Will circulating biomarkers help to deliver precision medicine in CRPC?

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Summary

• Why circulating Biomarkers?

• Proteins, hormones and other metabolites

• CTCs

• Nucleid Acids

• Take home message
Does precision medicine exist in CRPC?

- **Pre 2010**: Classical ADT, 2ry/3ry hormonal manipulations (Docetaxel (2004), Mitoxantrone)

- **2010**: Spirucel T (only US), Cabazitaxel

- **2011**: Abiraterone

- **2012**: Abiraterone, Enzalutamide

- **2013**: Radium-223 dichloride (pre-/post-docetaxel), No visceral disease

- **2014**: Docetaxel, Enzalutamide

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How precision medicine could Help

Treatments vs. Costs

Treatments

Benefits

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How precision medicine could Help

Prognostic test:
- Low risk
- Low risk
- Low risk
- High risk
- High risk

Predictive test:

Pharmacodynamic test:

Drug selection

Dose selection

Schwarznbach et al. nat Reviews, 2011
Hurdles for precision medicine in CRPC

Traditional

• Poor understanding of Prostate Cancer Biology
• Clinical heterogeneity and poor preclinical models
• Scarce effective treatment options
• Lack of benefit surrogate endpoints slows development

Ongoing hurdles

• Limited access to tumour tissue in advanced and CRPC disease in clinical practice outside trials/academic institutions
Advantages of Circulating biomarkers

- Blood represents an:
  - Attractive non-invasive source of tumour and host information
  - Repeatable
  - Easier implementation than tumour biopsies in:
    - Clinical trials
    - Routine practice
Have circulating biomarkers already contributed in CRPC management?

How would they contribute in the future of precision medicine in CRPC?
Proteins, hormones and metabolites
Proteins: serum, plasma & blood

<table>
<thead>
<tr>
<th>BIOMARKER</th>
<th>Prognostic basal</th>
<th>Predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Specific Antigen (PSA)</td>
<td>✔</td>
<td>✔/✖</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>✔</td>
<td></td>
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<tr>
<td>Lactate dehydrogenase</td>
<td>✔</td>
<td></td>
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<tr>
<td>Alkaline Phosphatase</td>
<td>✔/✖</td>
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COU-AA-301

Abiraterone 1000mg daily
Prednisone 5mg BID
n=797

Placebo daily
Prednisone 5mg BID
n=398

Primary end point:
• OS (25% improvement; HR 0.8)

Secondary end points:
• TTPP
• rPFS (Radiographic progression)
• PSA response

FACT-P questionnaire
Prospective data collection: Day 1 of Cycles 1, 4, 7, 10, and every 6 cycles thereafter until the end of study treatment

Stratification by:
- ECOG performance status
  - 0-1 vs 2
- Worst pain over previous 24 hours
  - BPI short form; 0-3 (absent) vs 4-10 (present)
- Prior chemotherapy
  - 1 vs 2
- Type of progression
  - PSA only vs radiographic with or without PSA

1195 patients with progressive mCRPC
Failed 1 or 2 chemotherapy regimens, 1 of which contained docetaxel

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2:1

Serum hormones in COU-AA-301

Serum hormones in COU-AA-301

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<tr>
<td>Testosterone</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>Androstenodione</td>
<td>✔</td>
<td>✗</td>
</tr>
<tr>
<td>DHEAS</td>
<td>✔</td>
<td>✗</td>
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</table>

Metabolomics in CRPC

- Metabolomic profiling has been proposed as a potential source for biomarker identification

- Metabolome is closer to Phenotype
Circulating Tumor Cells
Circulating Tumor Cells (CTCs)

- Peripheral blood epithelial cells shed, actively or passively, from tumor surface of cancer patients

- Isolation:
  - Enrichment
  - Detection
  - Enumeration

- Profiling

Yap, Lorente, Omlin, Olmos & de Bono. Clin Cancer Res. 2014
CTCs enumeration

- Single centre study: experimental therapies

- Multicentre study: standard therapies
CTCs count changes

Conversion from >5 CTC to <5 CTC

- CTC counts are prognostic
- CTC counts may indicate when treatment is effective
- **BUT**
- This does not establish ‘surrogacy’
- Prospective Phase III trials in which the evaluation of the marker (CTC number) are linked to the development of a drug are required

CTCs surrogacy: COU-AA-301

- Higher conversion rates with AA relative to placebo, and benefit for favorable (CTC < 5) and unfavorable (CTC ≥ 5) CTC subgroups
- Higher percentage of ≥30% declines in AA patients.

- Independent predictive factor of OS in MVA.

Scher et al. ASCO annual meeting 2011
Possible trial design to answer the question of CTCs in monitoring treatment benefit at a individual patient level.
# CTCs as surrogate tumour tissue

<table>
<thead>
<tr>
<th>Protein assays</th>
<th>Use/Applications</th>
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<tbody>
<tr>
<td>AR (Nuclear/Cytoplasmatic)</td>
<td>Target identification/Pharmacodynamic</td>
</tr>
<tr>
<td>EGFR</td>
<td>Target identification</td>
</tr>
<tr>
<td>HER2</td>
<td>Target identification</td>
</tr>
<tr>
<td>IGF-1R</td>
<td>Target identification</td>
</tr>
<tr>
<td>M30 (CK-M30)</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>γH2AX</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>pHH3</td>
<td>Pharmacodynamic</td>
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<tr>
<td>AR amplification</td>
<td>Marker of resistance</td>
</tr>
<tr>
<td>pTEN loss</td>
<td>Marker of resistance/Drug combinations</td>
</tr>
<tr>
<td>TMPRSS2/ERG</td>
<td>Taxonomic classification</td>
</tr>
<tr>
<td>Myc amplification</td>
<td>Tumor profiling</td>
</tr>
</tbody>
</table>

Olmos, Barker, Sharma et al. Clin Cancer Res. 2011

Attard, Swennenhuis, Olmos et al. Cancer Res. 2009
Monitoring tumour changes in CTCs

- AR mutations: Treatment selection and monitoring
  

- AR alternative splicing variants

Yap, Lorente, Omlin, Olmos & de Bono. Clin Cancer Res. 2014
CTCs *AR-V7* positive: predictive marker


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CTCs AR-V7 current limitations

- Single-centre experience
- Require immediate initial processing
  - Enrichment CTCs
  - Lysis and RNA capture
- Haemolysis
- Novel methods

Genitourinary tumours, prostate 2
Monday 29; 02:00 PM - 03:45 PM
Abstract 7570
-Galeterone in AR-V7
-EPIC AR-V7 detection on CTCs
Organoids and PDX from CTCs


Yap, Lorente, Omlin, Olmos & de Bono. Clin Cancer Res. 2014
Circulating Nucleid Acids
Whole blood RNA signatures

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Germline DNA

- >100 SNPs variants associated to cancer risk, SNPs variants also associated with toxicity.
- Screening of germline \textit{BRCA1 and BRCA2} mutations in >2000 Pca.
- \textit{gBRCA 2} mutations are an independent prognostic factor for survival\textsuperscript{1}. PARPi are very active in this population\textsuperscript{2}. Somatic?

Genitourinary tumours, prostate 2, Monday 29; 02:00 PM - 03:45 PM
LBA 20. Olaparib in sporadic CRPC patients

Circulating free DNA in CRPC

• Multiple clones in metastatic disease represented in cfDNA

• Dynamic clonal architectural heterogeneity

• Monitoring of disease i.e. AR mut or Amplif

Take home messages

• The backbone of precision medicine is about maximising benefit and minimising risk in our patients

• Circulating makers to help in the stratification and monitoring of CRPC are use everyday

• Blood is a source of information from the tumor and the host

• Novel technologies are helping in treatment selection and monitoring

• Still implementation is routine practice needs more validation work, reproducibility and efficiency
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