CONTROLLING THE IMMUNE RESPONSE IN GI CANCERS

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Tumor Immunology Overview

1. Priming and activation of T cells

2. IFN-γ-mediated upregulation of tumor PD-L1

3. PD-L1/PD-1-mediated inhibition of tumor cell killing

“Immunotherapy does not work in gastrointestinal tumors.”

– Everyone (everywhere, right now)
The Reality

GI Tumors are Immunogenic
- All speakers

Evidence of activity
- Dr. Segal - checkpoint inhibitors
- Dr. Morse and Jaffe – vaccines (colorectal and pancreatic)

Immune responses are inducible
- Immunogenic Cell death and modulation (standard cytotoxic agents, radiation)
- Vaccines
- Other Immunomodulators

Understanding underlying biology → Better use of agents and trial design → Increased activity
- Immune response induction
- Inhibition of immune checkpoints
- Combination with standard agents
- Immune targeting of resistance
Immunogenic Cell Death and Modulation

Radiation

- Upregulation of MHC-I
- Uploading of antigen processing machinery
- Peptide pools
- Adhesion molecules (ICAM-1) and death receptors (FAS)

Chemotherapy

- Effector immune infiltrate
- Translocation of cacteculin
- Release of tumor antigens (cascade)
- TAA Cross-presentation
- CD8 T-cells

Small molecule inhibitors

- Vascular normalization
- T-cell infiltration
- Chemokine release
- CD8 T-cells
- MDSC
- Treg cells

Activation of apoptosis
Blockage of cell cycle

Hodge Semin Oncol 2012
Immunotherapy Efficacy Evaluation

Immunotherapies work differently than cytotoxic agents

Old evaluation techniques may not apply well
Key Issues in Efficacy Evaluation

Overall Survival Benefit without PFS Benefit

PFS

OS

PROSTVAC PHASE 2

Kantoff, et al. JCO 2010
Key Issues in Efficacy Evaluation

Overall Survival Benefit without PFS Benefit

PROVENGE PHASE 3 TRIALS

PROVENGE Phase III

Small, et al. JCO 2006

Kantoff, et al. NEJM 2010
Key Issues in Efficacy Evaluation

Overall Survival Benefit without PFS Benefit

Hodi, 2010 NEJM
Tumor Growth Rate

Tumor Burden

Time

### Halabi Predicted Survival vs. Actual Survival

<table>
<thead>
<tr>
<th>NCI Docetaxel therapy (n=22)</th>
<th>All patients</th>
<th>Patients with Halabi predicted survival &lt; 18 mos</th>
<th>Patients with Halabi predicted survival ≥ 18 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted survival by Halabi score (mos)</td>
<td>16.5</td>
<td>13.0</td>
<td>21.0</td>
</tr>
<tr>
<td>Actual median overall survival (mos)</td>
<td>15.5</td>
<td>15.4</td>
<td>16.9</td>
</tr>
<tr>
<td>Difference (mos)</td>
<td>(-1.0)</td>
<td>2.4</td>
<td>(-4.1)</td>
</tr>
<tr>
<td>Patients survival longer than predicted by Halabi nomogram</td>
<td>11 of 22 (50%)</td>
<td>8 of 13 (62%)</td>
<td>3 of 9 (33%)</td>
</tr>
</tbody>
</table>

Tumor Growth Rate

![Graph showing tumor burden over time with annotations and arrows indicating changes or events at specific time points.](image-url)
Magic Sorting Hat?

Tumor Infiltrating Lymphocytes Predict Outcome at Diagnosis

Galon Science 2006
Population: Newly diagnosed colorectal CA high risk by Immunoscore (CD3$^{\text{CTLow}}$CD3$^{\text{IMLOW}}$)
Design: randomized phase II $\rightarrow$ standard therapy +/- vaccine (PANVAC, MVA-Brachyury)
Endpoint: recurrence free survival
Exploratory: at recurrence, TIL PD-1+ and tumor PD-L1 expression
Goal: Convert RFS at 2 years from 50% to 75%
Estimated n = 40 per arm
Vaccines may work best with minimal disease

- Minimal tumor burden creates an excellent environment for vaccination:
  - Relatively low Treg number (high effector:Treg ratio)
  - Tumor microenvironment is immunosuppressive (so lack of bulk may improve efficacy)
  - “Time” for augmentation of immune response with multiple vaccinations
  - Multiple modality treatment following vaccination available

- Vaccines can focus on causes of advanced disease
  - Epithelial to mesenchymal transition
  - Driver antigens
Potential Targets: Brachyury

Embryologic Transcription Factor: Over-expression Induces EMT in Epithelial Tumor Cells

PANC-1-pDNA

PANC-1-pBrachyury

Epithelial

E-cadherin

Plakoglobin

Mesenchymal

Fibronectin

Vimentin

Brachyury

Potential Targets: Brachyury

Fernando...Palena. J Clin Invest. 2010; 120:533-44.
Potential Targets: Brachyury

A

Primary localized tumor

Primary invasive tumor

Induction of EMT

Tumor dissemination

Circulation

Normal epithelial cell

Epithelial tumor cell

Mesenchymal-like tumor cell

Apoptotic tumor cell

Metastasis

Therapeutic resistance

Conventional anti-tumor therapy (chemotherapy, radiation)

B

Primary invasive tumor

Circulation

Tumor dissemination

Antigen presenting cell

CD8+ T cell

CD4+ T cell

Immunotheerapeutic intervention: vaccination against a driver of tumor EMT

Activation of CD8+ and CD4+ T cells specific for an EMT driver

Cancer vaccine

Skin

Anti-tumor immune response

Conventional anti-tumor therapy (chemotherapy, radiation)

Antitumor response
BRACHYURY EXPRESSION IN COLON CANCER

Collaboration with Drs. Guadagni and Roselli, Rome, Italy

Staining with Mab-54-1 rabbit anti-brachyury

ANOVA: F(3,76) = 38.045, p < 0.0001

% Positive nuclei

% Brachyury positive cells

Normal mucosa  Dysplasia  Tumor  Metastasis

Tissue Type

n=28  n=10  n=40  n=3

Dysplasia

Tumor

Tumor
Brachyury expression predicts poor prognosis at early stages of colorectal cancer

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Expression described in:
- Colorectal
- Breast
- Prostate
- Lung
- Chordoma
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