New Oncology Drugs: A Brief Primer

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Learning Objectives

• List novel chemotherapies and the indications of these newer agents
• Recognize the disadvantages and challenges of traditional cancer treatment
• Mechanism of monoclonal antibodies and associated toxicities (targeted therapies)
• Explain how immunotherapy works, evolving indications and associated toxicities
How did we get here?

• **Evolution**
  • Surgery
  • Radiation Therapy
  • Systemic Therapy
Cytotoxic Chemotherapy

- Use of anti-cancer drugs to slow or stop the growth of rapidly dividing cancer cells.
- Inhibiting different phases of the cell cycle, chemotherapy became an effective validity in cancer treatment.
- Challenge: associated toxicity involving normal cell functioning required for normal well being.
Toxicities

- GI toxicities
- Bone Marrow suppression
- Neurological toxicities
- Cardiac dysfunction
- Dermatological toxicities
- Constitutional symptoms
A New Era of Cancer Treatment

- Monoclonal antibodies
- Oral molecular target drugs
- Immunotherapy
Monoclonal Antibodies

• Rituximab
  • CD20 Inhibitor. NHL
• Bevacizumab
  • VEGF Blocker. GBM, NSLC, Colorectal cancers, Ovarian, cervical and RCC
• Transtuzumab, Pertuzumab
  • Her-2 Blockade. Breast, Gastric cancer
• Cetuximab
  • EGFR blocker, Head and Neck and Colorectal.
• Panitumumab
  • EGFR blocker, Colorectal.
• Ramucirumab
  • Vascular endothelial growth factor receptor 2 (VEGFR2). Lung, gastric and colorectal.
Monoclonal Antibodies Toxicity

Allergic and Infusion reactions
Hemorrhage
Hypertension and Proteinuria
Skin rash
Nose bleed
Delayed wound healing and wound dehiscence
GI Perforation
Monoclonal Antibodies

- Cetuximab
- Panitumumab

Small Molecule TKIs/STIs

- Erlotinib
- Imatinib
- Lapatinib
- Trastuzumab
- Bevacizumab
- Tipifarnib
- Lonafarnib
- Sorafenib

mTOR

HER1, HER2, HER3, or HER4

PI3-K

SOS

RAS

RAF

MAPK

MEK

Cell proliferation
Cell survival
Cell mobility and invasiveness

Transcription

Hudis CA. NEJM 2007;357(1):41
Oral Molecular Target Drugs

- Imatinib, Nilotinib, Dasatinib
  - TKI. CML. BCR/ABL inhibitor
- Sunitinib, Sorifinib, Pazopanib
  - Tyrosine Kinase Inhibitors.
    - RCC, HCC, STS
- Erlotinib, Afatinib, Gefitinib, Osimertinib
  - EGFR blockers. NSLC
- Lapatinib
  - Her 2 locker
- Regorafenib
- VEGF/TKI Blocker. CRC, GIST and HCC
- Vemurafinib, Tirametinib
  - B-raf inhibitor, Malignant Melanoma
Toxicity

Fatigue
Cytopenias
Hypertension
Cardiac dysfunction
Liver dysfunction
Thyroid dysfunction
Skin Rash
Pharmaceutical Research and Development Dept.

“We’ve run out of things to name our drugs. It’s time to invent some new alphabet letters.”
Immune Checkpoint Inhibitors

- Ipilimumab
  - Malignant Melanoma
- Nivolumab
  - Malignant Melanoma, NSLC, RCC, Squamous cell cancer of head and neck, Classical Hodgkin’s lymphoma, Urothelial cancer,
- Pembrolizumab
  - Malignant Melanoma, NSLC,, Squamous cell cancer of head and neck, Classical Hodgkin’s lymphoma,
- Atezolizumab
  - Urothelial carcinoma and NSLC.
Mechanism of Action

- **a** Tumour-specific IgG
  - Tumour cell
  - Tumour antigen
  - Complement
  - Effector cell

- **b** Angiogenesis inhibition
  - VEGFR
  - VEGF

- **c** Checkpoint blockade
  - T cell
  - CTLA4
  - PD1
  - PDL1
  - Ipilimumab
  - Nivolumab

- **d** Radioimmunotherapy
  - Immunoconjugates
  - Antigen-based retargeting of cellular immunity

- **e** Antibody–drug conjugate therapy
  - CD3

- **f** Bispecific antibody therapy

- **g** CAR T cells
CTLA-4, inhibitory receptor blocks T cell activation. Ipilimumab blocks CTLA-4 and augments T cell activation.

B7, co-stimulatory “ligand” activates co-stimulatory receptor Cd28 and stimulates T cell.
Cancer and Immune System

• Interaction between cancer and the immune system plays a pivotal role in cancer development.
• In cancer patients, the immune system is not sufficiently vigorous to eliminate cancer cells, suggesting that the antitumor immune system is suppressed.
• For instance, transplant recipients under continued immunosuppression displayed a significantly higher risk of developing de novo tumors.
• AIDS
• Autoimmune Disorders
What is cancer immunotherapy?

Treatment of cancer by immunologic approaches.

- Antibody-secreting (plasma) cell
- CDB+ cytolytic T lymphocyte (CTL)
- Natural killer (NK) cell
- Antigen-presenting cell (macrophage)
- B lymphocyte
- Antibody
- CD4+ helper T lymphocyte
- Dendritic cell
• PROGRAMMED CELL DEATH PROTEIN 1 (PD-1)
  Immunosuppressive molecule that is expressed on T-cells
  • Activated when it binds to its ligand (PDL-1)
  • Activation leads to impaired T-cell function
PD-1

- PROGRAM CELL DEATH LIGAND 1 (PDL-1)
- Ligand that binds to and activates PD-1
- PDL-1 is expressed on many cancer cells
PD-L1 Targeted Tumors

High PD-L1 Expression

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Estimated PD-L1 Prevalence</th>
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<tbody>
<tr>
<td>NSCLC (SCC)</td>
<td>50%</td>
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<tr>
<td>NSCLC (adeno)</td>
<td>45%</td>
</tr>
<tr>
<td>Colon</td>
<td>45%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>40%</td>
</tr>
<tr>
<td>RCC</td>
<td>20%</td>
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</tbody>
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- Nearly all human cancer types can express PD-L1
- Aberrant PD-L1 expression is associated with aggressive disease, poor prognosis, and poor survival

As one of the highest prevalent cancers, NSCLC represents a significant opportunity to leverage the effects of PD-1/PD-L1 blocking agents

Source:
PD-1
Toxicities

- Colitis
- Hepatitis
- Endocrinopathies
- Pneumonitis
- Nephritis/Renal dysfunction
- Dermatitis
Conclusion

• Cancer treatment Paradigm is rapidly changing.
• Monoclonal Antibodies and Targeted therapies allow selective action to attack cancer cells mainly and reduce risks of traditional toxicities.
• Immunotherapy is a novel but old concept in cancer treatment which recently changed the practice standards in several cancers.
Conclusion

- Durable response to treatment and long term treatment plans.
- Compliance issues with oral treatments.
- False impression of being cured from advance malignancy and tendency to stop treatment.
- Immunogenic side effects and role of high dose prednisone to counteract.
References

Hudis CA. NEJM 2007;357(1):41
