

17th Yahya Cohen Memorial Lectureship

NRAMP1 and hGPX1 Gene Polymorphism and Response to Bacillus Calmette-Gue'rin Therapy for Bladder Cancer **by Dr Edmund Chiong**

Background: The natural resistance-associated macrophage protein 1 (NRAMP1) gene is associated with susceptibility to Mycobacterium tuberculosis in humans and to bacillus Calmette-Gue'rin (BCG) in mice. The detoxification enzyme, human glutathione peroxidase 1 (hGPX1), is associated with recurrence of bladder cancer (BCa).

Objective: To determine whether NRAMP1 and hGPX1 gene polymorphisms correlate with response to BCG immunotherapy for non-muscle-invasive BCa (NMIBC).

Materials and Methods: DNA was obtained from the peripheral blood of 99 NMIBC patients who were prospectively randomized to receive postresection intravesical BCG (81 mg [n = 50] or 27 mg [n = 19]) or BCG (27 mg) with interferon alpha (IFN- α ; n = 30). The median follow-up time was 60 months. Restriction fragment length polymorphism (RFLP) analysis was performed to identify polymorphisms in the NRAMP1 promoter region (GT repeat number) and at position 543 (aspartate [D] and/or asparagine [N] expression) within the NRAMP1 protein (D543N) and position 198 (proline and/or leucine expression) within the hGPX1 protein (Pro198Leu). Data were analyzed using X2 analysis, multivariate analysis, and Kaplan-Meier curves.

Results and Limitations: On univariate analysis, the NRAMP1 D543N G:G genotype had decreased cancer-specific survival (CSS; $p = 0.036$). The hGPX1 CT genotype (Pro-Leu) had decreased recurrence time ($p = 0.03$) after BCG therapy. On multivariate analysis, patients with the NRAMP1 D543N G:G genotype and allele 3 (GT) n polymorphism had decreased recurrence time ($p = 0.014$ and $p = 0.03$) after BCG therapy. The limitation of this study was its small sample size.

Conclusions: Polymorphisms of the NRAMP1 and hGPX1 genes may be associated with recurrence of BCa after BCG immunotherapy.