Predictive Biomarkers for Tumor Immunotherapy: Are we ready for clinical implementation?

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Changing Paradigms in Cancer Treatment
Potential Uses of Biomarkers

- Adverse event monitoring
- Targets for drug discovery
  - Better systems for screening libraries
  - Providing “proof-of-principle” activity in pre-clinical setting
  - Help predict potential toxicity
- Clinical trial decision-making
  - Improved patient selection
  - Better selection of clinical endpoints
  - Reduce cost by optimizing dose selection
Requirements for Clinical Application of Biomarkers

- Must have a signaling characteristic
- Must be accurately measured
- Must be feasible to measure
- Must be validated

- Should be a commodity
- Should be cost-effective
Biomarkers in Tumor Immunotherapy

- Soluble factors
  - Serum proteins
  - Circulating DNA and tumor cells
- Tumor factors
  - Receptor expression
  - Cellular infiltrates
- Patient factors
  - Humoral and cellular immune responses
  - Immune system polymorphisms
- Mathematical predictions
Tumor Immunotherapy Biomarkers

• To date, no biomarker has accurately predicted clinical response to tumor immunotherapy

• But, there are trends that have been noted.....
Correlation of clinical response and antibody titers

Vaccine; CancerVax

Chung et al. JCO 2003
Correlation of clinical response and CD4+ T cell response

Vaccine: Allogeneic tumor cell-pulsed DC

Lopez et al. JCO 2009
Correlation of clinical response and CD8+ T cell response

Vaccine: V/F-CEA-MUC1-TRICOM

Correlation of clinical response and Tregs

Vaccine: MVA-5T4

Issues with current biomarkers

- Small sample sizes
- Limited extension to larger phase clinical studies
- Lack of acceptance by industry
- Expensive
- Largely retrospective (and unplanned) analyses
Can biomarkers be selected for prospective evaluation?
Overall Survival of IL-2 Patients

IL-2: Survival after treatment (2002-2007)

- Complete Response
- Partial Response
- Non-responders
Interleukin-2 Immunotherapy

• How does IL-2 mediate anti-tumor effects?
• Why does IL-2 induce anti-tumor responses in only 17%?
• Can we improve the number of patients who will respond to treatment?
• Is there a biomarker that can predict response to IL-2 treatment?
# Predictors of Response to IL-2 Therapy

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>Fyfe et al. JCO 1995</td>
</tr>
<tr>
<td>Number of organs involved*</td>
<td>Besana et al. Eur J Cancer 1994</td>
</tr>
<tr>
<td>Bone metastasis*</td>
<td>Rosenberg et al. JCO 1989</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Royal et al. J Immunother 2003</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Atkins et al. NEJM 1988</td>
</tr>
<tr>
<td>Rebound lymphocytosis</td>
<td>West et al. NEJM 1987</td>
</tr>
<tr>
<td>Erythropoietin production</td>
<td>Janik et al. JCO 2002</td>
</tr>
<tr>
<td>Increased TNF-α and IL-1</td>
<td>McDermott et al. Sem Oncol 2006</td>
</tr>
</tbody>
</table>

*Subsequently challenged  
** Renal cell only
Pre-treatment leukocytes and neutrophils predict response to IL-2-based immunotherapy

Schmidt H et al. JCO 2007;25:1562-1569
Expression of Ki-67 negatively correlates with survival following interferon-α and low-dose IL-2 in renal cell carcinoma

High CA-IX levels predict response to IL-2 in renal cell carcinoma

Atkins et al. Clin Cancer Res 2005
VEGF predicts survival following IL-2 treatment

Survival, by VEGF group

- <125 (n=39)
- >125 (n=20)

P=0.0031

Sabatino et al. J Clin Oncol 2009
Clonal T cell expansion

Malek and Bayer, Nature Rev Immunol 2004
The frequency of CD4^+CD25^{hi} T cells are elevated in patients with MM and RCCA

Cesana et al. JCO 2005
Tregs decrease to normal levels after the cycle 2 in objective responders.

Cesana et al. JCO 2005
The change in Treg frequency is associated with clinical response

<table>
<thead>
<tr>
<th>Time</th>
<th>PD</th>
<th>PR</th>
<th>CR</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Tx – Post 1</td>
<td>2.05%</td>
<td>1.52%</td>
<td>0.19%</td>
<td>0.826</td>
</tr>
<tr>
<td>Pre-Tx – Post 2</td>
<td>5.09%</td>
<td>2.37%</td>
<td>-7.85%</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Cesana et al. JCO 2005
Computational Modeling of IL-2

\[
\frac{dR_s}{dt} = -k_r \cdot L[t] \cdot R_S[t] + (k_r + k_{syn}) \cdot C_s[t] - k_r \cdot R_S[t] + \frac{V_S}{S} \quad (1)
\]

\[
\frac{dC_s}{dt} = k_r \cdot L[t] \cdot R_S[t] - (k_r + k_s) \cdot C_s[t] \quad (2)
\]

\[
\frac{dR_i}{dt} = -k_r \cdot L_i[t] \cdot R_i[t] + k_r \cdot C_i[t] + k_r \cdot R_S[t] - k_r \cdot R_i[t] \quad (3)
\]

\[
\frac{dC_i}{dt} = k_r \cdot L_i[t] \cdot R_i[t] - (k_r + k_h) \cdot C_i[t] + k_e \cdot C_i[t] \quad (4)
\]

\[
\frac{dL_i}{dt} = \frac{-k_f \cdot L_i[t] \cdot R_i[t] + k_r \cdot C_i[t]}{(V_e \cdot N_A)} - k_h \cdot L_i[t] \quad (5)
\]

\[
\frac{dL_i}{dt} = k_h \cdot C_i[t] \quad (6)
\]

\[
\frac{dL_i}{dt} = \frac{-k_r \cdot L_i[t] \cdot R_S[t] + k_r \cdot C_s[t] + k_h \cdot L_i[t] \cdot V_e \cdot N_A \cdot Y[t]}{(N_A)} \quad (7)
\]

\[
\frac{dY}{dt} = \text{Max}\left\{\frac{600 \cdot C_s(t)}{250 + C_s(t)} - 200,0\right\} \times 10^3 \quad (8)
\]

Fallon and Lauffenberger Biotechn Progr 2000
Hypothesis: IL-2 will preferentially affect nTregs at different doses

IL-2 100 U/ml

IL-2 1000 U/ml
Experimental: IL-2 preferentially affects naïve Tregs in a dose-dependent manner.
Are we ready for clinical implementation?

- Yes - for inclusion of putative biomarkers in clinical trial design
- Yes - for further validation in larger sample sizes
- Should be a high priority for academia, industry and government
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