The Clonal Evolution of Chemo-resistant Urothelial Cancer

Seth P. Lerner, MD, FACS
Professor, Scott Department of Urology
Beth and Dave Swalm Chair in Urologic Oncology
Baylor College of Medicine

4th FOIU July 3-5, 2018
Financial and Other Disclosures

- Off-label use of drugs, devices, or other agents: none
- Data from IRB-approved human research is presented

<table>
<thead>
<tr>
<th>I have the following financial interests or relationships to disclose:</th>
<th>Disclosure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>FKD</td>
<td>S</td>
</tr>
<tr>
<td>Roche/Genentech</td>
<td>S</td>
</tr>
<tr>
<td>JBL</td>
<td>S</td>
</tr>
<tr>
<td>Viventia</td>
<td>S</td>
</tr>
<tr>
<td>BioCancell, Nucleix, QED, UroGen</td>
<td>C</td>
</tr>
<tr>
<td>UroGen, Vaxiion</td>
<td>C</td>
</tr>
</tbody>
</table>
• The problem - solving cisplatin-based chemotherapy resistance
• Mechanisms of resistance
• What we can learn from NGS of bulk tumor
• Tumor heterogeneity
• Clonal evolution
• Novel insights into chemotherapy resistance
Metastatic Bladder Cancer
M-VAC vs Gemcitabine/Cis-platin - Overall Survival

Objective response rates were M-VAC (46%) and GC (49%)
But Long-term survival 15%

von der Maase, H et al J Clin Oncol 23:4602, 2005
Impact of No Response to NAC

Study design, mutation rates, and aggregate significant somatic mutations

Eliezer M. Van Allen et al. Cancer Discovery 2014;4:1140-1153
Blocking PGE\(_2\)–induced tumour repopulation abrogates bladder cancer chemoresistance

Antonina V. Kurtova\(^1,2\), Jing Xiao\(^3\), Qianxing Mo\(^4\), Senthil Pazhanisamy\(^4\), Ross Krasnow\(^4\), Seth P. Lerner\(^4\), Fengju Chen\(^3\), Terrence T. Roh\(^1,5\), Erica Lay\(^4\), Phillip Levy Ho\(^4\) & Keith Syson Chan\(^1,2,3,4\)

Celecoxib with Chemotherapy in Localized, Muscle Invasive Bladder cancer (BLAST)

Tx: GC x 4 cycles + Celecoxib 100mg qd

Primary aims:

1) mRNA expression in pre- and post-chemotherapy specimens

2) Toxicity

Integrated Mutation and Amplifications/Deletions

**MSig1**
High APOBEC; high mut and neoantigen load; highest 5-year survival (89%)

**MSig2**
Lowest mutation rate and poorest 5-year survival (22%)

**MSig3**
High APOBEC

**MSig4**
Enriched in both ERCC2 signature and ERCC2 mutations; highest levels in smokers
The luminal-papillary, luminal-infiltrated, basal/squamous, and neuronal subtypes broke down, respectively into 3, 2, 2, and 2 smaller groups.

Katie Hoadley - UNC
Cancer Evolution and Heterogeneity

Bulk tumor analysis

Field cancerization

Driver alterations

Distant metastasis

Or this population?

This population?
Shared clonal mutations

Metastasis specific mutations

Patient 1

LN mets

Patient 2

LN and stomach

Patient 3

LN and lung

Thomsen et al, Mol Onc 2016
WES of bulk tumors for identification of mutations with predicted functional impact

LMD of 33 tumor regions + normals

Deep amplicon sequencing (4250x mean coverage) of mutations identified from WES

Fluidigm expression profiling for subtype analysis

Thomsen et al, Scientific Reports 2017
Heterogeneity and Survival

- 30 matched pre- and post-NAC resistant tumors
- Whole exome sequencing

Clonal evolution of chemotherapy-resistant urothelial carcinoma

Bishoy M Faltas¹⁻³,¹⁰, Davide Prandi⁴,¹⁰, Scott T Tagawa¹⁻³, Ana M Molina¹,², David M Nanus¹⁻³, Cora Sternberg⁵, Jonathan Rosenberg⁶, Juan Miguel Mosquera¹,⁷, Brian Robinson¹,⁷, Olivier Elemento¹,⁸,⁹, Andrea Sboner¹,⁷,⁹, Himisha Beltran¹⁻³,¹¹, Francesca Demichelis¹,⁴,⁹,¹¹ & Mark A Rubin¹,³,⁷,¹¹
Shared in all samples
Shared in more than one but not all samples
Private primary
Private metastatic
Fraction of tumor cells
0% 100% Not assessed
Wild type

Divergent evolution point

WCM077
TCHH
CREBBP
ERCC3
HDAC3
JAK2
KDM8A
MET
PIK3CA
TP53

ALK
BCOR
BRCA1
BRCA2
FANCA
GATA3
RUNX1
TP53

AHNAK2
APC
ARID1A
RBM5

AIM1
BCOR
ERBB3
JAK1
KMT2A
KMT2B
KMT2D
NCOR1
RET

ASXL1
FANCD2
TP53BP1

*p.Y220C
**p.E271K
**p.E545K

KMT2D
PEG3

GATA1
SBDS

ERBB2
F2RL1
RBM5

KMT2A

FALTAS B et al. Nature Genetics 2017

WCM088
DAXX
KMT2B
KMT2D
NCOR1
RET

*p.K2654N
**p.S2140

FALTAS B et al. Nature Genetics 2017

WCM233

FANCD2

KMT2D

ERBB2

FALTAS B et al. Nature Genetics 2017

WCM168

*p.E726K
**p.D663H

FALTAS B et al. Nature Genetics 2017

WCM249

TP53
SMARCA4
E2F1
STAG1
CDKN2A
CTNNB1

ARID1B
ARID4B
FANCA
KDM5C
PGD
PDGFRC
WT1

ERBB2
FALTAS B et al. Nature Genetics 2017

WCM259

CASC5
TP53
ASXL1

ARID1B
ARID4B
KMT2A

EBF1
UDR5

ERBB2
FALTAS B et al. Nature Genetics 2017

FALTAS B et al. Nature Genetics 2017

A: Bladder primary
B: LN metastasis
C: Lung metastasis

A: Bladder primary
B: LN metastasis
C: Peritoneum metastasis

A: Bladder #1 primary
B: Bladder #2 primary
C: Bladder #3 primary
D: LN metastasis

A: Bladder primary
B: LN metastasis
C: Prostate bed metastasis

A: Renal pelvis primary
B: Liver #1 metastasis
C: Liver #2 metastasis

A: Bladder primary
B: LN #1 metastasis
C: LN #2 metastasis
D: Peritoneum metastasis

FALTAS B et al. Nature Genetics 2017
Sub-clonal SNVs in the primary tumor \(\rightarrow\) enriched in post-DR metastatic lesions

Shared in all samples

Shared in more than one but not all samples

Private primary

Private metastatic

Faltas B et al. Nature Genetics 2017
Cisplatin Resistance
Mutations and Mutation Signatures pre- and post-NAC

Cisplatin Mutation Signature

In-depth characterization of the cisplatin mutational signature in human cell lines and in esophageal and liver tumors

Boot, et al Genome Research; posted on line 9/17/2017

The Repertoire of Mutational Signatures in Human Cancer

Ludmil B Alexandrov¹*, Jaegil Kim²*, Nicholas J Haradhvala²,³*, Mi Ni Huang⁴*, Alvin WT Ng⁴, Arnoud Boot⁴, Kyle R Covington⁵, Dmitry A Gordenin⁶, Erik Bergstrom¹, Nuria Lopez-Bigas⁷,⁸,⁹, Leszek J Klimczak¹⁰, John R McPherson⁴, Sandro Morganella¹¹, Radhakrishnan Sabarinathan⁷,⁸, David A Wheeler⁵, Ville Mustonen¹², Gad Getz²,³,¹³,¹⁴**, Steven G Rozen⁴***, Michael R Stratton¹¹***, on behalf of the PCAWG Mutational Signatures Working Group and the ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Network

Posted on line 5/15/2018

• New signatures SBS31 and 35
  – Prior platinum chemotherapy
  – Characteristic single and dinucleotide substitutions
Conclusions

- Treatment resistance is a significant problem for neoadjuvant chemotherapy and treatment of metastatic disease
- TCGA bulk tumor analysis identifies significant heterogeneity within individual tumors and subtypes
- Branching evolution and metastatic spread are early events
Conclusions

- Chemotherapy-treated UCB is characterized by intra-patient mutational heterogeneity, and the majority of mutations are not shared.
- Chemotherapy increases the genomic diversity post treatment mediated in part by APOBEC mutagenesis.
- A novel cisplatin mutation signature recently described.
- Thanks to Bishoy Faltas and Lars Dyrsjkot who provided some slides for this presentation.