Jennifer Peterson MSN, RN, BMTCN, OCN, WCC

Jennifer Shamai MS, RN, AONCS, BMTCN

How the Experts Treat Hematologic Malignancies
Las Vegas, NV
March 16, 2017
DISCLOSURES

No Disclosures
Objectives

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

Preparative or Conditioning Regimens

• First part of the transplant schedule
• May be administered on an inpatient or outpatient basis
• Rationale for conditioning regimens: preparation of the soil in order to
  – Eradicate residual tumor cells
  – Create space for the donor cells
  – Suppress the recipient’s immune system
  – 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
- Goals of therapy
Conditioning Regimens

- Treatments given to patients to prepare their body to receive HPCs
  - Chemotherapy
  - Radiation therapy
  - Biotherapy
  - Immunotherapy
- Classification of conditioning intensity
  - Myeloablative
  - Reduced intensity / nonmyeloablative
INTENSITY OF THERAPY
Nonmyeloblative

Reduced Intensity

Myeloablative

Increasing toxicity and intensity

Increasing requirement of GVT effect
Myeloablative

- Used for autologous and allogeneic transplants
- Traditional regimen with chemotherapy and/or radiation therapy administered at lethal doses
- Toxic modality with high morbidity and mortality
- Goal of therapy is to eliminate tumor cells and create an immunosuppressed host
Nonmyeloablative/Reduced Intensity

- Used for allogeneic transplants
- Reduced/standard doses of chemotherapy +/- radiation therapy are administered
- Goal of therapy is to create enough immunosuppression to enable graft versus tumor effect
- Decreased morbidity and mortality
- Uses
  - Patients greater than 60 years old
  - Patients with comorbidities
Development of Nonmyeloablative HCT

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

1. Recurrence rate is lower in patients who manifest a GVT reaction than 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 potentially achieve remission
## Conditioning Regimens: Ideal Properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Allogeneic Myeloablative</th>
<th>Allogeneic Reduced intensity Nonmyeloablative</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>
<tr>
<td>Regimen</td>
<td>Disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose Melphalan</td>
<td>Multiple Myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludarabine/Melphalan</td>
<td>Multiple Myeloma, various others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludarabine/TBI</td>
<td>Multiple Myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan/Cyclophosphamide</td>
<td>Myeloid Leukemia, MDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide/TBI</td>
<td>Leukemias, NHL, MDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan/Fludarabine</td>
<td>Leukemia, MDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carmustine/Etoposide/Cytarabine/Melphalan [BEAM]</td>
<td>Hodgkin Lymphoma, NHL,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide/Carmustine/Etoposide [CBV]</td>
<td>Hodgkin Lymphoma, NHL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Intensity of Therapy and GVT

Deeg HJ, Sandmaier BM. Who is fit for allogeneic transplantation? Blood 2010;116(23):4762-4770
PREPARATIVE CHEMOTHERAPY
Chemotherapy

- May use single agent or multiple agents
- May be used with or without radiation therapy
## Common Regimens/Disease

<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, MDS</td>
</tr>
<tr>
<td>Cyclophosphamide/TBI</td>
<td>Leukemias, NHL, MDS</td>
</tr>
<tr>
<td>Busulfan/Fludarabine</td>
<td>Leukemia. MDS</td>
</tr>
<tr>
<td>Carmustine/Etoposide/Cytarabine/Melphalan [BEAM]</td>
<td>Hodgkin Lymphoma, NHL,</td>
</tr>
<tr>
<td>Cyclophosphamide/Carmustine/Etoposide [CBV]</td>
<td>Hodgkin Lymphoma, NHL</td>
</tr>
</tbody>
</table>
Chemotherapy Agents

• Alkylating agents: mainstay of many regimens due to favorable toxicity profile
  – Cyclophosphamide: hemorrhagic cystitis, cardiac toxicity, n/v, histamine reaction (burning in nose, jaw, facial pain, lip tingling)
  – Melphalan: cryotherapy to prevent mucositis, n/v, skin rash
  – Busulfan: seizure precautions (crosses blood-brain barrier), pulmonary toxicity, pharmacokinetic dosing, alopecia, skin changes

• Carmustine: nitrosoureas
  – Pulmonary toxicity, n/v, SOS, hemorrhagic cystitis, nephrotoxicity, infusion reaction
  – Requires pre- and post-hydration
Chemotherapy Agents Continued

- **Cytarabine**: antimetabolite
  - Mucositis, chemical conjunctivitis, bone pain, chest pain, n/v
  - Cerebellar toxicity

- **Etoposide**: plant alkyloid, topoisomerase inhibitor
  - Acute anaphylactic reactions, hypotension, diarrhea, rash, plantar and palmar burning, peripheral neuropathy

- **Fludarabine**: purine nucleoside analog
  - Synergizing effect with alkylating agents
  - Replaced cyclophosphamide in regimens to reduce toxicity
  - N/V, Diarrhea, alopecia
Side Effects of Chemotherapy

- **Hematologic**: Myelosuppression
- **Gastrointestinal**: Nausea/vomiting, anorexia, mucositis, diarrhea, constipation, anorexia
- **Genitourinary**: Electrolyte imbalances, hemorrhagic cystitis, renal toxicity
- **Cardiovascular**: Hypertension, hypotension, cardiotoxicity
- **Pulmonary**: Pneumonitis, fibrosis
- **Neurological**: Seizures, peripheral neuropathy, headache
- **Skin**: Hyperpigmentation, alopecia, erythema
- **Miscellaneous**: Hypersensitivity reactions, cataracts, conjunctivitis, secondary malignancy
ATG (Anti-T Cell Globulin)

- Immunosuppressive agent that inhibits T cells and other immune cells
  - Polyclonal immunoglobulins derived from horse, rabbit
- Used in conditioning regimens to enhance engraftment
  - Also used to prevent GVHD
- Given during an inpatient stay to allow for close monitoring due to potential side effects
  - Premedications required
RADIATION FOR CONDITIONING
Fractionated Total Body Irradation: FTBI

• Rationale for FTBI
  – Developed in 1940s-1950s following lessons learned from nuclear bombings
  – Early experiments with single, total dose were more toxic and had greater graft failure

• Dosage
  – Fractionation: fractions of total dose given over several days
    • Hyperfractionation: multiple fractions per day
When is FTBI Used

- Used in diseases that are sensitive to radiation
  - Leukemias
  - Lymphomas
- Used in allogeneic transplants to promote immunosuppression and prevent GVHD
- Careful considerations
  - Previous radiation exposure
  - Limited used in children
FTBI Dose and Administration

• Fully ablative regimens
  – Multiple treatments in order to reach determined dose
• Nonmyeloablative regimens
  – Single fraction of radiation
• Administration is institution specific
  – Requires careful measurement and planning
  – Blocks/shields used to protect vital organs
  – Boosts may be given to sanctuary sites such as testes
FTBI Administration

- Patient positioning
  - Standing
  - Sitting
  - Lying on floor
  - Special considerations for children
TBI

- Standing position for adults
- Patient is held in harness
- Lung shields are placed in plexiglass
Pediatric TBI

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 the bone marrow
Acute Radiation Side Effects

- Nausea/vomiting
- Immunosuppression
- Fever
- Fatigue
- Skin reactions
- Mucositis
- Alopecia
- Parotiditis
Chronic Radiation Side Effects

- Interstitial pneumonitis
- Cataracts
- Hepatic disorders
- Renal dysfunction
- CNS dysfunction
- Endocrine dysfunction
  - Thyroid
  - Growth
  - Infertility
- Secondary malignancy
BIOTHERAPY, IMMUNOTHERAPY, AND TARGETED THERAPY
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.
Actions of Biotherapeutic Agents

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

- Cuts off blood supply to tumor (angiogenesis)
- 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 cancerous cells
- Inhibits proteins and causes programmed cell death (apoptosis)
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®
Targeted Therapy

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

NCI, Targeted Therapies online tutorial retrieved December 20215
https://archive.org/details/gov.hhs.nci.therapies
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 agents to cancer cells
  - Can trigger an immune response
Monoclonal Antibody Features

• Infusion therapy
• Often in combination with chemotherapy
• Most common complication is infusion reactions
• Generally not considered hazardous
Harnessing the Power of the Immune System

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.

T cell Donor (Patient or Healthy Donor)

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
- 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
Immune Related Side Effects – Ir-SE

- Immunologic related side effects of biotherapy/targeted therapies can be significant and life-threatening
  - Hepatitis (elevation in AST and ALT)
  - Colitis (close attention to patients bowel patterns)
  - Dermatitis (most common)
  - Hypophysis (inflammation of the pituitary gland)
  - Uveitis
  - Neuritis
  - Nephritis
  - Pneumonitis
- Most often treated with steroids
- Fever is often associated, but expected and normal