Immunotherapy in NSCLC

hopes & challenges

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NSCLC: the reality today

- Number 1 cancer killer worldwide and in Europe
- High rates of fatal relapse due to chemo- and radioresistant residual disease
- Immunotherapy as a rational alternative/complementary treatment?
Immunological tumor destruction

William B. Coley 1862 - 1936

S. pyogenes toxin

sarcoma

Paul Ehrlich, 1905

In Immunity with Special Reference to Cell Life.

of the organism against elements standing biologically much higher in
the scale than erythrocytes and much more foreign to the body than
those exceedingly lowly organisms, the bacteria. I refer here to the
production of “Antikörper” against cells of the higher animal organi-
sation, e.g., ciliated epithelium (v. Dungern), spermatogonia (Kochstetter,
Metschnikoff, Moosvi), kidney cells, and leucocytes. These “Anti-
körper” are also of a complex nature. They obey the already de-
scribed law of elective absorption, and their origin is in keeping with
the rule that only the antibody of a serum directed against pa-
ray (merocytes). But even if in the immediate future no great practical
success is attained, we must remember that we are only at the very
beginning of a rational investigation of properties of cells which
hitherto have been too lightly regarded.

available for therapeutic application. The idea has already been
mooted by v. Dungern, of attacking epithelial new formations, particu-
larly carcinoma, by means of specific “antiepithelial sera,” and
Immunological tumor destruction
today’s view

Immunotherapy against lung cancer?
key assumptions...

- The immune system can sense the presence of lung carcinoma
- The immune system can eradicate chemo- and radioresistant cancer cell clones
- Immunological memory can guard against disease relapse
Evidence for anti-tumoral immune responses in NSCLC

Tumor-induced lymphoid aggregates in resectable NSCLC:
- contain T-cells and activated dendritic cells
- the number of activated DCs correlates with better survival

Dieu-Nosjean et al, J Clin Oncol 2008
Evidence for anti-tumoral immune responses in NSCLC

**Immunotherapy for NSCLC: recent trials**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Stage</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPI-501212/IV + chemo</td>
<td>IIIB/IV</td>
<td>stopped</td>
<td></td>
<td></td>
<td>no benefit over chemo</td>
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<tr>
<td>PF-05270730 + erlotinib</td>
<td>IIIB/IV</td>
<td></td>
<td></td>
<td></td>
<td>ongoing</td>
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<tr>
<td>L BLF-25 (Blimpovax)</td>
<td>IIIB/IV</td>
<td></td>
<td></td>
<td></td>
<td>median survival 17.4 mo (stat signal in IIIB)</td>
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<tr>
<td>CP2101</td>
<td>IIIB/IV</td>
<td></td>
<td></td>
<td></td>
<td>planned 68% 1-y survival</td>
</tr>
<tr>
<td>rEOF</td>
<td>IIIB/IV</td>
<td></td>
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<td></td>
<td>median survival 8.4 mo</td>
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<tr>
<td>MAUL-A3</td>
<td>III adjuv.</td>
<td></td>
<td></td>
<td></td>
<td>HR 0.76 vs placebo, p=0.122</td>
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<tr>
<td>GVAX</td>
<td>IIIB/IV</td>
<td></td>
<td></td>
<td></td>
<td>signal in IAC subset</td>
</tr>
<tr>
<td>GVAX in IAC</td>
<td>IIIB/IV</td>
<td></td>
<td></td>
<td></td>
<td>ongoing</td>
</tr>
<tr>
<td>belagenpimtanumab-L (Lucanix)</td>
<td>IIIB/IV</td>
<td></td>
<td></td>
<td></td>
<td>median survival 14.7 mo</td>
</tr>
<tr>
<td>Autologous DC-therapy</td>
<td>I-IV</td>
<td></td>
<td></td>
<td></td>
<td>64% immune response anecdotal clin. benefit</td>
</tr>
</tbody>
</table>
**Immunotherapy for NSCLC: recent trials**

- **MAGE-A3**
- **Placebo**

HR = 0.75 (95% CI 0.46-1.23)
One-sided logrank p = 0.122

Median follow up 44 months

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>NSCLC</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>122</td>
<td>103</td>
<td>19</td>
</tr>
<tr>
<td>69</td>
<td>33</td>
<td>13</td>
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<td>57</td>
<td>52</td>
<td>11</td>
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<tr>
<td>47</td>
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<td>7</td>
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<tr>
<td>23</td>
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<td>3</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

*J Clin Oncol 25 Suppl 18:398S, 2007*

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**Dendritic cells as cellular vaccines**

**How does a classical vaccine work?**

- **Antigen**
  - Listeria toxoid
  - HBs
  - MAGE-3
  - EGF
  - ...

- **Adjuvant**
  - Alum
  - Montanide ISA
  - TLR agonists
  - ASO2B
  - ...

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*Immunotherapy in NSCLC*
Classical vaccines act by targeting dendritic cells in the body

Cancer vaccines require a more sophisticated approach...

Classical vaccination...

- ...is a blind and random targeting of functionally heterogenous dendritic cell populations
- DCs in cancer patients are dysfunctional, immunosuppressive
- → risk of aggravating tolerance towards cancer antigens
- → inject activated, antigen-loaded DCs as a vaccine
Autologous dendritic cell cancer vaccines: the making of

- Monocytes
- Autologous tumor extracts
- Whole tumor mRNA
- Synthetic peptide
- Viral vectors
- 6-day culture in GM-CSF / IL-4

Immature DCs

Activated, antigen-presenting dendritic cells

Autologous DC vaccines in lung cancer: clinical trials so far

Author Manuscript
Published in final edited form as:
Lung Cancer. 2007 September; 57(3): 308-312.

Immunization of NSCLC Patients with Antigen-pulsed Immature Autologous Dendritic Cells

Edward A. Hirschowitz1,2, Terry Foskey1, Giovanna E. Hilgad3, and John R. Yannelli2,3
1Division of Pulmonary and Critical Care Medicine, University of Kentucky, Chandler Medical Center, Lexington, Kentucky
2Vanderbilt University Medical Center, Nashville, Tennessee
3Department of Microbiology and Immunology, University of Kentucky, Chandler Medical Center, Lexington, Kentucky

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K. Vermeeren Oct 20 2010

K. Vermeeren Oct 21 2011
### Autologous DC vaccines in lung cancer: clinical trials so far

**Hirschowitz et al Ling Cancer 2007**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Stage</th>
<th>Months from conventional treatment</th>
<th>Months from 2nd vaccine</th>
<th>Recurrence from 2nd vaccine (months)</th>
<th>Status at time of report</th>
<th>Immuneologic Response</th>
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<tr>
<td>DC17 IIB</td>
<td>51</td>
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<tr>
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<td>+</td>
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<td>Expired 12</td>
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<td>Progressive Local-regional Failure</td>
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<tr>
<td>DC21 IIIIB</td>
<td>Expired 6</td>
<td>Expired 2</td>
<td>2</td>
<td>Progressive Local-regional Failure</td>
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<tr>
<td>DC23 IIB</td>
<td>25</td>
<td>17</td>
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<tr>
<td>DC25 IIIA</td>
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<td>&lt;1</td>
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<tr>
<td>DL:09 IIIIB</td>
<td>21</td>
<td>10</td>
<td>1</td>
<td>Metastasis Skeletal Spread</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

- Primary endpoint: immune responses: 9/14 (64% response rate)
- Excellent toxicity profile
- No obvious clinical benefit
- Small, heterogeneous population; injection of immature DCs (???)

[Image of CT scans labeled A to D] Referenced sources: 
Immune-related response criteria

Response after Initial Increase in Total Tumor Burden

- Week 12: Initial increase in total tumor burden (in WHPD)
- Week 14: responding
- Week 20: response
- Follow-up ongoing

Patient treated with 10 mg/kg ipilimumab monotherapy in study CA104-000

DC cancer vaccines: great idea… small effects so far
DC cancer vaccines: great idea… small effects so far

Immuno-subversion in the lung cancer environment
DC vaccines today...

a “shot” in the dark

Unlocking DC vaccine potential

1. map immuno-suppressive landscape in NSCLC
2. disrupt dominant immuno-suppressive signals ("release the brakes")
3. targeted re-engineering of vaccine DCs

DC vaccines: “releasing the brakes”

- bevacizumab
- sunitinib
- sorafenib
- IL-10
- TGF-β
- VEGF
- PGE2
- ATRA
- STATTCA
- NO
- NOB
- Fadrozole
- HDACi
- defibrotide
- IDO
- CTLA4
- low-dose cyclophosphamide
- myoglobin
- GM-CSF

malignant myoid suppressor cell

macrophage

tumor-draining lymph node
DC vaccines in lung cancer
back to the mouse

<table>
<thead>
<tr>
<th>Image 1</th>
<th>Image 2</th>
<th>Image 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A mouse</td>
<td>A tumor</td>
<td>A heart</td>
</tr>
</tbody>
</table>

![Graph showing cancer progression and survival](image)

Percent survival vs. time (days)

- Tumor-loaded DCs
- Mock-loaded DCs
- Saline

L. Pyfferen et al., unpublished
DC immunotherapy in NSCLC: key priorities towards success

- **therapeutic setting:** define the dominant immuno-subversive mechanisms in NSCLC
  - tumor load
  - histology
  - optimal "debulking" treatment (surgery / chemo / radio / targeted Rx)
  - induce immunogenic cell death (choice of chemo/radio)
  - (prognostic/predictive signatures?)

- **adjuvant setting:** understand the immunological climate of residual disease (chemo/radio-resistant cells, cancer stem cell niche)
  - hypoxia vs immune response
  - immunomodulation by cancer stem cell-specific signals (Notch, Wnt, Shh...)
  - how long should we vaccinate?