OBJECTIVES

• Historical Perspectives
• Classical Approaches
• Paradigm Shifts
• Small Molecule Inhibitors
• Immunotherapy: Benefits & Risks
• “Gene” Therapy
Why is this topic important?

In 2019, an estimated 1,762,450 new cases of cancer will be diagnosed in the United States and 606,880 people will die from the disease.

Approximately 39.3% of men and women will be diagnosed with cancer at some point during their lifetimes (based on 2012-2016 data).

But, how are we doing?

- In the United States, the overall cancer death rate has declined since the early 1990s:
  - 1.8% per year among men from 1999 to 2016
  - 1.4% per year among women from 2002 to 2016
  - 1.4% per year among children ages 0–19 from 2009 to 2013
- This has led to an increase in survivors of cancer:
  - The number of people living beyond a cancer diagnosis reached nearly 15.4 million in 2016 and is expected to rise to almost 19 million by 2024.
• Dr. Rudolf Virchow entered medicine in the 1840s
• Sought to provide more unifying theories of disease instead of the traditional descriptors:
  • Miasmas, hysterias, bad / foul humors, neuroses
• Cellular theory
  • Hypertrophy
  • Hyperplasia
  • ... Neoplasia

HEMATOLOGY HISTORY

- THE FOUR HUMORS

- Yellow Bile
  - SERUM

- Phlegm
  - WBC

- Blood
  - OXYGENATED RBC

- Black Bile
  - DEOXYGENATED RBC

• (I’m sorry… really)
CLASSICAL APPROACHES
Cytotoxic chemotherapies & Success Stories
BEGINNINGS OF CHEMOTHERAPY

• 1946: Goodman and Gillman
  • Mustine, nitrogen mustard, SS John Harvey
  • The first patient: lymphoma

• 1947: Sidney Farber
  • Pathologist turned investigator
  • Childhood leukemia
  • Aminopterin (precursor of methotrexate)

DRUG DEVELOPMENT

• Progress has been met with more regulation, more controlled environments and stricter criteria for effectiveness

• NCI established in 1955

• Combination chemotherapy (ALL, 1965)

• Adjuvant therapy (Osteosarcoma, 1974)

Cytotoxic Chemotherapy

- Success stories have occurred in multiple tumor types:
  - Lymphoma (Hodgkin / Non-Hodgkin)
  - Testicular / Germ Cell Tumors
  - Childhood Leukemias
  - Adult Leukemias

- However:
  - Less successful in other histologies
  - Dose-response curve / AUC
  - Dose intensity
  - Adverse events

Limitations

- Toxicities
- Mortality
- Lack of response
- Mutagenic abilities of malignancies

PARADIGM SHIFTS
THE “FOUR MINUTE MILE OF CANCER”

- Chronic Myelogenous Leukemia
- The Philadelphia Chromosome
- bcr/abl
- Dr. Brian Druker
- STI571 / Imatinib

THE “FOUR MINUTE MILE OF CANCER”

• Imatinib, unprecedented success
  • Palpable sensation in the field that THE breakthrough for all cancer types was on the horizon
  • Editorial by Bruce Chabner, 1999

• ‘Perfect Inversion of the goals of cancer medicine’

SMALL MOLECULE INHIBITORS

• The bcr/abl payoff
• Vascular blockade
• BTK Inhibition
• CDK4/6 (Cell Cycle) Inhibition

• ...and the side effects
IMMUNOTHERAPY

Checks and Balances
• Currently approved therapies:
  • Cytokines / Cytokine stimulation
  • CTLA-4 inhibitors
  • PD-1 inhibitors
  • PD-L1 inhibitors
  • CAR-T cell therapy (more in a bit)
• Harnessing the power and potential of the innate and adaptive immune system has long been a goal of cancer therapy

• The first documented use of immunotherapy in cancer therapy was in the late 19th century
  • Dr. W. Coley & ‘Coley’s toxin’
  • Injected a mixture of live (!) bacteria into sarcomas
  • Had some results (tumor regressions)
  • Mechanisms weren’t understood
  • Patient deaths
  • Results weren’t repeatable / reproducible

• High Dose IL-2
  • Renal cell carcinoma (kidney cancer)
  • Melanoma (skin cancer)

• Whipping up an ‘immunologic storm’…
  • ... and hoping to win the lottery

• Proof of concept

• Toxicities: High fevers, confusion, low blood pressures, heart failure, swelling

MODULATING THE IMMUNE RESPONSE: CTLA-4

- Ipilimumab: first in class
- An attempt at ‘cleaner’ immunotherapy
- Removal of the natural ‘immunologic brakes’
Success in melanoma

‘Unprecedented numbers’; doubling the number of patients alive after 1 year (43%)

CHECKPOINT INHIBITION

• Old concept in cancer therapy becomes new

• Immunologic manipulation

• PD-1, and PD-L1

• Mutational burden

• irAE: a whole new class

MODULATING THE IMMUNE RESPONSE: PD-1

• Success in melanoma
• ‘Unprecedented numbers’; doubling the number of patients alive after 1 years (73%)

MODULATING THE IMMUNE RESPONSE: PD-1 / PD-L1

• With this success, research has expanded the scope of use of this concept:
  • Melanoma
  • Non-small cell lung cancer
  • Small cell lung cancer
  • Hodgkin Lymphoma
  • Kidney cancer
  • Bladder cancer
  • Colorectal cancer
  • Merkel cell carcinoma
  • Gastric cancer
  • …and more to come
IMMUNE RELATED ADVERSE EVENTS (IRAE)

• As the immune system is stimulated to act, an intentional expansion of the reach and volume of the immune system is anticipated

• At times, this is extraordinarily smooth in delivery with minimal side effects

• At other times, however...
• **Fatigue**
  - Occurs in 16-24% of PD-1/PD-L1 treated patients (All grades)
  - Can be up to 40% of CTLA-4-I treated patients
  - Generally mild

• **Infusion-related reactions**
  - Mild reactions (itching, etc) occurs in 25% of patients
  - Life threatening reactions (anaphylaxis) is quite rare (<2%) across the classes

**IRAE: DERMATOLOGIC**

- **Dermatologic**
  - Most common toxicity in this class of medications
  - Usually the earliest toxicity (~3 weeks)
  - Highly variable (can range from mild rash to vitiligo to alopecia to Stevens-Johnsons Syndrome)
  - Management is generally steroid based: topical / oral / systemic depending on severity of rash, duration of rash, necessity of continuation of the medication

**IRAЕ: GASTROINTESTINAL**

- **Colitis & Diarrhea**
  - Average time to onset is ~6 weeks
  - With ipilimumab, colitis can occur in 30% of cases; with 10% of those being severe (>7 stools per day)
  - **THIS DIARRHEA CAN BE LIFE THREATENING**
  - The earlier the recognition (and treatment initiation), the better the outcome
  - Colitis occurs in only 1-2% of cases with PD-1 / PD-L1 inhibitors

- Management: 1) Hydration, 2) High dose corticosteroids, 3) Infliximab

IRAE: HEPATIC

• **Hepatotoxicity**
  - Usually manifests as simple elevations of AST / ALT (and sometimes bilirubin)
  - Generally, is pretty rare:
    - 10% for ipilimumab
    - <5% for PD-1 inhibitors
    - 20% for ipilimumab + nivolumab

• Management:
  - Generally, these are asymptomatic situations that can be either simply be monitored or treated with corticosteroids
  - Some case literature using MMF for refractory patients

IRAE: LUNG

• **Pneumonitis**
  - Average time to onset is about ~ 3 months into therapy
  - **THIS SITUATION CAN BE LIFE THREATENING**
  - Occurs in 3-10% of patients
  - More prominent in patients who have underlying interstitial lung disease or who have had chest radiation in the past (radiation recall)
  - Generally presents as acute hypoxic respiratory failure with diffuse infiltrates

• Management:
  - Corticosteroids with long associated taper
  - If steroids do not work: infliximab, cyclophosphamide

IRAE: ENDOCRIPATHIES

• Autoimmune thyroid disease
  • Hyperthyroidism
  • Hypothyroidism

• Hypophysitis

• Adrenal insufficiency

• Acute onset Type 1 Diabetes

IRAE: OTHERS

- Nephritis
- Pancreatitis
- Guillain-Barre Syndrome
- Myocarditis
- Acquired Hemophilia
- Conjunctivitis / Uveitis / Episcleritis
- Arthritis
CAR-T “GENE” THERAPY
Chimeric Antigen Receptors (CAR) are synthetic, engineered receptors that are made in a laboratory.

The idea behind this approach is to essentially synthesize two approaches to cancer:
- Monoclonal (specific) antibodies
- T-cell therapy (immunotherapy)
This is a process that is heavy on biomedical / biochemical engineering

**Steps:**

1) Collect T-cells (blood draw) from the patient (specific to each & every patient)

2) In a lab, the T-cells are exposed to an inactivated virus in order to convince / train them to express an engineered receptor on its surface (this receptor doesn’t exist in nature)

3) T-cells are ‘expanded’ (grown) in the lab to number in the millions
**Steps (continued):**

- 4) **Patient receives dosing of chemotherapy** to kill their existing lymphocytes

- 5) **Re-infuse the expanded T-cell population** into the patient (like a blood transfusion)

- 6) The newly engineered T-cells further grow in the patient and, armed with their new machinery, **attack the cancer** entrenched in the body
CAR-T CONCEPTS

- T cells from peripheral blood
- Viral or non-viral insertion of genes into T cells
- T cell receptor (TCR) and chimeric antigen receptor (CAR)
- Antigen processed and presented by MHC
- Tumor cell
- Expand TCR gene-engineered T cells
- Cell infusion with IL-2
- Preconditioning with chemotherapy
Success in Acute Lymphoblastic Leukemia
  • Common leukemia in children and young adults
  • High rates of cure with chemotherapy, stem cell transplants
  • Minimal success if these standard therapies fail

In the first trial in ALL with CAR-T cell therapy:
  • 27/30 (90%) patients went into complete remission initially
  • 18/30 (60%) were able to maintain this remission

Early success in refractory lymphomas as well

CAR-T ADVERSE EVENTS

• Most feared side effect is cytokine release syndrome
  • Supraphysiologic response to immunotherapy
  • Manifestations:
    • Fever
    • Headache / Rash / Diarrhea / Myalgia / Arthralgia
    • Circulatory collapse
    • Altered mental status / Confusion

• Management:
  • Based on the grade of CRS (hypotension, hypoxia)
  • Supportive care
  • Tocilizumab
  • Steroids

CONCLUSIONS

• Exciting times
• Options abound
• Novel approaches coupled with critical, science based rational drug & clinical trial design are poised to lead to further advances in our field
• Early recognition and appropriate management of these new classes of side effects are critical for patient success
THANKS!

(Nudge the person sitting next to you who looks like this)