Advances in the Treatments of Blood Cancers

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Normal Blood Production

- Multipotential hematopoietic stem cell (Hemocytoblast)

  - Common myeloid progenitor
    - Erythrocyte
    - Mast cell
    - Myeloblast
    - Megakaryocyte
      - Thrombocytes
    - Basophil
    - Neutrophil
    - Eosinophil
    - Monocyte
      - Macrophage
      - Dendritic cell

  - Common lymphoid progenitor
    - Natural killer cell (Large granular lymphocyte)
    - Small lymphocyte
      - T lymphocyte
      - B lymphocyte
    - Plasma cell
Origins of Blood Cancer

- Splenic marginal-zone lymphoma
- DLBCL (ABC-type)
  - Primary mediastinal B-cell lymphoma
- Memory B cell
- B-CLL
- Hairy-cell leukaemia
  - Prolymphocytic leukaemia
- MALT lymphoma
- Multiple myeloma
- Germinal centre
- GC B cell
- Naive B cell
- Naive B cell
- B-CLL (unmutated V gene)
- Follicular lymphoma
  - Burkitt's lymphoma
  - DLBCL (GC-type)
  - Lymphocyte-predominant Hodgkin's lymphoma
- Classical Hodgkin's lymphoma
- Post-transplant lymphomas
- Mantle zone
- Plasmablast
- Plasma cell
- Mantle-cell lymphoma
  - B-CLL (unmutated V-region genes)
- Lymphoplasmacytic lymphoma
  - Primary effusion lymphoma

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Evolving Treatment of Hematologic Malignancy

1949: Methotrexate, Nitrogen mustard
1953: MOPP
1963: Doxorubicin, Vincristine
1975: CHOP
1978: VP-16
1983: ABVD
1997: Autologous stem-cell transplant, Cisplatinum, Rituximab, BEACOPP
1998: Dose-escalated BEACOPP
1999: R-CHOP, 2-CDA
2002: Lenalidomide, Vorinostat
2003: Everolimus, Bortezomib
2005: Pralatrexate, Romidepsin
2007: Bendamustine
2009: Brentuximab vedotin
2011: Ibrutinib
2013: Venetoclax, Copanlisib
2014: Nivolumab
2016: Tisagenlecleucel (CAR T cell)
2017: Axicabtagene ciloleucel (CAR T cell)
2018: Pembrolizumab

Era of chemotherapy
Era of targeted therapy
Immune therapies
Myeloma Success Story

History
- 1945: First documented case
- 1890: Description of plasma cells
- 1928: First large case series of myeloma
- 1958: Serum protein spike identified
- 1966: Light chain types (later termed kappa and lambda) recognized
- 1985: International staging system
- 1840: First documented case
- 1850: Abnormal urine protein, later termed Bence Jones protein
- 1890: Description of plasma cells
- 1928: First large case series of myeloma
- 1958: Serum protein spike identified
- 1966: Light chain types (later termed kappa and lambda) recognized
- 1985: International staging system

Treatment
- 1847: Urothene (N. Alawi)
- 1847: Methotrexate (N. Blokhin)
- 1950: Corticosteroids (R. E. Mass)
- 1950: Thalidomide (S. Singhal and B. Barlogie)
- 1992: Bortezomib (R. Z. Orlowski)
- 2002: Lenalidomide (P. G. Richardson and K. C. Anderson)

Blood. 2008 Mar 15; 111(6)2962-2972
Era of Chemotherapy

• Nitrogen mustard used in chemical warfare in WW I
• Induced bone marrow aplasia
• Developed to treat blood cancer
  – Tumors shrunk
  – Tumors grew back promptly
  – Would shrink again if given another dose (introduced the cycle concept)
• First chemotherapy drug in 1940’s
Mechanism of Chemotherapy

- Induces cell death by damaging DNA
  - Stops the ability of the cells to divide

- More active against cells that are rapidly dividing

- Unfortunately, also toxic to healthy normal cells

- Associated with a range of toxicities
  - Bone marrow suppression
  - Nausea and vomiting
  - Sore mouth and diarrhea
  - Tingling and numbness in hands and feet
  - Cardiac damage
  - Lung damage
  - Kidney damage
  - Risk of leukemia
Era of Chemotherapy

• Proof of Concept:
  – Methotrexate
    • First drug to treat pediatric ALL in 1948
    • Cured choriocarcinoma 1958
      • First solid tumor to be cured by chemotherapy
  – Resistance to chemotherapy develops
  – Most solid tumors are not curable with standard chemotherapy
What If We Just Increase the Dose?

Autologous Stem Cell Transplantation

- Higher doses of chemotherapy kills more cancer cells
- Too high a dose could harm the patient
- Toxicity to normal cells limits dose of chemotherapy
- Toxicity limits effectiveness of treatments

- Rational for high dose chemotherapy with stem cell rescue
Newer Agents and Combinations Developed

• Combinations of drugs with non-overlapping toxicities combined to try to cure cancer
  – R-CHOP
  – DA R-EPOCH
  – Hyper CVAD
  – PROMACE CYTOBOM
  – RICE
  – R-GDP
  – Etc...

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Era of Targeted Therapy

- Better understanding of cancer biology
- Identification driver mutations which are responsible for cell proliferation
- Drugs designed to specifically inhibit the critical pathways
  - Blocking antibodies
    - Trastuzumab in Her2 + breast cancer
    - Rituximab in NHL
  - Small molecules (TKI)
    - Gleevec in CML
    - Erlotinib in EGFR mutated lung cancer
- Birth of precision medicine
Era of Targeted Therapy: Proof of Concept

• CML was once universally fatal
  – Only curative treatment was allogeneic stem cell transplant
  – Allo transplant has a lot or risks
    • Immunosuppression
    • GVHD
    • Infections

• Discovery
  – CML is defined by BCR/ABL gene
  – Imatinib designed to precisely inhibits enzymes causing fusion gene
  – Controls the disease with minimal side effect
  – Bone marrow transplant no longer necessary in most cases
  – Disease easily controlled in most cases
New Paradigm

- Response rate in phase I trial was 90%
- Approved by FDA in 2001
- Revolutionized the paradigm of drug discovery
How Do We Identify the Targets?

- Cytogenetics
- PCR
- FISH
- Next generation sequencing
- Accelerated pace of discovery
- Shorter time from bench to bedside
• PROBLEM
  – Cancers all look the same under the microscope
  – Biologic behavior is not the same
  – Tumors are heterogeneous and evolve over time
  – There is no single driver mutation in most cancer cells
  – CML model did not translate into other cancer “cures”
Understanding Cancer Biology Yields New Treatments
Newer Targeted Therapies in AML

History of FDA Approved AML Therapy

1973 Cytarabine/Daunorubicin (7+3)

1977 First BM transplant

May 2000 Gemtuzumab ozogamicin

May 2002 Idarubicin

Jun. 2010 Gemtuzumab ozogamicin withdrawn

Aug./Sep. 2017 Gemtuzumab ozogamicin (returned), CPX-351, Enasidenib

Nov. 2018 Gilteritinib, Venetoclax, Glasdegib

Sep. 2020 Azacitidine (maintenance)
Era of Immunotherapy: T cell Immuno-oncology

EMPOWERING THE IMMUNE SYSTEM TO FIGHT CANCER

**Effector T-cell mechanisms**

<table>
<thead>
<tr>
<th>Activating</th>
<th>Inhibitory</th>
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<tbody>
<tr>
<td>ICOS</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>Oncolytic viruses</td>
<td>PD-1</td>
</tr>
<tr>
<td>LAG-3</td>
<td></td>
</tr>
<tr>
<td>TIGIT*</td>
<td></td>
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<tr>
<td>TIM-3</td>
<td></td>
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**Non-effector cell mechanisms**

<table>
<thead>
<tr>
<th>Activating</th>
<th>Inhibitory</th>
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<tbody>
<tr>
<td>NLRP3</td>
<td>CTLA-4</td>
</tr>
<tr>
<td>STING</td>
<td>CCR2/5</td>
</tr>
<tr>
<td>CD73</td>
<td>IL-8</td>
</tr>
<tr>
<td>CSF1R</td>
<td>TGFR</td>
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**NK-cell mechanisms**

<table>
<thead>
<tr>
<th>Activating</th>
<th>Inhibitory</th>
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</thead>
<tbody>
<tr>
<td>SLAMF7</td>
<td>KIR</td>
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</table>

Ongoing Immuno-Oncology research focuses on these pathways, either alone or in combination, to understand how they can be modulated to restore the body’s natural ability to fight cancer.

*Pathways are listed by primary mechanism. Secondary mechanisms may exist. APC=antigen-presenting cell; CCR2/5=chemokine (C-C motif) receptors 2/5; CSF1R=colony-stimulating factor-1 receptor; CTLA-4=cytotoxic T-lymphocyte antigen 4; EP4=prostaglandin E2 receptor 4; ICOS=inducible T-cell co-stimulator; IDO1=indoleamine 2,3-dioxygenase-1; IL-8=interleukin-8; KIR=killer cell immunoglobulin-like receptor; LAG-3=lymphocyte-activation gene 3; NLRP3=nucleotide-binding oligomerization domain-like receptor family, pyrin domain containing 3; NK=natural killer; PD-1=programmed death receptor-1; SLAMF7=signalling lymphocytic activation molecule family member 7; TGFR=transforming growth factor beta receptor; TIGIT=T-cell immunoreceptor with Ig and TIM domains; TIM-3=T-cell immunoglobulin mucin-3.
Mechanism of Action: CTLA4 and PD1 Antibodies
Widespread Use of PD1 Inhibitors

Source: U.S. FDA, IQVIA, National Sales Perspectives, Feb 2018; IQVIA Institute, Apr 2018
Notes: Met = metastatic; rec/met = recurrent/metastatic; 1L+ = 1st line; 2L+ = 2nd line; HCC = hepatocellular carcinoma.
Immune Mediated Adverse Events: “The Itises”

• GI
  – Hepatitis
  – Colitis
  – Pancreatitis
• Pulmonary
• Endocrine
  – Thyroiditis
  – Hypophysitis
  – Hyperglycemia/DM
  – Adrenalitis
• Dermatitis
  – Maculopapular rash
  – Pruritis
  – Blistering
• Cardiac
  – Myocarditis
  – Pericarditis
  – Decreased LV function
• Nephritis
• Neurologic:
  – Myasthenia Gravis
  – Transverse myelitis
  – Encephalitis
  – Peripheral neuropathy
  – Aseptic meningitis
• Ocular toxicity
• Musculoskeletal
  – Inflammatory arthritis
  – Myalgia/myositis
Bi-specific T cell Engaging Antibodies

**Engineering an Adapter From Two Monoclonal Antibodies**

BiTE® = Bispecific T Cell Engager

- Blinatumomab enables CD3-positive T cells to recognize and eliminate CD19-positive acute lymphoblastic leukemia (ALL) blasts
- Approved for use in patients with relapsed or refractory B-cell precursor ALL
- Scientist are working developing Bites with many different cancer types.
CAR T Therapy

- T cells are engineered to recognize cancer antigens
  - CD 19 targeting in B cell lymphoma and ALL
  - BCMA targeting in multiple myeloma
- Maybe a curative approach in some cases
- Can be used in patients unfit for stem cell transplant
- Can work with chemo refractory disease

Limitations
- Performed in specialized center with experience in cellular therapies
- Extreme cost
- Limited production capacity of commercial CAR-T products
- Timing is everything when cancer is aggressive
Why don’t we cure more cases of cancer: MRD

- “The surgeon got it all”
- “Your PET scan shows you have a complete remission”
Testing for Minimal Residual Disease

• MRD tests detect traces of tumor cells which were previously undetectable
• May be predictive of better outcomes
• Potential to avoid additional toxic therapies
  – Avoiding stem cell transplant
  – Stopping maintenance therapy
  – Predict which patients need more intensive treatment in 1st remission
• Under investigation in a variety of cancers
Where do we go next?