BLADDER CANCER

Better clinical outcomes with BCG Connaught than Tice

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The results of a randomized controlled trial, recently published in *European Urology*, reveal significantly better recurrence-free survival for patients with non-muscle-invasive bladder cancer (NMIBC) who received BCG Connaught than those who received the Tice strain.

There are currently at least eight different strains of BCG in use for the treatment of NMIBC around the world, resulting from the global distribution and serial passage of the original BCG strain (BCG Pasteur), developed in Paris in 1921. A number of geographically restricted substrains have become established since then, including BCG Tokyo and BCG Moscow.

BCG Connaught and BCG Tice were developed in the USA in the 1930s and have become the two most widely used strains for bladder cancer immunotherapy in North America and across Europe. Questions regarding differential clinical efficacy between substrains have arisen from studies of BCG as a tuberculosis vaccine, but whether the same is true for intravesical treatment of NMIBC is unclear.

To shed light on this issue, a team of researchers, led by George Thalmann, performed a prospective randomized controlled trial of BCG Connaught versus BCG Tice at the University of Bern in Switzerland. Initiated in 1998, the trial ran until 2010 when it was stopped early owing to the obvious superiority of BCG Connaught.

Data were analysed from 131 patients with high-risk NMIBC (defined as any high-grade tumour, low-grade tumours with >2 recurrences within 2 years or

carcinoma *in situ*) randomized to receive six weekly instillations of either BCG Connaught ($n = 71$) or BCG Tice ($n = 60$) after transurethral resection.

5-year recurrence-free survival was significantly better for those treated with BCG Connaught (74%, 95% CI 62.8–87.2) than those who received BCG Tice (48%; 95% CI 35.5–65.1). Adverse effects were similar between treatment groups.

After noting the superior survival outcomes, researchers turned to mice to investigate the immunogenicity of both strains. They found that BCG Connaught was associated with more-robust CD8⁺ T-cell priming, and induced greater recruitment of immune cells (including CD45⁺ leukocytes, T cells and natural killer cells) to the bladder, than BCG Tice.

Genetic analysis revealed that BCG Tice contains two single nucleotide polymorphisms (SNPs) and one indel that are not present in any other BCG strain. One of these SNPs was mapped to superoxide dismutase C and predicted to affect enzyme activity, which might limit *in vivo* survival.

Patients did not receive maintenance BCG therapy, which has been demonstrated to improve outcomes but was not introduced until after the study was started. Maintenance therapy might improve outcomes with BCG Tice, but whether BCG Connaught would still fare better is unclear.

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Original article Rentsch, C. A. *et al.* Bacillus Calmette-Guérin strain differences have an impact on clinical outcome in bladder cancer immunotherapy. *Eur. Urol.* doi:10.1016/j.eururo.2014.02.061