Strategies for enhancing the efficacy of immunotherapy

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Cancer Immunity Principles

Tumors express antigens recognized by immune cells
- Aberrant expression of embryonic antigens.
- Clonotypic neo-oncogenes (bcr/abl; B-cell idotype).
- Over-expression of low expression antigens on tumors.

Tumor Surveillance: immune system limits cancer
- Tumors may be eliminated before clinically detected.
- Tumor development represents failure of immunity due to lack of antigen-specific responses or immune paralysis.
- Patients with tumors may have tumor-specific memory T cells.

Augmenting immunity causes cancer regression
- Cytokine therapy- activate and expand T cells and NK cells
- Monoclonal antibodies- direct cytotoxicity or antibody-dependent cellular cytotoxicity (ADCC)
- Vaccine with to induce and amplify T-cell responses
- Immune check-point blockade to reverse anergy of T cells
- Infusion of antigen-specific T cells, NK cells
Immunological Modalities to Treat Cancer

- Vaccines
- Blocking counter-regulatory mechanisms
- Adjuvants and Cytokines
- Cellular Therapies
- Antibodies to Tumor Associated Antigens
Tumors that develop in an immuno-deficient host can be eliminated by a competent immune system.

Distinction between tumor-associated antigens and tumor-specific antigens

• Tumor associated: anti-CD20- Rituximab FDA approved in 11/26/1997 targets normal B-cells and CD20+ B-cell malignancies.

• Tumor specific: Neo-antigens created by oncogeneic mutations/translocations in tumors, recognized by TILS- T cells extracted from the tumor microenvironment and expanded ex vivo.
Mutation Density Varies Across Different Cancers
• Driver mutations (red) cause an increase in the cell's fitness.
• Mutations in housekeeper genes (pink) decrease a cell's fitness.
• Passenger mutations (green) have no effect on fitness
• Mutator mutations (yellow) leads to an increase in the cell mutation rate.

What Happens at the Beginning of Immune Responses?

- Activated Cytotoxic CD8+ T-cell CD45RO+ CD38+ CD57+
- Naïve CD8+ T-cell CD45RA+ CCR7+ CD62L+
- Apoptotic or Necrotic Cancer Cell

Antigen Processing and presentation of peptides on MHC I

- Antigen presentation by dendritic cell
- Immature dendritic cell: puptake of antigen from cancer cell
- Cytolysis of Cancer Cell
Checkpoint Blockade and the Immunological Synapse

Inhibition of antigen-specific T cells by PDL1 expression on tumors

Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab

Long-term Survival of Patients with Renal Cell Cancer Treated with High-dose IL-2

Fig 1. Survival of 156 patients with metastatic renal cell cancer randomly assigned to receive high-dose bolus interleukin-2. Overall survival stabilizes at approximately 15% beyond 6 years with maximum follow-up beyond 13 years.

Three Different Mechanisms of Cellular Immunotherapy

Treatment of a patient using adoptive cell therapy with TILs containing Vb22+ ERBB2IP mutation-reactive T cells

Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer.

Melinda Bachini
2016

Clinical Response and Persistence of Expanded T Cells in Vivo

Chimeric Antigen Receptor (CAR) T Cell Therapy

Signal 1 → activation (CD3ζ)
Signal 2 → co-stimulation

2nd gen → 4-1BB or CD28
3rd gen → 4-1BB + CD28

Complete regression of DLBCL three months following CART therapy
## DLBCL CAR T study: 59% Response Rate

<table>
<thead>
<tr>
<th>Best overall response (CR + PR)</th>
<th>Patients (N = 51)(^a)</th>
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<tbody>
<tr>
<td></td>
<td>59% (95% CI, 44.2-72.4)</td>
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<tr>
<td></td>
<td>(P &lt; .0001)</td>
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<tr>
<td>CR</td>
<td>43%</td>
</tr>
<tr>
<td>PR</td>
<td>16%</td>
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<tr>
<td>SD</td>
<td>12%</td>
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<tr>
<td>PD</td>
<td>24%</td>
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<tr>
<td>Overall response rate (CR + PR)</td>
<td>45%</td>
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<tr>
<td>at 3 months</td>
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<tr>
<td>CR</td>
<td>37%</td>
</tr>
<tr>
<td>PR</td>
<td>8%</td>
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\(^a\) The interim analysis was preplanned to include the first 50 patients treated with CTL019 and followed for at least 3 months or discontinued early.
Duration of Response:
79% Relapse-free at 6 Months

- Median DOR not reached (median follow up, 6.4 months)
- All responses at 3 months were ongoing at the time of cut-off
  - No responding patients went on to SCT
- Median OS not reached (median follow-up, 2.8 months; max, 11.7 months)

DOR, duration of response; OS, overall survival; SCT, stem cell transplant.
A. CD27 vs. CD28

Healthy Untreated DLBCL Heavily-treated DLBCL

B. % CD3+CD27+CD28-

p<0.05

C. % CD27-CD28-

r^2=0.3752

p<0.05
A. Pre-sort

B. Days of expansion

C. Total cells  CD27-CD28-depleted  CD27-CD28-

SSCA  FSCA  FSCW  # cells per well

SSCA  Sytox blue  CD3

SSCA  CD27  CD28

SSCA  CD27  CD28

SSCA  Sytox blue
Vasoactive intestinal polypeptide induces tolerogenic dendritic cells that limit inflammation

Waller EK. *Blood*. 2006;107(9):3423-3424.
Structural model of VPAC1 receptor and docking of VIP

CD8 T-cells in the graft mediate the anti-leukemia activity of VIPhyb

VIPhyb-treatment increased novel TCR-beta clones compared with donor and GvHD recipients

Donor T cells
2.5% Oligoclonal

GvHD T cells
26% Oligoclonal

GvL T cells
22% Oligoclonal

Strategies for cancer immunotherapy

- Improving the anti-cancer T cell repertoire
  - Vaccination with tumor-specific antigens
  - BMT CTN1401 DC-myeloma fusions
  - Dr. Al-Kadhimi myeloma peptide vaccine, MDSC depletion
  - Selecting non-anergic Tn and Tcm T cells for expansion
  - Ex vivo immunization with tumor-micro-vesicles
  - Optimization of antigen-specific T cell manufacturing

- NK cell infusions with super-agonist IL15

- Bi-specific antibodies to target T cells to tumor

- Combining Vaccines and check-point blockade

- In vivo vaccination with chemo/XRT combined with check-point blockade, cytokines
Evolution of Immuno-oncology

Off-target effects

Tumor Specificity

Paul Ehrlich, father of the “magic bullet” concept of chemotherapy and immunotherapy

“For the sake of brevity, that combining group of the protoplasmic molecule to which the introduced group is anchored will hereafter be termed receptor”

Ehrlich and Morgenroth 1900. Berliner Klinische Wochenschrift. 2:196-204.