Mobilization Strategies for Autologous and Allogeneic Hematopoietic Cell Transplantation

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Disclosures

I have served on the following advisory boards for the following companies:

- Amgen
- Bristol-Meyers Squibb
- Seattle Genetics

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Objectives

- Identify optimal mobilization strategies for hematopoietic stem cell collection (HCT)
- Review the efficacy and safety of mobilization agents available for use in HCT
- Discuss the pharmacoeconomic implications of different mobilization techniques

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Hematopoietic Stem Cells in the Bone Marrow Environment

- Hematopoietic stem cells (HSC)
  - Self renewal
  - Reconstitution of blood cell line lineages
  - Reside in bone marrow
  - Express CXCR4 receptor
- Key Components
  - Osteoblasts
  - Bone marrow endothelial cells
  - CXCL12
  - Perivascular leptin receptor positive cells

Becker PS. J Natl Compr Canc Netw 2014; 12: 1443-1449

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Moving HSCs out of the Bone Marrow

Physiologic systems

- Fibrinolytic system
- Bone remodeling
- Sympathetic nervous system
- Circadian rhythms

Pharmacologic agents

- Colony stimulating factors
- Plerixafor
- Natalizumab
- Thrombopoietin
- Stem cell factor
- Macrophage inhibitory protein
- Interleukin 8
- CXCL12 analog

Becker PS. J Natl Compr Canc Netw 2014; 12: 1443-1449

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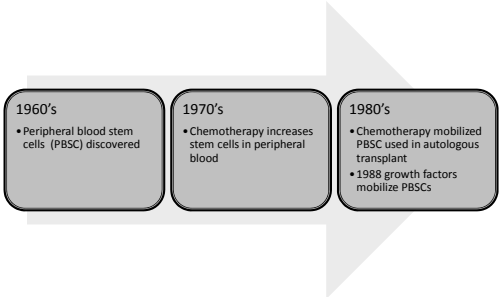
Historical Perspective



Tanhehco YC et al. Transfusion 2013; 53: 2314-2326

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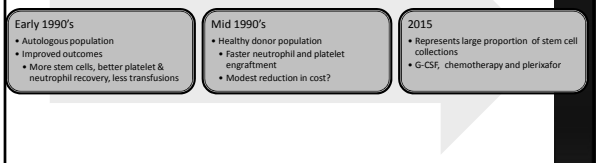
Historical Perspective



Holig K, Transfs Med Hemother 2013; 40: 225-2350
Hopman RD, DiPersio JF Blood Reviews 2014; 28: 31-40

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Stem Cell Mobilization

- Require coordination
  - Transplant program, apheresis, flow cytometry, cell processing laboratories
- Practices vary widely
  - Adapted practices
  - Variability
- Difficult to establish standards
  - Consensus guidelines developed

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Stem Cell Targets and Doses

- Stem cell and engraftment kinetics
  - Cell doses <1 X 10^6/kg
    - — Increased RBC transfusions, loss of engraftment
  - Cell doses <1.5-2.5 x 10^6/kg
    - — Delayed neutrophil & platelet recovery
  - Cell doses > 3-5 X 10^6 cells/kg
    - — Improved platelet recovery, reduced blood transfusions
- Higher stem cell doses
  - Improved neutrophil & platelet engraftment, reduced transfusions
  - More data needed

Giralt S et al. Biol Blood Marrow Transplant 2014; 20: 295-308

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ASBMT Recommendations for Stem Cell Targets and Doses

- Minimum stem cell dose
  - 2 X 10^6 cells/kg
  - Lower doses – consider circumstances
- Ideal target stem cell doses
  - 3-5 X 10^6 cells/kg
  - 2.5 X 10^6 cells/kg – single apheresis session
  - Higher targets for multiple transplants

Giralt S et al. Biol Blood Marrow Transplant 2014; 20: 295-308

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Autologous Stem Cell Mobilization: Initial Collection

- Optimal mobilization
  - Collection of targeted cell dose
  - Minimize number of apheresis
  - Reduce costs
  - Avoid complications
    - — Febrile neutropenia
- Prevention of mobilization failure
  - Traditional strategies 40%

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PBSC Mobilization Agents

Agent	Mechanism of Action	Advantages	Disadvantages
G-CSF	1. Reduction of SDF-1 via degradation by neutrophil elastase 2. Increase in CXCR4 3. Induces release of proteases into BM	Outpatient Low toxicity Predictable time to peak CD34+ cells Predictable timing of apheresis	Lower CD34+ cell yields vs combo regimens More apheresis needed Lower probability of stem cell products with high CD34+ cell content
Chemotherapy	1. Marrow aplasia with subsequent stimulation of hematopoietic recovery	Higher number of CD34+ cells vs G-CSF Fewer apheresis sessions Antitumor activity	May need hospitalization Unpredictable time to peak CD34+ cell content Unpredictable timing of apheresis Greater toxicity
Plerixafor	1. Reversible antagonist of CXCR4	Higher CD+34 compared to G-CSF Fewer apheresis sessions Higher likelihood of successful mobilization Predictable time to peak CD34+ cells	AWP = 24 mg: $8460.88 -single use vials

Tanhehco YC et al. Transfusion 2013; 53: 2314-2326

Initial Stem Cell Mobilization Strategies: Growth Factors

- G-CSF
  - Standard doses 5-16 mcg/kg/day
    - — Higher stem cell yield at higher doses: 40 mcg/kg/day
    - — Added toxicity and expense
  - Reported failure rates – 38%
    - — Wide range reported in the literature
- GM-CSF
  - Inferior to GSCF
    - — Stem cell collected
    - — Post transplant outcomes
    - — Consider in remobilization strategy

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Initial Stem Cell Mobilization Strategies: Growth Factors

Author	Patient Population	Regimen	CD34+ Yield (X 10^6 cells/kg)	Failure Rate (%)
Pusic 2008	MM Lymphoma	N = 976: CM + G-CSF N = 64: G-CSF	5.43 3.36	18.6 18.75
Alegre 1997	MM	N = 18: Cy + GMCSF N = 22: G-CSF	6.8 4.9	NR NR
Desikan 1998	MM	N = 22: G-CSF N = 22: Cy + G-CSF	5.8 33.4	23 18
Besinger 1995	MM, BC Lymphoma	N = 124: CM + G-CSF/GM N = 119: G-CSF	10.75 5.21	7 5
Narayanasami 2001	Lymphoma	N = 22: G-CSF N = 24: Cy + G-CSF	2.5 7.2	4.5 4.2
Dazzi 2000	NHL	N = 12: G-CSF N = 12: Cy + G-CSF	2.89 6.41	NR NR

Pusic et al. Biol Blood Marrow Transplant 2008; 14: 1045-1056
Alegre et al. Bone Marrow Transplant 1997; 20: 211-217
Desikan et al. J Clin Oncol 1998; 16: 1547-1553
Besinger et al. J Clin Oncol 1995; 13: 2547-2555
Narayanasami et al. Blood 2001; 98: 2059-2064
Dazzi et al. Leuk Lymphoma 2000; 39: 301-310
MM = multiple myeloma, CM = chemomobilization, BC breast cancer
Cy = cyclophosphamide , GM = GMCSF, NR = not reported

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Initial Stem Cell Mobilization Strategies: Pegfilgrastim

Author	Patient Population	Regimen	CD34+ Yield (X 10^6 cells/kg)	Failure Rate (%)
Bruns 2006	MM	N = 15 Cy + PEG 6 mg N = 15 Cy + PEG 12 mg N = 15 Cy + G-CSF	10 7.4 8.6	0 0 0
Hosing 2006	MM	N = 19 PEG 12 mg N = 8 G-CSF 10 mcg/kg	8.4 8.7	0 0
Unpublished trial data	Lymphoma N = 38	G-CSF 10 mcg/kg PEG 6 mg PEG 12 mg	37% collected 2 X 10^6 cells/kg	46 69 73
Costa 2012	MM NHL	N = 74 G-CSF 10 mcg/kg N = 57 PEG 12 mg	7.26 7.54	1 patient 1 patient

Bruns et al. Transfusion 2006; 46: 180-185
Hosing et al. Br J Haematol 2006; 133: 533-537
Costa et al. Transfusion 2012; 52: 2375-2381
Unpublished data available from: http://download.veritasmedicine.com/REGFILES/amgen/20020112.pdf
MM = multiple myeloma, CM = chemomobilization
Cy = cyclophosphamide , GM = GMCSF, NR = not reported
PEG = pegfilgrastim

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Initial Stem Cell Mobilization Strategies: Chemomobilization

Author	Patient Population	Regimen	CD34+ Yield (X 10^6 cells/kg)	Failure Rate (%)
Pusic 2008	MM Lymphoma	N = 976: CM + G-CSF N = 64: G-CSF	5.43 3.36	18.6 18.75
Alegre 1997	MM	N = 18: Cy + GMCSF N = 22: G-CSF	6.8 4.9	NR NR
Desikan 1998	MM	N = 22: G-CSF N = 22: Cy + G-CSF	5.8 33.4	23 18
Chao 2011	MM Lymphoma	N = 143: CM + G-CSF N = 84: G-CSF	18.6 7	4.2 16.7
Dingli 2006	Lymphoma	N = 22: G-CSF N = 24: Cy + G-CSF	2.5 7.2	4.5 4.2
Damon 2009	NHL	N = 69: EAR + G-CSF	15.9 6.41	0

Pusic et al. Biol Blood Marrow Transplant 2008; 14: 1045-1056
Alegre et al. Bone Marrow Transplant 1997; 20: 211-217
Desikan et al. J Clin Oncol 1998; 16: 1547-1553
Chao et al. Blood 2011; 118: 4048
Dingli D et al. Clin Lymphoma Myeloma 2006; 6: 384-388
Damon LE et al. J Clin Oncol 2009; 27: 6101-6108
MM = multiple myeloma, CM = chemomobilization, NR = not reported
Cy = cyclophosphamide , EAR = etoposide, cytarabine, rituximab

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Initial Stem Cell Mobilization Strategies: Chemotherapy Regimens

Author	Patient Population	Regimen	CD34+ Yield (X 10^6 cells/kg)	Failure Rate (%)
Wood 2011	MM	N = 152: VP-16 + G-CSF	12	0
Wood 2013	Lymphoma	N = 159: VP-16 + G-CSF	6.2	6
Zappasodi 2008	MM	N = 23: DCEP + PEG	5.7	13
Fruehauf 2007	MM	N = 26: CAD + PEG 12 mg	9.7	12
Isidori 2005	Lymphoma	N = 25: IEV + PEG 6 mg	8.7	4
Simona 2010	Lymphoma	N = 38: ESHAP + PEG 6 mg	9.42	17

Wood et al. Biol Blood Marrow Transplant 2011; 17: 141-146
Wood et al. Bone Marrow Transplant 2013; 48: 711-776
Zappasodi et al. Transfusion 2008; 48: 857-860
Fruehauf et al. Bone Marrow Transplant 2007; 39: 743-760
Isidori et al. Haematologica 2005; 90: 225-231
Simona et al. Transfus Apher Sci 2010; 43: 321-326
MM = multiple myeloma, VP-16 = etoposide; DCEP = dexamethasone, cyclophosphamide, etop
cisplatin; CAD = cytoxan, doxorubicin, dexamethasone, IEV = ifosfamide, epirubicin, etoposide

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Initial Stem Cell Mobilization Strategies: Cyclophosphamide dose

Author	Patient Population	Regimen	CD34+ Yield (X 10^6 cells/kg)	Failure Rate (%)
Hiwase 2007	MM	N = 61: Cy 1-2 gm/m2 N = 26: Cy 3-4 gm/m2	5.1 7.7	11 8
Sizemore 2009	MM	N = 37: Cy 2 gm/m2 + G-CSF N = 35: Cy 4 gm/m2 + G-CSF	NR NR	13.5 3
Sizemore 2010	NHL	N = 28: Cy 2 gm/m2 + G-CSF N = 28: Cy 4 gm/m2 + G-CSF	NR NR	32 4

Cyclophosphamide 3-7 gm/m2

- Higher yields
- Lower failure rates
- Improved engraftment kinetics

Hiwase et al. Cytotherapy 2007; 9: 539-547
Sizemore et al. Blood 2009; 114:4229
Sizemore et al. Biol Blood Marrow Transplant 2010; 16: (suppl 2) : S206
MM = multiple myeloma,, NR = not reported, NHL = non Hodgkin's lymphoma
Cy = cyclophosphamide

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Initial Stem Cell Mobilization Strategies: Plerixafor

Author	Patient Population	Regimen	CD34+ Yield (X 10^6 cells/kg)	Failure Rate (%)
DiPersio 2009	MM Phase III	N = 148: P + G-CSF N = 154: G-CSF	13 7.3	28 66
Shaughnessy 2011	MM NHL	N = 33: CM + G-CSF N = 22: P + G-CSF	11.6 10.7	0 0
Isola 2011	MM	N = 25: G-CSF N = 22: P + G-CSF	8.4 16.1	NA NA
Campen 2010	NHL	N = 34: Cy + G-CSF N = 8: P + G-CSF	NR NR	29.4 12.5
Adel 2011	MM	N = 98: Cy + G-CSF N = 35: P + G-CSF	NR NR	21 6
DiPersio 2009	NHL Phase III	N = 150: P + G-CSF N = 148 G-CSF	5.7 2	41/10 80/45

DiPersio et al. Blood 2009; 113: 5720-5726 Adel NG et al. Blood 2011; 118: 4059
Shaughnessy Biol Blood Marrow Transplant 2011; 17:729-736 DiPersio JF et al. J Clin Oncol 2009; 27: 5720-5726.
Isola et al. Blood 2011; 118: 2075 MM = multiple myeloma, CM = chemomobilization, NR = not reported
Campen et al. Biol Blood Marrow Transplant 2010; 61: S206 Cy = cyclophosphamide , P = plerixafor, NA = not applicable

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Poor Mobilization Risk Factors

Baseline

- Treatment related
  - Extensive chemotherapy
  - Previous melphalan, fludarabine, platinum regimens, alkylating agents or lenalidomide
  - Previous radiation therapy
- Patient related
  - Advanced age
  - Diagnosis of NHL
  - Diabetes
- Bone marrow-related
  - Bone marrow involvement
  - Thrombocytopenia

At Time of Mobilization

- Low steady-state CD34+ cell count
- Steady-state thrombocytopenia
- Low day 1 apheresis yield

Giralt S et al. Biol Blood Marrow Transplant 2014; 20:295-308

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Initial Stem Cell Mobilization Strategies: Preemptive and Risk Adapted Plerixafor

- Peripheral blood (PB) CD34+ cell counts
  - Added to steady state G-CSF
  - Improves collection efficiency
  - Reduces cost of mobilization attempts
  - Lowers mobilization failure rate
- Many institution specific protocols
  - Pre-established PB CD34+ thresholds

Giralt S et al. Biol Blood Marrow Transplant 2014; 20: 295-308

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Initial Stem Cell Mobilization Strategies: Preemptive and Risk Adapted Plerixafor

Author	Target CD34+ Yield (X 10^6 cells/kg)	Criteria for Plerixafor Administration	Regimen	Failure Rate (%)
Costa 2011 3	6 (MM)	PB CD34+: 25 PB CD34+: 14	N = 34 PEP N = 81 CM + G-CSF	2 22
Abhyankar 2011	2.5 (single) 5 (tandem)	Day 5 PB CD34+ <10 PB >10 & <20 for tandem start P Day 1 apheresis <50% desired	N = 159 PEP -104 G-CSF alone - 55 P+G-CSF	5
LaPorte 2011	4 (target) 2 (minimum)	Day 4 PB CD34+ <12 Daily aphresis yield <1.5 Or <50% of previous day yield	N = 68 PEP - 38 G-CSF alone - 30 P+G-CSF	1
Micallef 2013	2 minimum	Day 5 PB CD34+ <10 or <20 PB >10 & <20 for tandem start P Day 1 apheresis <1.5/kg or subsequent yield <0.5 /kg	N = 98	1

Costa et al. Bone Marrow Transplant 2011; 46: 523-528
Abhyankar et al. Bone Marrow Transplant 2011; 47:483-487
LaPorte et al. Blood 2011; 118: 4389
Micallef et al. Biol Blood Marrow Transplant 2013; 19: 87-93

MM = multiple myeloma, CM = chemomobilization
PB = peripheral blood, PEP = preemptive plerixafor,

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ASBMT Recommendations for Initial Mobilization Attempts

- Goal reduce overall failure rates to <5%
  - Minimize complications
  - Optimize resource utilization
- Preapheresis PB CD34+ cell count monitoring
  - Identify poor mobilizers
  - Preemptive plerixafor
- Areas for continued research
  - Chemomobilization + plerixafor + G-CSF

Giralt S et al. Biol Blood Marrow Transplant 2014; 20: 295-308

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ASBMT Recommendations for Initial Mobilization Attempts

- Multiple myeloma
  - G-CSF option (10-16 mcg/kg/day) for patients with no more than 1 line of chemotherapy
    - No melphalan or > 4 cycles of lenalidomide
  - Preemptive plerixafor monitoring
- Non Hodgkin's Lymphoma
  - G-CSF option (10-16 mcg/kg/day) for low risk patients
  - Higher failure rates, ease of scheduling
  - Preemptive plerixafor monitoring

Giralt S et al. Biol Blood Marrow Transplant 2014; 20: 295-308

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Audience Response Question 1

Higher doses of cyclophosphamide mobilization are associated with which of the following:

a. Higher CD34+ yields
b. Lower failure rates
c. More toxicity compared to G-CSF alone
d. All of the above

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ASBMT Recommendations for Initial Mobilization Attempts

- Chemomobilization vs. G-CSF
  - Direct comparisons equivocal
  - Patient populations respond differently
    - Early vs late stage MM
- Stand alone chemomobilization
  - Consider with suboptimal response to therapy
- Upfront plerixafor
  - Goal is highest possible CD34+
  - Fewest apheresis days possible
  - Real time PB CD34+ not available

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Remobilization Options

- Combination growth factors
  - More costly and as effective as high dose G-CSF
  - Failure rates >80%
- Chemomobilization
  - Historically recommended
  - Failure rates >70%
- Bone marrow harvest
  - Increased costs, decreased quality of life
  - Difficult in the event of failed PBSC collection

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ASBMT Recommendations for Remobilization

- Growth factors alone not recommended
- Chemomobilization
  - Option for single agent growth factor failure
- Plerixafor
  - Patients failed non- plerixafor regimen
  - May be helpful if failed plerixafor regimen
    - — Plerixafor + G-CSF
    - — Plerixafor + G-CSF + chemotherapy
- Bone marrow harvest
  - Third line option, not eligible for clinical trials

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ASBMT Allogeneic Stem Cell Mobilization Recommendations

- Single agent growth factors
  - G-CSF preferred agent for mobilization
    - — 10 mcg/kg/day, single or split dose
      - Higher doses higher collections, more toxicity
    - — Superior results compared to GM-CSF
      - Lower cell yields, more leukapheresis
    - — Some data with pegfilgrastim 6-12 mg
- Combination growth factors
  - G-CSF vs. G-CSF + GM-CSF
    - — G-CSF superior results

Duong HK et al. Biol Blood Marrow Transplant 2014; 20: 1262-1273

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ASBMT Allogeneic Stem Cell Mobilization Recommendations

- Plerixafor
  - Single agent
    - — No benefit over G-CSF alone
    - — Ongoing IBMTR trial
- Pediatric population
  - 10 mcg/kg/day
  - Retrospective analysis of 201 patients
    - — Target CD34+ cell yields achieved
      - Young age, male donor, more days apheresis – higher yield
      - Minimal toxicity

Duong HK et al. Biol Blood Marrow Transplant 2014; 20: 1262-1273

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Biosimilar G-CSF Mobilization

- Biosimilar G-CSF products
  - Europe multiple agents approved by EMA
  - United States
    - — 1 approved product, 1 pending approval (EP2006)
- World Marrow Donor Association
  - Use of biosimilars within clinical trials
- Executive Committee of the EBMT Association
  - 2009 – did not recommend use of biosimilars until further studies regarding efficacy and use are reported

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Biosimilar G-CSF Mobilization

- Review of literature
  - Included 904 patients
    - — Hematologic malignancies
      - HL, NHL, acute and chronic leukemia, germ cell tumors
    - — Healthy donors
      - Sibling and unrelated donors
    - — Ratiograstim®/Tevagrastim® (n= 520)
    - — Zarzio® (n = 384)

Schmitt M et al. Theranostics 2014; 4: 280-289

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Biosimilar G-CSF Mobilization

- Autologous transplant outcomes
  - Good mobilization of CD34+ stem cells
    - — Median CD34+ cell counts 3-10.1 X10 cells/kg
  - Similar side effect profile
    - — Bone pain, febrile neutropenia
  - Post transplant outcomes
    - — Median time to neutrophil engraftment: 11-15 days
    - — Median time to > 20,000 platelets: 12-19 days

Schmitt M et al. Theranostics 2014; 4: 280-289

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Biosimilar G-CSF Mobilization

- Allogeneic transplant outcomes
  - Good mobilization of CD34+ stem cells
    - — Median CD34+ cell counts 4.4-10.2 X10 cells/kg
  - Similar side effect profile
    - — Bone pain, flu-like symptoms, muscle pain
  - Post transplant outcomes
    - — Median time to neutrophil engraftment: 13-15 days
    - — Median time to > 20,000 platelets: 16-25 days

Schmitt M et al. Theranostics 2014; 4: 280-289

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The Cost of Mobilization Failure

Consequence	Outcome
Failure to mobilize sufficient number of CD34+ cells	• No transplant, subsequent relapse • Increased apheresis days • Need for bone marrow harvest • Added cost for remobilization • Increased resource utilization
Transplant with suboptimal CD34+ apheresis product	• Delayed, partial or failed engraftment • Prolonged hospitalization • Increased infections • Increased bleeding or need for transfusions
Unmeasured costs to patient/caregiver	• Transportation to/from apheresis center • Cost of housing/food • Psychological strain • Missed work time
Unmeasured costs to the center	• Weekend apheresis • Delay in treatment • Disruption in patient flow • Inability to proceed to transplantation

Shaughnessy P et al. Biol Blood Marrow Transplant 2013; 19: 1301-1309

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Standard Mobilization Costs

- Difficult to determine
  - Based on mobilization strategy
  - Growth factor mobilization
    - — Range $6,000-20,000
  - Chemotherapy mobilization
    - — $11,000 -52,000
    - — Additional expenses
      - Chemotherapy administration & complications
      - Admission to hospital for complications
        - $7,000-10,000
      - Cost containment strategies

Shaughnessy P et al. Biol Blood Marrow Transplant 2013; 19: 1301-1309

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Standard Mobilization Costs

- Plerixafor
  - Acquisition cost limit up-front use
    - — Budget constraints
    - — Economic evaluations guide use
  - Do the superior outcomes justify the price?
    - — Pharmacoeconomic analysis provides data

Shaughnessy P et al. Biol Blood Marrow Transplant 2013; 19: 1301-1309

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Overview of Health Economic Research

- Analyzes costs & consequences of interventions
  - Impact on individuals, healthcare systems, society
  - Variety of perspectives
    - — Patient, payer, institution, industry, society
- Types of analysis
  - Cost minimization, cost-effectiveness, cost-utility, cost-benefit and cost-consequence
  - Benefits and limitations

Shaughnessy P et al. Biol Blood Marrow Transplant 2013; 19: 1301-1309

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Evaluating Costs

- Cost-utility analysis
  - Gold standard
  - Facilitates comparisons of cost-effectiveness
    - — Uses common metric – QALY
- Challenges of cost analysis
  - Practical execution
    - — Costs, populations and care vary
    - — Can not always generalize data nationally
    - — Multi-center evaluations difficult
      - Reluctance to share proprietary information

Shaughnessy P et al. Biol Blood Marrow Transplant 2013; 19: 1301-1309

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Evaluating Costs

Quality adjusted life year = "QALY"

- Measure of disease burden –
  - — Quality and quantity of life lived
- Number of years added by intervention
  - — "Years lived in perfect health"
- Used to allocate healthcare resources
- Calculation
  - — 1 QALY = 1 year of life x 1 utility value
  - — Incorporated with medical costs -> cost / QALY

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Pharmacoeconomic Evaluation of Plerixafor for Stem Cell Mobilization

Author	Design	Mobilization Regimen	Outcomes Measured	Results
Shaughnessy 2011	Retrospective	N = 33: P+G-CSF N = 33: CM + G-CSF	Chemotherapy Drugs (P,G-CSF, other) Hospitalization, Transfusion Apheresis	100% mobilization Mean costs/pt P+G-CSF $20,298 CM+G-CSF $19,173 P+G: fewer G doses, hosp, transfusions
Kymes 2012	Retrospective	N = 10 G-CSF N = 10 P + G-CSF	Drug (P+G-CSF) Apheresis, Storage, Transplant, hosp	G-CSF + P results in 1.75 QALYs than G-CSF alone
Vishnu 2012	Prospective	N = 18 G-CSF N = 24 PEP + G-CSF	Drug (P, G-CSF), stem cell collection, lost revenue	95% mobilization vs 75% before PEP Cost savings /pt: $19,300

Shaughnessy et al. Biol Blood Marrow Transplant 2011; 17: 729-736
Kymes et al. Am J Manag Care 2012; 18:33-41
Vishnu et al. Transfusion 2012; 52: 55-62

P = plerixafor, CM = chemomobilization, G = G-CSF
hosp = hospitalization, PEP = preemptive plerixafor,
Pt = patient

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Pharmacoeconomic Considerations

- Prospective pharmacoeconomic data for plerixafor based mobilization is lacking
  - Multi-centered studies needed
  - Standardized endpoints needed
- Retrospective data
  - Plerixafor appears to be cost effective
  - Individual institution data difficult to extrapolate
  - Sample size

Shaughnessy P et al. Biol Blood Marrow Transplant 2013; 19: 1301-1309

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Audience Response Question 2

Which of the following outcomes is NOT associated with mobilization failure?

a. Delay in therapy
b. Fewer apheresis days
c. Increased infections
d. Psychological strain

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Safety of Stem Cell Donation

- Safety for donors is a priority
  - Monitoring is a group effort
    - NMDP, CIBMTR, World Marrow Donor Association
  - Donors have no direct medical benefit
  - Obligation to disclose risks
- NMDP developed monitoring tools
  - 14 key toxicities common to donors
  - Prospective data regarding toxicities

Pulsipher MA Blood 2013; 121: 197-206

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Toxicities Associated with PBSC Collection

Frequent	Rare
Bone pain	Splenic rupture
Headache	Anaphylaxis
Fatigue	Arterial thrombosis
Nausea	Glomerulonephritis
Fever	Pulmonary hemorrhage
Insomnia	Capillary leak syndrome
Mild allergic reaction	Thrombocytopenia
	Decrease in hemoglobin

Moalic V. Pathologie Biologie 2013; 61: 70-74

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Acute Toxicities: Bone Pain

- Start within 24 hours of G-CSF
  - Peaks 4-5 days into treatment
- Pathophysiology
  - Expansion of bone marrow, stimulation of afferent nerves, histamine release
- Treatment
  - Acetaminophen, NSAID's, narcotics
  - Loratadine
    - Case reports and patient testimonials
    - Phase II trials ongoing
      - CALGB - double blind randomized trial
      - NOLAN – open, naproxen vs loratadine

Romeo C. J Oncol Pharm Practice 2014; epub ahead of print doi: 10.1177/1078155214527858

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Rare Complications: Splenic Rupture

- Case reports
  - No fatalities in healthy donors
  - Presents severe sharp left upper quadrant pain
- Risk factors
  - Prolonged exposure, high G-CSF doses
- Mechanism
  - Increase in WBC, extramedullary myelopoiesis
- Avoid vigorous activity after donation
  - Spleen volume normal 7-10 days post donation

Moalic V. Pathologie Biologie 2013; 61: 70-74
Holig K. Transfus Med Hemother 2013; 40: 225-235

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Rare Complications: Arterial Thrombosis

- Case reports in healthy donors
  - Advancing age
- Mechanism
  - G-CSF receptor on platelets & megakaryocytes
  - Pro-thrombotic state
    - Coagulation stimulated via tissue factor
    - Conflicting findings
- Caution with healthy donors with clotting risks

Moalic V. Pathologie Biologie 2013; 61: 70-74
Holig K. Transfus Med Hemother 2013; 40: 225-235

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Rare Complications: Pulmonary Events

- Case reports
  Interstitial pneumonitis, pulmonary infiltrates, lung fibrosis and acute respiratory distress syndrome
- Pathophysiology
  - Unknown

Moalic V. Pathologie Biologie 2013; 61: 70-74
Holig K. Transfus Med Hemother 2013; 40: 225-235

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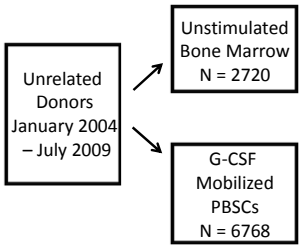
Acute Toxicities: A Comparison of BM and PBSC Collections



Endpoints
- Skeletal pain
- Fatigue
- Selected symptoms

Pulsipher MA et al. Blood 2013; 121: 197-206

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Acute Toxicities: A Comparison of BM and PBSC Collections

	Bone Marrow (%)	Peripheral Blood Stem Cell (%)
Infection Grade II – IV	1.5	0.55
Thrombocytopenia <100 / <50	0.3 0	26 <1
Anemia HgB < 8 g/dL	0.2 % males 5.7% females*	0.1 % males 0.2 females
Pain Peak pain scores	Localized 2 days post donation	Generalized Days 2-5 of G-CSF
Most common toxicity	Fatigue 60%	Fatigue 48%

*P = < 0.01

Pulsipher MA et al. Blood 2013; 121: 197-206

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Long Term Toxicities: Hematologic Malignancies

	Cancer Incidence	Hematologic Malignancies	Follow Up	Comments
NMDP N = 4015	Similar to general population	0	1 year	
EBMT N = 51,024 2009	0.4 and 1.2/10000 person years BM/PBSC	8 cases - BM 12 cases - PBSC	12 years	27,770 BM 23,254 PBSC
German Registry N = 3928 2009	12 donors (0.3%)	4 donors	12 years	All URD
Spanish Registry N = 736 2002	5 donors	0	10-64 months	

Confer DL, Miller JP. Br. J Haematol 2007; 137: 77-78
Halter J et al. Haematologica 2009; 94:94-101
Holig K et al. Blood 2009; 114: 3757-3763
De la Rubia et al. Transfusion 2002; 42: 4-9.

BM = bone marrow, PBSC = peripheral blood stem cell

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Audience Response Question 3

Which of the following was the most common toxicity reported by unrelated donors of PBSC and BM in the prospective trial sponsored by the NMDP?

a. Pain
b. Itching
c. Fatigue
d. Anxiety

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Novel Agents Under Investigation

Drug/Pathway	Mechanism of Action	Specific Agents	Clinical Trial Status
CXCL12/CXCR4 Modulators	CXCR4 antagonist CXCL12 neutralization	POL6326 BTK-140 TG-0054 NOX-A12	Phase I, II in progress Phase I/IIA complete Phase II in progress Phase II in progress
S1P agonists	Alteration of S1P gradient between PB and BM	SWE2871	Animal studies
VCAM/VLA-4 Inhibitors	Inhibition of VLA-4 mediated HSC adhesion to VCAM-1 in BM stroma	BIO 5192	Animal studies
Proteosome inhibitors	Alteration of VLA-4/VCAM-1	Bortezomib	Phase III in progress
Stabilization of HIF	Expression of VEGF A in the BM sinusoids leading to vasodilation	FG-4497	Animal studies

Hopman RD, DiPersio JF Blood Reviews 2014; 28: 31-40

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Summary

- Stem cell mobilization practices continue to be refined
  - ASBMT has developed recommendations for mobilization strategies for allogeneic and autologous transplant populations
  - More multi-centered prospective data is needed in order to understand costs associated with mobilization
- Stem cell mobilization is a relatively safe process

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Mobilization Strategies for Autologous and Allogeneic Hematopoietic Cell Transplantation

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