Therapeutic Cancer Vaccines

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Disclosures

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I will not discuss off-label use of any agents
Educational Goals

• To understand the rationale for anti-tumor vaccines

• To understand the role of “antigens” as targets for vaccine development

• To identify anti-tumor vaccine approaches approved or in advanced phase clinical trials

• To understand some of the challenges incorporating anti-tumor vaccines into clinical practice
Outline

• Introduction
  • Rationale for anti-tumor vaccines
  • History of vaccines
  • Role of antigens / antigen discovery
  • Anti-tumor vaccines in practice/advanced trials
  • Paradigm changes for the treating oncologist
Tumor Immunology - Types of approaches

- Infusion of cytokines
- Antibody therapy
- Adoptive immunotherapy
- Immunomodulation
- Vaccines

Passive

Active
What is an anti-tumor vaccine and how do they work?

- Cancer cell
- Protein
- Peptide
- Virus / bacteria
- Nucleic acid
- ADJUVANT
- Dendritic cell (Antigen-presenting cell)
- ADJUVANT
- Lymphocytes
- Antibodies
- Cytokines
Why use vaccines to treat cancers?

- Nature has already given us a specific and adaptive process
- Infectious diseases – “magic bullet”
- Greatest medical accomplishment of the 20th century (?) – vaccines
- Already evidence that immune system plays a role in anti-tumor surveillance
- Lots of evidence that they “work” in experimental models
Challenges with Anti-Tumor Vaccines

- Self versus non-self
- Autoimmunity …
- Protection from disease versus treatment of existing disease
- Generating antibody responses (only) may be insufficient
- Compensatory / regulatory mechanisms within tumors are complex
(Brief) History of Anti-Tumor Vaccines

• Discovery of mechanisms of T-cell recognition and action
• Discovery of antigen-presenting cells
• Led to a large effort to identify “tumor-rejection” antigens
• Multiple vaccine approaches to specifically elicit immune cells with anti-tumor activity
(Brief) History of Anti-Tumor Vaccines

- Early 1900’s: Inactivated tumors as vaccines
- Use of adjuvants
  - BCG
  - Cytokines

Dranoff ’93 PNAS 90:3539
(Brief) History of Anti-Tumor Vaccines

• Inbred mouse strains permitted the demonstration of antigen-specific anti-tumor immunity
What the cytolytic T cell sees and does
Identification of CTL antigens

Adapted from: Makalowski '13 DOI:10.5772/53619

Prepare cDNA library from tumor

Transfect reporter Cell line

Lysis?

evaluate cytolytic activity
Identification of CTL antigens

Tumor cell → Acid elute peptides → HPLC and sequence identify
Identification of other tumor antigens “SEREX”

- Grow bacterial lawn on agar
- Transfect – phage cDNA library
- Transfer to membrane
- Overlay with human sera
- Detect IgG

Sequence and identify gene encoding phage plaque
Tumor Vaccine Antigens

• Tumor-specific
  • Expressed only by tumor
  • Mutated, frameshift, translocation event
  • Abnormal post-translational modifications
• Oncofetal, differentiation antigens
  • Germ cell – “cancer-testis” antigens
• Tumor-associated
  • More highly expressed in tumor
• Viral oncogenes
Types of Anti-Tumor Vaccines

- Antigen not defined
  - Whole cell vaccines, cytokine-expressing whole cell vaccines, tumor nucleic acid transfected DC vaccines

- Antigen-specific vaccines
  - Protein
  - Peptide (e.g. binding specific MHC)
  - Genetic (viral, bacterial, plasmid DNA vectors)
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Antigen-Presenting Cell Vaccines – Sipuleucel-T

Sipuleucel-T Phase III Trial - D9901

Probability of non-progression vs. Time from randomization to progression (weeks)

- APC8015 (n=82)
- Placebo (n=45)

$P = 0.061$ (log-rank)

HR = 1.43 (95% CI: 0.98, 2.09)

Sipuleucel-T Phase III Trial - D9901

- **Sipuleucel-T (n=82)**
- **Placebo (n=45)**

\[ P = 0.010 \text{ (log rank)} \]
\[ HR = 1.7 [95\% CI: 1.13, 2.58] \]
Median survival benefit: 4.5 months

Sipuleucel-T Phase III “Impact” Trial - D9902B

9902B – Phase III “IMPACT” Trial

Metastatic CR Prostate Cancer

512 patients

Vaccination q14 days x 3

Placebo vaccination q14 days x 3

Trial Endpoints:

Primary: Overall survival

Secondary: Symptomatic, radiographic progression
Sipuleucel-T Phase III “Impact” Trial - D9902B

p=0.032 (Cox model)
HR = 0.775 (95% CI: 0.614, 0.979)

Median survival benefit = 4.1 mo

Adverse Events – IMPACT Trial

Grade 1 or 2 events 2x higher in sipuleucel-T than placebo group:

- Chills
- Fever
- Headache
- Flu-like illness
- Hypertension
- Sweating
- Groin pain

Grade 3 or 4 events: All < 5%

Sipuleucel-T was FDA-approved April 2010 for the treatment of asymptomatic, metastatic, castrate-resistant prostate cancer

First approval of an anti-tumor vaccine (for humans) in the U.S.
Viral Vaccines – Prostvac-VF

Viral Vaccines – Prostvac-VF
Randomized Phase II Trial

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Randomized Phase II Trial

Median survival benefit: 8 mo

Viral Vaccines – Prostvac-VF
Randomized Phase III Trial

“PROSPECT” Trial – NCT01322490

- Prostvac-V/F + GM-CSF
- Prostvac-V/F alone
- Double placebo

Metastatic CR Prostate Cancer
1200 patients

Trial Endpoints:

Primary: Overall survival
Secondary: Symptomatic or radiographic progression at 6 months
What about other diseases?

And simpler vaccines?
Protein Vaccine - NSCLC
MAGE-A3 – Cancer-Testis Antigen

“MAGRIT” Adjuvant Trial – NCT00480025

IB, II or IIIA NSCLC Expressing MAGE-A3
2289 patients

MAGE-A3 + Adjuvant

Placebo

Trial Endpoints:

Primary: Disease-free survival
Secondary: Overall survival, lung cancer-specific survival
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Why no association with PFS?

- APC8015 (n=82)
- Placebo (n=45)

\[ P = 0.061 \text{ (log-rank)} \]
\[ HR = 1.43 \text{ (95\% CI: 0.98, 2.09)} \]


Model of Treatment Effect Arising from Multiple Immunotherapy Trials

Adapted from: Madan (2010) *Oncologist* 15:969
Model of Treatment Effect Arising from Multiple Immunotherapy Trials

Adapted from: Madan (2010) Oncologist 15:969
So What Have We Learned?  
Guidance for the Treating Oncologist

• Minimal adverse events (compared with traditional anti-cancer therapies)
• No difference in time to radiographic progression, few PSA “responses,” but survival prolonged
• In the case of sipuleucel-T, subgroup analysis suggests magnitude of survival benefit greater in patients with lower disease burden (lower PSA, lower LDH, no prior chemotherapy, greater time from diagnosis)
• “Optimal” treatment time, consequently, not as salvage but rather in early asymptomatic patients who don’t require emergent management
What Else Have We Learned?

Challenges for the Treating Oncologist

• Which patients are likely to benefit?
  The future: Which vaccine for which patient?

• No good markers (yet) to know if an individual patient has “benefited”
  (Kind of like adjuvant therapy for metastatic disease)

• Difficult to know when to proceed on to next therapy
  How should these be sequenced or used with other therapies (like chemotherapies or corticosteroids)?
So What’s in the Future for Cancer Vaccines?

- “Off-the-shelf” vaccines are feasible (and cheaper)
- Earlier stages of disease
- New (better) targets
- Biomarkers of response and likelihood of response (“personalized” medicine)
- Combination with other treatments
  - Traditional therapies
  - Other immunological therapies
Vaccines Don’t Need to Be Too Complicated (or Expensive)
Antigen-Specific DNA Vaccine - Oncept
First Anti-Tumor Vaccine Approved in US

Vaccines May Modulate Effect from Subsequent Therapies

“Immunomodulation”
Immune Checkpoint Inhibitors

The Future of Vaccines with Other Immunomodulating Agents

Vaccines

T-cell checkpoint inhibitors
Tumor microenvironment modulators
Regulatory and immunosuppressive mechanisms

Immunomodulating Agents

OX-40 agonist
Cytokines