gp100 (209-2M) peptide and High Dose Interleukin-2 in HLA-A2+ Advanced Melanoma Patients

Cytokine Working Group
Experience
# Metastatic Melanoma - Progress in Past 30 years

<table>
<thead>
<tr>
<th>Approved Therapies</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ DTIC</td>
<td>1970’s</td>
</tr>
<tr>
<td>♦ High Dose Interleukin-2</td>
<td>1998</td>
</tr>
</tbody>
</table>
INTERLEUKIN-2 TREATMENT REGIMEN

IL-2
600,000 or
720,000 IU/kg
Q8H by
15 min infusion
Over 5-6 days
Max 14-15 doses

Rest

IL-2
600,000 or
720,000 IU/kg
Q8H by
15 min infusion
Over 5-6 days
Max 14-15 doses

Repeat at 8-12 weeks if responding

Maximum 3 or so courses
High Dose IL-2 Therapy* in Advanced Melanoma

- RR: 16% (43 / 270)
- Durable responses
  - Median 8.9 mos
  - CR: median not reached
- Toxic
- Inpatient
- Expensive
- Use limited to selected pts and Rx Centers

*Atkins et al JCO, 1999 (N=270)
High Dose IL-2: Survival in Melanoma

<table>
<thead>
<tr>
<th>median (mos)</th>
<th>range</th>
</tr>
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<tbody>
<tr>
<td>overall</td>
<td>12.0</td>
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</table>

11% (30/270) remain alive at minimum 5 year f/up
### Peptides

<table>
<thead>
<tr>
<th>Allele</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
<th>P9</th>
</tr>
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<tbody>
<tr>
<td>HLA-A*0201</td>
<td>L</td>
<td>I</td>
<td>R</td>
<td>R</td>
<td>K</td>
<td>R</td>
<td>I</td>
<td>L</td>
<td>V</td>
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<td></td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>V</td>
<td>V</td>
<td>L</td>
<td>V</td>
<td>F</td>
</tr>
<tr>
<td>HLA-A3</td>
<td>L</td>
<td>I</td>
<td>R</td>
<td>L</td>
<td>K</td>
<td>R</td>
<td>I</td>
<td>L</td>
<td>V</td>
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<tr>
<td></td>
<td>L</td>
<td>I</td>
<td>R</td>
<td>L</td>
<td>K</td>
<td>R</td>
<td>I</td>
<td>L</td>
<td>V</td>
</tr>
<tr>
<td>HLA-A*6801</td>
<td>E</td>
<td>V</td>
<td>A</td>
<td>V</td>
<td>A</td>
<td>V</td>
<td>A</td>
<td>A</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>V</td>
<td>A</td>
<td>V</td>
<td>A</td>
<td>V</td>
<td>A</td>
<td>A</td>
<td>R</td>
</tr>
<tr>
<td>HLA-B7</td>
<td>P</td>
<td>P</td>
<td>Q</td>
<td>P</td>
<td>Q</td>
<td>P</td>
<td>P</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
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<td>P</td>
<td>P</td>
<td>Q</td>
<td>P</td>
<td>Q</td>
<td>P</td>
<td>P</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>G</td>
<td>R</td>
<td>I</td>
<td>D</td>
<td>K</td>
<td>P</td>
<td>I</td>
<td>L</td>
<td>K</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>R</td>
<td>I</td>
<td>D</td>
<td>K</td>
<td>P</td>
<td>I</td>
<td>L</td>
<td>K</td>
</tr>
</tbody>
</table>

### Pocket Diagram

- **Peptide**: $\text{NH}_3^+$
- **Pockets**: A, B, D, C, E, F
MALIGNANT MELANOMA: PEPTIDE VACCINES

T cell defined epitopes shared by HLA-matched melanomas

HLA-A2 Epitopes (nonapeptides)

\[
\begin{align*}
gp100(209-2M) & \quad IT(M)DQVPFSV \\
MART-1(26) & \quad AA(L)GIGILTV \\
Tyrosinase(368) & \quad YMN(D)GTMSQV \\
\text{Heteroclitic peptides} & \quad \text{modified to be more effective for T cell activation}
\end{align*}
\]
Findings at the NCI-Surgery Branch with gp100 209-2M alone and with high Dose Interleukin-2

*10/11 patients respond immunologically ELISPOT and tetrarmers to gp209-2M + IFA, while 0/11 clinical responses (Nat Med. 4, 1998)*

*Later followup report shows 0/32 clinical responses (Nat Med. 10, 2004)*
A

gp209-2M
+
IFA
D-5
IL-2 720,000 IU/kg
Q8 h x 14 doses
Repeat q3 Wks

B

gp209-2M
+
IFA
D-1
IL-2 720,000 IU/kg
Q8 h x 14 doses
Repeat q3 Wks

C

gp209-2M
+
IFA
Wk1

gp209-2M
+
IFA
Wk4

gp209-2M
+
IFA
Wk7
D-1
IL-2 720,000 IU/kg
Q8 h x 14 doses
Repeat q3 Wks
IL-2 + gp100 209-2M Peptide Vaccine

- $13/31$ (42%) respond to gp209-2M + HD IL-2 with 12 PR and 1 CR, while only 16% with immune response to peptide
- Follow-up (update) $15/47$ (32%) respond clinically (14 PR and 1 CR) to peptide + HD IL-2

*Rosenberg et al Nat Med 4:1998*
IL-2 + gp100 209-2M Peptide Vaccine in Melanoma

♦ NCI disseminate trial as phase III (concern results not sufficient)
♦ NCI SB Consortium Phase III Trial
  HD IL-2 +/- vaccine (underway)
♦ This Report:
  CWG Three Arm Phase II trial
  Vaccine + various HD IL-2 Schedules
May Repeat q12 Wks, Max. 3 Courses

IL-2 600,000 IU/kg
Q8 h x 14 doses

G209-2M + Montanide ISA-51

Wk1

D-1

Wk4

Wk7

Wk10

May Repeat q12 Wks, Max. 3 Courses

IL-2 600,000 IU/kg
Q8 h x 14 doses

G209-2M + Montanide ISA-51

G209-2M + Montanide ISA-51

G209-2M + Montanide ISA-51

Wk4

Wk7

Wk10

Administer q3 Wks x 4

IL-2 600,000 IU/kg
Q8 h x 14 doses

G209-2M + Montanide ISA-51

D-1

Wk1

Wk4

Wk7

D-1
CWG IL-2 + Mutated gp100 Melanoma Peptide Protocol for Metastatic Melanoma

- **Cohort 1**: Week 1, Week 2, Week 3, Week 7, Week 10
- **Cohort 2**: Week 1, Week 2, Week 7
- **Cohort 3**: Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10

- **Week**
  - 1
  - 2
  - 3
  - 4
  - 5
  - 6
  - 7
  - 8
  - 9
  - 10
  - 11
  - 12

- **Symbols**:
  - * = Tumor measurements and T cell assays
  - ▼ = Melanoma Peptide
  - □ = IL-2

- **Legend**:
  - **Cohort 1**: Week 1, Week 2, Week 3, Week 7, Week 10
  - **Cohort 2**: Week 1, Week 2, Week 7
  - **Cohort 3**: Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Week 7, Week 8, Week 9, Week 10
Eligibility Criteria

- Must have histologically confirmed melanoma which is advanced and measurable.
- Must be HLA typed and be shown to be HLA-A2+
- Must have a good performance status (ECOG 0 or 1)
- Must have adequate organ function (as for High dose IL-2)
- Must not have received prior IL-2. Patients who have received one prior chemotherapy regimen are eligible
- Patients with active brain metastases are ineligible.
CWG Three arm phase II trial of gp100 209-2M peptide and high dose IL-2

♦ 131 enrolled with follow-up available on 121 eligible patients
  • 46 (42) pts on cohort 1
  • 43 (40) pts on cohort 2
  • 42 (39) pts on cohort 3
CWG Three arm phase II trial of gp100 209-2M peptide and high dose IL-2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=121</th>
</tr>
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<tbody>
<tr>
<td>M/ F</td>
<td>72/ 49</td>
</tr>
<tr>
<td>Median age</td>
<td>50 (20-76)</td>
</tr>
<tr>
<td>ECOG PS (0/ 1)</td>
<td>99/ 22</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>34 (46% )</td>
</tr>
<tr>
<td>Normal</td>
<td>40 (54% )</td>
</tr>
<tr>
<td>Unknown</td>
<td>47</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
</tr>
<tr>
<td>IFNα</td>
<td>44 (36% )</td>
</tr>
<tr>
<td>Chemotx</td>
<td>16 (13% )</td>
</tr>
</tbody>
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CWG Three arm phase II trial of gp100 209-2M peptide and high dose IL-2

Patient Characteristics
Cohort 3 (39 patients) had slightly less favorable characteristics
Otherwise very balanced

Prior therapy
- IFNα 18 (46%)
- Chemotx 6 (18%)
### HD IL-2 + gp100 209-2M Peptide Vaccine Trial

#### Results

<table>
<thead>
<tr>
<th>Therapy</th>
<th>IL-2 doses</th>
<th>Median (of max)</th>
<th>(range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>20 of 28</td>
<td>(11-27)</td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>20 of 28</td>
<td>(9-27)</td>
<td></td>
</tr>
<tr>
<td>Cohort 3</td>
<td>35 of 56</td>
<td>(8-51)</td>
<td></td>
</tr>
</tbody>
</table>

- 15 patients (12%) did not receive IL-2 due to disease progression
- 12 (30%) of those pts not receiving IL-2 in cohort 2
### HD IL-2 + gp100 209-2M Peptide Vaccine Trial

#### Response (by WHO criteria):

<table>
<thead>
<tr>
<th>Cohort:</th>
<th>Eval</th>
<th>CR</th>
<th>PR</th>
<th>RR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>121</td>
<td>10</td>
<td>10</td>
<td>16.5%</td>
</tr>
<tr>
<td>Cohort 1</td>
<td>42</td>
<td>6</td>
<td>4</td>
<td>23.8%</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>40</td>
<td>3</td>
<td>2</td>
<td>12.5%</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>39</td>
<td>0</td>
<td>4</td>
<td>10.2%</td>
</tr>
</tbody>
</table>
Characteristics of Responses

♦ Follow-up range from 17 to 62 months
♦ Median Follow-up of 44 months

♦ Complete Responses (10)
  • 8/10 progression-free at (18+, 26+, 27+, 27+, 29+, 35+, 37+, 62+ months)
  • 2 progressed at 17 and 51 months

♦ Partial Responses (10)
  • Only 1 progression-free at 17 months
  • 6 progressed in less than 12 months, 2 progressed at 15 months and 1 progressed at 29 months
## Clinical Outcome in PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>mean days</th>
<th>median days</th>
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<tbody>
<tr>
<td><strong>Progression Free Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>248d</td>
<td>84d</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>mean yrs</th>
<th>median yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival</strong></td>
<td>1.47</td>
<td>1.24</td>
</tr>
</tbody>
</table>
Assess degree of immune dysfunction

- Percent of CD3+ expressing ζ chain (↓)
- Percent of CD4+CD25+ Regulatory T cells (↓)
- Percent of CD15+, CD14-CD18+ (Immature Myeloid Cells) (↓)

Assess Specific T cell response

- Percent gp100-209 tetramer expressing CD8+ T cells (↑)
- Control percent Flu tetramer expressing CD8+T cells

Compare Pre-treatment, Post-treatment, and change from pre- to post-treatment
Immune Assays Performed Pre-Tx and at Week 12

♦ Preliminary Results

- Complete sampling on 52 patients (Pre- and Week 12))
  - Including 10 responders (6 CR, 4 PR)
  - Including 13 PFS > 12 months (PFS responders)
- For % CD3+, ζ expressing cells
- For % CD4+, CD25+ cells
- For % CD15+, CD18+, CD14- cells
- For % CD8+, gp100 tetramer+ cells
  - No significant difference in Pre- and Post-Treatment levels or change in levels in CR/PR responders (10) compared to non-responders (42)
  - No significant difference in Pre- and Post-Treatment levels or change in levels in PFS responders (13) compared to non-responders (39)
Conclusions

- **gp100 209-2M vaccine does not appear to greatly enhance** high dose IL-2 clinical activity in HLA-A2 + advanced melanoma patients

- **No correlation of Immunologic Assays** (Pre-, Post- and change from Pre- to Post-Treatment with clinical outcome in PFS and objective responses)
Conclusions (continued)

Low overall response rates-in cohort 3- IL-2 and vaccine every 3 weeks

- Prognostics characteristics of tumor were poor??
- Difficulty in tolerance to increased IL-2 doses??

- Many patients (12; 30%) in cohort 2 do not receive IL-2 after 6 weeks of vaccine

- Results support the early initiation of standard HD IL-2 after the diagnosis of advanced melanoma in lieu of a clinical trial and the continued need to search for approaches to enhance IL-2’s clinical effectiveness
Special Thanks

♦ Carol Carrillo, BS
♦ David Panka, PhD- laboratory correlates
♦ Bonnie LaFleur, PhD- statistics