Immunotherapy for lymphoma: The time is now

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Outline

• Nuts and bolts of the immune system and how it recognizes and attacks cancer cells.

• Cancer immune escape.

• Types of cancer immunotherapy.

• Clinical results of immunotherapy for lymphoma
The immune system

- Evolved to provide protection against viruses and bacteria
- Immune cells are created from bone marrow stem cells
- Consists of cells and proteins whose purpose is to recognize and kill micro-organisms
- The immune system is “educated” to attack foreign invaders, but at the same time, leave healthy, self-tissues unharmed
- The immune system can sometimes recognize and kill cancer cells
- 2 main branches
  - Innate immune system – Initial responders
  - Adaptive immune system – Tailored attack
Immune cells develop in the bone marrow

Hematopoietic Stem Cell

Innate immune cells
- Neutrophils
- Monocytes
- Macrophages
- DCs
- NK cells

Adaptive immune cells
- T cells
- T<sub>REG</sub> cells
- B cells
How T cells recognize their targets

Antigen – a substance recognized by receptors on immune cells
How are cancer cells seen as “abnormal” by the immune system?
Cancers can effectively “hide” from the immune system

- Reversing cancer-induced immune escape pathways can re-awaken the immune system to fight cancer
The PD-1 / PD-L1 axis in cancer
Cancer immunotherapy makes its mark

Immunotherapy – Treatments that take advantage of the immune system to fight cancer
Immunotherapy for lymphoma - approaches

Cancer vaccines
  • Anti-idiotype vaccines

Adoptive T cell therapy
  • Chimeric antigen receptor (CAR) therapy – genetically engineered T cells that can recognize cancer cells (CD19)

Immune checkpoint blockade
  • PD-1 blockade therapy
  • CD47 blockade therapy
Checkpoint Inhibition as Cancer Immunotherapy

Drake et al, Nat Rev Clin Oncol 2014
PD-1 blockade is effective against many human cancers
PD-1 blockade is effective in relapsed Hodgkin lymphoma

- Nivolumab treatment of 23 patients with relapsed HL
- 80% had prior stem cell transplant, and 80% received brentuximab
- Response rate was 87% (17% complete response rate)
- 86% in remission at 6 months
- Few serious side effects

Ansell et al, NEJM 2015
PD-1 blockade is effective in relapsed primary mediastinal B cell lymphoma

Pembrolizumab in Relapsed or Refractory Primary Mediastinal Large B-Cell Lymphoma

- KEYNOTE-013 and 170 – phase I and II studies of anti-PD-1 antibody in PMBL
- Response rate of ~45% in both studies
- Some patients achieved complete responses
- No patient in complete response experienced a disease recurrence
Mmmm…. good – macrophages feed on cancer

FACT OF THE DAY

Macrophages—literally “big eaters” of the immune system—can devour tumor cells.
The CD47-SIRPα axis – a second key checkpoint pathway in lymphoma

Veillete, A. et al. Trends Immunol 2018
CD47 blockade therapy is effective in relapsed DLBCL

CD47 Blockade by Hu5F9-G4 and Rituximab in Non-Hodgkin’s Lymphoma

Ranjan Advani, M.D., Ian Flinn, M.D., Ph.D., Leslie Poplewell, M.D., Andres Forero, M.D., Nancy L. Bartlett, M.D., Nilanjan Ghosh, M.D., Ph.D., Justin Kline, M.D., Mark Roschewski, M.D., Ann LaCasce, M.D., Graham P. Collins, M.D., Thu Tran, B.S., Judith Lynn, M.B.A., James Y. Chen, M.D., Ph.D., Jens-Peter Volkmer, M.D., Balaji Agoram, Ph.D., Jie Huang, Sc.D., Ravindra Majeti, M.D., Ph.D., Irving L. Weissman, M.D., Chris H. Takimoto, M.D., Ph.D., Mark P. Chao, M.D., Ph.D., and Sonali M. Smith, M.D.

Table 2. Clinical Responses to Combination Therapy with 5F9 and Rituximab.*

<table>
<thead>
<tr>
<th>Response</th>
<th>All Patients (N = 22)</th>
<th>Patients with DLBCL (N = 15)</th>
</tr>
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<tbody>
<tr>
<td>Objective response</td>
<td>11 (50)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Complete response</td>
<td>8 (36)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (14)</td>
<td>1 (7)</td>
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<tr>
<td>Stable disease</td>
<td>3 (14)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8 (36)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Disease control</td>
<td>14 (64)</td>
<td>9 (60)</td>
</tr>
</tbody>
</table>
Conclusions

• The immune system can recognize and kill cancer cells

• Cancers express antigens that can be seen as “foreign” to T cells of the immune system

• Although immune responses are generated against lymphoma in some patients, they are suppressed and ineffective

• 3 main types of immunotherapy for lymphoma are: CAR T cell therapy, PD-1 blockade therapy, and CD47 blockade therapy

• PD-1 blockade therapy works well in Hodgkin lymphoma and in PMBL. It is easy to administer and is relatively safe

• CD47 blockade therapy works well in diffuse large B cell and follicular lymphoma. It is easy to administer and well-tolerated

• Immunotherapy has revolutionized the way we treat cancer. More to come....