Immunotherapy for the treatment of GIST

Division of Surgical Oncology
Office of Therapeutic Development
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Outline

• **Immunotherapy for solid tumors**

• Unmet clinical need

• Immune response to GIST

• Building an anti-KIT CAR
1890

American Journal of the Medical Sciences.
May, 1890.

The treatment of malignant tumors by repeated inoculations of erysipelas: with a report of ten original cases.

By William B. Coley, M.D.,
Assistant Surgeon to the Hospital for Fuplerted and Crippled; Instructor in Surgery in the Post-graduate Medical School, New York.

Whether this principle could be isolated or outlined in the form of a process and admitted to the practice in the office of the physician, with the help of a few cases familiar with the process, is a matter that might as well be given a few words of interest. The process of the process, rendering it a run of a few times would be under the care of the physician. The process of the process, rendering it a run of a few times would be under the care of the physician. The process of the process, rendering it a run of a few times would be under the care of the physician.
2003
2015
CANCER CARE
SURGERY
CHEMO
XRT
IMMUNO
2020

CANCER CARE

$25-40 billion market

50% of medical oncology market share
Cancer Immunotherapy Treatment Shows More Promise
Treatment Eradicated Tumors in 14 of 16 Patients With Advanced Leukemia in Study

New Immunotherapy Drug Data Show Promise in Treating Cancer
Drugs From Bristol-Myers and Merck Shown to Prolong Lives of Some Cancer Patients

New Cancer Technology Gives Investors a Shot in the Arm
Immunotherapy’s promise is drawing some marquee financiers
F.D.A. Allows First Use of a Novel Cancer Drug

By ANDREW POLLACK  SEPT. 4, 2014

Breaking Through Cancer’s Shield

By GINA KOLATA  OCT. 14, 2013

New System for Treating Cancer Seen as Hopeful

By ANDREW POLLACK  JUNE 2, 2014
Breakthrough of the Year 2013

CANCER IMMUNOTHERAPY
Broad Interest
Normal Immune Response
Skinned knee: First barrier of protection is broken.

An invader enters the body through the cut, where immune cells have begun to gather to protect the body.

The immune cells begin to destroy and digest the invader and its antigens.

Some of the immune cells transform into antigen-presenting cells that tell the T cells about the invader.
Anti-Tumor Immune Response

1. Tumor cells release tumor antigens.
2. APCs gather tumor antigens and prepare to present to naive T cells.
3. Naive T cells are activated by the APC.
4. Activated T cells find the tumor cells with the same tumor antigens and destroy them.
Immunotherapy Categories

Non-specific Immunostimulation
- BCG
- IL-2 and IFNα

Vaccines
- Antigen-loaded APCs
- Direct antigen administration

Cellular
- TILs
- CAR-T Cells

Immunomodulation
- Anti-PD-1
- Anti-CTLA-4

Caspi. Nat Rev Imm. 2008
Core Principles of Immunotherapy

DEFINE TARGET

BUILD WEAPON

TUMOR

ATTACK ENEMY DEFENSES

DELIVER WEAPON
Is the enemy thyself?

- Cancer tissue is a variant of normal
- Immune cells may not be able to distinguish
- *KIT* present on tumor and normal cells
- *Delicate balance between immune attack* and organ damage
Checkpoint Inhibitors
Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma
Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma
CAR-T Cells

- Genetic re-engineering of patient T cells
- Chimeric antigen receptor (CAR)
  - Fusion protein
  - Antibody confers tumor antigen specificity
  - T cell receptor components
  - Co-stimulatory components
- Focus on CD19 CAR for leukemia and lymphoma
- Solid tumors more challenging

Anti-CEA CAR
LIQUID ≠ SOLID
Pattern of GIST Metastases

<table>
<thead>
<tr>
<th>Site</th>
<th>n</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All liver</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>Liver only</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>Any peritoneal</td>
<td>20</td>
<td>21</td>
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<td>Any node</td>
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<td>6</td>
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<tr>
<td>Any bone</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Any lung</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Liver and peritoneal cavity main sites of GIST metastases.
Phase I Hepatic Immunotherapy for Metastases
Study of Intra-Arterial Chimeric Antigen
Receptor-Modified T-cell Therapy for CEA Liver
Metastases


ORIGINAL ARTICLE
Neutrophil:lymphocyte ratios and serum cytokine changes after hepatic artery chimeric antigen receptor-modified T-cell infusions for liver metastases

A Saled, L Licata, RA Burga, M Thorn, E McCormack, BF Stainken, EO Assanah, PD Khare, RD Davies, NJ Espat, RP Junghans and SC Katz
Plan of Attack

Tumor Marker Response to CAR-T Cells

![Graph showing tumor marker response over time after CAR-T cell infusions.](image-url)
Response to CAR-T Cells
CAR-T Cells Mediated Tumor Cell Death

10X

40X

BL

Post-Infusion
This is why we are all here…

Alive at >3 years
Intraperitoneal CAR-T delivery
IPC
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Rationale for GIST Immunotherapy

- 30% recur within 2 years after surgery
- Resistance to TKIs
- No advances in first-line therapy since 2002
- Immune infiltrate in GIST demonstrated
- TKI and immunotherapy may be synergistic
Gastrointestinal Stromal Tumor (GIST)

- Recurrent or Metastatic Disease
  - Consider Resection of Primary with Minimal Metastatic Disease especially when Symptomatic
  - Unresectable or Resection Requiring Extensive Surgery
    - Imatinib
      - Response/ Stable Disease
      - Focal Progression
      - Diffuse Progression
        - Surgery* Embolization* RFA*
        - Sunitinib Other New Agents
          - Continue Imatinib
  - Diffuse Progression

* RFA = radiofrequency ablation

LIMITED OPTIONS FOR ADVANCED TKI RESISTANT DISEASE

Gold & Dematteo Ann Surgery 2006
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GIST Immune Cells Predict Outcome

- NK cell density predicts progression
- T cell density predicts progression
- Immuno-surveillance is occurring
- Potential biomarkers

Immune Cells in GIST

*In need of assistance*

- High level of macrophages and T cells
- T cell balance skewed toward suppression
- Abundance of M2 anti-inflammatory macrophages
- Level of M2 cells correlated with Treg
- More M2 cells in metastatic GIST

Checkpoints Exploited

- T cells in GIST tumors express checkpoint molecules
  - PD-1, TIM-3, LAG-3
- Imatinib increases GIST TIL PD-1 expression
- Imatinib decreased GIST tumor PD-L1 expression

TKI Effect on Immune Cells

• More than direct effect on tumor cells
• KIT expressed on immune cells
• Targeting tumor and patient
• Enhances immune response to GIST
• Improved T cell tumor killing
• Reverses immunosuppression
• Synergy with checkpoint blockade

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Adoptive Cell Immunotherapy – Renewed Optimism

- Tumor infiltrating lymphocyte (TIL) therapy
  - Derived from resected specimens or biopsies
  - Response rates up to 51-72% in patients with melanoma\(^1,2\)
  - Applicable to a limited number of diseases and patients

- CAR-T cells
  - Applicable to wide variety of cancer types
  - Need to define surface target
  - Derived from peripheral blood leukocytes
  - Introduction of genes for chimeric antigen receptors (CAR)
  - Success with CLL (anti-CD19 CAR with CD137)\(^3\)

1 Dudley. JCO; 23: 2346 (2005)
2 Dudley. JCO; 26: 5233 (2008)
3 Porter. NEJM; 365: 8 (2011)
Anti-KIT designer T cells for the treatment of gastrointestinal stromal tumor

Steven C Katz¹*, Rachel A Burga¹, Seema Naheed¹, Lauren A Licata¹, Mitchell Thorn¹, Doreen Osgood¹, Cang T Nguyen¹, N Joseph Espat¹, Jonathan A Fletcher³ and Richard P Junghans²
Anti-KIT CAR Constructs

KL-TCR (1st Generation)

KL (215 aa)  Zeta TM (21 aa)  Zeta cyt (112 aa)

KL-CD28-TCR (2nd Generation)

KL (215 aa)  CD28 ED (44 aa)  CD28 TM (25 aa)  CD28 Cyt (42 aa)  Zeta Cyt (112 aa)
anti-KIT CAR-T Transduction Efficiency
anti-KIT CAR-T 1\textsuperscript{st} & 2\textsuperscript{nd} Generation
Proliferate on exposure to KIT+ tumor

\[ \downarrow \text{CFSE} = \uparrow \text{proliferation} \]
anti-KIT CAR-T Kill KIT+ Tumor Cells
Infiltration of anti-KIT CAR-T Within GIST Xenografts
In Vivo Activity in Xenograft Model

**NO IL2**
- CTRL (n=6)
- 1st gen (n=6, p=0.05)
- 2nd gen (n=6, p=0.17)

**IL2**
- CTRL (n=4)
- 1st gen (n=6, p=0.06)
- 2nd gen (n=3, p<0.001)
Necrosis of GIST Xenografts Induced By anti-KIT CAR-T With IL-2
Summary

• Immunotherapy for solid tumors promising
• Regional delivery for GIST metastases
• Immune response to GIST biologically meaningful
• Anti-KIT CAR-T for GIST under development
• Target the tumor and the host
Thank you

MENTORS
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- Sam Singer
- Richard P. Junghans
- N. Joseph Espat

COLLABORATORS
- Jonathan A. Fletcher

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