Gene Therapy: Melanoma Theory to Practice

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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**

Fang L, et al. J Invest Dermatol 2008;128:2956-2605

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 complexs 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

  Pilla L, et al. Cancer Immunol Immunother 2006

Melanoma: Autologous Tumor-Derived Heat Shock Protein gp96 Peptid 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

Testori A, et al. JCO 2008

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**

Testori A, et al. JCO 2008

Melanoma: Vaccine Therapy

- **Whole-cell vaccines**
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Dendritic Cells (DC)

- **Most effective antigen presenting cells (APCs) capable of capturing, processing and presenting antigens to T-and B- lymphocytes.**
- **Catagories 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**

Lesterhuis WJ, et al. Critical Rev Oncol Hematol 2008

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
- Enpoints:
  - primary: objective response
  - Secondary: toxicity, overall survival, progressive free survival

Schadendorf D, et al. Ann Oncol 2006

Dendritic Cell-Based

Therapy	No	OR	CR	PR + SD	
Peptide or tumor lysate	32	8	2	6	Nestle, 2006
Peptide vs peptide +GMCSF	13	1	0	2	Slingluff, 2003
Peptide/lysate vs DTIC	53	3	0	10	Schalendorf, 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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Schadendorf D, et al. Ann Oncol 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
- 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

Schadendorf D, et al. Ann Oncol 2006

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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

    Rosenberg SA, et al. Nat Med 1998

    Miller AM, et al. Cancer 1981
  - 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

Cohort	No.*	CR	PR	RR	95% CI (%)
Trial 1	42	6	4	23.8	12 to 40
Trial 2	40	4	1	12.5	4 to 27
Trial 3	39	1	4	12.8	4 to 27
Overall	121	11	9	16.5	10 to 26
HD IL database	270	17	26	15.9	12 to 21

* 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

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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 recieiving 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**

	HR (98% CI)	p value
Obs	1.02 (0.77, 1.36)	0.85
VAC	1.0 (0.75, 1.34)	0.99

- **Distant Metastatic Free Survival**

	HR (98% CI)	p value
Obs	1.33 (0.77, 2.28)	0.08
VAC	1.32 (0.76, 2.30)	0.10

Eggermont AM, et al. JCO 2008 (abst)

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)

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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 ⇒ cell death**

Melanoma: CD8 T-Cell Response

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
- Apopototic 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

