BMTCN REVIEW COURSE

PREPARATIVE REGIMENS

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How the Experts Treat Hematologic Malignancies
Las Vegas, NV
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DISCLOSURES

No Disclosures
Objectives

• Review various agents used to prepare patients for transplant
• Review intensity of therapy used in preparation for transplant

Note: the primary reference source for this course is Ezzone, S. (2013) Hematopoietic stem cell transplantation: a manual for nursing practice. Oncology Nursing Society, Pittsburgh, PA
Preparative or Conditioning Regimens

- First part of the transplant schedule
- May be administered on inpatient or outpatient basis.

Rationale for conditioning regimens:
- Preparation of the soil in order to:
  - Suppress the recipient’s immunity
  - Create space for the donor cells
  - Eradicate residual tumor cells
  - Avoid overlapping toxicities
Conditioning Regimen: Purpose

- Eradicating malignant cells
- Inducing immunosuppression (Allo)
- Augmenting anti-tumor immune response
Conditioning Regimen Selection

- Disease
- HPC source
- Type of transplant
- Organ function
- Goal of therapy
Conditioning

- Treatments given to patients to prepare their body to receive hematopoietic progenitor cells (HPCs)
  - Chemotherapy
  - Radiation
  - Immunotherapy
  - Biotherapy
  - Targeted therapies

- Classification of conditioning intensity
  - Myeloablative
  - Reduced intensity/Non-myeloablative
Chemotherapy

- May use single agent or multiple agents
- May be used with or without radiation therapy
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose Melphalan</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Fludarabine/Melphalan</td>
<td>Multiple Myeloma, various others</td>
</tr>
<tr>
<td>Fludarabine/TBI</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Busulfan/Cyclophosphamide</td>
<td>Myeloid Leukemia</td>
</tr>
<tr>
<td>Cyclophosphamide/TBI</td>
<td>Leukemias, MDS, NHL</td>
</tr>
<tr>
<td>Busulfan/Fludarabine</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Carmustine/Etoposide/Cytarabine/Melphalan [BEAM]</td>
<td>NHL, Hodgkins Lymphoma</td>
</tr>
</tbody>
</table>
# Conditioning Regimens: Ideal Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Allogeneic Myeloablative</th>
<th>Allogeneic Reduced intensity</th>
<th>Autologous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppression</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Eradicate underlying disease</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Make space for new marrow</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid/minimize overlapping toxicity</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Conditioning Regimens: Myeloablative

- Myeloablative
  - Traditional
    - High dose chemotherapy
    - +/- radiation therapy
    - +/- immunotherapy
  - Toxic modality
    - Morbidity
    - Mortality
Conditioning Regimens: Reduced Intensity

• Reduced intensity
  • Standard dose chemotherapy
  • Immunotherapy
  • +/- Reduced dose radiation therapy

– Goals
  • Decreased toxicity
    – Decreased peri-transplant morbidity
    – Decreased peri-transplant mortality
Side effects of chemotherapy

- **Hematologic**: Myelosuppression
- **Gastrointestinal**: Nausea/vomiting, mucositis, diarrhea, constipation, anorexia
- **Genitourinary**: Electrolyte imbalance, hemorrhagic cystitis, renal toxicity
- **Cardiovascular**: Hypotension, hypertension, cardiotoxicity
- **Pulmonary**: Pneumonitis, fibrosis
Side effects of chemotherapy

- **Neurological**: Seizures, peripheral neuropathy, headaches
- **Skin**: Hyperpigmentation, alopecia, erythema
- **Miscellaneous**: Hypersensitivity reactions, cataracts, conjunctivitis, secondary malignancy
RADIATION FOR CONDITIONING
Fractionated Total Body Irradiation: FTBI

• Rationale for FTBI
  – Developed in 1940-50’s following lessons learned from nuclear bombs
  – Early experiments with single, total dose were more toxic and had greater graft failure

• Dosage
  – Fractionation
  – Fractions given over several days
When is FTBI used

- Used in diseases that are sensitive to radiation
  - Leukemia
  - Lymphoma
- Used in allogeneic transplants to promote immune suppression and prevent GVHD
- Careful consideration:
  - Previous radiation exposure
  - Limited in children
FTBI: Dose and Administration

- Fully ablative regimens
  - Multiple treatments in order to reach determined dose
- Non ablative regimen
  - Single fraction of radiation
- Administration is institution specific
  - Careful measurement and planning
  - Blocks/shields protect vital organs
  - Boosts may be given to tumor sanctuary sites such as the testes
FTBI Administration

• Patient positioning may be:
  – Standing
  – Sitting
  – Lying on floor
  – Children – special consideration
Total Body Irradiation

- Standing position for adults
- Patient is held in harness
- Lung shields are placed in Plexiglass
- Boosts given to lung fields
Pediatric FTBI

Lung block placement

Pediatric FTBI position
Total Marrow Irradiation (TMI)

- Approach for radiation therapy
- Combines computed tomography (CT) with radiation therapy machine
- Increases precision of treatment
- Target of radiation is bone marrow – thus the name
Radiation Side Effects - Acute

- Nausea & vomiting
- Immunosuppression
- Diarrhea
- Fever
- Fatigue

- Skin reactions
- Mucositis
- Alopecia
- Parotiditis
Radiation Side Effects - Chronic

- Interstitial pneumonitis
- Cataracts
- Hepatic disorder
- Renal dysfunction
- CNS dysfunction

- Endocrine function
  - Thyroid function
  - Growth
  - Fertility

- Second malignancy
INTENSITY OF THERAPY
Myeloablative

- Used for autologous and allogeneic transplants
- Chemotherapy or radiation are administered at lethal doses
- Goal of therapy is to eliminate tumor cells and create an immunosuppressed host
Non-myeloablative/Reduced Intensity

- Used for allogeneic transplant
- Reduced doses of chemotherapy or radiation are administered
- Goal of therapy is create immunosuppressed host to enable graft versus tumor effect
- Uses:
  - Patients greater than 60 years old
  - Patients with co morbidities
Development of Nonmyeloablative BMT

- Toxicity of transplant in younger patients
- Limited use in older patients
- Diseases that can be cured by an allogeneic transplant are more common in the elderly
- Recognition of the contribution of GVL in the cure of disease
Evidence for Graft Versus Tumor Effect in Patients

1. Recurrence rate is lower in patients who manifest a graft versus host reaction than for those who do not.
2. Identical twins: recurrence rate is higher following stem cell transplant than if a matched sibling is utilized.
3. Removal of T cells from the donor graft before transplant increases the recurrence rate.
4. In patients who relapse, withdrawal of immune suppression or infusion of more donor T cells can sometimes achieve remission.
5. Mini-transplant.
Biotherapy, Immunotherapy, Targeted Therapies in HCT

**Biotherapy**
A type of treatment that uses substances made from living organisms to treat disease. These substances may occur naturally in the body or may be made in the laboratory. Some biotherapies stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases.

**Immunotherapy**
A type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system.

**Targeted Therapies**
A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells.
How targeted therapies work

- Identify targets that play role in cancer growth and survival
- Proteins more abundant in cancer cells than normal cells

NCI, Targeted Therapies online tutorial retrieved December 2021
https://archive.org/details/gov.hhs.nci.therapies
Actions of biotherapeutic agents

Can have one or more single or overlapping actions, including:

- Cuts off blood supply to tumor (antiangiogenesis)
- Prevents cell signaling which in turn prevents cell growth
- Blocks growth factors
- Targets mutant proteins
- Carries agent(s) which are cytotoxic to tumor cells
- Augments immune system response to attack cancer
- Inhibits proteins and causes programmed cell death (apoptosis)
Examples of Targets for Therapy

- Human epidermal growth factor receptor 2 protein (HER2)
  - Expressed at high levels on some breast and stomach cancers
    - Example: Trastuzumab (Herceptin®)

- Targets which produce mutant (altered) proteins that drive cancer progression
  - BRAF mutation
    - Example: Vemurafenib (Zelboraf®)

- Targets which block inhibitors of immune responses to cancer cells
  - PD1 inhibitors or check point inhibitors
    - Example: Pembrolizumab (Keytruda®)

- Chromosomal abnormalities
  - Creates fusion protein that drives cancer development
    - Example: Imatinib (Gleevec®)
Biotherapy: Cytokines

Interferon / Interleukins
- IL-2 Proleukin®
- Interferon alpha Intron A®
- Interferon gamma Roferon®

Colony stimulating growth factors
- GCSF Filgrastim Neupogen®
- Pegfilgrastim Neulasta®
- GMCSF Sargramostim®
- Plerixafor Mozobil®

Erythrocyte Growth Factors
- Epoetin alfa Aranesp® Procrit®

Keratinocyte Growth Factor
- rHuKGF Palifermin®
Biotherapy: Granulocyte Colony Stimulating Factors

- **Filgrastim (Neupogen®)**
  - Indications:
    - Prevention of post chemo neutropenia
    - Mobilization of stem cells for collection and transplant
  - Administered subcutaneously daily
  - Dose 300 mcg or 480 mcg

- **Pegylated filgrastim (Neulasta®)**
  - NCCN guidelines for risk of Neutropenia of >10%
  - Dose 6 mg SC 24 hours following chemotherapy
  - Given via SC injection or ONBODY injector
Biotherapy: Erythroid Stimulating Agents (ESA)

Action
- Stimulate erythropoiesis via same mechanism as endogenous erythropoietin

• Indications:
  - Anemia of chronic disease and chronic renal failure
  - Anemia associated with chemotherapy for non-myeloid malignancies

Contraindication:
- When goal of chemotherapy is curative
  - Worse survival outcomes were identified when patients received ESAs (Bohlius et al., 2009)

• Black box warning
  - Hypertension, Stroke, Thrombotic events

• Requires REMS (Risk Evaluation and Mitigation Strategy)
Targeted Therapy Categories

- Monoclonal Antibodies
- Small Molecule Inhibitors
- Proteosome Inhibitors
- Immunotoxins/Biologic Response Modifiers
- Genetically modified T Cell therapy
- Vaccines
Monoclonal Antibodies

• Interaction on target signaling molecules on cell membrane activates pathways inside cell
  – Can prevent molecules on cell membrane from interacting
  – Can deliver radioactive molecules or toxins/chemotherapy agent to cancer cells
  – Can trigger an immune response
Monoclonal Antibodies Features

- Infusion therapy
- Often in combination with Chemotherapy
- Most common complication is infusion reactions
- Generally not considered hazardous
Monoclonal antibodies

Conjugated
- Antibody Drug Conjugate
  - Brentuximab
  - Ado trastuzumab
- RIT
  - Ibritumomab tiuxetan

Unconjugated
- Cell Surface markers: CD 20, CD 52, etc.
- EGFR
- HER2
- VEGF
- CTLA-4
- PDI Receptors
Conjugated Monoclonal Antibodies: RIT and ADC

Radioimmunotherapy (RIT)
Ibritumomab tiuxetan (Zevalin®) — attaches yttrium-90 radioactive isotope which attaches to CD 20 and induces B cell damage

Antibody Dependent Cytotoxicity (ADC)
Brentuximab vedotin (Adcetris®)
Anti-CD30 antibody attached to a cytotoxic agent

NCI, Targeted Therapies online tutorial retrieved December 2015
https://archive.org/details/gov.hhs.nci.therapies
ADC image by permission
Polovich, Olsen & LeFebvre, 2014
Small Molecule Inhibitors

• Small Molecules
  – Cross cell membranes
  – Interfere with proteins on cell surface or inside cell
  – Modify enzyme activities or its interaction with other molecules

• Usually given via oral route
  – Considered hazardous drug with excretion precautions
Small Molecules
Proteosome Inhibitors

• Inhibits proteosomes’ enzymatic function resulting in disruption of cellular stability and can lead to cell death
• Given intravenously/subcutaneous
• Indications are primarily multiple myeloma
• Toxicities - Myelosuppression, cardiopulmonary toxicities, tumor lysis
Small Molecule Inhibitors Less Common Side Effects

- Nausea and vomiting
- Constipation
- Mouth sores
- Shortness of breath
- Cough
- Fatigue
- Headache
- Swelling in hands and feet
- Cytopenias

American Cancer Society, 2014
Immunotoxins / Biologic Response Modifiers

• Immunotoxin – protein used to treat cancer
  – Example: Denileukin diftitox (Ontak®)
    • CD25+ cutaneous T cell lymphoma
• Biologic response modifiers
  – Mechanism unclear
  – Examples used to treat multiple myeloma
    • Lenalidomide (Revlimid®)
    • Pomalidomide (Pomalyst®)
    • Thalidomide (Thalomid®)
Harnessing the Power of the Immune System for Cancer Therapy

Cytotoxic T-Lymphocyte: A specialized white blood cell responsible for eliminating unwanted body cells (e.g. cancer) is killing a cell infected with the influenza virus in this image.

Courtesy of Stephen J. Forman, MD
Genetically Modified T-cells

• T-cells are part of the immune system that recognizes virus, bacteria and fungus

• T-cells have receptors on them that recognize foreign tissue antigens (organ transplant)

• Tumors have antigens on surface too

• Can T-cells be “educated” to recognize tumor antigen?
Adoptive Therapy using CAR-Engineered T cells

1. Leukapheresis (Remove immune cells from blood)
2. Isolate and activate T cells
3. Genetically engineer T cells with tumor-specific chimeric antigen receptor (CAR)
4. Stimulate replication of tumor-specific engineered CAR T cells
5. Infuse engineered CAR T cells
Vaccine Therapy

• Belong to the class of biologic response modifiers
• Goal is to activate the body’s immune system, to prevent, recognize and defend against cancer cells
  – Prevent cancer (prophylactic vaccines) e.g.
    • Hepatitis B vaccine
    • Human Papillomavirus vaccine
  – Treat cancer (therapeutic vaccines) e.g.
    • Cytomegolovirus vaccine

Polovich, Olsen & LeFebvre, 2014
Ir-SE – Immune related side effects

• Immune related side effects of biotherapy / targeted therapies can be significant and life-threatening
  – Hepatitis (elevation in AST and ALT)
  – Colitis (close attention to patient’s bowel patterns)
  – Dermatitis (most common)
  – Hypophysitis (inflammation of the pituitary gland)
  – Uveitis
  – Neuritis
  – Nephritis
  – Pneumonitis
• Most often treated with steroids
• May require hospitalization
• Fever is often associated, but expected and normal
Limitations of Targeted Therapy

• Resistance may develop
  – Use in combination treatments
  – Drug holidays
  – Use of similar agents

• Drug costs and medication management
  – Average cost of new biologics on the market is ~ $10,000 / month
  – Procurement and adherence issues
Patient Education

- Help patients to appreciate the side effect profile of the particular targeted therapy
  - Different than what they may have expected with traditional chemotherapies
- Report any adverse effects which have not been identified as a side effect of the treatment
- Goal of therapy – with many targeted therapies, it is often stable disease, not complete remission
- Help patients with medication/herb/supplement management and chemotherapy adherence
- Ensure patients know how to access healthcare team on a 24 hour basis
FDA Approved Drugs* (and study drugs) for Melanoma

Targeted Therapies

- **BRAF inhibitors**
  - Vemurafenib*
  - Dabrafenib*
  - Encorafenib (LGX818)

- **MEK inhibitors**
  - Trametinib*
  - Cobimetinib
  - Binimetinib (MEK162)
  - Selumetinib (AZD6244)

- **CKIT inhibitors**
  - Imatinib
  - Dasatinib
  - Nilotinib

- **Combinations**
  - Dabrafenib + trametinib*
  - Vermurafenib + cobimetinib
  - Encorafenib + Binimetinib

Immunotherapies

- **Anti-CTLA-4 antibody**
  - Ipilimumab*
  - Tremelimumab

- **Anti-PD-1 antibody**
  - Pembrolizumab*
  - Nivolumab*

- **Anti-PD-L1 antibody**
  - MPDL3280A
  - MEDI4736

- **Other**
  - Interleukin-2 (IL-2)*

- **Combinations**
  - Ipilimumab + nivolumab

*FDA approved for Melanoma

Slide courtesy of Krista M. Rubin, MS, RN, FNP-BC
Massachusetts General Hospital
Future directions

• Change in paradigm of chemotherapy and radiotherapy
  – Using the immune system to target cancer cells
• Nurse must have a high index of suspicion for subtle or unusual symptom expression because of impact of biotherapies on the patient’s own immune system
• New therapies being FDA approved and released into clinical practice with frequency
• This website links FDA notices and updates on approval and new indications: (set it up to email you alerts)

http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm