CancerCare Manitoba

# Extreme Gardening:

## Stem Cell Transplantation in Multiple Myeloma


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# Disclosures

**FINANCIAL DISCLOSURE**

**Grants/Research Support**: Clinical trial funding from Celgene, Janssen, Onyx, Merck, Bristol Myers Squibb, Millenium

**Speaker bureau/Honoraria amounts**: None

**Consulting fees**: None

**Other**: None

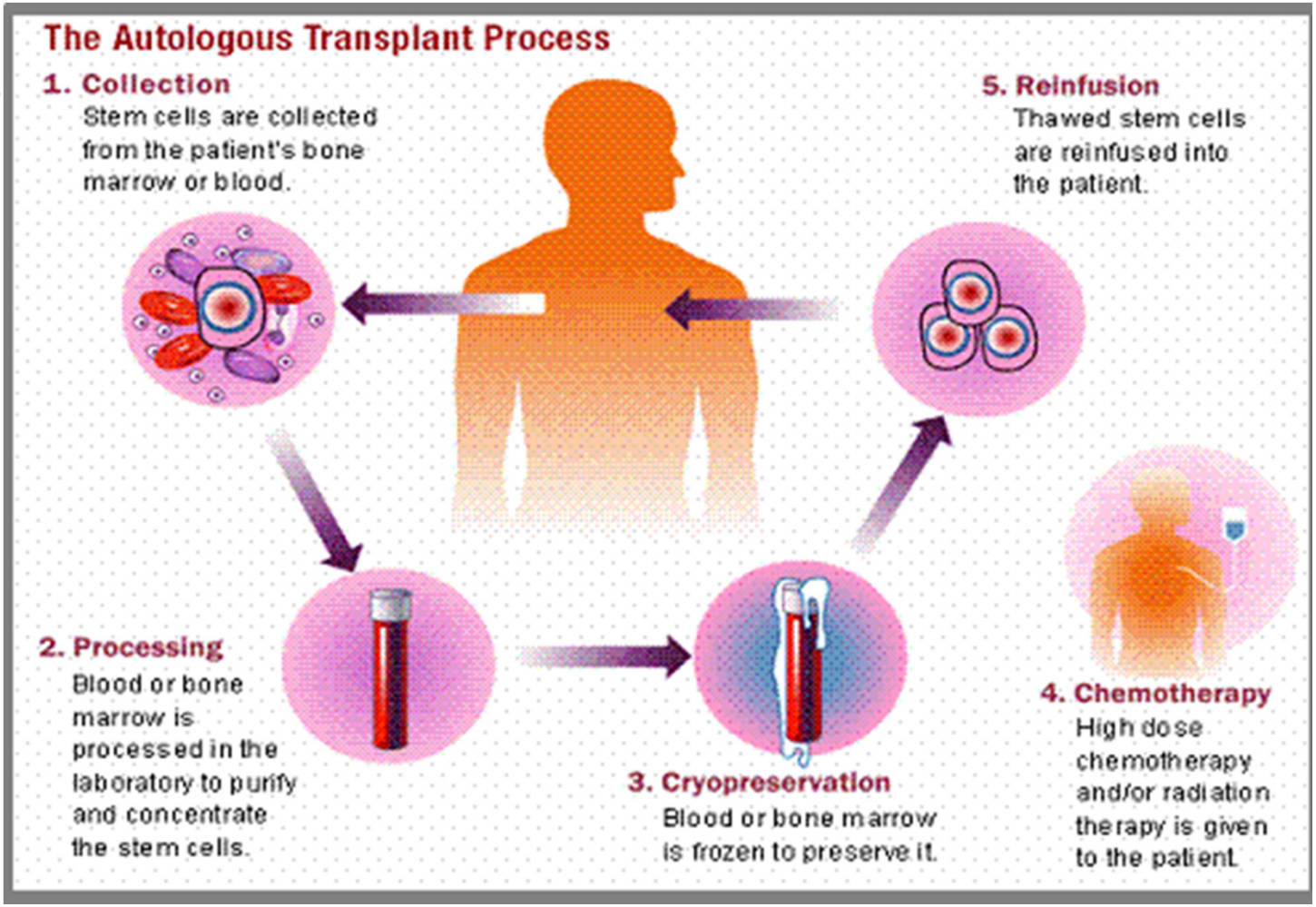
# Objectives

By the end of this session, learners should be able to:

1) Appreciate the process of autologous stem cell transplantation
2) Understand the indication for stem transplantation in myeloma
3) Discuss common and severe adverse effects of stem transplantation and know how to address them

# Background

- Autologous Stem Cell Transplantation
  - a procedure in which blood-forming stem cells (cells from which all blood cells develop) are removed, stored, and later given back to the same person
- Allogeneic Stem Cell Transplantation
  - Source of stem cells is another person


The Autologous Transplant Process
1. Collection
Stem cells are collected from the patient's bone marrow or blood.
5. Reinfusion
Thawed stem cells are reinfused into the patient.
2. Processing
Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.
3. Cryopreservation
Blood or bone marrow is frozen to preserve it.
4. Chemotherapy
High dose chemotherapy and/or radiation therapy is given to the patient.

# Diseased Bone Marrow

# Induction Chemotherapy

# Stem Cell Harvesting

# Conditioning (High Dose Chemotherapy)

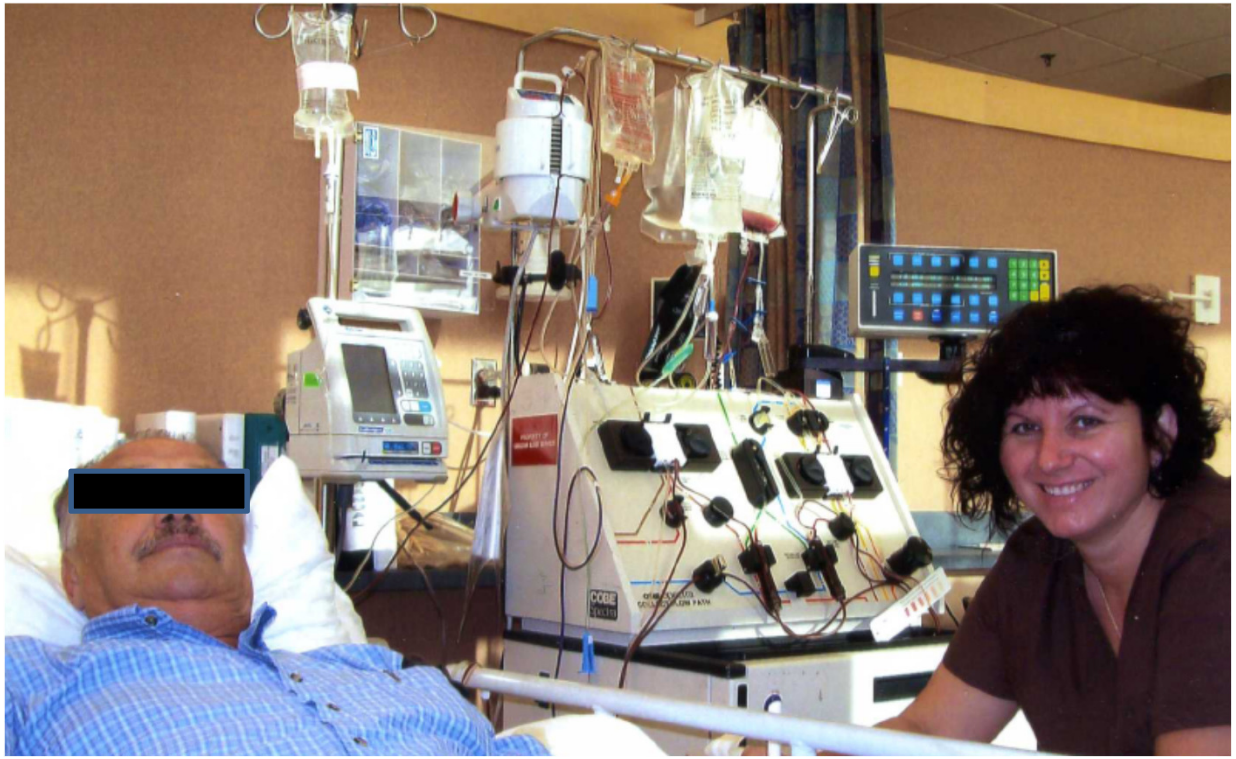
# Stem Cell Re-infusion

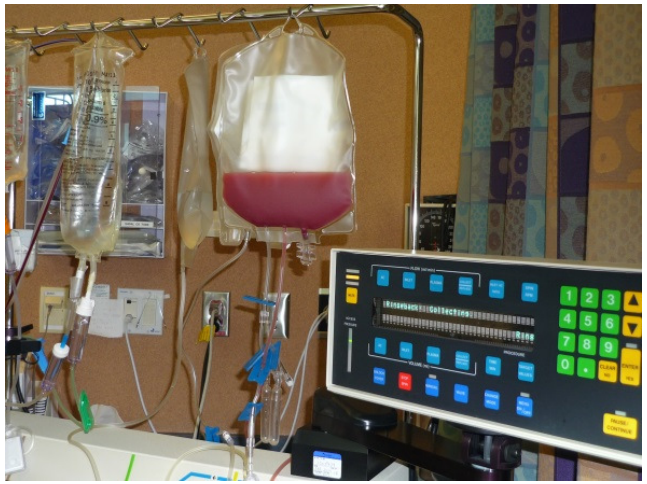
# Engraftment

# Stem Cell Source

# Bone Marrow Harvest

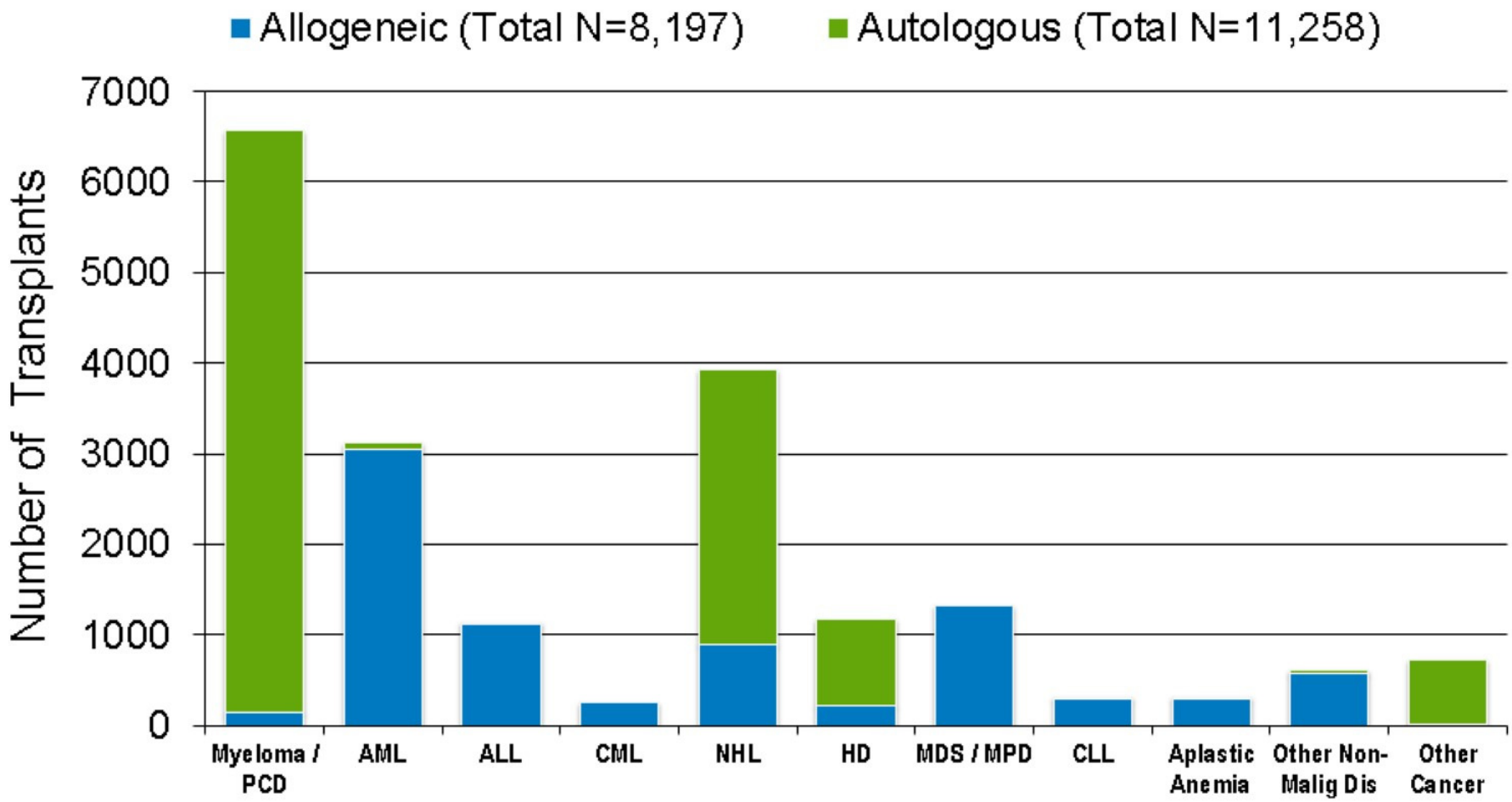
# Peripheral Blood Collection





Granulocyte Colony stimulating factor (GCSF) to mobilise progenitor cells

# Indications for Hematopoietic Stem Cell Transplants in the US, 2013

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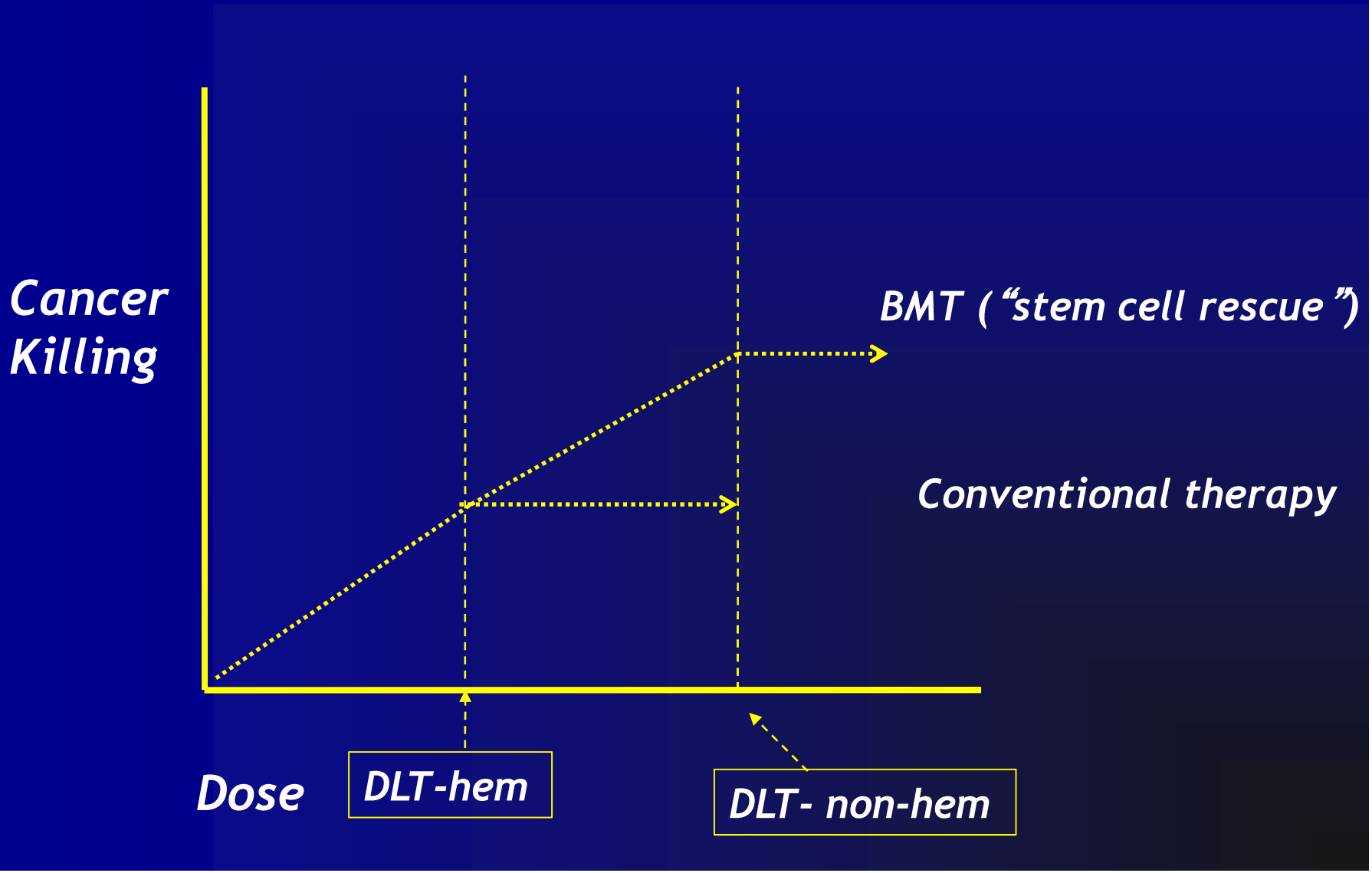
# What is the rationale for high dose chemotherapy?

# Myeloablation and "dose limiting toxicity"



# Why Do We Do ASCT in Myeloma?

- Randomized 200 newly diagnosed myeloma patients <65 years old to standard chemotherapy vs autologous bone marrow transplant
  - Standard chemo – alternating 3 week cycles of VMCP and BVAP (18 cycles) → IFN until relapse
  - ASCT – 4-6 alternating cycles of VMCP and BVAP followed by bone marrow harvest and melphalan 140mg/m2 + 8 Gy TBI → IFN until relapse

Attal et al, NEJM 1996

# Why Do We Do ASCT in Myeloma?

| | Conventional chemo | High Dose Therapy |
|---|---|---|
| CR | 5% | 22% |
| VGPR | 9% | 16% |
| PR | 43% | 43% |
| EFS | 18 months | 27 months |
| OS | 37.4 months | Not reached |

Attal et al, NEJM 1996

# Why Do We Do ASCT in Myeloma?

- Five other randomized trials comparing transplant to standard chemotherapy:
  - ORR improved 60-80% vs 50-55%
  - CR or VGPR improved 40-50% vs <20%
  - PFS 25-30 months vs 15-20 months
  - ASCT either upfront or at relapse improves median OS to 50-55 months vs 36 months

Harousseau et al NEJM 2009

# Patient Selection

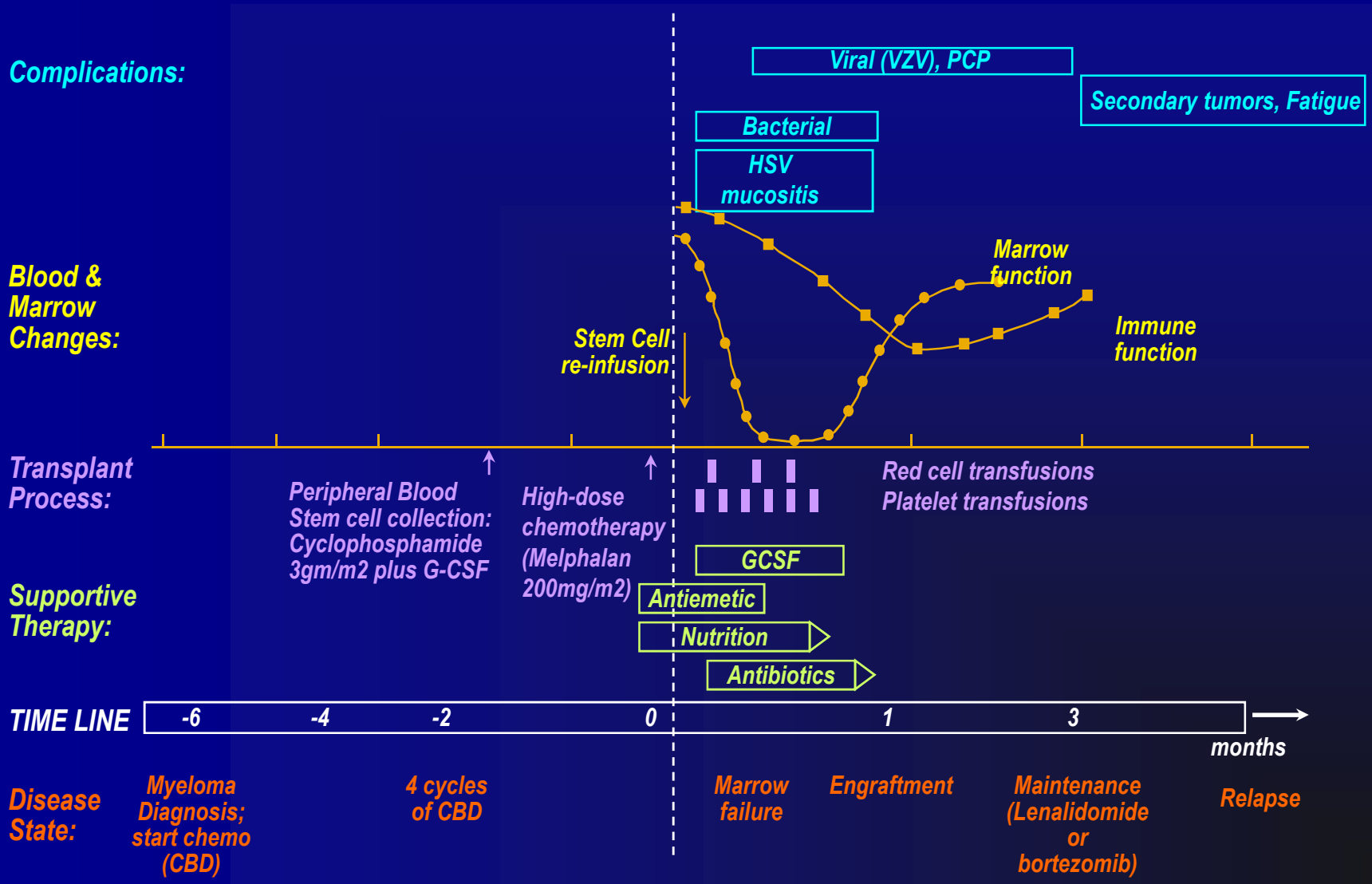
- Patients up to the age of 70 years
  - Most studies used a cut off of 65 years
  - Some US centres do not use an age cut off (determined by "biological age")
- Good performance status
- Absence of significant medical co-morbidities (i.e. severe cardiac, lung, liver disease)
  - Note: renal failure including ESRD on dialysis is not a contraindication but may require modification of conditioning regimen

# Complications of ASCT

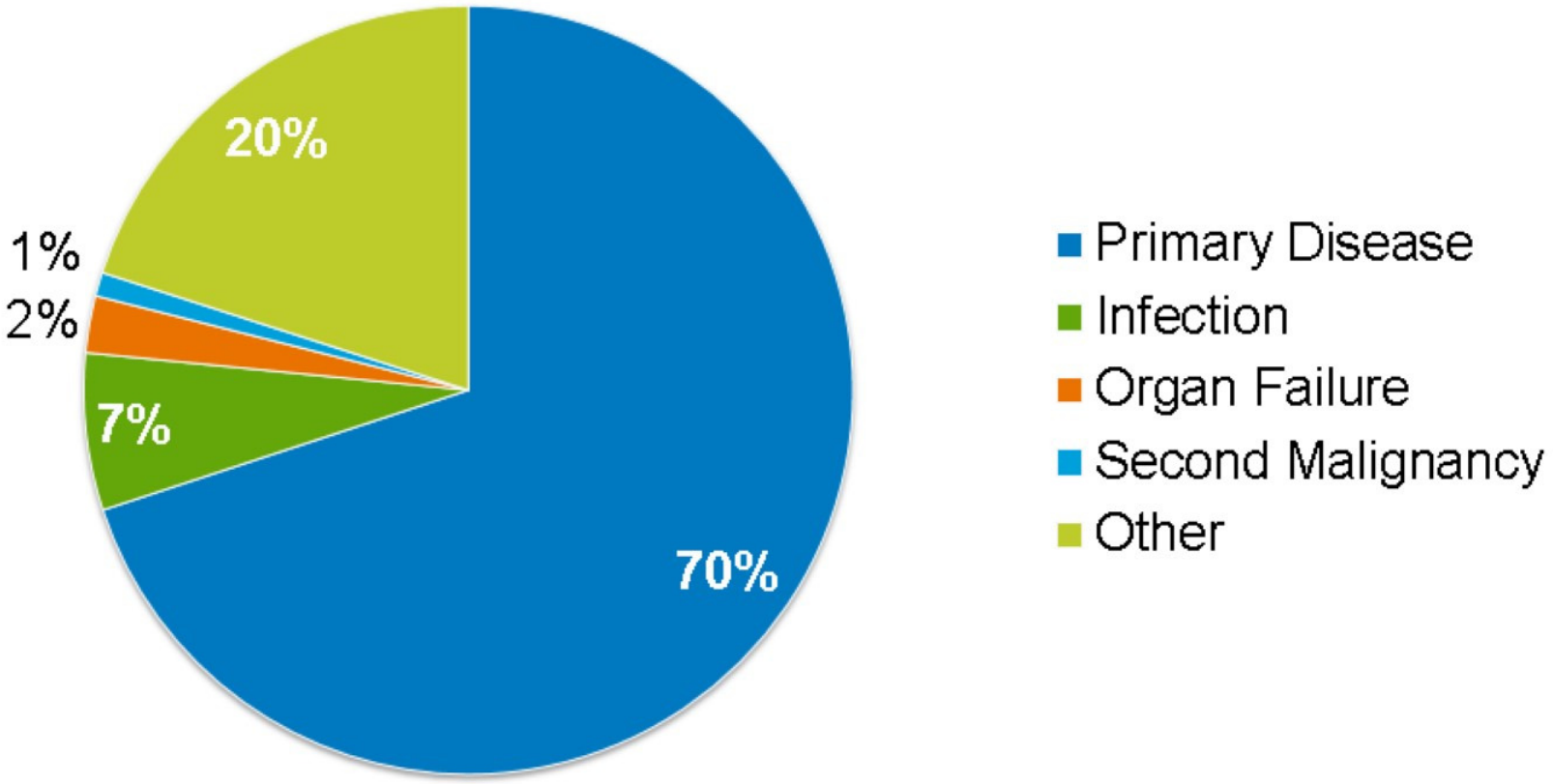
- Early complications
  - Mucositis
  - Febrile neutropenia
    - Usually bacterial organisms
  - Varicella Zoster Reactivation 7% (MBMT 2006-2007)
  - Renal insufficiency/Electrolyte disturbance
  - Dehydration
- Late Complications
  - Impaired Immune recovery
    - Re-immunization
  - Hypogonadism/Infertility
  - Impaired bone Health
  - MDS/AML ~4% at 7 years
  - Secondary solid tumors
  - Fatigue

Note: Graft vs host disease (GVHD) is not on the list as this is seen only with allogeneic stem cell transplantation

# Stem Cell Transplant Timeline



# Causes of Death after Autologous Transplants done in 2012-2013




100 day transplant related mortality only 1%

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# Case

- 62 year old female
- ISS III myeloma kappa light chain restricted
- Comorbidities:
  - Type II DM (Diet controlled), Hypertension
- Partial response with 3 cycles of bortezomib and dexamethasone
- Autologous Collection: Cyclophosphamide 2.5g/$m^2$ + G-CSF
- High Dose Chemotherapy: Mel 200 mg/$m^2$

# Inpatient Complications

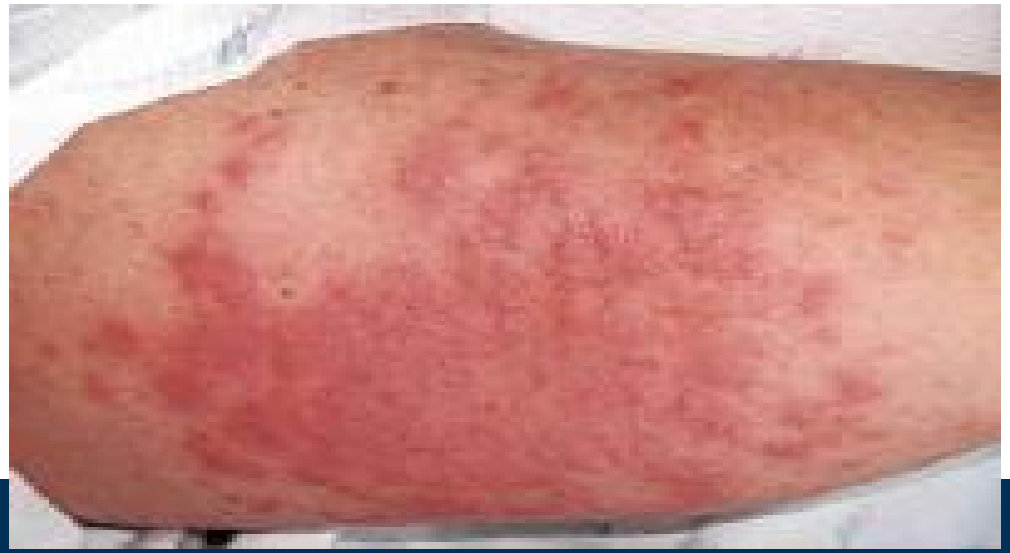
- Mucositis: Grade III Day +5
- FNE day +6
  - Cultures grew S. Viridans
  - Completed 10 days of IV antibiotics
- Acute Renal Insufficiency
- D/C day +25 due to poor oral intake
  - renal status normalized, mucositis resolved
  - D/C Meds: Sulfamethoxazole/Trimethoprim, valacyclovir, pamidronate (monthly), metformin 1g bid, ramipril 10 mg po od

# Day +28

- Nurse Assessment in Clinic
  - Patient not feeling quite right, poor oral intake
  - Exam: HR: 120 BP 90/60 RR 20 Temp 37
  - Bloodwork
    - Na 125 mM, K 5.0 mM  BUN: 25 mM Cr 250 uM
    - PO4 0.5 mM, Mg 0.5 mM
    - CBC ANC 1.5 Plt 100 Hb 100 g/L
  - Diagnosis: dehydration and renal insufficiency
  - Treatment: Outpatient IV hydration plus electrolyte replacement (hold metformin and ramipril)

# Day +50

- After a brief hospitalization, patient felt much better, C Diff toxin negative.
- Patient may have benefited from
  - Daily assessment following D/C
  - Passes for a few days before D/C
- **Doc can you look at my rash**?



R. Arm

# Rash

- Differential Diagnosis
  - Drug Rash – TMP/SMX
  - Photosensitivity induced by SMP/SMX
  - Viral exanthem
  - Contact dermatitis
- Action: Stopped TMP/SMX; rash went away – Dapsone substituted
  - (Consider G6PD assay in appropriate populations)

# Post ASCT Assessment

- First appt 48-72 hours post discharge then at 1 week then at 4 weeks
- Complete history and physical
  - Nutrition, volume status, mouth sores, infection, rash, etc
- Bloodwork
  - CBC with diff, lytes, BUN, Creatinine, ALT, AST, ALP, GGT, LDH, protein, magnesium, phosphate, calcium, albumin

# Post ASCT Assessment

- Medication Review
  - Antiemetics, pain meds, regular home medications
  - Anti-infective prophylaxis
    - PJP prophylaxis until day +180 (TMP/SMX or dapsone or pentamidine)
    - VZV prophylaxis until day +180 with valacyclovir
  - Bisphosphanates
    - Monthly pamidronate or zoledronic acid
- Day 70 seen by BMT team and care returned to myeloma team
- Initiate maintenance therapy (lenalidomide or bortezomib) at day 100
- Re-vaccination schedule

| Approximate timing after BMT | 3 months after BMT " Month 0 " | 4 months after BMT " Month 1 " | 5 months after BMT " Month 2 " | 12 months after BMT " Month 9 " | 14 months after BMT " Month 11 " | 24 months after BMT " Month 21 " | 27 months after BMT " Month 24 " |
|---|---|---|---|---|---|---|---|
| **< 7 years old** **DTaP-IPV-Hib** (diphtheria, tetanus, acellular pertussis, inactivated polio, haemophilus influenzae type B) | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | |
| **≥ 7 years old** **Tdap-IPV** (tetanus, diphtheria, acellular pertussis, inactivated polio ) | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | |
| **≥ 7 years old** **HIB** (haemophilus influenzae type b) | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | |
| **Pneu-C-13** (pneumococcal conjugate) | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | | | | |
| **Pneu-P-23** (pneumococcal polysaccharide) | | | | ____/____/____ ❶ MM / DD / YY | | ____/____/____ MM / DD / YY | |
| **Men-C-ACYW -135** (meningococcal conjugate) | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | | |
| **HAHB** (hepatitis A & B) ❷❸ (Twinrix Adult® to be used for pediatric and adult patients) | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | |
| **2 to 12 years old** **MMRV** (measles, mumps, rubella, varicella) ❹❺❼ (Priorix-Tetra®) | | | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY |
| **> 12 years old** **MMR** (measles, mumps, rubella) ❹❺ | | | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY |
| **> 12 years old** **Var** (varicella) ❹❺❻❼ (Varivax III ®) | | | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY |
| **Females 9 to ≤ 26 years old** **HPV** (human papillomavirus) (Gardasil ®) | | | | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | ____/____/____ MM / DD / YY | |
| **Influenza** | **Lifelong seasonal administration starting 6 months after date of transplant ❽** | | | | | | |
| **Td** (tetanus, diphtheria) | **Every 10 years for continued protection** | | | | | | |

❶ Following the primary series of 3 doses of Pneu-C-13, administer 2 doses of the 23-valent polysaccharide pneumococcal vaccine (Pneu-P-23) to broaden the immune response. For patients with chronic GVHD who are likely to respond poorly to Pneu-P-23, a fourth dose of the Pneu-P-13 should be considered instead of Pneu-P-23 at 12 months after HSCT.

❷ Cost covered by Manitoba Health due to increase risk of Hepatitis A & B resulting from transplant related hepatotoxicity.

❸ Post-vaccination testing for antibody to hepatitis B surface antigen is recommended 1-2 months after the 3rd dose to ensure protection. If testing indicates inadequate protection, provide an additional 3 doses of hepatitis B vaccine. Retest anti-HBs one month after the second series of hepatitis B vaccine.

❹ Administer **only if off** all immunosuppressive therapy for at least 3 months and currently not receiving immunomodulatory drugs (eg. lenolidomide, bortezomib)

❺ Interval between IVIG and a live vaccine is dependant upon the dose of IVIG used and ranges between seven and eleven months. Refer to the Canadian Immunization Guide www.phac-aspc.gc.capublicat/cig-gci/p01-10-eng.php

❻ Varicella vaccine may be administered during the same visit but at a separate injection site as MMR vaccine, DTaP-IPV-Hib vaccines, adolescent/adult diphtheria-tetanus-acellular pertussis (Tdap), inactivated polio, pneumococcal polysaccharide, meningococcal conjugate, hepatitis A&B, and influenza vaccines. If not given during the same visit as other live virus vaccine (MMR), administration of the two live vaccines should be separated by at least 4 weeks.

❼ Varicella vaccine is only given to recipients who have not experienced primary varicella infection or herpes zoster between Day 0 and Day 730 (2 years) post-transplant**. Zoster (shingles) vaccine should never be used**

❽ For children aged 6 months to 8 years who are receiving influenza vaccine for the first time, 2 doses should be administered

# Bottom Line – ASCT is not as complicated as it seems