Bladder Cancer: Non-invasive II

Podium 17

Saturday, May 16, 2015 3:30 PM-5:30 PM

PD17-01

NATURAL RESISTANCE-ASSOCIATED MACROPHAGE PROTEIN 1 (NRAMP1) GENE POLYMORPHISMS AND RESPONSE TO BACILLUS CALMETTE-GUERIN THERAPY IN ASIAN NON-MUSCLE INVASIVE BLADDER CANCER PATIENTS

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INTRODUCTION AND OBJECTIVES: The NRAMP1 gene has been implicated in susceptibility to tuberculosis and to Bacillus Calmette-Guerin (BCG) response in murine models. We previously showed that genetic polymorphisms in two NRAMP1 gene loci correlate with response to BCG therapy in patients with non-muscle invasive bladder cancer (NMIBC). We aim to determine the predictive role of polymorphisms in all NRAMP1 gene loci in NMIBC recurrence and BCG immunotherapy outcome.

METHODS: Peripheral blood DNA was prospectively obtained from122 evaluable EORTC intermediate to high risk NMIBC patients, who underwent post-transurethral resection intravesical regimes of BCG (81mg or 27mg) or BCG (27mg) with interferon alpha (IFNa). Blood DNA was also obtained from 149 healthy volunteers as controls. A total of 14 NRAMP1 gene polymorphisms spanning across the gene (NG_012128.1) were evaluated with high resolution melt (HRM) analysis followed by DNA sequencing. The Kaplan-Meier together with Log-Rank test and Cox regression method were used to analyze the data.

RESULTS: Genotype frequencies were similar between the NMIBC patients and controls in accordance to the Hardy-Weinburg equilibrium. Two SNPs rs2695342 and rs17215556 showed no variation in the NMIBC cohort. 47 (38.5%) patients experienced recurrences. Median follow-up was 98.15 months (0.7 - 210.5). Overall mean time to recurrence and progression was 76.23 months (95%, CI 65.02-87.43) and 92.06 months (95%, CI 81.06 - 103.06) respectively. Age at diagnosis was significantly associated with recurrence (HR 1.054, p= 0.019) and overall survival (HR=1.066, p=0.014), but not progression (HR= 0.981, p= 0.685) in the multivariate analysis. On Kaplan-Meier analysis, individuals carrying three NRAMP1 genotypes rs2695343 (13672A/A) (p=0.047), rs2279015 (17519A/A) (p=0.038) and rs1059823 (18093 A/A) (p=0.044) were associated with lower recurrence-free survival after BCG therapy overall. On Cox regression analysis, individuals carrying NRAMP1 genotypes rs 2276631 (C/C) (HR=37.02,p=0.024), rs3731865(G/C)(HR=13.38,p=0.049), rs2695343(A/A) (HR=33.01,p=0.012) are more likely to have shorter time to recurrence. No association of NRAMP1 genotypes with progression-free survival was found.

CONCLUSIONS: Our findings suggest that polymorphisms in the NRAMP1 gene correlate with response to BCG therapy in NMIBC patients. They may serve as molecular markers to predict BCG failure and cancer recurrence.

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PD17-02

IS INTRAVESICAL BCG ALONE STILL THE ONLY TRULY EFFECTIVE INTRAVESICAL THERAPY FOR NON-MUSCLE INVASIVE BLADDER CANCER?

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INTRODUCTION AND OBJECTIVES: In a randomized prospective trial it has been shown that intravesical sequential bacillus Calmette-Guerin (BCG) and electro-osmotic delivery (IVED) of mitomycin (MMC) is superior to BCG alone in patients with stage pT1 bladder cancer. A 5-year and 10-year contemporary cost-effectiveness study of these 2 treatment strategies suggests that sequential therapy is also cost-effective in this indication. After an additional 6 years of follow-up, we report estimated 10-year results.

METHODS: From January 1994 through June 2002, we randomly assigned 212 patients with stage pT1 bladder cancer to either 81 mg BCG once a week for 6 weeks (n=105) or to 81 mg BCG once a week for 2 weeks, followed by IVED of 40 mg MMC (intravesical pulsed electric current 20 mA for 30 min) once a week, and this cycle was repeated 3 times (n=107). Complete responders underwent maintenance treatment: those assigned to BCG alone had one instillation of 81 mg BCG once a month for 10 months, and those assigned to sequential therapy had 40 mg MMC once a month for 2 months, followed by 81 mg BCG once a month and this cycle again repeated three times. The primary endpoint was disease-free interval; secondary endpoints were time to progression; overall survival; and disease-specific survival. Analyses were done by intention to treat.

RESULTS: Median follow-up was 121 months (IQR 70.5−163.5). Patients assigned to sequential BCG and IVED of MMC had higher disease-free intervals than those assigned to BCG alone (79 months [95% CI 27−139] vs 26 months [11−113]; log-rank p=0.0002. Patients assigned to sequential BCG and IVED of MMC also had a lower recurrence rate (45% [35−55] vs 62% [50−72], log-rank p=0.0002; progression (12% [3−21] vs 28% [17.5−38.5], log-rank p=0.003); overall mortality (44% [33−55] vs 59% [43−75], log-rank p=0.01; and disease-specific mortality (9% [2.5− 15.5] vs 23% [11−34], log-rank p=0.0055. Side-effects were mainly localised to the lower urinary tract. MMC pharmacokinetics showed that plasma levels remained well below toxic concentrations.

CONCLUSIONS: These long-term data confirm former studies and suggest that intravesical sequential BCG and IVED of MMC is a superior and cost-effective treatment that has the potential to be integrated into hospital and health systems as a standard of care.

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PD17-03

"TUMOR BUDDING", A NOVEL PROGNOSTIC INDICATOR FOR PREDICTING STAGE PROGRESSION IN T1 BLADDER TUMORS

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INTRODUCTION AND OBJECTIVES: Tumor budding was defined as an isolated single cancer cell or a cluster composed of fewer than 5 cancer cells scattered in the stroma at the invasive tumor margin (Figure 1). It is a strong predictor for lymph node metastasis in T1 colorectal cancer and current guidelines recommend additional excision after endoscopic therapy when tumor budding is positive. We introduced this concept to T1 non-muscle invasive bladder carcinoma (NMIBC) and evaluated whether tumor budding could have a prognostic impact on T1 NMIBC clinical outcome.