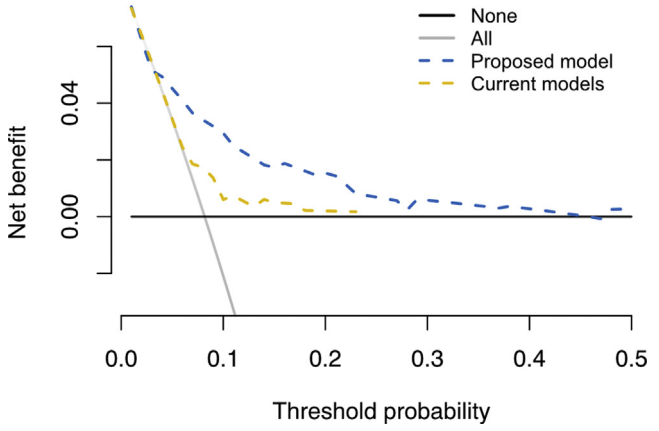

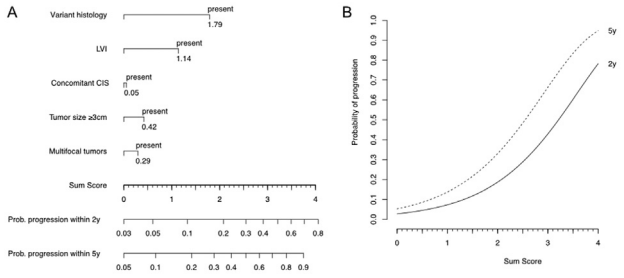

Source of Funding: none

PD66-10

IDENTIFYING POLYMORPHISMS THAT MODULATE RESPONSE TO BACILLUS CALMETTE-GUERIN THERAPY IN PATIENTS WITH NON-MUSCLE INVASIVE BLADDER CARCINOMA

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INTRODUCTION AND OBJECTIVES: Bacillus Calmette-Guerin (BCG) immunotherapy has a considerable failure rate. Various centres have found associations between polymorphisms in genes involved in the immune inflammatory pathways and treatment outcomes. We evaluated a panel of polymorphisms in a prospectively maintained cohort of Asian non-muscle invasive bladder carcinoma (NMIBC) patients. MicroArray analysis was also performed to assess candidate variants and their association with BCG immunotherapy response.

METHODS: 218 NMIBC patients that had received BCG therapy and 200 normal controls from the Chinese University of Hong Kong and National University Hospital of Singapore were recruited for the study. Single Nucleotide Polymorphisms (SNP) were classified by High Resolution Melting analysis and Sequence analysis. 18 SNPs from the Natural Resistance-Associated Macrophage Protein1 (NRAMP1)gene and 8 SNPs from the immune response gene family were evaluated. Kaplan-Meier together with Log-Rank test and Cox regression methods were used to analyse the data. Illumina Infinium OncoArray-500K BeadChip MicroArray were then used to interrogate 12 BCG responders and 12 non-responders (6 recurrences and 6 progressions).

RESULTS: Polymorphism genotype distributions were similar between controls and patients, in accordance to the Hardy-Weinberg equilibrium. NRAMP1 rs34448891 Allele 3/3 were associated with increased incidence of cancer progression ($p=0.014$) compared to Allele 3/2. Patients carrying the Interleukin 17A rs2275913 G/A and G/G genotype were also found to have shorter time to recurrence ($p=0.004$). The Interleukin 18 receptor 1 rs3771171 A/A genotype was associated with shorter time to recurrence ($p=0.04$) and time to progression ($p=0.043$). The MicroArray Analysis revealed that rs8125878 (GA) of chromosome 20 and rs6569926 (AG) of chromosome 6 both carried prognostication value, with all responders having a homozygous genotype and all non-responders having a heterozygous genotype.

CONCLUSIONS: Our findings show that specific polymorphisms in NRAMP1, IL17A and IL18R1 correlate with response to BCG therapy in Asian NMIBC patients. Further functional studies should be performed to elucidate the significance of these genes in the management of bladder cancer and potential therapy implications.

Source of Funding: This study is funded by National Medical Research Council Grant: NMRC/CIRG/1347/2012.

PD66-11

HYPERTHERMIC INTRAVESICAL CHEMOTHERAPY FOR BCG-UNRESPONSIVE NON-MUSCLE INVASIVE BLADDER CANCER

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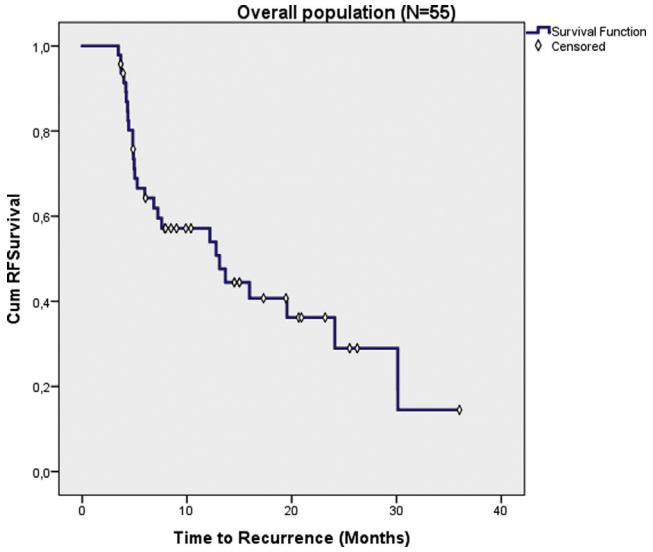
INTRODUCTION AND OBJECTIVES: Adjuvant intravesical instillations with bacillus *Calmette-Guerin* (BCG) is the recommended treatment option for patients with intermediate and high-risk non-muscle invasive bladder cancer (NMIBC). Despite adequate BCG treatment, a large proportion of patients experiences a recurrence. Although radical cystectomy is the Gold Standard for BCG-unresponsive NMIBC, a number of patients are unfit for or unwilling to consider this option. The optimal therapy in such cases is unknown. The objective of the present study was to assess the efficacy of hyperthermic intravesical chemotherapy (HIVEC®) in BCG-unresponsive intermediate and high-risk NMIBC patients.

METHODS: From October 2014 to July 2017 NMIBC patients who were defined BCG-unresponsive (recurrence of high-grade disease after having had a minimum of 5/6 induction and 2/3 maintenance BCG instillations) were prospectively included at three academic institutions. All patients were planned to receive HIVEC® treatment, consisting of an induction phase followed by maintenance therapy. Only patients who had a minimum of 5 HIVEC® instillations were included in the present analysis. Patients were followed by cystoscopy and cytology every three months and a CT-scan yearly. The primary outcome was the recurrence-free survival (RFS). The Common Terminology Criteria for Adverse Events (CTCAE) was used to assess side-effects.

RESULTS: The study population consisted of 59 BCG-unresponsive NMIBC patients (8% intermediate- and 92% high risk) of whom 55 underwent $\geq$5 HIVEC® treatments. Histology was urothelial carcinoma in all patients and T-stage was pTis in 31, pTa in 10, pT1 in 9, pT1+CIS in 3 and pTa+CIS in two patients. The median age and follow-up was 72 years and 9.0 months [IQR 7.1 - 19.5]. The overall recurrence rate was 58% and the mean RFS was 16.6 months [SE 2.1] (Fig.1). In patients having carcinoma in situ (n= 36), the recurrence rate was also 58% and the mean RFS was 16.2 months [SE 2.8]. Progression occurred in 3 patients and two patients experienced severe side-effects (CTCAE $>$2).

CONCLUSIONS: HIVEC® seems a valid treatment option for BCG-unresponsive intermediate- or high-risk NMIBC patients. We report a mean RFS of $>$1 year, potentially avoiding or postponing the need for radical surgery in these patients.



Source of Funding: none

PD66-12

PATIENT CENTERED OUTCOMES OF INTRAVESICAL BACILLUS CALMETTE-GUERIN (BCG) PLUS INTERFERON

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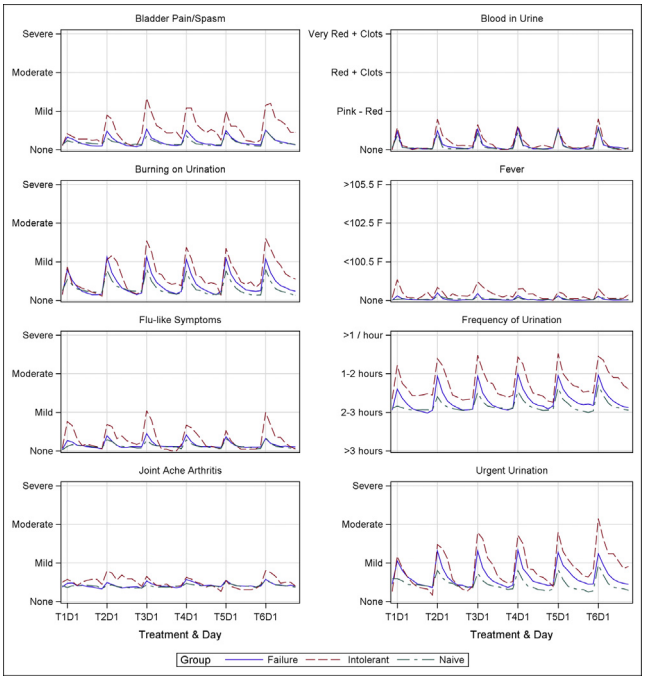
INTRODUCTION AND OBJECTIVES: There is a paucity of patient-reported outcomes with intravesical Bacillus Calmette-Guerin (BCG). We now report 2 patient-centered metrics evaluating BCG with interferon (IFN) induction as part of the Phase 2 BCG/IFN national trial.

METHODS: Patients were treated with intravesical BCG (full dose for BCG naive (BCG-N), 1/3 dose for prior BCG failures (BCG-F), 1/10 dose for patients deemed BCG intolerant (BCG-I)) plus IFN for 6 weekly treatments. A Quality of life index (QoL), a validated 4-part questionnaire evaluating patients' views of various aspects of their life, was administered prior to and immediately following completion of induction therapy. A Quantitative symptom score (QSS), a survey of common side effects (ie dysuria, urgency, frequency, hematuria) rated from none (0) to severe (3), was completed immediately prior to each instillation, after each instillation, and daily following each instillation until the next instillation. Statistical analysis was performed using linear mixed regression ($p<0.01$).

RESULTS: Of 984 patients who submitted at least 1 survey of either type, 777 pre-induction and 786 post-induction QoL surveys were collected. A statistically significant but clinically insignificant change in pre-to-post QoL scores was noted in the BCG-N and BCG-F groups but not in the BCG-I group. There were no differences in the mean change in QoL score between all groups ($p=0.74$). An average of 713 QSS surveys were submitted after each instillation. All side effects were worse immediately after instillation and dissipated over the following 2-3 days (Figure 1). Frequency, urgency, and dysuria were the most severe side effects in all groups. BCG-I patients tended to have more severe symptoms than BCG-N and BCG-F but a significant difference in symptom severity trend during treatment was only seen in bladder pain/spasms.

CONCLUSIONS: BCG/IFN was tolerated well by all groups, regardless of prior BCG exposure, with no clinically significant difference in QoL after BCG induction. In all groups, symptoms were worst immediately after instillation but rapidly improved. BCG-I patients tended to have worse severity scores. This study demonstrates the general tolerability of BCG and provides data for physician counseling prior BCG therapy.



Source of Funding: None