Gene Therapy for Prostate Cancer

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Learning Objectives

- Identify the advantages & disadvantages of combination gene therapy in low-risk and high-risk prostate cancer patients with localized disease
- Describe the role of immune modulators like granulocyte-monocyte colony stimulating factor (GM-CSF) in cancer cell vaccines
- Correlate available safety and efficacy data utilizing vaccines and antisense oligonucleotides as treatments for metastatic prostate cancer

Gene Therapy for Localized Disease

<table>
<thead>
<tr>
<th>Combination Gene Therapy</th>
<th>Phase</th>
<th>Patients</th>
<th>Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-suicide1</td>
<td>I</td>
<td>16</td>
<td>PSA ↓ ≥ 25% in 7</td>
</tr>
<tr>
<td>Ad5-CD/TK/rep + 5FC/GCV</td>
<td></td>
<td></td>
<td>PSA ↓ ≥ 50% in 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>At 5-yrs2: PSADT ↑ from 17 to 31 mo (p = 0.014)</td>
</tr>
<tr>
<td>Trimodal3</td>
<td>I</td>
<td>10</td>
<td>PSA ≤ 0.5 ng/mL in 5</td>
</tr>
<tr>
<td>Ad5-CD/TK/rep + 5FC/GCV + EBRT</td>
<td></td>
<td></td>
<td>4-yrs (n=9)4: intermediate-risk – no disease evidence</td>
</tr>
</tbody>
</table>

Adenovirus Vector

Adapted from http://user.chollian.net/~epker/Zeado003.gif
Accessed 9/26/09

Combination Gene Therapy + ADT

Low-risk n = 29
- Days 0, 14 Adv-TK intraprostatic (5 x 10¹¹ vp)
- Valacyclovir
- IMRT

High-risk n = 26
- Days 0, 56, 70 Adv-TK intraprostatic (5 x 10¹¹ vp)
- Valacyclovir
- IMRT
- Androgen deprivation therapy

Low-risk and high-risk arm biopsy results showed no evidence of prostate carcinoma at 24 months

True or False

- Replication-competent adenovirus-mediated suicide gene therapy may lengthen prostate-specific antigen doubling time and delay the need for androgen suppression therapy in patients with low-risk prostate cancer.

- True

PROSTVAC-VF

Recombinant vaccinia vector as primary vaccination

Multiple booster vaccines with fowlpox vector

PSA-TRICOM are transgenes for PSA and T-cells

Antigen Presenting cells

TARGETED IMMUNE RESPONSE AND TUMOR CELL DESTRUCTION

Adapted from Expert Opinion on Investigational Drugs 2009;18:1001-1011

ECOG 9802 PROSTVAC-VF + TRICOM

N = 29
P = 0.002

Median PSADT


GVAX Allogenic Whole Cell Vaccine

Antigen Presenting cells

Adapted from Cancer Letters 2008;266:116-134

VITAL-2 Phase III Clinical Trial of GVAX for Prostate Cancer

N = 408

GVAX + Docetaxel 75 mg/m² q 3 wk + Prednisone 10 mg/day

Docetaxel 75 mg/m² q 3 wk + Prednisone 10 mg/day

P-value

Docetaxel cycles completed (no.)

5

7

0.01

Overall survival (mo.)

12.2

14.1

0.0076

95% CI (1.15-2.53)

Deaths

67

47

Study stopped prematurely due to an imbalance in deaths in GVAX arm


Results of D9901 & D9902A with Sipuleucel-T in Advanced Prostate Cancer

Sipuleucel-T

Placebo

Hazard ratio

N = 147

N = 78

23.2

18.9

1.5 (1.1-2.05)

P = 0.011

9.7

11.1

1.26 (0.95-1.68)

P = 0.111

Note: Hazard ratio is expressed as risk in placebo treated patients divided by the risk for patients treated with sipuleucel-T

Adapted from Cancer 2009;115:3670-3679

Leukopheresis
Prostate acid phosphatase fused to GM-CSF
**D9902B**

A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Immunotherapy With Autologous Antigen Presenting Cells Loading with PA2024 (Sipuleucel-T, APC8015) in Men with Metastatic Androgen Independent Prostatic Adenocarcinoma

**Metastatic Androgen Independent Prostate Cancer**

N = 500

Sipuleucel-T  Placebo

Primary Objective: Overall survival
Secondary Objectives: Time to disease progression

Adapted from www.clinicaltrials.gov
Accessed 9/17/09

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**Antisense Oligonucleotides**

- Chemically modified DNA-like molecules 17-22 nucleotides in length

\[
\text{mRNA} + \text{Antisense oligonucleotide} \rightarrow \text{Resulting inhibition of gene expression}
\]

Current Opinion in Urology 2007;17:182-187

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**Docetaxel/Prednisone + OGX-011 in Metastatic Prostate Cancer**

- Granulocyte-monocyte colony stimulating factor (GM-CSF)-secreting cancer cell vaccines induce anti-tumor immune responses by recruiting antigen presenting cells and activating CD4+ and CD8+ T-cells.

- True

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**Docetaxel + Oblimersen Sodium (Bcl-2 Antisense Oligonucleotide)**

<table>
<thead>
<tr>
<th></th>
<th>Docetaxel N = 57</th>
<th>Docetaxel + Oblimersen N = 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed PSA response (%)</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Partial response (RECIST) (%)</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>Major toxic events (%)</td>
<td>22.8</td>
<td>40.7</td>
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Primary end points of study were not met with docetaxel-oblimersen

Adapted from Annals of Oncology 2009;20:1264-1269

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**True or False**

- Oblimersen should be combined with docetaxel in all patients with castrate-resistant prostate cancer.

- False
Conclusions

- Limiting factors of current trials:
  - Efficiency
  - Selectivity
  - Immunogenicity
  - Lack of specific outcome improvement
- Continue research in transcriptional targeting
- Future gene therapy trials are needed combining hormonal, chemotherapy and radiation

Questions?

Thank you for your attention.

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