Focus on Immunotherapy as a Targeted Therapy

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Disclosures

• I have nothing to disclose that is relevant to this presentation.
Current treatments for cancer

- Surgery
- Radiation therapy
- Chemotherapy
- Hormonal therapy
- Targeted therapies (antibodies, small molecules)

New!

Immunotherapy
The immune system
T cells can recognize and destroy cancer cells
T cells can recognize and destroy cancer cells

3 requirements:
• Antigens
• Access
• Activity
Recognition of tumor cells by T cells

Antigen (epitope)
- self protein → tolerance
- mutated protein (neoantigen)
- cancer-testis (CT) antigen
- oncofetal protein
- overexpressed protein
- endogenous retroviral ORFs
- viral protein (e.g. HPV, EBV)

MHC

T Cell Receptor

Costimulatory Receptor
T cells can recognize and destroy cancer cells

3 requirements:
• Antigens
• Access
• Activity
Tumor-infiltrating lymphocytes (TIL) in ovarian cancer

Multi-colour IHC with Nuance imaging

CD8+ killer T cells
CD4+ T cells
CD20+ B cells
Tumor cells

Katy Milne, unpublished
Tumor-infiltrating lymphocytes (TIL) in ovarian cancer

Three cases of HGSC:

- **Cold**: Few TIL
- **Warm**: Weak TIL, *T cells in stroma*
- **Hot**: Robust TIL, *T cells and B cells in epithelium & stroma*
T cells and B cells show a combined effect on survival

Kaplan-Meier based on TIL patterns in HGSC (n=167, optimally de-bulked)

- No TIL (n=20)
- CD8 TIL alone (n=17)
- CD8 + CD4 TIL (n=58)
- CD8 + CD4 + CD20 TIL (n=72)

Log-rank
P<0.0001

Why aren’t hot tumors rejected?

Three cases of HGSC:

- **Cold**
  - Few TIL

- **Warm**
  - Weak TIL
  - T cells in stroma

- **Hot**
  - Robust TIL
  - T cells and B cells in epithelium & stroma

CD4+ T cells
CD8+ T cells
CD20+ B cells
T cells can recognize and destroy cancer cells

3 requirements:

- Antigens
- Access
- Activity
Immune evasion mechanisms:
Inhibitory signals (immune checkpoints)

PD-L1/PD-1 binding inhibits T cell killing of tumor cell

- PD-L1
- PD-1
- Antigen
- T cell receptor
- T cell
- Tumor cell
Immune evasion mechanisms: Inhibitory signals (immune checkpoints)

PD-L1/PD-1 binding inhibits T cell killing of tumor cell

- Tumor cell
- PD-L1
- PD-1
- Antigen
- T cell receptor
- T cell
Immune evasion mechanisms: Inhibitory signals (immune checkpoints)
Immune evasion mechanisms: Inhibitory signals (immune checkpoints)

CD8+ T cells (good guys)

PDL1+ macrophages (bad guys)
Immune evasion mechanisms:
Inhibitory signals (immune checkpoints)

CD8+ T cells (good guys)
PDL1+ macrophages (bad guys)
Stimulatory and inhibitory pathways in T cells
T cells have very sophisticated control mechanisms.
Immunotherapy modalities

- Antibodies (e.g. anti-PD-1)
- Other immune modulators
- Vaccines
- Oncolytic viruses

Adoptive T cell therapy
- Natural (e.g. TIL)
- Engineered (e.g. CAR-T cells)
Immune modulation: Checkpoint blockade

PD-L1/PD-1 binding inhibits T cell killing of tumor cell

Blocking PD-L1 or PD-1 allows T cell killing of tumor cell

Tumor cell

PD-L1

Antigen

T cell receptor

T cell

PD-1

Tumor cell death

Anti-PD-L1

Anti-PD-1

PD-1

T cell
**Checkpoint blockade: clinical successes**

*anti-CTLA-4 (eg, Ipilimumab)*

- Metastatic melanoma – FDA approval

*anti-PD-1 (eg, Nivolumab, Pembrolizumab, others):*

- Metastatic melanoma – 38% Objective Responses (Hamid, NEJM 2013), 53% Objective Responses with Ipilimumab (Wolchok, NEJM 2013) and FDA approval
- Non-small cell lung cancer – 18% Objective Responses and FDA approval
- Kidney cancer – 27% Objective Responses (Topalian, NEJM 2012); 52% ORR nivolumab + sunitinib (Amin, JCO abstract, 2014), FDA approval
- Bladder cancer – 52% Objective Responses (Powles, Nature 2014), FDA approval
- Hodgkin’s Lymphoma – 87% Objective Responses (Ansell, NEJM 2015), FDA approval
- Colorectal cancer (MSI) – 40% Objective Responses (Le, NEJM 2015), FDA Breakthrough Status 2015
- Any adult or pediatric metastatic solid tumor with mismatch repair deficiency (dMMR), FDA approval
- Replacing frontline chemotherapy for melanoma, lung cancer and renal cell cancer (so far)
Mutation load predicts response to checkpoint blockade (imperfectly)

Where checkpoint blockade is more likely to work

TCGA data mining reveals a correlation between mutation load and CD8+ TIL.
Immune modulation: current challenges

**Toxicities**

Efficacy

- many cancers (e.g., ovarian, breast) have low response rates (10-20% range)
- responses are often transient (e.g., lung)
Stimulatory and inhibitory pathways in T cells
Immune modulation: current challenges

**Cost**

- approx. $100k/treatment cycle
- combinations may be required for some cancers (e.g., Ipi + Nivo for melanoma)
- long-term use may be required for some cancers
Immunotherapy modalities

- Antibodies (e.g. anti-PD-1)
- Other immune modulators
- Vaccines
- Oncolytic viruses

Adoptive T cell therapy
- Natural (e.g. TIL)
- Engineered (e.g. CAR-T cells)
Adoptive T cell therapy

Identify/engineer tumor-reactive T cells

Expand T cells

Infuse T cells with immune modulation

Tumor or blood sample
Mouse breast tumour before T cell therapy

anti-CD3 (T cell marker)
Mouse breast tumour 5 days after T cell therapy

anti-CD3 (T cell marker)
Clinical grade T cell production unit
BCCA’s Deeley Research Centre, Victoria
BC Cancer Gyne TIL Trial (2019)

Relapsed cervical and MMR deficient ovarian and endometrial cancers

Years from diagnosis

CA-125

Harvest T cells from tumor sample

Chemo

Lymphodepletion
T cell infusion
Systemic IL-2

Chemo

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Engineering T cells to better recognize and destroy cancer cells
Chimeric Antigen Receptors (CARs)

Antibody binds the tumor cell

Receptor activates the T cell

- Antibody portion (e.g. α-CD19)
- Spacer and transmembrane domain
- Co-stimulatory domain from CD137 or CD28
- T cell receptor signaling domain
CD19 CAR-T cell clinical results

- 90% Complete Responses (67% sustained) in pediatric and adult B-ALL (Davila, Sci Trans Med 2013; Maude, NEJM 2014)
- 50-80% Objective Responses in lymphoma (Kochenderfer, JCO 2014)
- FDA approved for pediatric B-ALL (2017) and adult B cell lymphoma (2017, 2018)
CD19 CAR-T cell challenges

- Cytokine release syndrome
- Neurotoxicities of unclear etiology, with some fatalities
- Loss of healthy B cells for as long as the CAR-T cells are present
- About 1/3 of patients relapse, often with CD19-negative tumors
- Cost: US$400-500,000 per patient, just for the T cells
CAR-T Cell Wish List

• Lower toxicity
• Apply to other types of cancer
• Better penetration of solid tumours
• Fine-tuned control
• Failsafe stop mechanisms
• Affordable, feasible, sustainable
Canadian CAR-T Program

First trial: CD19 CAR-T cell for B cell malignancies (2019)

BC Cancer
CAR T Production
Vector Production

Ottawa
CAR T Infusion
T cell Collection

Rob Holt
John Webb
Brad Nelson
Dean Fergusson
Natasha Kekre
Harry Atkins
John Bell
Automated CAR-T Cell Manufacturing

BC Cancer’s Deeley Research Centre, Victoria
Automated CAR-T Cell Manufacturing

BC Cancer’s Deeley Research Centre, Victoria
The first cars...
...100 years later
Immunotherapy Program

Cancer cell

T cell