BCG and bladder cancer

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The overall lifetime risk of developing bladder cancer is said to be 1 in 28 and it is three times more common in men than women. It is currently the most expensive cancer from diagnosis to death in the United States. The aetiology is multifactorial being a combination of exogenous environmental factors and endogenous molecular factors. At presentation, approximately 70–75% of these tumours are confined to the mucosa (75%) or lamina propria (25%)—i.e. are non-muscle invasive—with the most common pathological subtype being transitional cell carcinoma (in 90%).

Non-muscle invasive tumours are initially treated by complete endoscopic resection with all visible lesions being removed. Intravesical chemotherapy or immunotherapy can be used perioperatively or postoperatively to prevent recurrence and progression following initial trans-urethral resection of bladder tumour (TURBT).

The most common immunomodulatory agent used, since its introduction for this purpose in the 1970s, has been Bacillus Calmette-Guerin (BCG). Typically this is commenced several weeks after tumour resection, once healing of the urothelium has occurred, as an induction course followed by maintenance therapy for up to 3 years. The mechanism of action of this agent is thought to involve a massive local immune response following direct binding of BCG to fibronectin in the bladder wall. A cell-mediated cytotoxic mechanism is thought to be responsible for the efficacy of BCG.

The article by Akbulut and colleagues in this issue of the Journal describes an unfortunate sequence of events following the inadvertent intravenous administration of BCG (which is an attenuated mycobacterium initially developed as a vaccine). Although serious, for obvious reasons this is not one of the side-effects commonly seen in practice but is a timely reminder nonetheless.

Intravasation usually occurs only if the BCG is given in the presence of gross haematuria, active urinary tract infection, following traumatic catheterisation or if given too soon after TURBT and may result in severe systemic symptoms. More usual are mild irritative voiding symptoms, mild fever and haematuria. Occasionally two or three drug anti-mycobacterial therapy is required for periods of up to 6 months when symptoms are severe.

BCG is particularly useful for the treatment of carcinoma-in-situ (CIS) with initial tumour-free response rates of up to 80%, although long-term progression for this ‘high-risk’ disease may still be seen in 20% of these initial responders. Tumour recurrence rates are generally reduced by around 40% overall when compared to TURBT alone in non-muscle invasive disease. Unlike chemotherapy, progression to higher stage disease can also be reduced by 20–30% though an overall survival advantage has yet to be demonstrated.

A common conundrum in clinical practice is defining and managing BCG failures. These patients have a 50% chance of disease progression and death with ongoing intravesical treatment. A second 6-week induction course will result in ‘salvage’ of a
further 15–20% of cases but beyond this, further intravesical therapy with interferon, gemcitabine and taxanes is considered experimental.

‘Early’ cystectomy (i.e. before evidence of muscle-invasive disease) can be considered following BCG therapy, for any sign of tumour recurrence unless it is a delayed recurrence with low-grade disease. In this situation up to 40% of patients will be proven to have muscle-invasive disease and/or positive lymph nodes at the time of surgery. At 5 years however, most patients who have cystectomy for early disease will be cured.

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References: