Immunotherapy 101 for GIST

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How does our immune system fight cancer?

1. Antigen-presenting cells patrol the body, picking up evidence of threats (like cancer).
2. Antigen-presenting cells present evidence of cancer to T cells in the lymph node.
3. T cells become activated, multiply, and head out to hunt for the cancer.
4. T cells recognize and kill the cancer.

UCIR.org website – AWESOME source for patient-friendly explanations of immune therapy!
Why does the immune system fail to kill off cancer?

• Cancer cells look more like “ourselves” than viruses or bacteria (foreign)
• The more genetically “broken” or mutated the cancer cell is, the more funny-shaped proteins get produced by the cancer cell and the better chance to be recognized
Goals for treatment

So for MOST patients – immune therapy needs to address:

- Lack of “foreign-ness” – not enough, or the wrong antigens
- The immune cells specific for the tumor are not able to get into the tumor
- Tumor-specific immune cells are shut down by other suppressive factors
- How do we try to fix these issues?
How does cancer immunotherapy work?

Cancer immunotherapy can involve:

- Boosting existing immune responses to cancer
- Triggering new immune responses to cancer
- Adding cancer-fighting immune components to the body

- Checkpoint protein inhibitors
- Vaccines, Virus therapies, Chemotherapy/radiation
- Cellular therapy

UCIR.org
What immune cells are in GIST?

A lot!

- T cells
- Macrophages
- NK cells

- Regulatory T cells
- Macrophages

Tan et al, Cancer Gen Ther 2017
Van Dongen et al, Int J Cancer 2010
What immune cells are in GIST?

- In localized GIST, improved PFS with
  - Low T regs
  - High CD3+ infiltrates
  - High CD3+ and NK cells

Effect of imatinib on immune cells

- Increases CD8+ cytotoxic T cells
- Decreases suppressive regulatory T cells
- Decreases production of IDO (suppressive cytokine)
- Increases PD-1 and PD-L1 expression on immune and tumor cells
- Reverts back with resistance to imatinib…

Balachandran et al, Nat Med 2011
Munn et al, Trends Immunol 2013
The immune system is recognizing SOMETHING about GIST…

• Low mutations but immune cells are there
  • Quality over quantity…
• Imatinib might work not just on slowing the growth of GIST but potentially through immune activities
• Can we harness/intensify the immune system?
How to boost or bypass immune recognition of cancer cells

Chemotherapy/targeted therapy?

1. Release of DAMP and PAMPs Type I Interferons
2. T cell
3. Activated T cell
4. Suppressive Angiogenesis
5. T cell infiltration
6. CD8+ T cell
7. Low Tumor Mutation Burden Silencing of MHC I

Give T cells already programmed to recognize targets

Target key pathways that promote immune cell “stalling” (suppression in the tumor environment)

Checkpoint inhibitors
IDO inhibitors
VEGF inhibitors

Florou & Wilky, Cancer Drug Res, 2022
Future directions – adoptive cellular therapies

**Known antigen target that is recognized by T cells**

**Presumed tumor-specific T cell population**

- CAR-T cells
- Engineered T cells
- TIL therapy
Immune therapy in GIST – summary…

• Cellular therapies – need more targets
• Some efforts to develop KIT CAR-Ts, but on other normal cells as well – risks of toxicity…
• Not ready for primetime yet

• Overall takehome –

From immunology perspective – immune therapy should help in GIST… but HOW and for WHOM is still a mystery.

• Now to hear about specific efforts for immunotherapy in GIST…
THANK YOU...

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