Predicting Response to Immunotherapy in Bladder Cancer

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Immunotherapy: The story of BCG

- BCG most effective therapy for NMIBC
  - Reduces recurrence, progression; prevents deaths

- However, ~30% patients fail BCG therapy
  - In non-responders, disease often progresses before curative cystectomy - decreased survival

- If we can identify non responders early, offer alternate therapy at earlier time point
Progression after BCG = Decreased Survival

- Micropapillary Bladder Cancer
- Median time to progression: 8 mo.
- Median survival: 35 mo.
- 5 yr DSS = 24%
  - 56% radical cystectomy
  - 50% primary chemotherapy

Willis, ... Kamat et al, J Urol, 2015
Predicting Response to BCG

Available Now (March 2018)

1. Gender, Grade and Stage of Tumor, +/- CIS
2. Depth of Lamina Propria Invasion (T1 ab, T1me)
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.

---

T1 HG disease: Sub-stage & Progression

T1 a/b

Survival Functions

T1 sub-stage

T1a

T1b

T1c-censored

T1d-censored

Cum Survival

p = 0.00

5

progression follow up

T1 m/e

Survival Functions

stage of pT1-

sub-class

reviewed

T1a

T1b

T1c-censored

T1d-censored

Cum Survival

p < 0.001

progression follow up

Slide: Bas Van Rhijn
Variant Histology
Micropapillary T1HG Progresses with Intravesical BCG

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

T1 on reTUR predicts response to BCG

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

Herr et al, JNCCN, 2015
Herr J Urol, 2007
Tumor Biomarkers

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

- Same problem with Ki-67, Rb ....
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

Published in 1981
Cytokines (eg IL-2) and BCG response

Recurrence after 6+3

Progression after 6+3

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
• 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
Proportional Hazards Model to Predict Time to Recurrence

<table>
<thead>
<tr>
<th>Cytokine*</th>
<th>Coefficient</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>I((\Delta_{IL-2} \geq 200))</td>
<td>-1.90</td>
<td>0.15</td>
<td>0.0574</td>
<td>0.02 - 1.06</td>
</tr>
<tr>
<td>I((\Delta_{IL-6} \geq 425))</td>
<td>-2.39</td>
<td>0.09</td>
<td>0.0102</td>
<td>0.02 - 0.57</td>
</tr>
<tr>
<td>I((\Delta_{IL-8} \geq 1500))</td>
<td>-0.78</td>
<td>0.46</td>
<td>0.0805</td>
<td>0.19 - 1.10</td>
</tr>
<tr>
<td>I((\Delta_{IL-18} \geq 40))</td>
<td>-3.20</td>
<td>0.04</td>
<td>0.0030</td>
<td>0.01 - 0.34</td>
</tr>
<tr>
<td>IL-1r</td>
<td>0.0025</td>
<td>1.003</td>
<td>0.0005</td>
<td>1.001 - 1.004</td>
</tr>
<tr>
<td>TRAIL</td>
<td>0.0021</td>
<td>1.002</td>
<td>0.0055</td>
<td>1.001 - 1.004</td>
</tr>
<tr>
<td>IFN-(\gamma)</td>
<td>-0.0009</td>
<td>0.999</td>
<td>0.0384</td>
<td>0.998 – 1.000</td>
</tr>
<tr>
<td>IL-12(p70)</td>
<td>0.24</td>
<td>1.27</td>
<td>0.0003</td>
<td>1.12 - 1.45</td>
</tr>
<tr>
<td>TNF-(\alpha)</td>
<td>0.006</td>
<td>1.01</td>
<td>0.0011</td>
<td>1.002 - 1.01</td>
</tr>
</tbody>
</table>

* Change from before to just after 6th instillation of BCG
Risk function for $\Delta$IL-8 with 6th BCG

[Graph showing the natural log of the odds ratio against the increase in IL-8 (pg/ml).]
Risk Assessment Calculator to Predict Recurrence

- $\eta = 0.2267 - 2.8594 \times I(\Delta IL-2 \geq 200) - 4.6366 \times I(\Delta IL-6 \geq 425) - 1.0933 \times I(\Delta IL-8 \geq 1500) - 5.4155 \times I(\Delta IL-18 \geq 40) + 0.00428 \times \Delta IL-1r + 0.00459 \times \Delta TRAIL - 0.00235 \times \Delta INF - \gamma + 0.4328 \times \Delta IL-12(p70) + 0.0123 \times \Delta TNF-\alpha$

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

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||

Recurrence & Progression Rates at 2 yrs

<table>
<thead>
<tr>
<th>Baseline FISH</th>
<th>FISH at 6 weeks</th>
<th>Recurrence by 24 months (%)</th>
<th>Progression by 24 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>12.8</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>60.0*</td>
<td>40.0</td>
</tr>
</tbody>
</table>

*Significant difference.
Can your own immune system kill cancer?

FDA Grants Atezolizumab Accelerated Approval as Initial Treatment for Some Advanced Bladder Cancers

AstraZeneca immunotherapy wins first approval in bladder cancer

Pfizer immuno-oncology drug wins U.S. approval for bladder cancer
FAKE NEWS!
Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

- PD-L1 Status
- Molecular Subtyping (TCGA, MDACC, etc.)
- Tumor Mutational Burden
- Immune Gene Expression Profiling

Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

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• Immune Gene Expression Profiling
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
UC: SP263 uses tumour and immune cell scores

**Definition**

**Tumour Cell:**
Proportion of tumour cells with membrane staining for PD-L1 at any intensity above background staining

**Immune Cell:**
Proportion of tumour associated immune cells with staining for PD-L1 at any intensity above background staining

<table>
<thead>
<tr>
<th>Assay</th>
<th>Cut offs for PD-L1 High</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP263</td>
<td>TC ≥25% or IC ≥25%</td>
</tr>
</tbody>
</table>

*Slide: Bellumunt, 2017*
UC: SP142 uses immune cell score

Definition
The proportion of tumour area occupied by PD-L1 expressing tumour-infiltrating immune cells of any intensity

Assay | Cut offs for PD-L1 High
---|---
SP142 | ≥5%

Slide: Bellumunt, 2017
UC: 22C3 uses Combined Proportion Score (CPS)

Definition
The percentage of PD-L1 expressing tumour and infiltrating immune cells relative to the total number of immune cells.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Cut offs for PD-L1 High</th>
</tr>
</thead>
<tbody>
<tr>
<td>22C3</td>
<td>≥10%</td>
</tr>
</tbody>
</table>

Slide: Bellumunt, 2017
## PD-L1 Expression as a Predictor of Checkpoint Blockade Sensitivity in UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Agent</th>
<th>Companion IHC Antibody</th>
<th>Threshold for Positivity</th>
<th>Target Cells</th>
<th>Assay Associated with Response?</th>
</tr>
</thead>
</table>
Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

- PD-L1 Status
- Molecular Subtyping (TCGA, MDACC, etc.)
- Tumor Mutational Burden
- Immune Gene Expression Profiling
Figure 3: Molecular subtype classification of bladder cancer and breast cancer
IMvigor 210 Trial: Atezolizumab

• Basal Clusters had highest prevalence of IC 2/3 PD-L1 (60% vs 23%) and TC 2/3 (39% vs 8%)
• Highest response in luminal cluster II subtype (ORR=34%, *P*=0.0017)
  • luminal cluster I, basal cluster I, and basal cluster II: ORR 10%, 16%, and 20%

However…

- Phase II CheckMate 275 (nivolumab)
  - TCGA basal I subtype showed highest proportion of responders (7/23, ORR 30%).
  - Luminal cluster II tumors ORR: ~25%.
  - Interferon-γ genes enriched in responders vs those with progressive disease ($P<0.01$)

Correlation of MDACC Subtypes with Response to BCG

MDACC Analysis of Chungbuk (Korean) cohort, Choi et al
Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

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- Molecular Subtyping (TCGA, MDACC, etc.)
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Tumor Mutational Burden/Neoantigen Burden

Tumor Mutational Burden/Neoantigen Burden

- IMvigor 210 Cohort II; 315 genes
  - Higher mutation load in responding vs non-responding patients (12.4 vs 6.4 per megabase, \( p < 0.0001 \))
  - Smoking status and TCGA subtype did not correlate with mutational burden
- Cohort I of IMvigor 210
  - Improved OS in highest quartile of TMB (>16 to <62.2 mutations per MB) vs quartiles 1–3
  - Estimated survival probability 75% at 1 year

\begin{itemize}
  \item \textbf{Cohort 2}\textit{ Platinum-treated mUC}
  \item \textbf{Cohort 1}\textit{ 1L cisplatin-ineligible mUC}
\end{itemize}

\begin{itemize}
  \item Improvement in OS independent of TCGA subtype; responses noted in all four subgroups
  \item Patients in the lowest 3 quartiles similar; Top quartile with increased response rate and overall survival benefit; ? threshold effect
\end{itemize}

MB, mutational burden; TMB, tumor mutational burden.
Interrogating the Tumor Microenvironment for Potential Biomarkers for Immunotherapy

• PD-L1 Status
• Molecular Subtyping (TCGA, MDACC, etc.)
• Tumor Mutational Burden
• Immune Gene Expression Profiling
Multiparameter Immune Gene Expression Profiling

- RNA can be quantified from multiple cell types within a specimen
- More fully representative of the tumor microenvironment
- Accurately determine the inflammatory status of a tumor ("hot" tumors)

Multiparameter Immune Gene Expression Profiling

- CheckMate 275: nivolumab in mUC
- 25-gene IFN-γ signature in 177 pretreatment samples
- IFN-γ gene signature correlated with response to nivolumab
  - High IFN-γ signature: CR or PR in 20/59 patients
  - Medium or low IFN-γ signature: CR or PR in 19/118 patients, p=0.0003

NPV problematic as some responses noted in non-inflamed cytokine signature

Proposed Prognostic Model for Advanced UC

405 pts receiving post-platinum atezolizumab in locally advanced or metastatic UC as frontline therapy or following progression occurring >12 mo after neo/adj chemo

6 prognostic factors:
• ECOG performance status (HR, 1.64; \( P=.002 \))
• Liver metastasis (HR, 1.45; \( P=.014 \))
• ↑ platelet count (HR, 1.73; \( P=.010 \))
• ↑ neutrophil-lymphocyte ratio (HR, 1.84; \( P<.001 \))
• ↑ lactate dehydrogenase level (HR, 1.54; \( P\leq.001 \))
• Anemia (HR, 1.60; \( P=.004 \))

Not significant:
• PD-L1 status
• Site of primary/metastases
• Stage at diagnosis
• Smoking
• Number of prior therapies

Overall Survival

<table>
<thead>
<tr>
<th>Number of Factors</th>
<th>Survival Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 factors</td>
<td>19.4-10.6 mo</td>
</tr>
<tr>
<td>2-3 factors</td>
<td>5.9-7.2 mo</td>
</tr>
<tr>
<td>4+ factors</td>
<td>2.6-2.8 mo</td>
</tr>
</tbody>
</table>

Predicting Response to Intravesical Bacillus Calmette-Guéрин Immunotherapy: Are We There Yet? A Systematic Review


Table 1 Consensus classification of factors as 'Definitely useful' and 'Probably useful' in predicting response. Evidence not robust enough to be classified is listed as 'Emerging strategies'.

<table>
<thead>
<tr>
<th>DEFINITELY USEFUL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before treatment</strong></td>
</tr>
<tr>
<td>Clinicopathologic features (Level of evidence)</td>
</tr>
<tr>
<td>Grade (+++), Stage (+++), Recurrent tumors (++)</td>
</tr>
<tr>
<td>Multiplicity (++), CIS (+), Female gender (+)</td>
</tr>
<tr>
<td>Age (+)</td>
</tr>
</tbody>
</table>

| **During and after treatment**                         |
| FISH pattern on cytologic examination                  |
The Richard Peto Effect

“Aspirin didn’t seem to work as treatment for heart attack if you’re born under Libra or Gemini, but it produced halving of risk if you were born under Capricorn. It’s just complete junk.

And, actually, a lot of subgroup analyses are junk”.  
-Professor Sir Richard Peto
Thank You

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