Immunotherapy versus Targeted Therapy

Maysa Al-Hussaini, MD FRCPath
Consultant Histopathologist, Cytopathologist
and Neuropathologist
Chair; Institutional Review Board
King Hussein Cancer Center
I know that most of the audience dislike pathology, but I will try to change your minds
Outline

• What is targeted therapy
  – Tyrosine kinase receptor inhibitor

• What is immunotherapy
  – Immune checkpoint inhibitors
  – T-cell mediated immunotherapy
  – Vaccines

• Immunotherapy versus targeted therapy; similarities

• Immunotherapy versus targeted therapy; differences
Targeted Therapy

Target
Anything specifically fired at
Avoid collateral damage
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we’ve been waiting for?
Differences with the more Traditional Therapies

Traditional therapies
• Affect cells that are doubling
• Not very specific
• Cytotoxic

Targeted therapies
• Drugs that inhibit a more specific target in the cell
• Mixture of cytostatic and cytotoxic
Mechanisms for Targeted Therapy

- Anti-receptor Antibodies ± Toxins
- Tyrosine Kinase Inhibitors
- Farnesyl Transferase Inhibitors
- Apoptosis Agonists
- Hormone Agonists/Antagonists
- Antisense
- Antimetabolites Microtubule inhibitors
- Growth Factor Receptors
- Intracellular Signaling Molecules
- Nucleus
- Tumor Cell
- Immune System Activation (Vaccines, Monoclonal antibodies)
- Metalloproteinase Inhibitors
- Matrix Degradation (Collagenases, Gelatinases & Stromelysins)
- Angiogenesis Inhibitors (Angiostatin, Endostatin & Anti-VEGF)
Actionable Mutations

• Actionable genomic events
• Potentially responsive to a targeted therapy
Targeted Cancer Therapy

Companion Tests

1. Molecular Profiling
2. Prognostic Markers
   - Markers predictive of drug sensitivity/resistance
   - Markers predictive of adverse events
Examples in Targeted Therapies and Companion Tests

- **Trastuzumab**: HER2/neu -- breast cancer
- **Cetuximab and panitumumab**: KRAS/NRAS -- colorectal cancer
- **Gefitinib/erlotinib and crizotinib**: EGFR and ALK -- non-small cell lung cancer
- **Vemurafenib**: BRAF -- melanoma
- **Imatinib**: Ph Ch -- chronic myelogenous leukaemia
Example of Targeted Therapy

Trastuzumab

- **HER2/neu-2** (also known as ErbB-2) stands for "Human Epidermal growth factor Receptor 2."
- A cell membrane surface-bound tyrosine kinase receptor.
- Encoded by the ERBB2 gene, a proto-oncogene located at the long arm of human chromosome 17(17q21-q22).
- Normally involved in the signal transduction pathways leading to cell growth and differentiation.
Example of Targeted Therapy

Trastuzumab

30% of women with breast cancer have HER2 positive breast cancer which is more aggressive than regular breast cancer.
Example of Targeted Therapy
Trastuzumab

• HER2/neu is important as the target of the monoclonal antibody trastuzumab (marketed as Herceptin).

• Trastuzumab is effective only in breast cancer where the HER2/neu receptor is overexpressed.
Her-2/ Neu Companion Testing

IHC of HER-2 neu 1+
Breast Carcinoma

IHC of HER-2 neu 2+
Breast Carcinoma

IHC of HER-2 neu 3+
Breast Carcinoma
Her-2/ Neu Companion Testing

IHC

IHC of HER-2neu 1+ Breast Carcinoma

IHC of HER-2 neu 2+ Breast Carcinoma

IHC of HER-2 neu 3+ Breast Carcinoma

FISH
Her-2/ Neu Companion Testing

IHC of HER-2neu 1+
Breast Carcinoma

IHC of HE
Breast Carcinoma

FISH

Normal breast cancer cell

Signal

Nucleus

Normal amount of HER2 receptors
send signals telling cells to grow
and divide.

1
Her-2/ Neu Companion Testing

Abnormal HER2+ breast cancer cell

Too many HER2 receptors send more signals, causing cells to grow too quickly.

IHC

FISH

R-2 neu 2+ carcinoma

IHC of HER-2 neu 3+ Breast Carcinoma
Outline

• What is targeted therapy
  – Herceptin as an example
• What is immunotherapy
  – Immune checkpoint inhibitors
  – T-cell mediated immunotherapy
  – Vaccines
• Immunotherapy versus targeted therapy; similarities
• Immunotherapy versus targeted therapy; differences
What if your immune system could be taught to kill cancer?
Immunotherapy

• In 1890 William Coley, a surgeon at Memorial Sloan Kettering noticed that cancer patients who suffered from infections after surgery often fared better than those who did not.

• His finding led to the development of Coley’s toxins, a cocktail of inactive bacteria injected into tumors that occasionally resulted in complete remission.
New York Times - July 29, 1908

ERYSIPelas GERMS AS CURE FOR CANCER

Dr. Coley’s Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer at the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York. It came out yester-
History of Cancer Immunotherapy

- 1863: Description of immune infiltrates in tumors by Virchow
- 1898: Cancer immuno-surveillance hypothesis (Burnet, Thomas)
- 1957: Treatment of bladder cancer with BCG
- 1976: IL-2 therapy for cancer
- 1983: Discovery of human tumor antigens (Boon, others)
- 1985: Adoptive cell therapy
- 1991, 4: FDA approval of sipuleucel-T (DC vaccine) in prostate cancer
- 2002: Adoptive T cell therapy
- 2009: HPV vaccination in VIN
- 2010: FDA approval of anti-CTLA4 (ipilimumab) for melanoma
- 2011: FDA approval of anti-PD1 for melanoma
- 2014: Further developments in cancer immunotherapy
Immunotherapy

Harness immune system components to enable the patient’s immune system to specifically recognize and kill cancer cells.
Targeted Therapy

Target
Anything specifically fired at.

Avoid collateral damage
Cancer Immunology

- Cancer cells are essentially “self”—part of the host.
- They often display unusual or inappropriate proteins on their cell surface that allow the immune system to identify them as “non-self”.
- An antitumor immune response is often mounted.
Cancer cells have evolved a number of mechanisms to enable evasion of this immune response and render it ineffective.

A state of immune tolerance has been established.
Immune Checkpoint Inhibitors

- The programmed death 1 receptor, PD-1 (also known as CD279) and its ligands programmed death ligands, PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273).
- Members of the CD28 and B7 families
- The PD-1 receptor is expressed on the surface of activated T cells.
- PD-L1 and PD-L2 are expressed on the surface of APCs such as dendritic cells or macrophages.
Immune Checkpoint Inhibitors

Activated T-lymphocytes

APC/ macrophages

PD-L1

PD-1

PD-L2
Immune Checkpoint Inhibitors

• Play critical roles in T cell co-inhibition and exhaustion.
  – When the ligands bind to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation.

• PD-L1 is the predominant ligand, while PD-L2 has a much more restricted expression pattern.
Immune Checkpoint Inhibitors

Activated T-lymphocytes

APC/ macrophages

Immune response

Protective mechanism
Mechanisms of Immune Evasion

Cancer cells exploit the PD-1 pathway to create an immunosuppressive environment, allowing cancer cells to thrive.

A. CD8+ T cell
   - IFNγ

B. CD8+ T cell
   - Attack
   - Induce
   - PD-L1

C. CD8+ T cell
   - Attack
   - Block
   - PD-L1

T-cell exhaustion

Cancer cell exploit the PD-1 pathway to create an immunosuppressive environment, allowing cancer cells to thrive.
Immune Checkpoint Inhibitors

Monoclonal antibodies blockading the PD-1/PD-L1 pathway will enhance T-cell function
PD-L1 as a Biomarker for Cancer Immunotherapy

- PD-L1-positive cancers are associated with poorer prognosis
- A correlation of PD-L1 expression and overall response rate was demonstrated in patients with the highest levels of PD-L1 expression (IHC 3; defined as $\geq 10\%$ PD-L1-positive tumor-infiltrating immune cells)
PD-L1 Companion Testing by IHC
Examples of PD-L1 IHC Staining of NSCLC Samples Using the Clinical Trial Assay

PS <1%
PS 1-49%
PS ≥50%

Brown chromogen: PD-L1 staining.
Blue color: hematoxylin counterstain.
Cancers with Overexpression of PD-L1

- Melanoma
- Non-small-cell lung cancer (NSCLC)
- Renal cell carcinoma
- Bladder cancer
- Ovarian carcinoma
Nivolumab (BMS-936558)

- The first agent targeting the PD-1 pathway to enter clinical testing
- It is a fully human IgG4 mAb
Combination of Immunotherapies

- Nivolumab is being evaluated in a phase I trial in combination with the CTLA-4-targeting agent ipilimumab (NCT01024231)
- Rapid and deep tumor regression observed in many patients
Combination with Chemotherapy

• Nivolumab is combined with platinum-based chemotherapy (gemcitabine/cisplatin, pemetrexed/cisplatin, or carboplatin/paclitaxel) in patients with chemotherapy-naïve, advanced NSCLC
Side effects

• Autoimmune adverse events
  – hepatitis, endocrinopathies, and dermatitis
  – Rash, pruritus, fatigue, and diarrhea elevated lipase levels
Immunotherapies

- Immune checkpoint inhibitors
- T-cell immunotherapy
- Vaccines

Immunotherapy
T-cell Immunotherapy

• Adoptive immunotherapy (cell therapies or living therapies)
  – Passive transfer of immune cells, which may or may not be modified / genetically altered to express a desired set of traits and / or features.
    • Chimeric antigen receptor (CAR) T-cell
    • T-cell receptor (TCR)
    • Tumor infiltrating lymphocyte (TIL) based therapies
Chimeric Antigen Receptor (CAR) T-cells

T cells are isolated from patient

T cells are engineered to express CARs that recognize cancer cells

Modified T cells are grown and expanded in culture

Modified T cells are infused into patient
T-cell Immunotherapy

• Some types of lymphoma; CLL
• Leukemia; refractory ALL and more recently AML
Side Effects

• Tumor lysis

• Weakening of the immune system in the recovery phase after fighting the “tumor” like fighting an infection.

• Cytokine release syndrome; fever, myalgia and severe hypotension.

• Neurotoxicity; ataxia, aphasia, confusion, delirium and hallucination.
Immunotherapies

- Immune checkpoint inhibitors
- T-cell immunotherapy
- Vaccines

Immunotherapy
Therapeutic Cancer Vaccines

Types of cancer vaccines

- Tumor cell type-based vaccines
- Peptide vaccines
- DNA-based
- Vector-based
- Dendritic cell-based
Therapeutic Cancer Vaccines

Tumor Cell-based Vaccines

Therapeutic cancer vaccines involve the use of tumor cells to stimulate the immune system and fight cancer. This process typically involves the following steps:

1. **Irradiation** of tumor cells to enhance their ability to stimulate the immune system.
2. **Genetic modification** of the tumor cells to ensure they are recognized by the immune system.
3. **Injection** of modified tumor cells into the patient to activate the immune system.

These vaccines can enhance the body's ability to recognize and fight cancer cells, potentially leading to improved outcomes for patients.
Therapeutic Cancer Vaccines

Peptide Vaccines

Tumor cells

Peptides

Artificial synthesis

Adjuvant

Inject

Tumor

CTL
Therapeutic Cancer Vaccines

DNA Vaccines

[Diagram showing the process of DNA vaccine administration into muscle cells, leading to stimulation of the immune system against cancer cells.]
Therapeutic Cancer Vaccines

Vector-based Vaccines

Viral vector
Therapeutic Cancer Vaccines

Dendritic Cell-based Vaccines
Immunologic Memory

- Immune checkpoint inhibitors
- T-cell immunotherapy
- Vaccines

Immunotherapy
Immunologic Memory

• A hallmark feature of “adaptive immune system”
• Can attack and thus prevent the re-appearance of antigically similar cancer cells
• Can help to keep the patient cancer free
• This is a lacking feature of other types of therapies
• Transferring the concept of cancer into a “chronic disease”.
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• What is Immunotherapy
  – Immune checkpoint inhibitors
  – T-cell mediated immunotherapy
  – Vaccines

• Immunotherapy versus targeted therapy; similarities

• Immunotherapy versus targeted therapy; differences
Immunotherapy versus Targeted therapy

Similarities

• Both modalities can essentially be considered “targeted” therapies.
• Both modalities target tumor cells and avoid normal cells.
• Many of the targeted therapies are approved along with a specific molecular test or companion diagnostic kit, making the precision molecular diagnostics a mandatory prerequisite for the cost-effective use of targeted treatment.
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Differences

- In targeted therapy, the cancer cells are directly targeted through trying to block actionable mutations in the cancer cells in one or more oncogenic drivers.
  - Specific mutation
  - Although targeted therapy offers a robust response rates in patients with a driver mutation resistance is often inevitable.

- In immunotherapy, cancer is indirectly targeted, as it tries to effectively boost the body's own immune system to eliminate the cancer.
  - No specific mutation
  - Immunologic memory allowing for long term remissions or even cure.
An Additional Difference

Cost!
**Immunotherapy versus Targeted therapy**

**Differences**

- **In targeted therapy**, the cancer cells are **directly** targeted through trying to block **actionable mutations** in the cancer cells in one or more oncogenic drivers.
  - Specific mutation
  - Although targeted therapy offers a robust response rates in patients with a driver mutation **resistance** is often inevitable
  - Cheaper

- **In immunotherapy**, cancer is **indirectly** targeted, as it tries to **effectively boost the body's own immune system** to eliminate the cancer.
  - No specific mutation
  - **Immunologic memory** allowing for long term remissions or even cure
  - More expensive
Conclusions

• Immunotherapy and targeted therapy are essentially “targeted therapy”.
• Both modalities specifically target tumor cells and avoid normal cells.
• Targeted therapies act on actionable mutations in tumor cells.
• Immunotherapies act on enhancing the immune system of the host to fight the cancer cells.
• Immunologic memory is an important feature of immunotherapies associated with long remissions and potential cures.
• Cost remains an important determinant of the choice of treatment.
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References

Thank you!