TREATMENT OF HIGH RISK MDS AND THE INDICATION FOR STEM CELL TRANSPLANT

Prapti Patel, MD
Assistant Professor of Internal Medicine
Division of Hematology Oncology
University of Texas Southwestern
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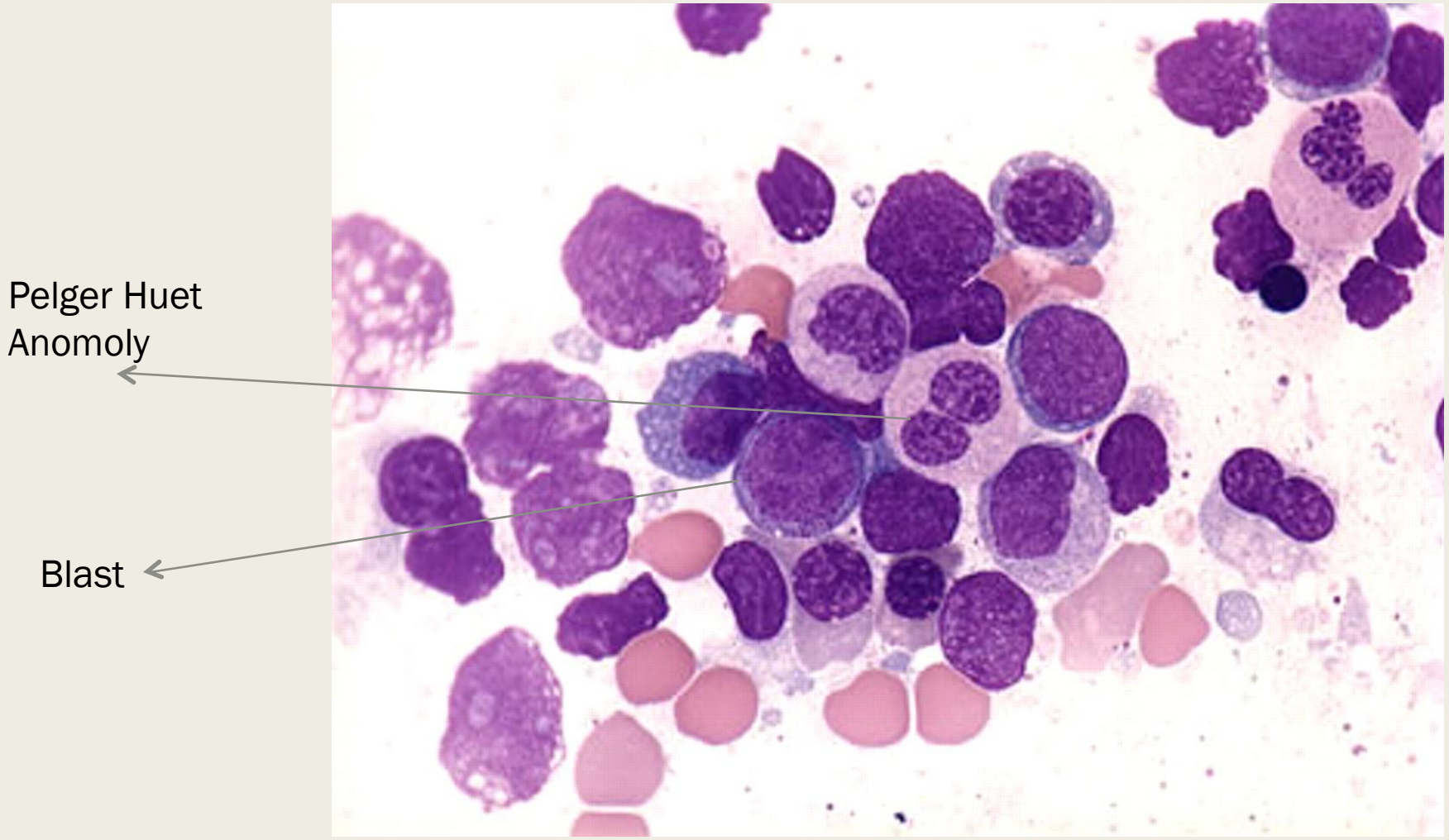
Outline

- Definition of high risk MDS
- Hypomethylating agents
- Stem cell transplant
- Pre-transplant hypomethylating agents
- Post-transplant hypomethylating agents
- Clinical trials available at UTSW

What is High Risk MDS?

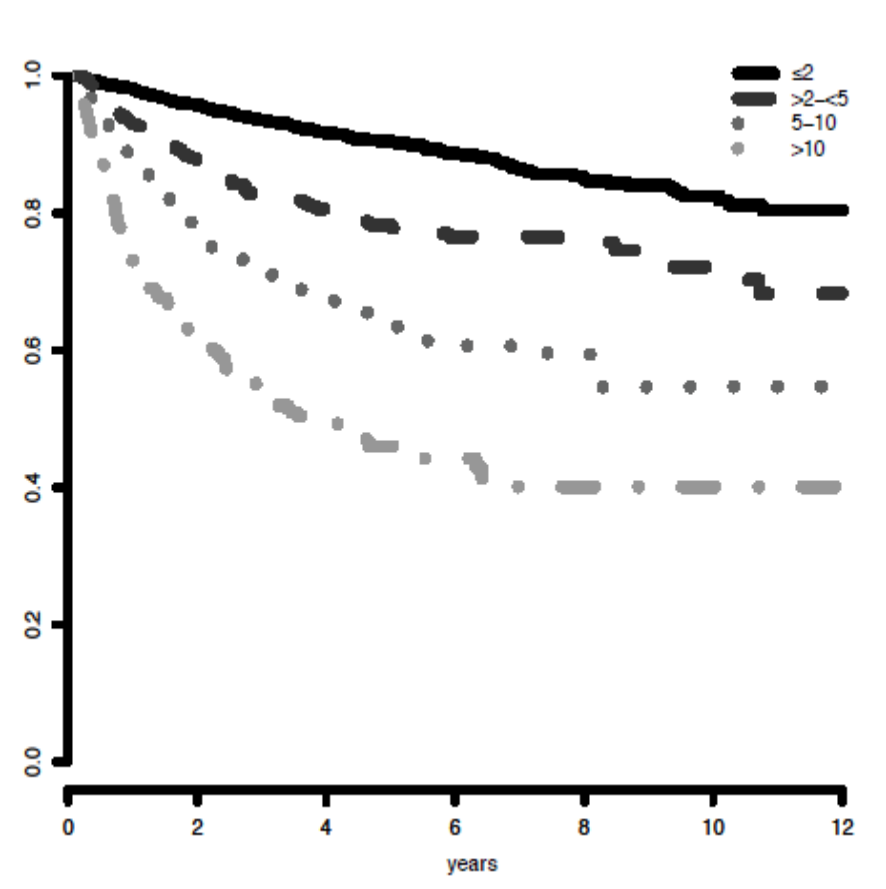
- Defined by R-IPSS
  - blast count
  - Number of cytopenias
  - Cytogenetic abnormalities
- What does it mean for the patient:
  - High risk of complications
  - High risk of transformation to acute leukemia

Refractory Anemia with Excess Blasts - 2.

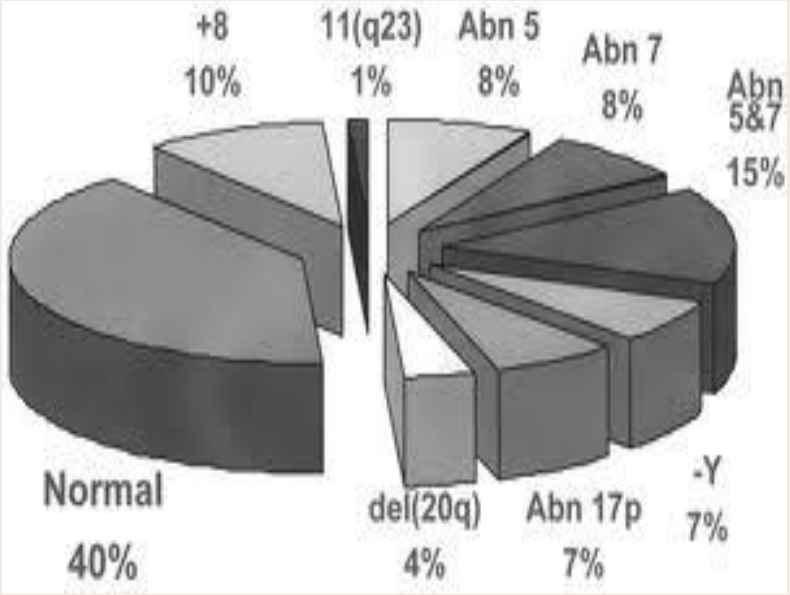


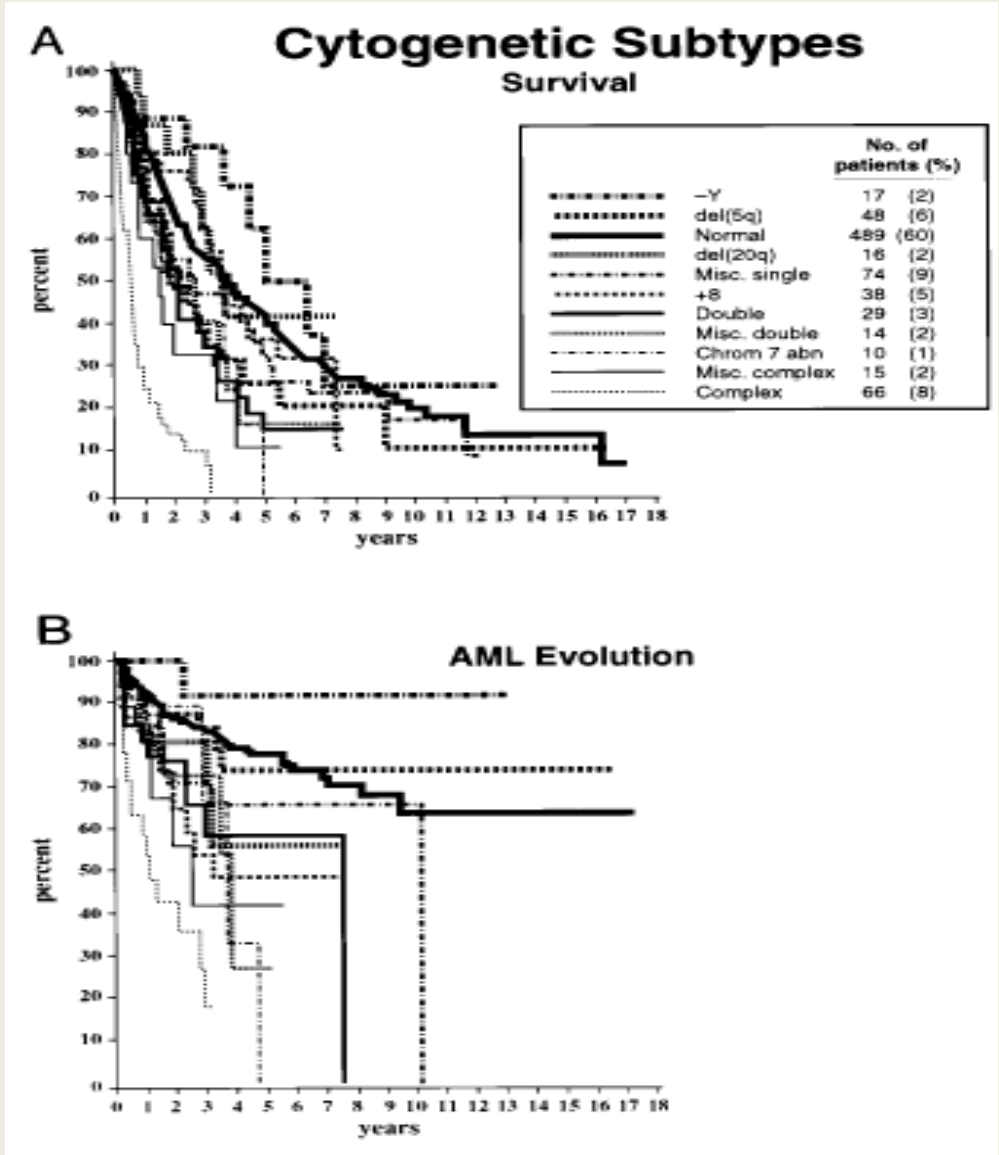
Peter Maslak, ASH Image Bank 2011; 2011-2536

% BM Blasts and Risk of Transformation to AML



Cytogenetics Abnormalities in MDS





IPSS-R

Table 3. IPSS-R prognostic score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	—	Good	—	Intermediate	Poor	Very poor
BM blast, %	≤ 2	—	> 2%- < 5%	—	5%-10%	> 10%	—
Hemoglobin	≥ 10	—	8- < 10	< 8	—	—	—
Platelets	≥ 100	50-< 100	< 50	—	—	—	—
ANC	≥ 0.8	< 0.8	—	—	—	—	—

Table 4. IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	≤ 1.5
Low	> 1.5-3
Intermediate	> 3-4.5
High	> 4.5-6
Very high	> 6

- Very good -Y, del(11q)
- Good Normal, del 20q, del 5q, del 12p
- Intermediate +8, 7q-, 1(17q), +19, +21
- Poor -7, del3(3)q21/q26, complex (3 abnormalities)
- Very poor >3 abnormalities

IPSS-R

Table 5. IPSS-R prognostic risk category clinical outcomes

	No. of patients	Very low	Low	Intermediate	High	Very high
Patients, %	7012	19	38	20	13	10
Survival, all*		8.8	5.3	3.0	1.6	0.8
		(7.8-9.9)	(5.1-5.7)	(2.7-3.3)	(1.5-1.7)	(0.7-0.8)
Hazard ratio		0.5	1.0	2.0	3.2	8.0
(95% CI)		(0.46-0.59)	(0.93-1.1)	(1.8-2.1)	(2.9-3.5)	(7.2-8.8)
Patients, %	6485	19	37	20	13	11
AML/25%*†		NR	10.8	3.2	1.4	0.73
		(14.5-NR)	(9.2-NR)	(2.8-4.4)	(1.1-1.7)	(0.7-0.9)
Hazard ratio		0.5	1.0	3.0	6.2	12.7
(95% CI)		(0.4-0.6)	(0.9-1.2)	(2.7-3.5)	(5.4-7.2)	(10.6-15.2)

Therapy of MDS

Low Risk

- Goal: try to increase the function of the normal cells in the bone marrow
- Method: myeloid growth factors

High Risk

- Goal: killing neoplastic clone causing MDS and preventing transformation to AML
- Method:
  - *Hypomethylating agents*
  - *Allogeneic stem cell transplant*

High Risk MDS Treatment: Azacitdine

- Randomized phase III study of SQ Aza in all stages of MDS
  - *BSC v Aza 75 mg/m2 D1-7 Q 28 days x 4 cycles*

	BSC	AZA
# pts	92	99
CR	0 (0%)	7 (7%)
PR	0 (0%)	16 (16%)
Improved	5 (5%)	37 (37%)
Total	5 (5%)	60 (60%)
Time to AML	12 months	21 months

- When using the IWG IPSS criteria, the response rate fell to 40-50%

Better treatments needed!

JCO. 2002; 18;2414.

Azactadine Survival Study

- Randomized Phase III
  - *AZA 75 mg/m2 z 7 days Q28D (n=179)*
  - *Conventional Care (BSC, low dose AraC of 20 mg/m2/d x 14d q 28-42 days, standard induction chemo*
- 2 y OS
  - *51 v 26%*

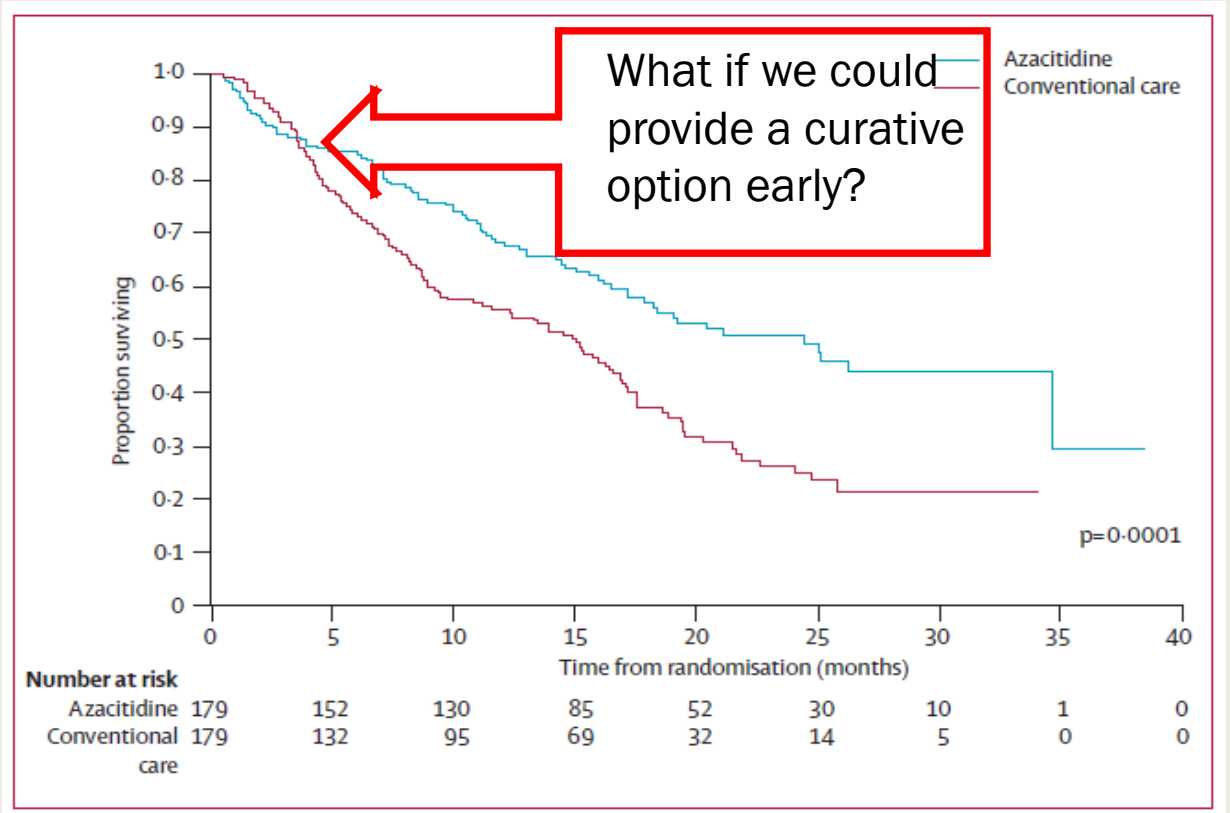


Figure 3: **Overall survival**

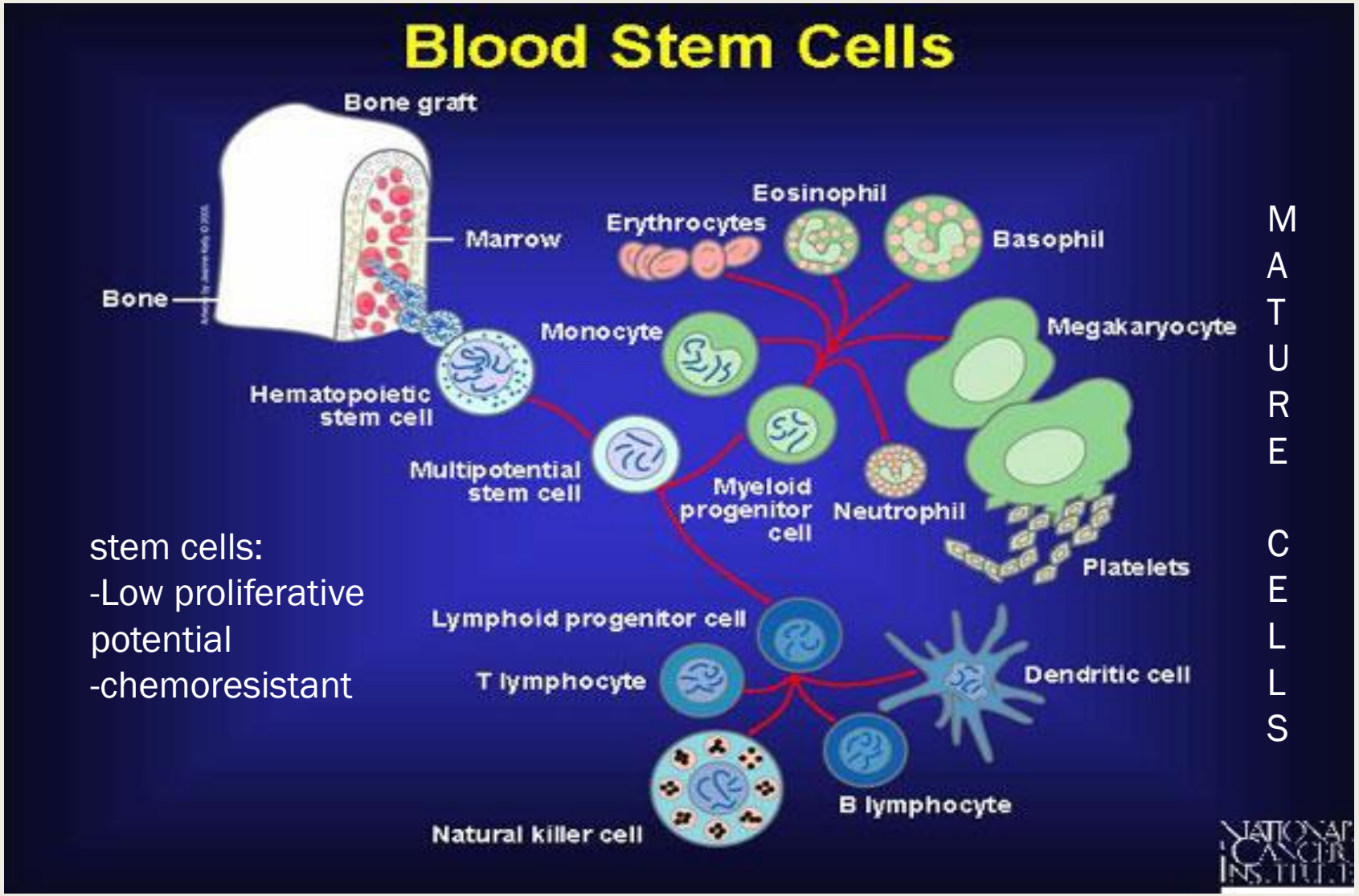
Lancet Oncology. 2009; 10:223.

Purpose of Allo Transplant

- Clean, chemo-naïve stem cells
- Graft versus tumor effect
- More effective in treating aggressive malignancies that may not be cured by chemotherapy alone

Only 1 stem cell needed to repopulate entire bone marrow

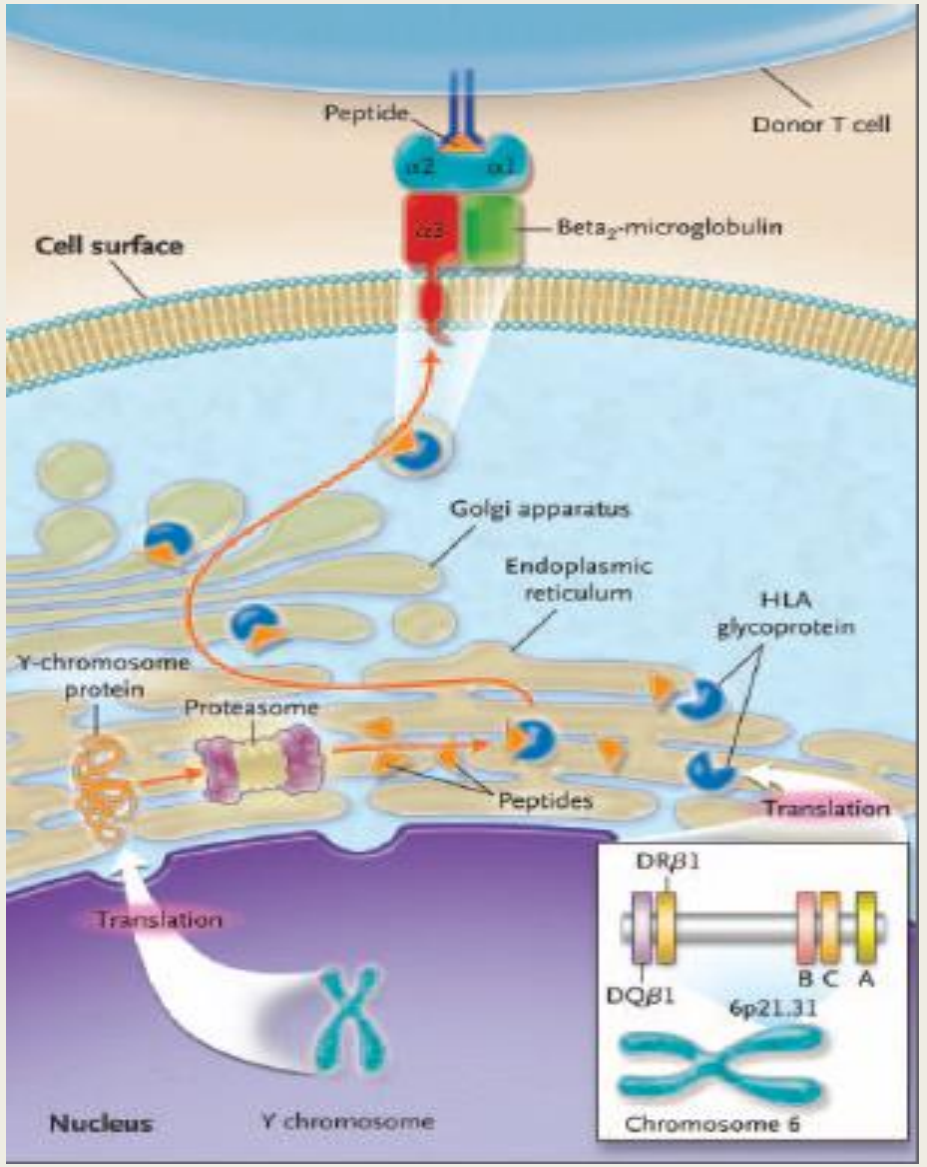
Only 1 in 1 million leukemic blasts is stem cell, can result in sustained leukemia



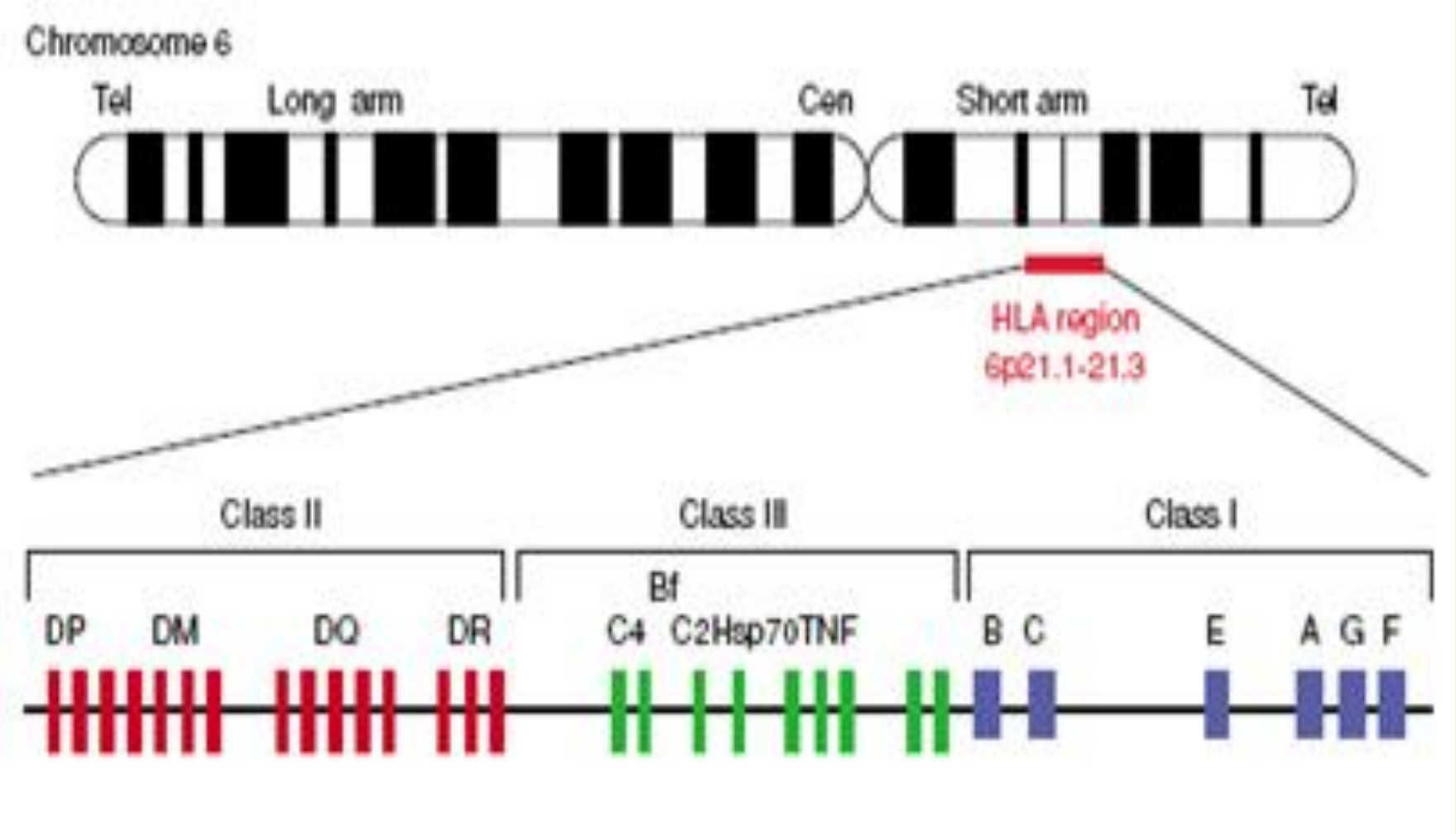
stem cells:
-Low proliferative potential
-chemoresistant

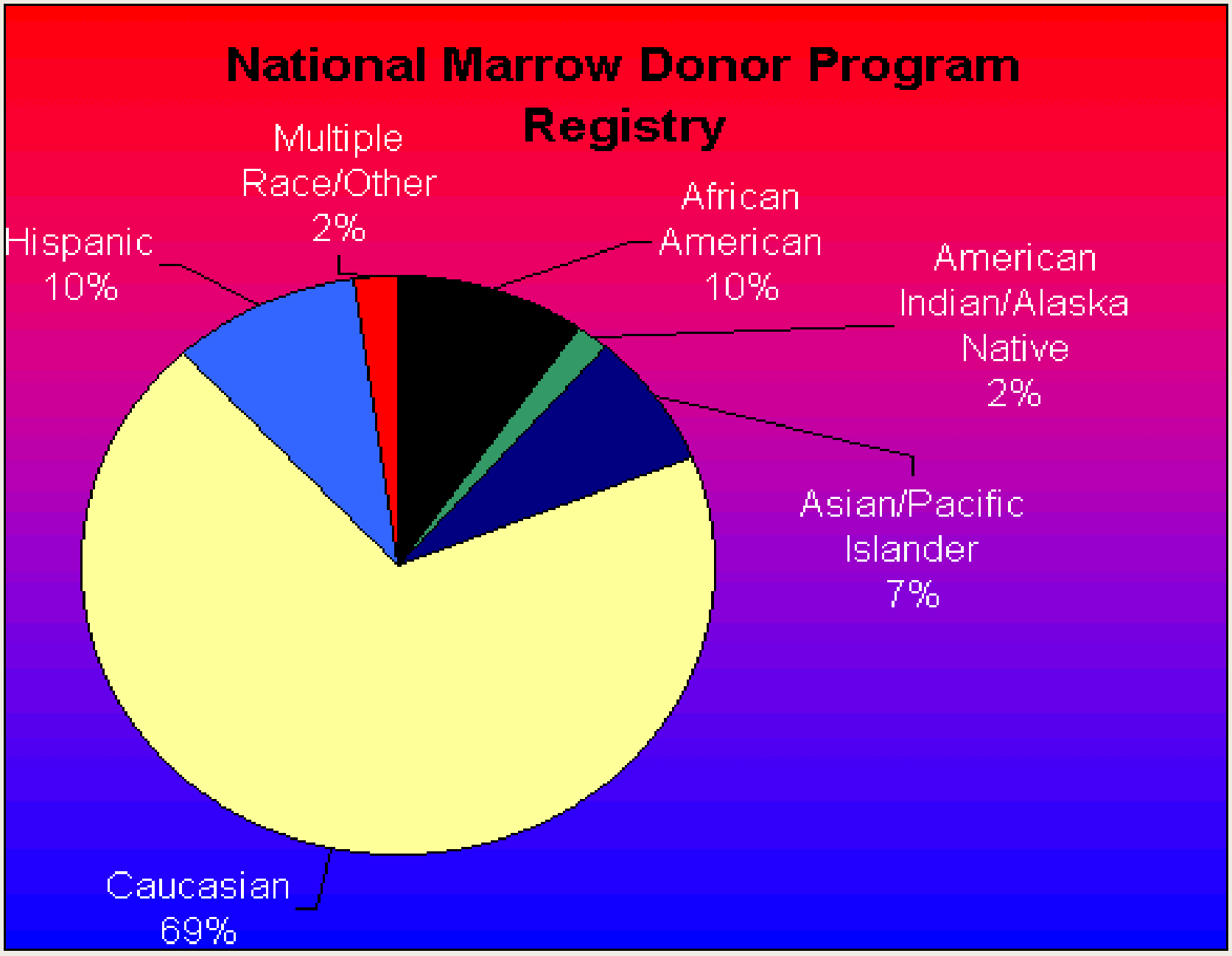
Graft vs Tumor Effect

- Allogeneic grafts initiate immune reactions against host tissue based on the proteins that are on WBC (known as human leukocyte antigens, HLA)
- Severity of reaction depends on degree of incompatibility of the HLAs
- Mediated by T Cells
  - *Recipient T cells can recognize donor T cells as foreign and reject graft*
  - *Donor T cells recognize recipient antigens as foreign/aberrant and cause GVHD/GVT*

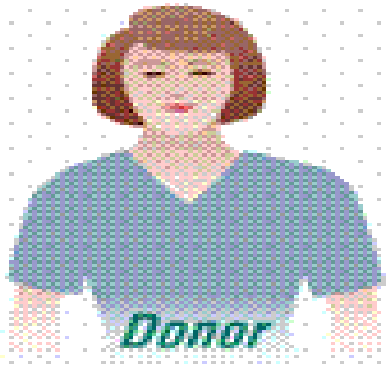


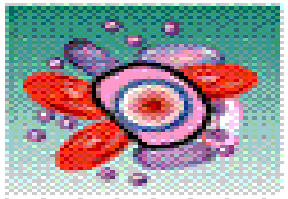
HLA typing


Chromosome 6
Tel
Long arm
Cen
Short arm
Tel
HLA region
6p21.1-21.3
Class II
Class III
Class I
Bf
DP
DM
DQ
DR
C4
C2Hsp70TNF
B
C
E
A
G
F


National Marrow Donor Program
Registry
Multiple Race/Other 2%
African American 10%
Hispanic 10%
American Indian/Alaska Native 2%
Asian/Pacific Islander 7%
Caucasian 69%

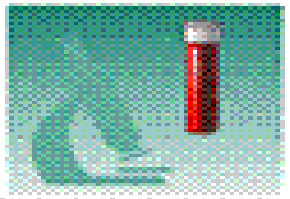
The Allogeneic Transplant Process





1 Collection

Stem cells are collected from the patients bone marrow or blood.

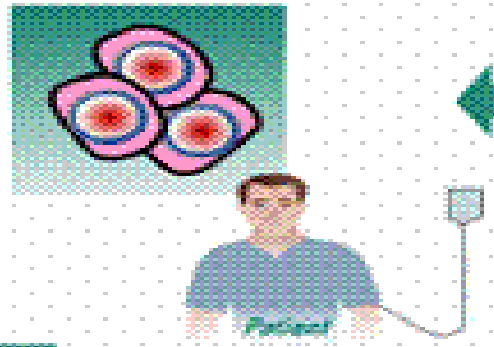


2 Processing

Bone marrow or periferal blood is taken to the processing laboratory where the stem cells are concentrated and prepared for the freezing process

3 Cryopreservation

Bone marrow or blood is preserved by freezing (cryopreservation) to keep stem cells alive until they are infused into the patient's bloodstream.



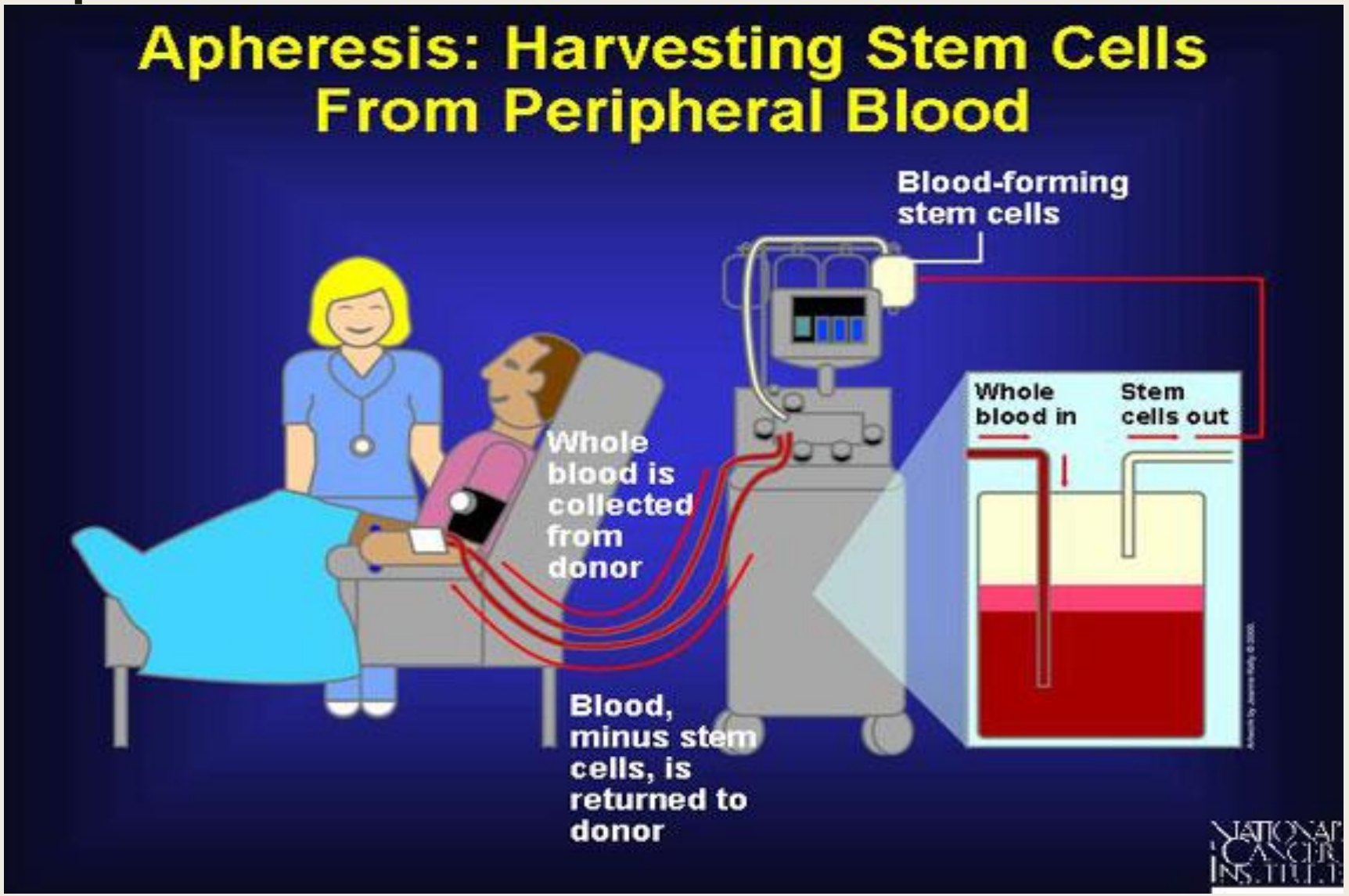
4 Chemotherapy

High dose chemotherapy and/or radiation therapy is given to the patient.

5 Infusion

Thawed stem cells are infused into the patient.

Peripheral Blood Collection



When to transplant?

- Recommendations by ASBMT consensus statement
  - *Early transplant:*
    - High risk patients
    - Low risk patients that are refractory to treatment
  - *No recs on:*
    - Induction chemo
    - Type of donor
    - Preparative regimen

Timing of Transplant and Survival (yrs)

	Immediate SCT	SCT in 2 yrs	SCT at PD
Low	6.51	6.86	7.21
Int-1	4.61	4.74	5.16
Int-2	4.93	3.21	2.84
High	3.20	2.75	2.75

- Downsides to this analysis:
  - Done before the age of HMAs (would treatment with an HMA change survival?)
  - Only included patients <60
  - Only included patients that received high dose chemotherapy, therefore more transplant related mortality

Blood. 2004; 104:579–585.

Treatment Options for Patients Who are Unfit for Allogeneic Stem Transplant

- Many are not candidates for allogeneic stem cell transplant
- Can't tolerate complications of transplant;: infection, GVHD, chemotherapy toxicity
  - *Other medical problems*
  - *Age (>72 years)*
- No treatment that is curative other than stem cell transplant.
  - *New treatments on the horizon in the form of clinical trials*

There is hope!!

Clinical Trials at UT Southwestern

- First Line treatments
  - *Combination therapy with HMA and new medications*
- Relapsed refractory treatments
  - *Immunotherapies*
  - *Targeted therapies*
- PRECISION MEDICINE in MDS
  - *STOP MDS Trial*
- Oral HMA!!

Summary

- High risk MDS is defined by low counts, high blasts, and lots of chromosome abnormalities
- Must be treated because there is a high risk of transformation to acute leukemia and complications from low counts
- Hematopoietic stem cell transplant is the only curative option
  - *Timing is important*
  - *Can give post transplant HMA to help prevent relapse*
- Lots of new therapeutic options are available