GRAND RIVER
Regional Cancer Centre

AN INTEGRATED PROGRAM OF GRH | a cancer care ontario partner

Autologous Stem Cell Transplant Toxicities

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  - **Other:** n/a

Objectives

- Review indications for Autologous Stem Cell Transplant (ASCT)
- Outline ASCT transplant process
- Review anticipated side effects
- Supportive care principles and agents used

Autologous Stem Cell Transplant (ASCT)

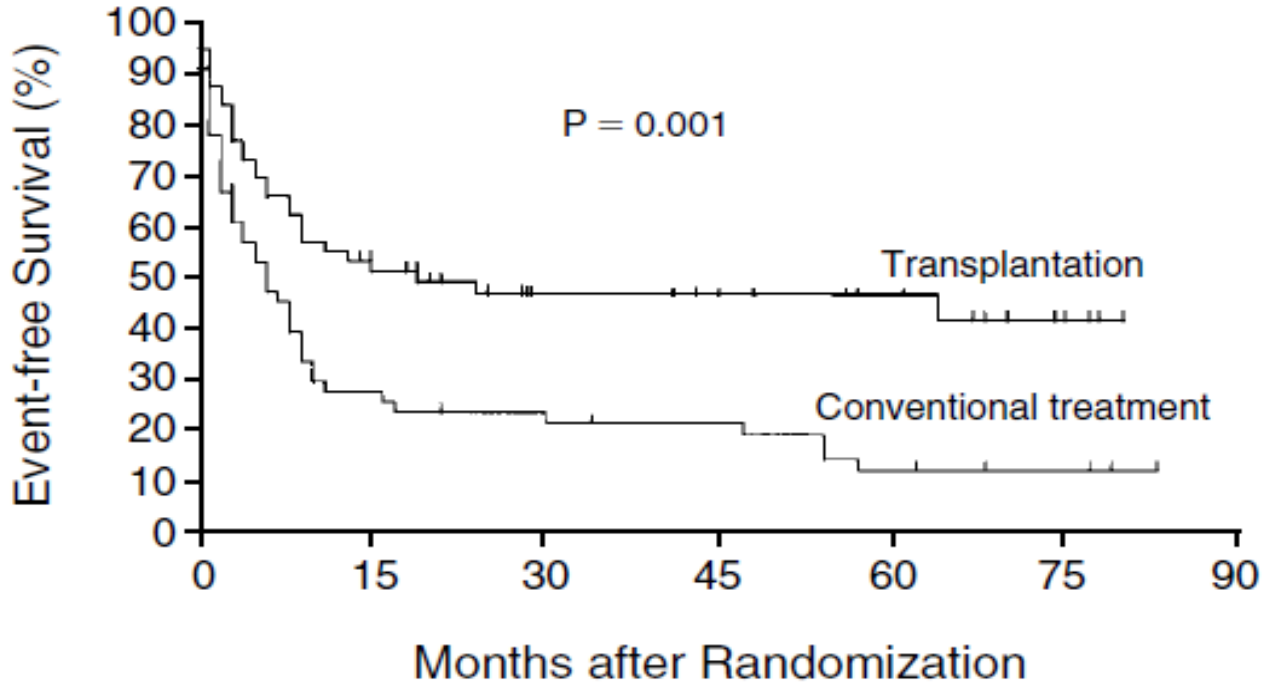
- A strategy to deliver high doses of chemotherapy (melphalan, busulfan, etoposide)
- At the dose given, would potentially be lethal, due to severe and prolonged bone marrow suppression
- Hematopoietic stem cells (HSC) are used as a hematopoietic rescue
- Patient's own HSC, harvested from peripheral blood
- Treatment related mortality is between 1-3%

Indication for ASCT: Myeloma

- Standard first line care for myeloma patients, currently no age limit although typically <70
- Tandem ASCT for some patients who obtain less than a very good partial response, and have no progressive disease before the second transplant. Can also be used for patients with some specific cytogenetic markers
- ASCT can be repeated in patients who relapse after a remission of > 2 years.
- Patients diagnosed with primary AL amyloidosis or POEMS syndrome.
- **Goal:** disease control, non-curative

Kolm, K. (2016)

Indication for ASCT: Lymphoma



PARMA trial NEJM Philip, T. et al. (1995)
N=54 ASCT vs n=55 conventional

High dose chemotherapy followed by ASCT demonstrated improvements in even-free survival (EFS) and overall survive (OS).

The goal of treatment:

DLBCL and Hodgkin's curative intent

Mantle cell lymphomas/follicular – non-curative intent

Indications for ASCT: Lymphoma

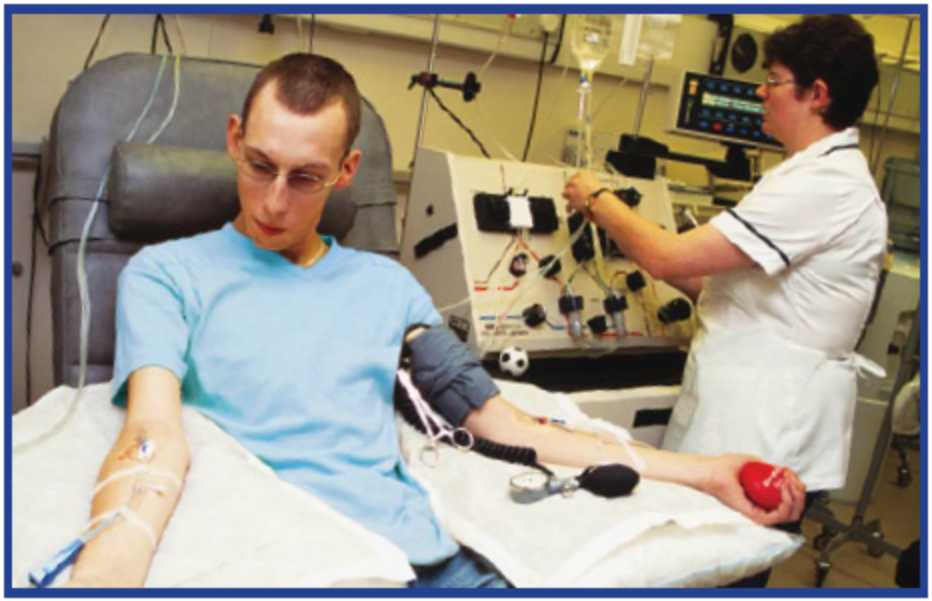
Non-Hodgkin's Lymphoma

- Chemo-sensitive patients, with aggressive lymphoma relapsed/refractory
- Select patients with high-risk aggressive NHL at first line treatment (eg. Plasmablastic lymphoma)
- Mantle cell lymphoma (at least partial response to chemotherapy)
- Select patients with relapsed follicular lymphoma
- Select CNS lymphoma (relapsed or part of induction)
- Burkitt's lymphoma beyond first remission

Hodgkin's Lymphoma

- Relapsed/refractory to first line treatment (ABVD)

Grand River and Juravinski Cancer Center
Day +1 Autologous Stem Cell Transplant Program



Juravinski is responsible for the pre-transplant work, and we support the patient/family through engraftment and recovery

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Transplant Process

- Assessment and Eligibility for transplant
- Pre-engraftment phase
- Engraftment
- Post transplant care

Transplant Process: Eligibility

Lymphoma

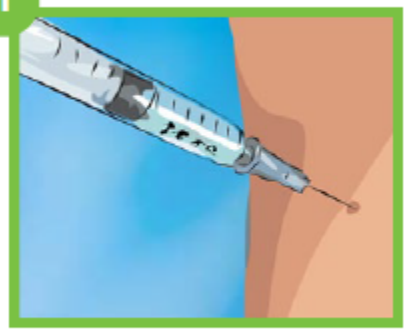
- Demonstrate response post salvage chemotherapy (GDP (gemcitabine, dex, cisplatin) usually 2-3 cycles)

Multiple Myeloma

- Demonstrate response to systemic therapy
  - CyBorD (cyclophosphamide, bortezimib, dex)
  - Revlimid/dex
  - RVD (revlimid, bortezimib (velcade), dex)

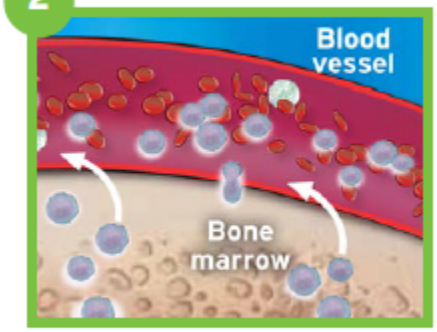
Transplant Process: Pre-engraftment

1 Injections



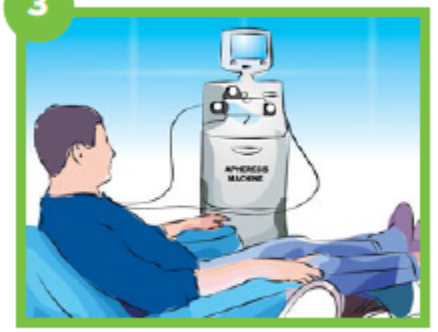
Injections of mobilisation agents

2 Mobilisation



Stem cells are stimulated to move into the bloodstream from the bone marrow space

3 Collection

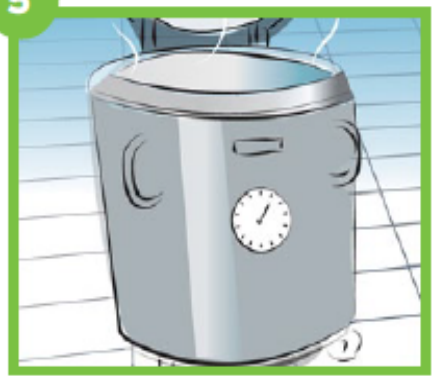


Collection of mobilised stem cells from the blood using the apheresis machine

4 Preparation for Storage

Stem cells collected are stored in infusion bags

5 Cryopreservation



Freezing of stem cells for use after completion of preparative regimen

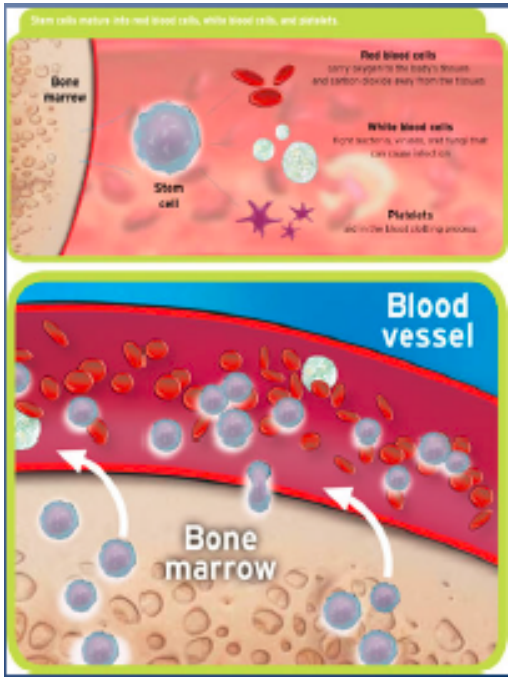
6 Chemotherapy and/or Radiation

Administration of preparative regimen intended to kill any remaining cancer cells and make a space for new cells to live

Transplant Process: Mobilization

Mobilization of Hematopoietic stem cells (HSCs) , using:

- G-CSF (filgrastim) with cyclophosphamide
- G-CSF
- Plerixafor

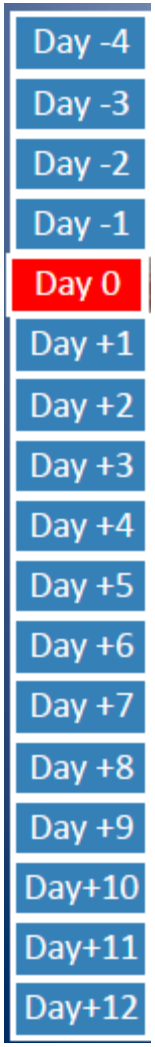


Case Study: Conditioning

Important considerations

- Lymphoma patients will be receiving a larger volume of fluid, therefore they may come with increased swelling (first few daily weight will not reflect true weight)
- Treatment occurs over two days, cells cannot be re-infused until 48 hours after conditioning treatment completed.

Stem Cell Reinfusion Day 0



- Common side effects: bad taste, flushing, abdominal cramping, distinctive odour (can last from 24- 48 hours).
- Circulatory overload: related to rapid administration
- DMSO toxicity: related to histamine release
- Rarely: allergic/anaphylactic reaction
- There is a possibility of pink-tinged urine related to breakdown in red blood cells (McAdams & Burgunder, 2013)
- Patients receives a large volume of fluid with cells and fluid support (approx 2-3 liters).

Day + 1

Day of Transfer to Grand River Hospital From Juravinski.

Day +1: Transfer day

- Bed held at GRH for day of transfer
- Patient assessed for medical stability
- Report from NP at Juravinski to the NP/GPO at Grand River Hospital
- Transportation arranged
- Patient to arrive before 1600
- Patient sent with all inpatient Juravinski records

Day 3: Pre-engraftment

- Nausea/vomiting
- Diarrhea Intravascular volume depletion
- Electrolyte imbalances (standard orders)
- GERD
- Anorexia, can be prolonged
  - Megace 800mg po bid (*not evidence based)
- Mucositis
- Myelosuppression and febrile neutropenia/sepsis

Kolm, K. (2016)

GI Toxicity: Nausea and Vomiting

- Multiple factors – chemotherapy, DMSO, mucositis, medications, constipation
- Consider underlying cause i.e. constipation treat with laxatives
- Combinations of antiemetic medications maybe required.
- Add one class at a time (CCO, 2010)
  - Prokinetic Agent (Maxeran), OR phenothiazine (stemitil)
  - Atypical psychotic (olanzapine 2.5-5mg PO BID)
  - 5-HT3 antagonist (ondansetron (zofran), granisetron (kyril))
  - Benzodiazepine (ativan)
  - Cannabinoid (Nabilone 0.5-2mg PO BID).

GI Toxicity: Nausea and Vomiting

Non-Pharmacological

- Small Frequent Meals, limit food odours (cold food)
- Sip on water/other fluids throughout the day
- Liquids and solids separately
- Limiting fluid and oral intake after vomiting (30-60min). Then slowly reintroduce.
- Referral to dietician

Nausea and vomiting can be persistent and last for <u>months</u>, it is important to help the person develop strategies that help them management their symptoms and maintain an adequate fluid and oral intake.

GI Toxicity: Diarrhea

- Frequently experienced side effect, often a result of mucositis causing abdominal pain/cramping and watery diarrhea.
- Mucositis of the GI tract can result in malabsorption resulting in malnutrition and electrolyte imbalances (Ezzone, 2013).

GI Toxicity: Diarrhea

- Multiple factors i.e. conditioning regimen, infectious, medications, mucositis, cdiff
- Important to monitor for fluid balance, electrolytes, skin breakdown and malnutrition.

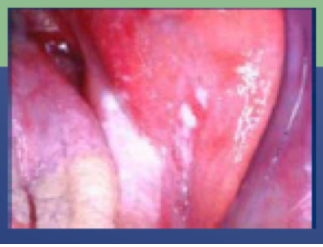
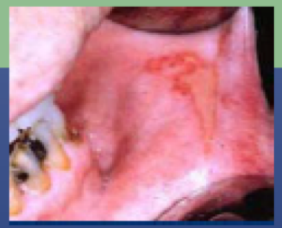
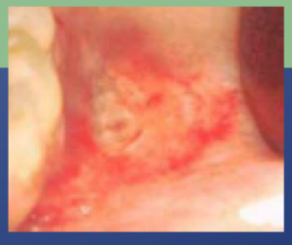
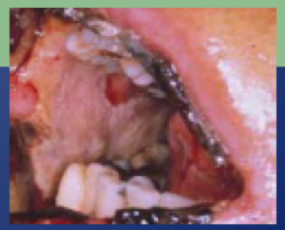
Management

- Review of medications
- Stool samples
- Imodium
- Fluid and electrolyte replacement
- Opioids
- Daily weights
- Small frequent meals, avoiding caffeine, insoluble fiber and irritants.
- ***Peri-anal care**

GI Toxicity: Oral Mucositis

- Occurs in up to 60-80% and most distressing toxicity.
- Higher incidence and severity in Lymphoma versus Myeloma (Blijlevens et al., 2017)
- Infra red oral cryotherapy significantly decreases the incidence (Tayyem, 2014)

GI Toxicity: Oral Mucositis

Grade				
0	1	2	3	4
None	Soreness +/– erythema No ulceration	Erythema, ulcers Patients can swallow solid diet	Ulcers, extensive erythema Patients cannot swallow solid diet	Mucositis to the extent that alimentation is not possible
				

GI Toxicity: Oral Mucositis

Oral hygiene

- Encourage brushing with a soft toothbrush
- Mouth rinse after every meal/snack and before bed with bland rinse
- Avoid flossing when plts <50
- Artificial saliva products

GI Toxicity: Oral Mucositis

Pharmacological

- Mouth rinses (magic mouthwash, lidocaine, xylocaine viscous 2%)
- Antimicrobial agents (chlorhexidine, half strength peroxide and Biotene)
- Analgesics (morphine, dilaudid, fentanyl)
- Antifungal (nystatin)

GI Toxicity: Oral Mucositis

Mouth Rinses

- **Chlorhexidine** can be used for plaque removal and antimicrobial properties, however, it can also cause teeth staining.
- **Biotene** also has antimicrobial properties and does not include alcohol. Therefore, does not cause the same level of burning/drying.
- **Half strength hydrogen peroxide** was used for debridement and loosening hemorrhagic accumulations. There is some evidence to suggest that it can cause fibroblast dysfunction and dry out the mucosa, therefore is no longer recommend for use. However, if lose tissue is causing gagging and choking it, can be used to debride the mouth.
- There, is also only limited evidence to support the use **of magic mouthwash and other antimicrobial agents**. The goal is to help maintain oral intake and manage pain, while limiting bacteria exposure. Good oral hygiene, with frequent mouth rinses is the goal.

(CCO, 2012, Ezzone, 2013)

GI Toxicity: Oral Mucositis

Analgesics

- When pain related to mucositis is continuous (moderate to severe), regularly scheduled pain medication can help to improve patients oral intake and their ability to engage in oral hygiene.

- Ideally oral medications should be given 60 minutes before meals/brushing.

- Lidocaine rinses can be used 10 minutes before meals/brushing.

(CCO, 2012, Ezzone, 2013)

GI Toxicity: Oral Mucositis

- Palifermin (kepivance): keratinocyte growth factor
- effective at avoiding PCA use
  - Myeloma 13% vs 53%
  - Lymphoma 46% vs 68%
- No difference in
  - days to neutrophil engraftment
  - Length of stay
  - Overall survival
- Median additional cost for myeloma patient $24 620, for lymphoma patient $19 980

Ajay K. Nooka Biol Blood Marrow Transplant 2014 Jun; 20(6)

GI Toxicity: Oral Mucositis

- Kepivance
  - 6 doses (3 pre chemotherapy, 3 post)
  - 60 mcg/kg/day; 70kg = 4200mcg/d
  - 6.25mg/ml (6250mcg/ml) 1ml = $8000
  - 1 dose = $5376
  - 6 doses = $32 256

GI Toxicity: Oral Mucositis

- Swab for HSV
- Magic mouth rinse (*not evidence based)
- Gentian violet 1% solution (*not evidence based)
- Cyklokapron (transexemic acid) mouth rinse (*not evidence based)
  - Limited stability (5 days refrigerated)
  - 4.8% solution: Take 1 500mg tablet, crush into fine powder and mix with 10.42ml sterile water. M: 250 or 500cc. Swish and SPIT 10mL qid
- PCA may be required

Electrolyte Replacement: K+

- K+ depletion sufficient to cause serum K+ 3.0 requires a total K+ deficit of 100meq. Then for each further decrease of 0.5 ~ 200meq additional deficit.
- For daily maintenance need 20mmol (1500mg) a day
- Maximum kidney can excrete is 400mmol/d
- Kdur 1 tab = 20mmol (1500mg)
- microK 1 tab = 8meq
- sloK 1 tab = 600mg = 8meq = 8mmol
- Kelixir prescribe in mmol
- KCl IV
  - Maximum concentration 40meq/L
  - Maximum rate 20meq/hour

Electrolyte Replacement
Mg and PO4 and HCO3

- K+ will not correct until Mg is corrected
- MgS04 2g in 250cc NS over 2h
- MgSO4 4g in 1L over 6h
- Mg Rougier 30cc po bid or MgSO4 tabs (diarrhea)
- KPO4 15mmol of PO4 (5cc) in 500cc NS over 6h (can increase concentration if central line but still run over 6 hours)
- Note – KPO4 infusion is NOT adequate K+ replacement in setting of diuretic use. Need KCl to correct because need Cl to absorb Na, otherwise the kidneys exchange Na for K+ and will have ongoing K+ losses.
- NaHCO3 drip NaHCO3 3 amps in 1L D5W at 100-200cc/h

Toxicity: Myelosuppression

- Depletion of stem cells resulting in severely decreased red blood cells white cell and platelet production.

- The chemotherapy given before the ASCT causes myeloablation (severe myelosuppression)

Toxicity: Myelosuppression

Associated risks:

- Febrile neutropenia (low neutrophils)
  - Threshold <1.0
- Anemia (decreased red blood cells)
  - Prbc transfusion threshold: 70-75
  - 1U prbc at a time
- Bleeding (low platelets)
  - Standard plt transfusion if platelets <10 (<20 if febrile)
  - Cykokapron 1g IV/po q8h prn

Toxicity: Myelosuppression

Myeloma Patient

	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11
WBC	3.3	5.2	4.9	3.1	2.5	2.8	2.2	3.4	.5	.1	.1	.3.	1.3	6.7
ANC	1.8	4.1	4.1	2.8	2.2	2.6	2.1	3.1	.4.	0	0	.1.	0.7	5.1
Hbg	134	120	116	120	126	129	129	124	124	124	122	120	119	124
Plt	200	189	196	188	165	120	101	65	36	22	41	75	28	64

Lymphoma Patient

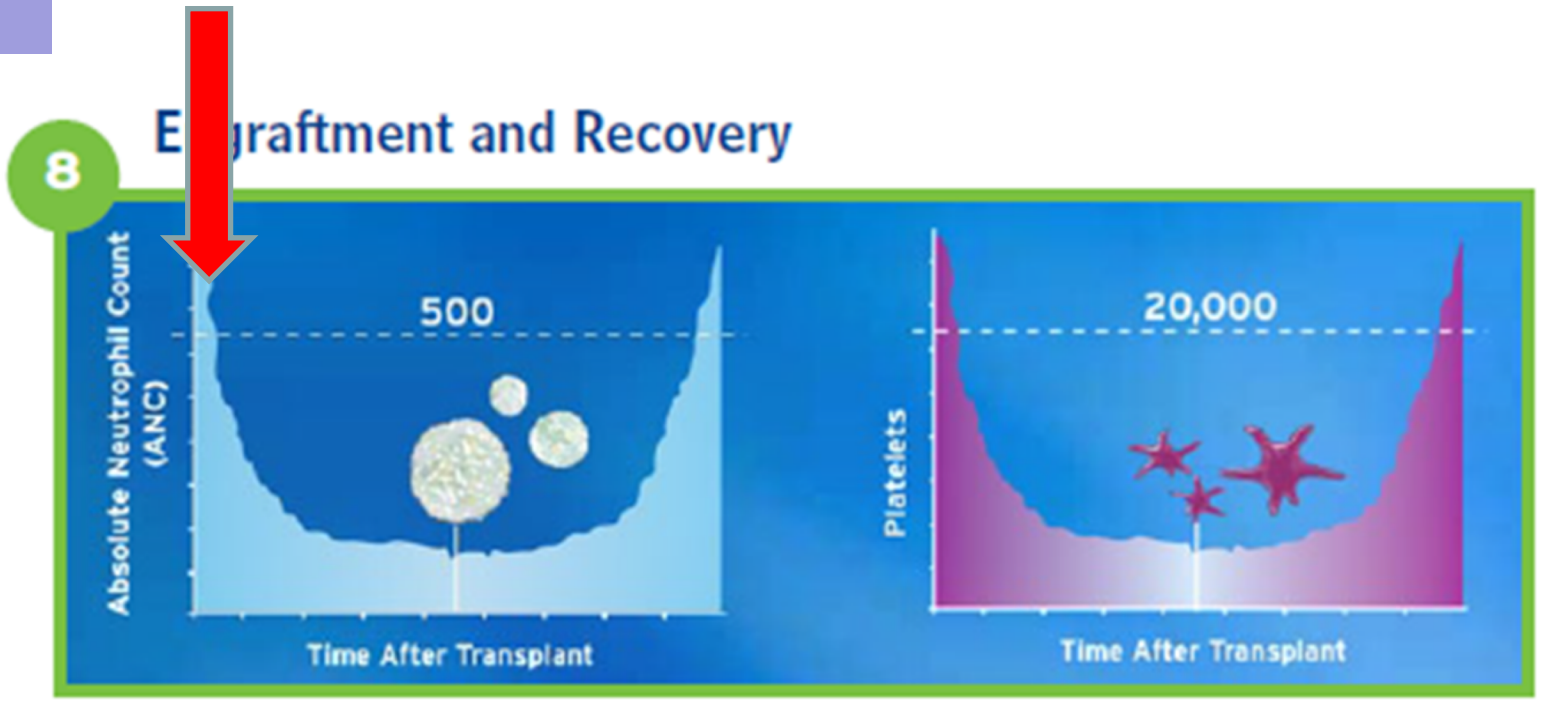
	-2	-1	0	1	2	3	4	5	6	7	8	9	10	11
WBC	7.5	6.1	5.7	5.5	2.1	.1.	.1	.1	.1	.1	.1	.3.	.8	2.2
ANC	7.1	5.8	5.5	5.2	2	.1	0	0	0	0	0	0	.2	1.2
Hbg	85	86	90	86	86	82	78	97	96	95	99	99	96	96
Plt	64	60	53	43	31	20	33	6	30	18	11	37	27	19

Pre-engraftment: G-CSF (Filgrastim)

G-CSF (Filgrastim) is used to encourage engraftment and decrease the length of Neutropenia.

- Multiple Myeloma
  - Begins on Day +5
  - Continues until ANC > 1 for 3 days
- Lymphoma
  - Begins on Day +7
  - Continues until ANC >1 for 3 days

Daily G-CSF injections begins as the WBC/ANC begins to decrease (Day +5 or Day +7), therefore begin regardless of ANC



One aim of autologous stem cell transplant is for infused stem cells to mature into functional blood components such as neutrophils and platelets. The first signs of engraftment and recovery include increasing absolute neutrophil and platelet counts

Prophylactic Treatment

Antibiotic (Multiple Myeloma and Lymphoma)

- Ciprofloxacin 500mg Po Q12h
- Given until ANC $\geq$ 1

Antiviral – Mulitple Myeloma

- Acyclovir 400mg PO/IV Q8h
- Continues for 6 months post transplant

Antiviral – Lymphoma

- Acyclovir 400mg PO/IV Q8h
- Given until ANC $\geq$ 1

Consider fungal and PCP prophylaxis i.e. Septra

Febrile Neutropenia

- Blood cultures x2 central (central, peripheral)
- Urine C&S
- CXR
- Immediate Antibiotic therapy
  - Tazocin 4.5g IV q8h
  - If hypotensive, or ANY sign of impending sepsis have a very very low threshold to start meropenum 500mg IV q6h +/- and aminoglycoside (eg. Tobramycin)

Engraftment

The establishment of HSCs in the marrow, from the peripheral blood, and begins producing blood cells.

Determined by:

- Platelets > 20 for 3 days
- ANC > 0.5 for 3 days

Post Transplant: Supportive Care

Follow-up in Nurse led clinic

- Routinely seen once a week (twice if required)
- Transferred back to hematologist between day 28 and 30, when eating and drinking improved
- Able to contact Nurse directly via Blackberry or call to inpatient unit (6 Oncology) with symptoms
- Apheresis line removed when drinking well

Post Transplant

- Ongoing symptoms (3 to 6 Months):
  - Lack of appetite
  - Fatigue/sleep disturbances
  - Depression/anxiety
  - Diarrhea
  - Nausea/vomiting
- Post transplant infections
- Immunizations (may not require full revaccination – can have serology testing)
- By 6 to 12 months most symptoms have improved.

Reference

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With thanks….

I think we learn from medicine everywhere that it is, at its heart, a human endeavor, requiring good science but also a limitless curiosity and interest in your fellow human being. And that the physician-patient relationship is key; all else follows from it. *Abraham Verghese*