Mobilization & Pre-Transplant Conditioning Regimens
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Mobilization
• A technique used to increase the number of circulating hematopoietic stem cells from the bone marrow into the bloodstream
• Only used for patients undergoing a peripheral blood stem cell transplant (not bone marrow transplant)

The premise of mobilization is based on the following...
• Progenitor cells begin rapid reproduction when depletion is recognized
• Depletion occurs by natural processes (aging/illness) and by artificial means (cell depletion by chemotherapy)
• Artificially causing depletion will result in an increase in progenitor cell counts
• Excess progenitor cells in the bone marrow will be forced into the peripheral blood
• Stem cells can be harvested, or collected, from the peripheral blood

Who gets “mobilized”?

The patient
• Auto PBSCT
• The patient is the donor
• May receive:
  • Growth factor ONLY (in remission or autoimmune disease)
  • Chemo AND growth factor (please present)

The donor
• Allo PBSCT
• Family member or unrelated donor
• ONLY growth factor (because the donor has no disease)
**Mobilization: Growth Factor Alone**

- **Standard (those who JUST need recovery after chemo):** 300-480mcg daily until after chemotherapy nadir
- **Mobilization dosing:** 10-32mcg/kg QD (or divided and administered BID) until apheresis complete
  - Basically 2-4x dose, which means more significant s/e

**Side Effects**
- Bone Pain (reported at 86%)
  - Spine, hips, pelvis, ribs and sternum
- Headache (reported at ~40%)
- Injection-site irritation
- Flu-like symptoms
- Extremely Rare - Splenic rupture
- Long-term sequelae are unknown but following healthy donors for more than 20 years has shown no greater health complications than healthy siblings

**Mobilization: Chemotherapy & Growth Factor – Autologous only**

- Many chemo regimens that are being used simply to treat disease have been used successfully as mobilization chemotherapy with the addition of G-CSF
- Some patients are more difficult to mobilize and may receive more than one “round” of mobilization chemotherapy
- High-dose cyclophosphamide is the most common agent used in mobilization and can be used alone, in combination with dexamethasone or in combination with other chemotherapy drugs
- Patient will be apheresed about 24 hours after the WBC has recovered to >1,000 or when the CD34+ counts are > 5 in the peripheral blood
- Growth Factor is discontinued after final day of apheresis

**Advantages**
- Additional “cell kill” for known or microscopic disease
- Additive effect for mobilization by using both chemotherapy and growth factor

**Disadvantages**
- Large doses of chemotherapy are used, placing patient at risk for complications from prolonged neutropenia
- Patient may experience fevers, mucositis, pain, nausea, vomiting, diarrhea, dehydration, malnutrition, and fatigue

**Plerixafor**

- Administered with GCSF to improve mobilization for patients that do not mobilize well.
- Most commonly used for patients who have had many previous rounds of chemo and marrow is slower to recover
- In a study of MM patients, patients receiving plerixafor had 3.5X higher CD34+ counts and 2.5X higher cell yield in apheresed product.
- Very expensive (around $12K per injection).
- Timing of apheresis collection important, it must be started 10-14 hours after the injection given.
- Side effect to GI tract more common, loose stool or diarrhea.

**Pre-transplant Conditioning Regimens**

- Donor scheduled in apheresis for orientation and vein check to determine appropriate access
- Check pregnancy test prior to administration of G-CSF (unsafe for pregnant women to receive G-CSF at these doses)
- Review side effects and management
- Begin injections on patient’s day -5 (after conditioning has started)
- Give injections in am (so peak effect is prior to apheresis, peak is soon after admin)
- Draw labs and monitor counts (WBCs and/or CD34+ counts)
- Assess daily for bone pain, fever, allergic reactions
- Donor will be apheresed on patient’s day –1 +/- patient’s day 0, G-CSF should be given 3-4 hours before apheresis on these days
- G-CSF is discontinued when an adequate number of stem cells have been collected (usually >5 X 10^6/kg)
- Answer any donor questions about the collection process.
What is Conditioning?
- “Preparative” regimens which condition or “prepare” the patient’s bone marrow to accept transplanted stem cells
- May involve high-dose chemotherapy with or without radiation therapy and/or radioimmunotherapy
- Typically lasts 4-10 days
- These are the days immediately preceding transplant and are “countdown” days

BMT “Roadmap”

What is Conditioning?
- Chemotherapy only
- High Dose Chemotherapy and TBI
- Chemotherapy and Radioimmunotherapy
- Lower Dose Chemotherapy and single dose TBI (non-myeloablative)

Goals of Conditioning
- Eradicate residual malignancy
- Suppress patient’s immune system to prevent graft rejection
- “Ablate” the patient’s bone marrow completely to allow space for donor stem cells (myeloablative)
- “Create space within” the patient’s bone marrow enough to allow the patient to accept the donor stem cells (non-myeloablative)

Type of Regimen Depends Upon…
- Disease (malignant or nonmalignant)
- Type of transplant (autologous or allogeneic; myeloablative or non-myeloablative)
- Medical condition of patient
- Patient/provider preference

Inpatient or outpatient?
- What is the conditioning?
- What is the supportive care necessary?
- How is the patient tolerating the conditioning?
- Is there a protocol requirement?
- Does the patient have pre-existing comorbidities?
- Pediatric patients are generally admitted if under 18
Conditioning Chemotherapy

• Major component of most conditioning regimens
• Single agent or combinations of agents with or without TBI and/or radioimmunotherapy

Conditioning Chemotherapy: Agents

• Cyclophosphamide (Cytoxan)
• Busulfan
• Etoposide (VP-16)
• Melphalan
• Fludarabine

Cyclophosphamide

Dosing

<table>
<thead>
<tr>
<th>Standard/ non-transplant dose</th>
<th>Transplant dose</th>
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<tbody>
<tr>
<td>• Lymphoma: 750mg/m2</td>
<td>• Myeloablative doses 100-200 mg/kg (non-myeloablative doses 30-60 mg/kg)</td>
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<tr>
<td>• Breast: 600mg/m2</td>
<td>• Total dose divided over 2-4 days</td>
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<td></td>
<td>• Administration</td>
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<td>• IV over 1 hour (doses &gt;5000 mg over 2 hrs)</td>
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Cyclophosphamide

Side Effects

• Nausea/Vomiting
  - Incidence in high dose therapy about 90%
  - Onset: 6-12 hours after one hour infusion
  - Duration: vomiting rarely lasts >24 hours, nausea may last longer

• Hemorrhagic Cystitis
  - Incidence 10-40%
  - Onset: hours to weeks post-therapy
  - Prevention:
    - Adequate hydration
    - Mesna
    - Continuous bladder irrigation

• Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
  - Onset: 12-48 hours after IV infusion of cyclophosphamide

• Cardiotoxicity
  - May occur with dose ranges from 120-270 mg/kg
  - Risk increases with prior anthracycline therapy

Cyclophosphamide

Nursing Considerations

• Antiemetics: begin 30-60 min. pre & continue 24 hours post

• Preventing hemorrhagic cystitis
  - IV hydration 4 hours pre & continue 24 hours post. Usually 2X maintenance fluids
  - Bladder protection
    - Mesna (MUST BE GIVEN ON TIME 15 min before then 3,6,8hrs post)
    - Continuous bladder irrigation if ordered

• Monitor fluid status
  - BID weights, postural BP, frequent I & O, maintain adequate urine output

• Monitor urine for blood (dipstick)
• Monitor electrolytes (especially K and NA)
• Baseline EKG pre-therapy (done as part of pre-transplant workup)
**Busulfan**

**Dosing**
- **Oral**
  - Protocol specific, typically 1mg/kg/dose in adults
  - Total dose 12-16mg/kg
  - Divided over 3-4 days & given Q6 hrs
  - Administration
    - NPO 1 hr pre & 1 hr post dose
    - Sips clear fluid only
    - 2mg tablets in gelatin capsules
    - Children < 5yrs: typically IV
- **IV**
  - Protocol Specific
  - 0.8 – 1 mg/kg IV every 6 hours for total of 8-16 doses (dependent on protocol and patient’s age) or 3.2mg-4mg/kg/day for 3-4 days
  - Administration
    - Infuse over 2-3 hours

**Side Effects**
- Nausea/Vomiting
- Seizures
- Mucositis
- Alopecia
- Skin hyperpigmentation
- Pneumonitis
- SOS
- Late Effects: sterility, pulmonary fibrosis

**Nursing Considerations**
- Antiemetics 30-60 min. prior to each dose
  - If patient vomits ORAL dose:
    - Do not repeat dose unless whole tablets seen
    - Count # whole tablets & re-administer with a provider order
    - NG administration: repeat only if vomiting occurs within 5 minutes
- Seizure Prophylaxis
  - Loading dose dilantin 10-15 mg/kg given 6 hours prior to first Busulfan dose
  - Maintenance dose: start 12 hours post loading dose and continue until 24 hours after last does of Busulfan given
  - May also receive levecitiram, does not require loading dose
- Pharmacokinetics
  - Goal is to maintain steady state blood levels
  - Targeted levels: Blood levels drawn according to protocol
  - Nursing P&Ps exist to guide Busulfan targeting

**Etoposide (VP-16)**

**Dosing**
- **Standard/Non-transplant doses**
  - 3.3mg/kg
  - 100mg/m2
- **Administration**
  - Standard dilution
  - 0.4mg/ml

**Transplant doses**
- Protocol specific
  - 450mg to 2 gms/m2
- **Administration**
  - Conditioning doses are so high the drug is administered undiluted. Standard IV tubing will crack; use nitroglycerin tubing
  - Administer with concurrent IVF with stopcock at hub of catheter
  - Refer to institutional policy for administration

**Side Effects**
- Hypotension
- Skin toxicities (blisters, redness, hyperpigmentation)
- Uric acid nephropathies and hemorrhagic cystitis
- Nausea/Vomiting
- Alopecia

**Nursing Considerations**
- Hydration 4 hrs pre until 24 hrs post (1.5 X maintenance)
- Frequent vital signs during infusion (BP, pulse Q30 min)
- Hypotension:
  - NS bolus until BP stabilizes
  - Resume infusion at slower rate
- Hyperpigmentation onset 2-3 weeks, resolves over 2-3 months
- Allopurinol started on first day of VP-16, discontinued on transplant day -1
- Frequent voiding
- Fall precautions due to high ethanol content of undiluted drug
### Melphalan

**Dosing**
- **Dosage**: 50-60 mg/m² IV
- **Administration**: Infuse over 15-30 minutes. May infuse over longer period of time but infusion should not exceed 1 hour from mixing time due to short stability

**Side Effects**
- Hypersensitivity
- Cardiovascular: Vasculitis, chest pain, hypotension
- Alopecia
- GI: Nausea, vomiting, diarrhea, SOS
- Respiratory: Pulmonary fibrosis, interstitial pneumonia

**Nursing Considerations**
- Hydration at 1.5 X maintenance 1-2 hours pre and 24 hours post
- Monitor for anaphylaxis
- Order from pharmacy immediately prior to infusing—limited drug stability

### Fludarabine

**Dosing**
- **Dosage**: Protocol Specific
- **Administration**: 30 mg/m² for 3 days (total dose 90 mg/m²)

**Side Effects**
- Immunosuppression
- Interstitial pneumonitis
- TLS with bulky disease
- Renal insufficiency
- Rash
- Fatigue, weakness
- Chills, fever, myalgia

**Nursing Considerations**
- Fairly well tolerated
- Immunosuppression is major side effect
Anti-Human Thymocyte Globulin Equine (ATG) - ATGAM
- Depletes T cells
- Used as conditioning for autoimmune or aplastic anemia
- Dosage
  - Protocol specific
  - Usual conditioning dose: 30mg/kg daily X 3 days
- Administration
  - 50mg/hr, 100mg/hr, remaining over 4-10 hrs (titrating slowly)
  - In-line 0.2-1.0 micron filter

Anti-Human Thymocyte Globulin Rabbit (ATG) - Thymoglobulin
- Depletes T cells
- Used as conditioning for autoimmune or aplastic anemia
- Dosage
  - Protocol specific
  - Usual conditioning dose:
- Administration
  - First dose over 6 hours, subsequent doses over 4 hours
  - In-line 0.2 micron filter

Anti-Human Thymocyte Globulin (ATG): Side Effects
- Sensitivity reactions, anaphylaxis
- Fever, chills, headache
- Rash
- Hyperkalemia
- Abdominal pain, diarrhea
- Weakness
- Dyspnea

Anti-Human Thymocyte Globulin (ATG): Nursing Considerations
- Skin test @ 1 hr prior to first dose of ATGAM, not Thymoglobulin
  - NO EMLA/LMX
- Anaphylaxis medications at bedside
- Premed with methylprednisolone (ATGAM only)
- Transfuse platelets after ATG infusion - ATG eats platelets
**Conventional Radiation vs TBI**

- **Conventional Radiation**
  - 180–200/day
  - One time a day
  - For 4–8 weeks

- **Mini TBI**
  - 200 Gy one time dose
  - Adults: May be at SCCA or UWMC
  - Peds: UWMC only

- **Myeloablative TBI**
  - 150–200 Gy two times a day for 3–4 days
  - Each dose 4–6 hours apart
  - All will be at UWMC
  - Pediatric patients under the age of 6 are sedated

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**TBI Pretreatment Preparation**

- Consult and Simulation
- Pretreatment planning
- X-ray of lungs taken
- Lead Blocks developed to shield lungs - used for 3 of 6 or 4 of 8 treatments
- Orientation to TBI and education
- Confirm orders written, signed CCO sheet in place, transportation arranged if needed

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**TBI Pretreatment Preparation**

**Patient/Family Teaching**

- Purpose of TBI
- Treatment location
- Anticipated duration of treatment
- Where family members accompanying patient can wait
- Patient monitoring - no one is in the room but a camera is focused on the patient
- Anticipated side effects/management
- NO CHG baths during RT

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**TBI: Side Effects**

- **Fatigue**
  - Almost all patients report decrease in energy level and inability to concentrate
  - Onset of fatigue typically 3rd or 4th TBI treatment day

- **Nausea/Vomiting**
  - Usually peaks 1.5–2 hours after TBI
  - Prophylactic antiemetics always given before treatments
  - PRN antiemetics for breakthrough nausea and vomiting up to 48 hours after last treatment; may be administered ATC

- **Diarrhea**
  - Onset generally within 48 hours of therapy
  - Duration - may continue for week or two after TBI - consider contribution of other conditioning agents and other causes

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**TBI: Side Effects (continued)**

- **Xerostomia**
  - Almost all patients experience dry mouth by 3rd or 4th treatment day
  - Dental consults prior to TBI
  - Reinforce oral hygiene programs taught before treatment started

- **Alopecia**
  - Usually occurs gradually within 2 weeks

- **Mucositis**
  - Develops 5–7 days after treatment started
  - Tends to worsen over next week
  - Usually resolves 3–4 weeks after treatment

- **Skin Reactions**
  - Mild erythema of skin common in first few days following TBI
  - More common in patients receiving cyclophosphamide or thiotepa prior to TBI
  - Moist erythema may develop over elbows, heels, fingertips
  - Hyperpigmentation may occur 2–3 weeks following TBI

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**Patient Preparation**

**Prior to TBI Transport**

- Remove all jewelry, metal, tight fitting garments (check pajamas for metal)
- Remove all ointments, creams, powders, deodorants, perfumes or lip balms
- Remove contacts
- Pick out music
- Void
- Pre-hydration
- Anti-emetics and/or sedatives
- Nursing Handoff
TBI: Side Effects, Late

- Gonadal Dysfunction
  - 95 - 100% of females develop early menopause and sterility
  - 90 - 95% of males have absent spermatogenesis
- Thyroid Dysfunction
- Cataracts
  - Approximately 20% of patients develop cataracts within 3 years of treatment
- Pulmonary Damage
  - Interstitial pneumonitis
  - Restrictive pulmonary disease
- Neurologic complications
  - Leukoencephalopathy
  - Chronic neurologic changes
- Secondary malignancies
- Growth impairment in children

Conclusion

- Side effects of treatment and a patient’s course through transplant will greatly depend upon their conditioning regimen
- Mobilization may change, Conditioning may change but the end goal will never change:
  
  Eradicate disease and increase event-free survival!

Questions?