Melanoma: Targeting the Immune System

Melanoma is one of the most immunogenic of all solid tumors:
- spontaneous regression
- identification of tumor associated antigens, tumor antigen-specific antibodies, tumor-specific cytotoxic T cells
- CD8 T cells has been shown to prevent tumor formation in vivo and in vitro, and the presence of infiltrating CD8 T cells within tumors is positively correlated with better prognosis in cutaneous melanoma
- many immunotherapy strategies have been evaluated to increase tumor control and patient survival

Melanoma: Vaccine Therapy

- Whole-cell vaccines
- Dendritic cell vaccines
- Peptide vaccines
- Ganglioside vaccines
- DNA vaccines
- Viral vectors

Lens M. Expert Opin Biol Ther 2008

Melanoma: Whole-Cell Vaccines

- Autologous whole-cell vaccines
- Heat-shock proteins
- Allogeneic whole-cell vaccines
  - Canvaxin™
  - Melacine®
- Allogeneic vaccines prepared from vaccinia melanoma lysates
**Melanoma Vaccines: Heat Shock Proteins**

- Heat-shock proteins (HSP) expression is increased when cells are exposed to stressful conditions and act as “chaperones” to upregulated antigens on antigen-presenting surfaces
- Patients with metastatic melanoma vaccinated after surgery with autologous tumor-derived HSP peptide complexes gp96 have been shown to develop class I HLA-restricted tumor-specific T cell immunity
  
  Belli F, et al. JCO 2002
- Phase II trial combined GM-CSF given at the site of the HSPPC-96 injection in combination with interferon alfa
  

**Melanoma: Autologous Tumor-Derived Heat Shock Protein gp96 Peptide Complex Vaccine (Vitespen)**

- Aim: Assess antitumor activity of autologous, tumor-derived HSP gp96 peptide complex in patients with stage IV melanoma
- Method:
  - Phase III multinational study
  - Patients randomized 2:1 to receive vaccine versus physician’s choice (PC)*
- Endpoint:
  Primary: overall survival

* PC = dacarbazine or temozolomide or IL2 or resection

Melanoma: Autologous Tumor-Derived Heat Shock Protein gp96 Peptid Complex Vaccine (Vitespen)

- Patient treatment:
  - Physician choice:
    - 107 assigned ⇒ 79.8% received Vitespen
    - 215 assigned ⇒ 61.9% received
    - number of injections ranged 0 to 87; median 6

Results:
- ITT analysis no statistical difference in OS
- Patients in the M1a and M1b substages receiving a larger number of immunization survived longer than those receiving fewer treatments


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Melanoma: Vaccine Therapy

- Whole-cell vaccines
- **Dendritic cell vaccines**
- Peptide vaccines
- Ganglioside vaccines
- DNA vaccines
- Viral vectors
Dendritic Cells (DC)

- Most effective antigen presenting cells (APCs) capable of capturing, processing and presenting antigens to T-and B- lymphocytes.
- Categories of DC:
  - plasmacytoid DC
  - myeloid DC
  - inflammatory DC
- DC vaccination
  - development of techniques to generate large number of these cells *in vitro* from blood monocytes or CD34+ progenitor cells

Dendritic Cell Vaccination Trials

- Proof of principle studies performed in 1990s
- Clinical studies:
  - DC-vaccination with non-matured DC
  - DC-vaccination with mature DC
- Responses
  - Objective responses: 5-10%
  - Type of responses: stabilization of disease, mixed responses
- Changing the way we look at results:
  - Immunologic responses
  - Conventional RECIST criteria may not be appropriate
  - Redefining dose

Melanoma: Dendritic Cell Vaccine

- Phase III evaluation of autologous peptide-loaded dendritic cell vaccine vs dacarbazine in patients with metastatic melanoma
- Treatment:
  - Dacarbazine 850 mg/m2 IV q 4 weeks
  - DC vaccines loaded with MHC class I and II – restricted peptides applied SQ every 2 weeks x 5, then q 4 weeks
- Endpoints:
  - Primary: objective response
  - Secondary: toxicity, overall survival, progressive free survival


Dendritic Cell-Based

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<th>Therapy</th>
<th>No</th>
<th>OR</th>
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<td>6</td>
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<td>Peptide/lysate vs DTIC</td>
<td>53</td>
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<td>10</td>
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Nestle, 2006
Slingluff, 2003
Schandendorf, 2006
Melanoma: Dendritic Cell Vaccine

- Phase III evaluation of autologous peptide-loaded dendritic cell vaccine vs dacarbazine in patients with metastatic melanoma from the Dermatologic Cooperative Oncology Group
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  - DC vaccines loaded with MHC class I and II – restricted peptides applied SQ every 2 weeks x 5, then q 4 weeks
- Endpoints:
  - primary: objective response
  - secondary: toxicity, overall survival, progressive free survival


Melanoma: Dendritic Cell Vaccine

- Phase III evaluation of autologous peptide-loaded dendritic cell vaccine vs. dacarbazine in patients with metastatic melanoma from the Dermatologic Cooperative Oncology Group
- Results:
  - at time of first interim analysis 108 patients enrolled
  - OR was low: VAC 3.8 % vs. dacarbazine 5.5%
  - Data Safety & Monitoring Board recommended closure of the study
  - Unscheduled subset analyses: patients with normal LDH and/or stage M1a/b survived longer in both arms
  - Observed association of performance status and HLA haplotype and survival in patients treated with vaccine

Melanoma: Vaccine Therapy

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- DNA vaccines
- Viral vectors

Melanoma: Peptide Vaccines

- Immunogenic peptides
  - tissue specific antigens
  - cancer testis antigens
  - mutated cancer-specific antigens
- A peptide derived from tissue specific antigen (gp100) has been synthesized in a mutated form to enhance HLA-A2.1 binding ⇒ T cell stimulation
  - initial small clinical trials demonstrated increase immune response but no antitumor response
  - combination therapy with interleukin-2 is a method that may increase antitumor effects

Combination Therapy for Advanced Melanoma: gp100 Peptide and Interleukin-2

- Three separate Phase II trials evaluating the combination of high-dose interleukin-2 (HD IL2) and gp100 peptide vaccine in patients with advanced melanoma
- Treatment:
  - gp100 (210M) peptide SQ during week 1, 4, 7, 10
  - HD IL-2
    - Trial 1: week 1 and 3
    - Trial 2: week 7 and 9
    - Trial 3: week 1, 4, 7 and 10

Sosman JA, et al. JCO 2008

Combination Therapy for Melanoma: gp100 Peptide and Interleukin-2

- N= 130 patients (Sept 1998 – Nov 2003)
- Median follow-up time of 60 months

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<tr>
<th>Cohort</th>
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<th>PR</th>
<th>RR</th>
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<td>12 to 21</td>
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* number assessed

Sosman JA, et al. JCO 2008
Combination Therapy for Melanoma: 
gp100 Peptide and Interleukin-2

Immune Correlates for Response:
- Paired samples from peripheral blood obtained prior to treatment and on week 12 (n=53)
- There was insufficient power to detect differences between responders and non-responders in any single trial.
- Limitation of immune testing is the amount of intra subject variation inherent in the assays.

Sosman JA, et al. JCO 2008

Melanoma: Vaccine Therapy

- Whole-cell vaccines
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- Viral vectors
Melanoma: Adjuvant Therapy  
EORTC Study 18961

- Aim: Detect difference in disease free survival (DFS) at 5 years between patients receiving adjuvant vaccine (ganglioside GM2-KLH21) treatment versus observation
- Methods:
  - Phase III trial
  - Stage II melanoma post resection of melanoma
  - Stratification by sentinel lymph node staging, depth, ulceration, gender, treatment center
  - Recruited from March 2002 – Dec 2005

Eggermont AM, et al. JCO 2008 (abst )

Melanoma: Ganglioside Vaccines

- Aim: Detect difference in disease free survival (DFS) at 5 years between patients receiving adjuvant vaccine (ganglioside GM2-KLH21) treatment versus observation
- Treatment strategy:
  - Ganglioside GM2-KLH/Q3-21 vaccine subcutaneously weekly x 4, then q 3 months from week 12 for 2 years, then q 6 months during 3rd year (#14)
  - Observation
- Endpoint:
  - Primary: DFS
  - Secondary: survival, toxicity

Eggermont AM, et al. JCO 2008 (abst )
Melanoma: Adjuvant Therapy
EORTC Study 18961

From randomized ITT population (n=1314):

- **Disease Free Survival**
  
<table>
<thead>
<tr>
<th></th>
<th>HR (98% CI)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Obs</td>
<td>1.02 (0.77, 1.36)</td>
<td>0.85</td>
</tr>
<tr>
<td>VAC</td>
<td>1.0 (0.75, 1.34)</td>
<td>0.99</td>
</tr>
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</table>

- **Distant Metastatic Free Survival**
  
<table>
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<tr>
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<th>HR (98% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obs</td>
<td>1.33 (0.77, 2.28)</td>
<td>0.08</td>
</tr>
<tr>
<td>VAC</td>
<td>1.32 (0.76, 2.30)</td>
<td>0.10</td>
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</tbody>
</table>

Eggermont AM, et al. JCO 2008 (abst)

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Melanoma: Adjuvant Therapy
EORTC Study 18961

- EORTC IDMC reviewed safety and efficacy data and recommended that the trial be stopped and vaccinations be halted in patients receiving VAC.

- **Conclusion:** This strategy of vaccine was ineffective and may even be detrimental in patients with stage II melanoma.

Eggermont AM, et al. JCO 2008 (abst)
Melanoma: Vaccine Therapy

• Whole-cell vaccines
• Dendritic cell vaccines
• Peptide vaccines
• Ganglioside vaccines
• DNA vaccines
• Viral vectors

T-Cell Activation

T cells require two signals from dendritic cells for full activation:
  ▪ binding of major histocompatibility complex – antigen to the T cell receptor
  ▪ binding of co-stimulatory molecules expressed on mature dendritic cells
Melanoma: CD8 T-Cell Response

Criteria for antitumor response:
- generation of sufficient quantity of antitumor specific CD8 T cells
- CD8 T cells must be able to infiltrate into the tumor
- activation of CD8 T cells within the tumor $\Rightarrow$ cell death

Strategies to optimize CD8 T-cell response for treatment:
- Non-specific stimulation of anti-tumor immune responses
  - stimulation of endogenous effector cells
  - removing inhibitory signals for T cell activation
- Active immunization to enhance endogenous anti-tumor responses in vivo
  - vaccines
- Adoptive cell-transfer therapy
Melanoma: Adoptive Cellular Therapy

- Cytotoxic T lymphocyte therapy (CTL)
- Tumor infiltrating lymphocyte therapy (TIL)
  - TILs and interleukin-2
  - non-myeloablative lymphodepleting preconditioning ⇒ TILs and interleukin-2
  - generate and adoptively transfer engineered autologous T cells that express high affinity for melanoma-specific antigens

Melanoma: Options for Pharmacotherapy

- Chemotherapy
- Immunotherapy
  - cytokine (IL-2, interferon)
  - cytotoxic T-lymphocyte antigen-4 antibodies
  - vaccines
- Targeting signal transduction pathways
- Apoptotic therapy
- Antiangiogenic therapy
Melanoma: Options for Pharmacotherapy

- Melanoma vaccines can induce cellular immune and/or antibody responses
- The science of melanoma vaccines:
  - Best target(s)
  - Best delivery
- Clinical trials with melanoma:
  - Small numbers
  - Endpoints: immune response vs. clinical response
  - Strategy: vaccine vs. vaccine + adjuvant vs. combination
  - Timing: early disease vs. late disease