operations were carried out sooner, at a mean of 8 months versus 24 months. Mortality at a median of 6 years was 32% for controls and 14% in the BCG arm. The Southwest Oncology Group[26] compared doxirubicin with BCG and showed progression of 37% and 15% respectively. Pagano[27] followed 133 patients to stage T2 or higher and again found BCG to be superior with 4% progressing compared with 17% of controls. Lamm[20] tied all three studies together in a review giving a cumulative progression rate of 28% for controls and 14% for those treated with BCG.

Herr's enthusiasm for BCG was maintained at his 10-year follow-up, in which the progression-free rate was 62% in the BCG group compared with 37% in the control group[28]. At 15-year follow-up there was no difference in progression or time to progression between the two groups[29], but the controls with recurrence had crossed over to treatment with BCG; also, maintenance BCG was not used in this series.

BCG has also been compared with intravesical chemotherapy. Martinez-Piniero[30] compared it with doxorubicin and thiotepa over 31 months. BCG again proved to be better, with a progression rate of 1.5% compared with 3.6% for thiotepa and 7.5% for doxorubicin.

Table 2 **Summary of outcome of several trials of intravesical therapy given for recurrence prophylaxis of superficial bladder cancer**

Author	*Patient No.*	*Comparison*	*Follow-up (No.)*	*Outcome*	*Comment*
Lamm (Ref 20)	3166	Thiotepa, MMC, doxorubicin, epirubicin	—	BCG better	Large review of 20 chemotherapy and 5 BCG papers
Lundholm (Ref 21)	261	MMC, Danish BCG	39	BCG better	2 yr treatment in both groups
SWOG (Ref 22)	377	MMC, Tice BCG	—	BCG better	Terminated early
Rubben (Ref 23)	77	BCG, control	—	No difference	Controls had a low recurrence rate
Vegt (Ref 24)	437	RIVM-BCG, Tice BCG, MMC	35	RIVM-BCG and MMC equal	6 weeks' BCG treatment and 6 months' MMC. Large number low-grade Ta tumours

SWOG=South West Oncology Group; MMC=mitomycin C; BCG=bacille Calmette-Guérin

There seems to be less difference when BCG is compared with MMC. Lundholm[21] followed 261 high-risk patients randomized to BCG or MMC for 39 months and, although BCG was superior in terms of prophylaxis, the progression rate of 13% was similar in the two groups. Dutch researchers[24] compared two strains of BCG (TICE and RIVM) with MMC and again at 36 months the progression rate was similar for all three at around 5%. A multicentre study by Krege[31] had three arms—TUR alone; MMC alternate weeks for a year and monthly for a second year; and BCG weekly for 6 weeks and then monthly for 4 months. Progression rate was 4.2% in all groups, including the controls, which perhaps indicates that they were dealing with less dangerous disease. MMC was also given for 2 years, whereas BCG was given for only 6 months.

MAINTENANCE

The impact of maintenance therapy is difficult to assess because of large variations in the way it is used. It may be given monthly, quarterly or twice a year, and the dose may be a single instillation or weekly instillations for three weeks. The aim is to lower the risk of recurrence and progression, but the concern is that maintenance therapy increases the side-effects. Lamm[32] reported a study in which patients were randomized to maintenance or not after the initial induction. The regimen was three weekly instillations at 3, 6 and 12 months and then every 6 monthls to 3 years. Immunologically this is reasonable because, once a patient has had an induction course of BCG, only three further doses are needed to obtain the maximum immune response. Indeed, less than three may be needed and in this study patients were not given all three instillations at each cycle if side-effects were increasing. This probably explains why no severe side-effects were reported (only 16% of patients received all possible instillations). Those in the maintenance group had significantly better recurrence-free survival, and the *P* value for overall survival was 0.08. The median follow-up is approaching 10 years. Comparisons with previous studies suggest that maintenance given as a single instillation either monthly or quarterly is no better than standard 6-week induction without maintenance.

SIDE-EFFECTS

Side-effects are either specific or non-specific to BCG. The non-specific risks relate to the procedure of retrograde urethral catheterization before BCG instillation. Prevention of these relies on an atraumatic technique performed under strict aseptic conditions.

BCG-specific side-effects can be grouped into 'usual' and 'undesirable'. The most common side-effects[33] are abacterial cystitis and dysuria (80%), haematuria (40%) and low-grade ($<38.5\,^{\circ}C$) fever (30%). These usually settle within 48 hours and require little more than paracetamol, although occasionally the symptoms are more severe or longlasting. The BCG treatments can continue, but if the side-effects are troublesome then one can consider increasing the time between treatments or reducing the dose. Urinary symptoms mimic those of bacterial urinary tract infection and if empirical antibiotics are felt necessary then quinolones, which have some action against live BCG, should be avoided[34].

Granulomatous prostatitis is noted in about 1% of patients[33] and is probably more common. The recommended treatment for symptomatic patients is 3 months of rifampicin and isoniazid[33]. Epididymitis occurs in just 0.2% and requires similar treatment. Granulomas can occur anywhere including liver, lung and kidney. Renal granulomas may represent either haematogenous spread or local spread secondary to ureteric reflux. Ureteric reflux is not a contraindication to intravesical BCG. The recommended management of such granulomas is cessation of BCG treatment and tuberculosis triple therapy for 3–6 months[33].

Allergic reactions, such as arthritis and rashes, occur in under 1% of patients. BCG antigens cross-react with components of cartilage proteoglycans[33]. Treatment is symptomatic only and BCG is usually stopped. If further BCG treatment seems warranted then the patient should be closely monitored for the first few hours in case of a more severe reaction.

The most severe complication is generalized 'BCG-itis', very rare but potentially lethal. It usually occurs immediately after instillation of BCG and is most likely to happen if the urinary mucosa has been breached by a traumatic catheterization or recent bladder resection[35]. The mycobacterium gains access to the bloodstream, the patient develops high fever ($>38.5\,^{\circ}C$), and multiple organ failure supervenes with impaired haemodynamic status, abnormal liver function, leukopenia and bilateral lower lung crepitations. Treatment includes, tuberculosis triple therapy, empirical Gram-negative antibiotic cover and high-dose steroids.

CONCLUSIONS

Present research is aimed at further unravelling the mechanism of action and towards improving efficacy and reducing side-effects. These clinical targets may improve with better patient selection, regimens with lower doses, combination of BCG with other agents and wider utilization of maintenance therapy. There are trials in progress looking at these options. It is the side-effects that prevent this successful therapy from being more widely used.

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