Predicting Response to Intravesical Immunotherapy (BCG) in NMIBC

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BCG is the ORIGINAL CANCER IMMUNOTHERAPY

After more than 40 years we still cannot reliably predict responders prior to treatment
Predicting Response to BCG

Available Now (Aug 2017)

1. Gender, Grade and Stage of Tumor, +/- CIS
2. Depth of Lamina Propria Invasion (T1 ab, T1 me)
3. Variant Histology
4. reTUR data
5. Prior Intravesical Therapy
6. FISH patterns
CUETO Score
BCG Response Prediction

1062 patients treated with BCG in four CUETO trials

Recurrence:
gender, age, grade, tumor status, multiplicity, Tis.

Progression:
age, grade, tumor status, T category, multiplicity, Tis.

Prognostic Factors and Risk Groups in T1G3 NMIBC Treated with BCG: 
Results of a Retrospective Multicenter Study of 2451 Patients

Adverse prognostic factors:
1. age ≥ 70 yr
2. size ≥ 3 cm
3. CIS +

No. at risk
0 Adverse 460 203 58 6 0
1 Adverse 786 260 64 4 0
2 Adverse 376 102 26 5 0
3 Adverse 75 21 4 0 0

Variant Histology
Micropapillary T1HG Progresses with Intravesical BCG

- 89% recurred
- 67% progressed (median 8 mos)
  - 6 (22%) metastatic disease

Kamat et al, J Urol, 2006; Kamat et al Cancer, 2007; updated
Willis et al, 2015
T1 on reTUR predicts response to BCG

- T1 HG patients
- 5 yr progression
  - =T1 on re-TUR: 82%
  - <T1 on re-TUR: 19%
Tumor Biomarkers

• Tumor P53
  ▪ Correlated: Saint, 2004; Lopez-Beltran, 2004; Palou, 2009
  ▪ Not correlated: Lebret, 1998; Zlotta, 1999; Peyromaure, 2002; Esuvarananathan, 2007

• Same problem with Ki-67, Rb ....
Intra-vesical BCG

B-cell

APC-cytokine/chemokine release

PMN recruitment

monocyte/macrophage recruitment

IL-8

Phagocytosis of BCG by macrophages

IL-6

Local T-cells

IFN-γ

TNF-α

Phagocytosis of BCG by tumor cells

HLA-DR expression by tumor cells

PMN activation

Tumor cell death

TRAIL release

TNF release

NK cells

TGF-β

PMN apoptosis

Inflammation

IL-6

IL-12

IL-10

IFN-γ

IL-2

T-cell activation

Resolution of inflammation

Jinesh G & Kamat A, Oncoimmunology, 2012
Can the immune response markers predict response to BCG?

Can immune biomarkers be used to design optimal dose, duration & schedule of BCG?
Antibody Responses to *Bacillus Calmette-Guérin* during Immunotherapy in Bladder Cancer Patients

Wendell D. Winters and Donald L. Lamm

*Departments of Microbiology [W.D.W.] and Urology [D.L.L.], University of Texas Health Science Center, San Antonio, Texas 78284*
Cytokines (eg IL-2) and BCG response

Recurrence after 6+3

Progression after 6+3

Cytokines (eg IL-8) and BCG response

Sagnak L et al, Clin Genitourin Cancer, 2009
36 new biomarkers for BCG induced bladder inflammation

1. Plasma proteins
   - IgM
   - alpha-2 Macroglobulin
   - fibrinogen
   - SHBG
   - von Willebrand Factor
   - serum amyloid P
   - apolipoprotein CIII
   - PAI-1
   - apolipoprotein H
   - α1 antitrypsin
   - C reactive protein
   - IgA
   - thyroxine binding globulin
   - BDNF
   - adiponectin

2. Stromal cell derived
   - G-CSF
   - MMP-9
   - RANTES
   - TIMP-1
   - VEGF

3. Cellular immune response
   - IL-1β
   - IL-6
   - IL-8
   - IP-10
   - MCP-1
   - GM-CSF
   - TNFα
   - EN-RAGE
   - ENA-78
   - IL-10
   - IL-16
   - IL-18
   - IL-1ra
   - IL-2
   - MIG
   - MIP-1
   - MPO

Statistically significant values, induced after 4h BCG on week 3
p < 0.05 using FDR correction for multiple analyte testing

Slide: Matthew Albert, Pasteur Institute
Prospective Trial: Markers of Response to Intravesical BCG

Hypotheses

• Comprehensive Panel of Cytokine response to BCG will differentiate responders from non-responders

• Innate intricacies of the immune response

• Genes which regulate inflammatory mechanisms will impact the response to BCG

• Cytogenetically abnormal cells: patterns will predict clinical tumor recurrence

PI: Kamat; NCT01007058
Cytokines and BCG Response

- **Cytokine** response to BCG does differentiate responders from non-responders

  - Responders have **higher levels** of BCG induced cytokines at BCG #6

  - **Magnitude of induction** of cytokines correlates with recurrence rate and time to recurrence

  - Complex **interplay** of cytokines
ΔIL-8 with 6th BCG

\[ p = 0.0041 \]
Risk function for ΔIL-8 with 6th BCG
Risk Assessment Calculator to Predict Recurrence

- η = 0.2267 - 2.8594 * I(ΔIL-2 ≥ 200) - 4.6366 * I(ΔIL-6 ≥ 425)
  - 1.0933 * I(ΔIL-8 ≥ 1500) - 5.4155 * I(ΔIL-18 ≥ 40)
  + 0.00428 * ΔIL-1r + 0.00459 * ΔTRAIL - 0.00235 * ΔINF-γ +
  0.4328 * ΔIL-12(p70) + 0.0123 * ΔTNF-α

- Cutpoint: Predict recurrence if η ≥ -0.1527
Cytokine Panel for Response to Intravesical Therapy (CyPRIT): Nomogram of Changes in Urinary Cytokine Levels Predicts Patient Response

Ashish M. Kamat, Graciela M. Hummel, Ferran Prat

Department of Urology, Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX

IL-2 pg/ml Change
IL-6 pg/ml Change
IL-8 pg/ml Change
IL-18 pg/ml Change
IL-1ra pg/ml Change
TRAIL pg/ml Change
IFN-γ pg/ml Change
IL-12(p70) pg/ml Change
TNF-a pg/ml Change
Total points
Linear predictor
Probability of recurrence

Area under ROC curve = 0.85

Patent No. PCT/US2013/028891

Kamat et al, Eur Urol, 2015
Use of Fluorescence In Situ Hybridization to Predict Response to Bacillus Calmette-Guérin Therapy for Bladder Cancer: Results of a Prospective Trial

Ashish M. Kamat,* † Rian J. Dickstein,‡ Fabrizio Messetti,‡ Roosevelt Anderson,‡ Shanna M. Pretzsch,‡ Graciela Noguera Gonzalez,‡ Ruth L. Katz,§ Abha Khanna,‡ Tanweer Zaidi,‡ Xifeng Wu,‡ H. Barton Grossman‖ and Colin P. Dinney¶

<table>
<thead>
<tr>
<th>Recurrence &amp; Progression Rates at 2 yrs</th>
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<td>Baseline FISH</td>
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<td>Negative</td>
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Polymorphisms in Oxidative Stress Genes

Recurrence-free median survival time [MST] = 42.3, 12.5, and 5.6 months for low, medium, and high risk patients,

Wei, Kamat ... Wu et al, PloS One 7:e38533, 2012
Gene Expression/Signature T1

Limitations: No Maintenance BCG; 13% G1; 66% G2

Genes (12 recurrence & 12 progression)
Cell mediated immune response; Inflammatory response; Cellular Growth; Proliferation

Kim YJ et al, CCR, 2010
BCG reduces progression only when maintenance is used

Meta analysis of 24 RCT of BCG with 4,863 pts

BCG Maintenance: **Not Created Equal**
Only SWOG protocol shows clear benefit

![Graphs showing tumor recurrence and disease-free rates](image)

Kamat & Porten, Eur Urol, 2014
80% progression events occurred in patients with class 2 tumors
Cohort limited in power (only 6.7% progressed)

Only 18% patients received BCG
PD-L1 as a Resistance Mechanism to BCG Therapy in NMIBC

Figure A: PD-L1(-) NMIBC

Figure B: PD-L1(+) NMIBC Post-BCG Treatment Granuloma

Inman et al, Cancer 2007
Th2/Th1 ratio Predicts BCG Response

Nunez-Nateras R, Urol Onc, 2014
Multiplex analyses of NMIBC with integration of multiple immune markers

CD$_4$ (green), CD$_8$ (red), PD-L$_1$ (white), FoxP$_3$ (yellow)

Sharma, Kamat et al 2016
What Now?
What Now?

- Patient Factors
- Tumor Histology
- Real Time 'Markers'

Age, Sex
Re-TUR Data
Grade, Stage Variant Histology Size, Number
FISH Data Response to BCG
What Next?

Subtypes, miRNAs (155, 21, 29, 146a)

FoxP3, Treg, CD4+ ICOS+

Patient Factors e.g. Gene Profile

Tumor MicroEnvironment

Inducible Factors e.g. Cytokine response

TAMs, CD68; TIDCs, CD83; GATA-3+; T - Bet+

IL-6, IFN-γ, TNF-a, IL-2, IL-1b, IL-8, IL-10, IL-12(p40), IL-12(p70), IL-18 and TRAIL.

Optimal BCG Therapy
Thank You

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