Precision Medicine in Advanced Bladder Cancer: Where Are We Today?

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- and -

I will not discuss off label use and/or investigational use in my presentation.
Lecture Objectives

- Review **principles of precision medicine** in cancer, including biomarker types

- Understand how **personalized medicine** can impact **urologic oncology** practice through several examples that address major clinical issues in bladder cancer

- Become aware of **caveats and challenges** of implementing personalized medicine in medical practice
Sir William Osler

“If it were not for the great variability among individuals, medicine might as well be a science and not an art”

Empirical Medicine

Substantial heterogeneity in diagnostic accuracy and treatment response

Stratified Medicine

Reduce variation and improve accuracy based on group characteristics

Personalized/Precision Medicine

Right Patient
Right Treatment
Right Time

Dr Francis Collins
(NIH Director)
Personalized Oncology: Biomarkers + Targeted Drugs

Predisposition Markers

Prognostic Markers
“disease aggressiveness”

Predictive Markers
“therapy response”

“who to treat”
“what to treat with”

Risk Prediction Testing

Follow

Testing

Treat with Drug X

Treatment Success 43%

Do Not Treat

Trial

Treat with Drug X

30%
1. **Improve Primary Diagnosis**
   - Predict individuals at high risk to develop bladder cancer

2. **Optimize Surveillance of Non Muscle Invasive (NMI) Ds**
   - Predict natural history: recurrence and progression

3. **Reduce Mortality of Muscle Invasive (MI) /Metastatic Ds**
   - Identify patients with occult nodal metastasis
   - Identify high risk patients that are ALSO responders to systemic therapy (chemo, targeted, immuno)
   - New Therapeutic Targets / New Drugs
How Molecular Medicine Can Help

Predisposition Markers

- Identify patients at-risk
- Genome-wide association (GWAS)

Prognostic Markers

- Optimize surveillance of Non Muscle Invasive Ds
- FGFR3 mutations
- Identify occult nodal metastasis
- 20 gene predictor of nodal metastasis

Predictive Markers

- Stratification of patients as responders/non-responders
- Gene predictors of sensitivity chemotherapy

New Therapeutic Targets

- New targets
  - Identification
  - Drug discovery
Neoadjuvant chemotherapy

- Meta-analysis of 10 trials (2688 pts)
  - 13% reduction in risk of death
  - 5% absolute benefit at 5 yrs
  - OS from 45% to 50%
  - High Stage patients benefit most
- Adoption in community <20%

Can we increase adoption by limiting treatment to High Risk (i.e. node + patients)?

Can we identify High Risk patients that respond?

Reference:
Predicting + Nodes at Cystectomy

Training and Model Development

Laval Cohort
pN0 N=17

Wilcoxon P-value

Laval Cohort
pN1-3 N=73

Top Probes Ranked by P-Value

MSKCC Cohort

Test Sample

WNN Classifier

High Risk

Low Risk

20 Gene Model

Validation

Prospective Cohort (N=168)

20 Gene Model

Develop for Clinical Practice

Lancet Oncol. 2011 Feb;12(2):137-143
Prediction of treatment outcome in patients treated with neoadjuvant MVAC

**Tx:** Neoadjuvant MVAC (N=45) + surgery or XRT

**Outcome:** Downstaging, and Overall survival

**MSKCC & UVA**

**NCI-60 Panel**

**COXEN**

**31 Gene Model**

**Evaluation of Model on Human Tumors**

Takata

*Clin Can Res; 11(7): 2625 (2005)*

Overall Survival vs. COXEN Score

**High Score**

**Low Score**

P = 0.000656

**SWOG S1314 Trial**

**PI** Thomas Flaig MD

**Translational Science: Theodorescu**

*Proc Natl Acad Sci U S A. 2007 04(32):13086*
*Cancer Res. 2009;69(21):8302*
*Cancer Res. 2010;70(5):1753*
SWOG 1314: COXEN-directed neoadjuvant chemo

Biomarker validation and Biomarker discovery

Primary study objective: To characterize the relationship of MVAC-and GC-specific COXEN scores in terms of pT0 rate in patients treated with neoadjuvant chemotherapy

Selection Criteria SWOG 8710 (T2-T4a N0M0, cisplatin eligible)

Randomize to chemo n=184

Gem-Cis

DD-MVAC

Cystectomy Pathology

Collection Tissue (>P0), blood, urine

Molecular Analysis Gene expression Sequencing microRNA SNP

Collection Tissue, blood, urine

Molecular Analysis Gene expression Sequencing microRNA SNP
NGS has accelerated *biomarker* discovery and *targeted therapy trial* development coinciding with increased industry interest in bladder cancer.
Next Generation DNA Sequencing (NGS)

Prognostic Markers
Predictive Markers
Therapeutic Targets

NGS Bladder Cancer

Hallmarks of Cancer

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Immune activating anti-CTLA4 mAb
- Telomerase inhibitors

- Aerobic glycolysis inhibitors
- Sustaining proliferative signaling
- Evading growth suppressors
- Avoiding immune destruction
- Enabling replicative immortality
- Tumor-promoting inflammation
- Selective anti-inflammatory drugs

- Proapoptotic BH3 mimetics
- Resisting cell death
- Inducing angiogenesis
- Activating invasion & metastasis
- Inhibitors of VEGF signaling
- Inhibitors of HGF/c-Met

- Cell. 2011; 144(5):646
- Clin Cancer Res. 2014; 20(18):4935
Many tumors have cell cycle pathways altered

CDK4/6 inhibitors:
- Palbociclib
- LEE001
- LY2835219

MDM2 inhibitors:
- RG-7112
- RO5503781
- DS-3032b
- CGM097
- MK-8242
- SAR405838

CDK4/6

p53/Rb pathway
93% altered

CDKN2A
- 5% 47%

CDKN1A
- 14% 6%

CCNE1
- 0% 12%

E2F3
- 0% 18%

RB1
- 10% 15%

CCND1
- 0% 10%

MDM2
- 0% 9%

TP53
- 49% 21%

ATM
- 12% 16%

Apoptosis

Cell Cycle Progression

Therapeutic Targets

Left box: mutation
Right box: copy number
Red: activated / amplified
Blue: inactivated / deleted
Gene enrichment Analysis:
Cell cycle genes are biomarkers of progression

- Cell cycle related genes are the most consistently prognostic class of biomarkers in bladder cancer
- 15 gene model constructed to reflect optimal cell cycle related genes

Score from model predicted progression/survival in bladder cancer patients

Cell cycle related genes are the most consistently prognostic class of biomarkers in bladder cancer

15 gene model constructed to reflect optimal cell cycle related genes

False discovery rate (%)

0 5 10 15

Cell cycle phase
cell cycle process
mitotic cell cycle
cell cycle
M phase
mitosis
nuclear division
M phase of mitotic cell cycle
ectoderm development
regulation of cell proliferation

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Predictive Markers

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Agents targeting FGFR3, ERBB2, PIK3CA, TSC1/mTOR are all in clinical trials

- Activity observed in some patients
- Mechanisms of response as well as de novo and acquired resistance are unclear
“Drugging Downstream” of Ras: mTOR/TSC1

- Patient treated on Phase II trial of Everolimus (mTOR inhibitor)
- NGS revealed TSC1 and NF2 inactivating mutations
- In vitro evaluation shows TSC1 sensitizes urothelial cancer cells to mTOR inhibition

Conclusions:
- Loss of function mutations in TSC1 and NF2 associated with drug escape
- Overall study negative—exceptional responders valuable
- Combination therapy

Iyer et al. Science 2012;338:221
“Drugging Downstream” of the Ras Oncogene

**RAL Genes**
1. Ral are GTPases (molecular switches)
2. Two family members: RalA and RalB
New Approach: Blockade of Ral Activation

AIM TO DISCOVER THIS

Upstream Signals

Inactive Ral GDP

GDI

GEF

GTPase Cycle

Conformational change

Active Ral GTP

Downstream Signaling pathways

Cannot bind GTP

NO Conformational change

Cannot bind RalBPI

Growth

Metastasis
Defining Allosteric Binding Pocket and Screening

Define “Collapsing” Allosteric Binding Pocket

Computational Screen (953,032 compounds)

88 Ral “Hits”
Evaluation of Ral Hits: Biochemical [x] Biological

88 “Hits” from Computational Screen

RalA-ALPHA Screen

RalA-FLAG ELISA

Cell Spreading Assay

NMR Binding

Cancer Cell Growth In Vitro and In Vivo

PK and PD

Cancer Cell Growth In Vitro and In Vivo

Structural Similarity of Ral GTPases

RalA-GDP (18uz)

RalB-GDP (threaded)
Evaluation of Ral Hits: Xenograft Growth

- 10 nude mice per group, 1 inoculation site/mouse with 200K H2122 cells
- Treatment started day of inoculation (50 mg/kg/day)
- Drug delivered IP daily except on weekends

**Graph:**
- **Tumor Volume (mm^3)**
  - DMSO CTL.MEAN
  - Ral Drug.MEAN
  - Comparison

**Comparison:**
- **Ral A+B siRNA**
  - siCTL.MEAN
  - siRal A+B.MEAN
  - P < 0.05

**Study Details:**
- **DMSO-CTL vs. RBC8**
- **RBC8 (IP)**

**Notes:**
- **P<0.05**
**Biomarker Driven Randomized Phase II Trial Concept**

**Patient Selection Approach**
- Tumor Sample
- Ral IHC
- Gene Expression
- Ral Signature Score

**Cystectomy**
- RalA IHC
- RalB IHC

**Trial Enrollment**
- RalA Signature Level
  - P<0.001
  - P=0.01

**Clinical Trial**
- RBC8

**Hope!**
- RBC8 SOC

**Graphs**
- % Progression Free
  - RalA Signature Positive
  - RalA Signature Negative
  - P=0.01

**Months Following Radical Cystectomy**
The story of p53 in Bladder Cancer

- p53 is a tumor suppressor
- Usually inactivated by point mutation
- Point mutations result in increased protein half-life
- Detectable IHC staining in >10-20% cells has sensitivity/specificity of approximately 85%
**Retrospective**

- USC/Norris CC Experience
- p53 IHC in Bladder Cancer (N=243)
- Post cystectomy recurrence free survival

**Prospective**

- SWOG Trial (N=499)
- Post-cystectomy patients with pT1/T2N0M0 (pre-op or operative staging)
  - If p53 positive (>10% nuclear stain) – offered 3 cycles of MVAC vs. observation
  - If p53 negative, no chemotherapy offered

N Eng J Med, 1994, 1259-64,  
J Clin Oncol. 2011, 29(25):3443
Implementing Personalized Medicine

Molecular understanding of disease drives discovery and development of BIOMARKERS+ Targeted Drugs

Will PM change economics of healthcare?

Will PM benefit be cheaper or more costly?

The regulatory landscape and public policy will determine success or failure of PM

Changes in medical practice to appropriately deliver personalized medicines to patients

Reimbursement for PM will drive delivery