What’s new in melanoma therapy?

Paul B. Chapman, MD
Activity of single agents in melanoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTIC</td>
<td>10-15%</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>10-18%</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>14-29%</td>
</tr>
<tr>
<td>IL-2</td>
<td>16%</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>10-14%</td>
</tr>
<tr>
<td>Taxol</td>
<td>14%</td>
</tr>
<tr>
<td>Vincristine</td>
<td>12%</td>
</tr>
</tbody>
</table>
Combination regimens that have been compared with DTIC

- Cisplatin, vinblastine, bleomycin
- DTIC/BCNU/cisplatin/tamoxifen
- DTIC/tamoxifen
- DTIC/IFNα
- DTIC/bcl2 antisense
<table>
<thead>
<tr>
<th>Drug</th>
<th>&quot;Attenuated&quot;</th>
<th>&quot;Full&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>20 mg/m² x 3</td>
<td>25 mg/m² x 4</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>1.2 mg/m² x 3</td>
<td>1.5 mg/m² x 4</td>
</tr>
<tr>
<td>TMZ</td>
<td>150 mg/m² x 5</td>
<td>150 mg/m² x 5</td>
</tr>
</tbody>
</table>

60% and 80% indicate the percentage of full dosages.
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Full dose</th>
<th>Attenuated dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>28</td>
<td>59</td>
</tr>
<tr>
<td>% men</td>
<td>61%</td>
<td>66%</td>
</tr>
<tr>
<td>Median age</td>
<td>66 (41-79)</td>
<td>61 (34-85)</td>
</tr>
<tr>
<td>Stage III</td>
<td>2 (7%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>26 (93%)</td>
<td>55 (93%)</td>
</tr>
<tr>
<td>M1a</td>
<td>2 (7%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>M1b</td>
<td>3 (11%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>M1c</td>
<td>21 (75%)</td>
<td>39 (66%)</td>
</tr>
<tr>
<td>Prior chemo</td>
<td>68%</td>
<td>51%</td>
</tr>
<tr>
<td>Median # cycles</td>
<td>3 (1-7)</td>
<td>2 (1-10)</td>
</tr>
</tbody>
</table>
Response to CVT chemotherapy
MSKCC 3-yr experience

% responding

- Attenuated dose
- Full dose
Survival by response

0 6 12 18 24 30 36

0 20 40 60 80 100

p<0.001

Median 5.3 months

Responders

Non-responders

Months

Percent survival
Chemotherapy in melanoma

- Little exploration of comb. chemo.
- Dose matters
- There are responses
- Responders live longer
Response proportions to high-dose IL-2 in 270 patients treated on 7 NCI-sponsored trials: 1985-1993

<table>
<thead>
<tr>
<th>Response</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>PR</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>CR + PR</td>
<td>43</td>
<td>16</td>
</tr>
</tbody>
</table>

Atkins et al. JCO 17:2105, 1999
High dose IL-2 – Durability of responses

Atkins et al. JCO 17:2105, 1999
Figure 15.44a  The Biology of Cancer (© Garland Science 2007)
Fig 1. Lymphodepletion and adoptive cell transfer-induced regression of metastatic disease in diverse anatomic sites

Challenges for Adoptive Immunotherapy in the future

- Can it be done outside of the NCI?
- How effective will it be, really?
- What kind of T cells should we be giving?
- Should we give a vaccine with it?
T-Cell Activation Is A Complex Process

Antigen-specific T-Cell Activation
- TCR : Antigen MHC
- CD28 : B7 Co-stimulation

Activated T cell
- IL-2 secretion
- Proliferation
- Effector function
- Induction of CTLA-4

CTLA4 : B7 suppression Termination of response
CTLA-4 Blockade Activates Antigen Specific T-Cell Responses
Pretreatment
**Pre-treatment**

- Week 12 (10/06): 4 blinded doses ipilimumab

**12/06**

- 4 10 mg/kg doses ipilimumab

**5/07**

- No drug
Challenges for Anti-CTLA4 therapy in the future

- Who responds, who doesn’t?
- How frequently does it have to be given?
- Should we give a vaccine with it?
ERK
Raf-A, B, C
MEK 1,2
To nucleus

Adapted from: Molecular Cell Biology, Freeman H.(ed.) 4th ed
Response to Imatinib

Response to MEK inhibitor

Pretreatment

Post-treatment
Challenges for Anti-STB therapy in the future

- Are we really blocking the pathway?
- How completely do you have to block it?
- Which tumors should we treat?
- Should we combine anti-STB drugs?
- Should we give chemotherapy with it?