Toward Personalized Bladder Cancer Management: Molecular Pathologic Advancements in Urothelial Carcinoma

George J. Netto, M.D.
Professor and Chair of Pathology
University of Alabama at Birmingham

Overview

• The Dual Universes of BC
  NMIBC vs MIBC

• The Impact of Genomics on BC
  Novel TAXONOMY?
  Prognostics
  Predictive
  Rx Targets
  Early Detection/Surveillance
Bladder Cancer (BC)
Disease Costs and Management Opportunities

- Major health care cost burden:
  - Frequent cystoscopy, high rate of recurrence etc...
  - $3-4 Billion per year in USA alone
  - HIGHEST COST per patient for any type of cancer

- Unique amenability to applying molecular detection methods (e.g. TERT)

Urothelial Carcinoma
Two Phenotypes?

- (Superficial) Non-muscle invasive BC (NMI-BC)
  - 70-80%

- Muscle Invasive BC (MI-BC)
  - 20-30%

Bladder Urothelial Carcinoma
Two Distinct Molecular Pathways

- **NMIBC**
- **H-RAS/FGFR3/mTOR**
- **PUNLMP**
- **Low Grade Papillary UrCa**
- **High Grade Papillary UrCa**
- **Invasive UrCa**

The Not So Distant Past?
Clinico-Pathologic Prognostic Factors
Predicting Recurrence and Progression in Individual Patients with Stage Ta T1 Bladder Cancer Using EORTC Risk Tables: A Combined Analysis of 2596 Patients from Seven EORTC Trials

Sylvester et al. Eur Urol 2006
- 2596 pts from 7 EORTC trials
- Predictive Model Parameters:
  - Number of Tumors
  - Tumor Size: 3 cm
  - Prior Recurrence Rate: 1 Rec/yr
  - pT
  - CIS
  - WHO grade

Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients

Stein et al J Clin Oncol 2001
- 1054 pts; 10.2 yrs median F/U
- Rad. Cystectomy + Adj Chemo radiation
- DFS 68% at 5yr and 60% at 10 yrs
- pTnm (OC vs Non-OC) only predictor of DFS/OS
  - OC LN neg group: 85% DFS at 5yr
  - Non OC LN neg group: 58% DFS at 5yr
  - LN positive group: 35% DFS at 5yr

MIBC Neoadjuvant Chemotherapy (NAC)

NAC Regimens:
- GC
- MVAC
- DD-MVAC
- Can we predict Response????

UIrol Oncol 2015
Two Genomic Circuits:

- **FGFR3** mut/Ampl; **CCND1** mut; 9q (CDKN2A) deletions
- **E2F3** ampl; **RB1** del; **PTEN** del; **CDKN2A; CCND1** loss, 5p gain

**P53/MDM2** alterations in both circuits at advanced Dz

Comprehensive molecular characterization of urothelial bladder carcinoma
The Cancer Genome Atlas Research Network

Nature: March 2014

- Integrated genomic Analysis of 131 URCa

- Average Genetic Alterations per tumor:
  - 302 mutations
  - 204 segmental CNA
  - 22 rearrangements

- Recurrent mutations in 32 genes:
  - Cell-cycle regulation
  - Chromatin regulation
  - RTK signaling pathways
  - Nine genes not frequently mutated in cancers (MLL2, ERCC2, ELF3, KLF5, RXRA, CDKN1A)

- Rx Targets in 69% of MIBC

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NEW GENOMIC TAXONOMY?
TCGA

INTEGARTED GENE EXPRESSION SUBTYPES

PAPILLARY-LIKE
BASAL / SQUAMOUS-LIKE
LUMINAL / BREAST-LIKE
Genomic Based Novel Therapeutic Targets

Rx Targets in 69% of URCa:
- mTOR/PIK3CA
- RTK/MAPK (ERBB2)
- ER

| mRNA/miRNA/Protein
| Genomic Based Novel Therapeutic Targets
| Genomic Based Novel Therapeutic Targets
| MIBC TCGA: TARGETS of Rx

- mTOR/PIK3CA
- RTK/MAPK (ERBB2)
- ER
Genomic Based Predictor of Neoadjuvant ChemoRx Response

Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy

- Whole genome mRNA expression profiling
- Three molecular subtypes of MIBC: Basal/Luminal/p53-like
- Shared molecular features with basal and luminal breast cancers
- Active p53 gene signature "p53-like" MIBC
  - resistant to neoadjuvant cisplatin-based ChemoRx
MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer


Ott et al Clin Can Res 2013

J. Hedegaard et al., Cancer Cell Jul. 2016.
MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer


Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial


Netto GJ. Lancet 2016

Role for anti-PD-L1 immune checkpoint inhibitor in advanced urothelial carcinoma

SP142 assay (Ventana) IC: 0,1,2,3
Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial

<table>
<thead>
<tr>
<th>Nivolumab</th>
<th>PD-L1&lt;1% (n=43)</th>
<th>PD-L1&gt;1% (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed objective</td>
<td>15% (4/26)</td>
<td>11% (9/78)</td>
</tr>
<tr>
<td>Partial response</td>
<td>16% (7/43)</td>
<td>22% (17/78)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>38% (16/43)</td>
<td>21% (16/78)</td>
</tr>
<tr>
<td>Progression</td>
<td>28% (12/43)</td>
<td>10% (8/78)</td>
</tr>
<tr>
<td>Unstable to establish</td>
<td>6% (3/43)</td>
<td>3% (2/78)</td>
</tr>
</tbody>
</table>

Best overall response: complete response 5% (1/22) and partial response 12% (3/22) for Nivolumab PD-L1<1%.

Nivolumab PD-L1>1% complete response 3% (2/60) and partial response 12% (7/60).

Data are number (%). Some percentages do not add up to 100 because of rounding.

Dako 28-8
Any Tumor Cell

PD-L1 IHC 22C3 pharmDx assay (Dako)
% of Tumor cell AND IC positivity
Could TERT mut be a Molecular Urine Marker for BC?

Could a Multi-genes Panel be developed with SafeSeq

Ludwig Cancer Research
JHU Pathology
JHU Brady Institute

- Two Application Settings
  - Surveillance
  - Primary Screen (Hematuria no prior TCC)

- TERT + UroSeq panel (11 genes)
- JHGBC Institute
- NIH SBIR Award
- International Collaborators
  - Osaka University, Japan
  - AC CAMARGO Cancer Ctr, Brasil
  - Hacettepe University, Turkey
- >2800 Urine and 400 FFPE Sequenced

Conclusions

- Genomics Impact on Bladder Cancer Management is FINALLY Here:
  - PGx
  - Predictive
  - Rx Targets
  - Early Detection/Surveillance

- New GENOMIC TAXONOMY is being refined and awaits
  TRANSLATION INTO OUR LABS

- So More Work Remains……..

Thank You !!!