

# Where in the TED Does HCT Stuff Go?

Diane J. Knutson



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## Key Concepts

- ◆ What is an HSCT?
- ◆ Why perform one?
- ◆ Who can benefit?
- ◆ Mechanics of transplant
- ◆ Early and Late complications
- ◆ Where on "new" TED?



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## Introducing Pre-TED & Post-TED



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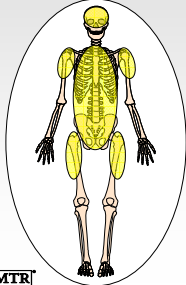
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## Blood is Made in the Bone Marrow



- ◆ Axial skeleton
- ◆ Inner spongy bone
- ◆ Bone marrow is in the holes
- ◆ Bone marrow is a highly organized/regulated organ



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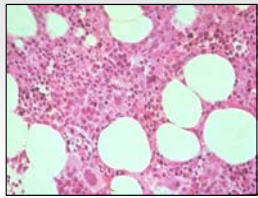
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## Bone Marrow: The Source of Blood and Our Immune System



Normal bone marrow

- ◆ Blood stem cells
  - Pluripotent
  - Self renewing
- ◆ Highly regulated production
  - Cytokines (SCF, IL3)
  - Growth factors (G-CSF)



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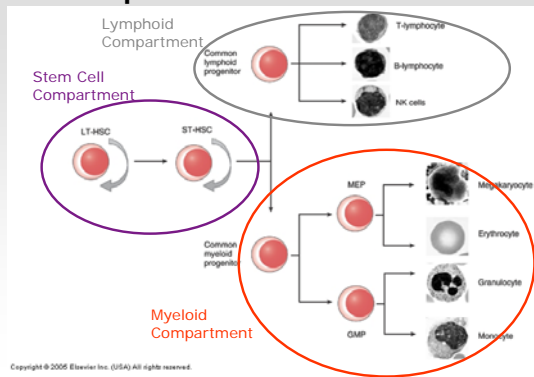
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## Hematopoiesis Scheme



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## Goals of HSCT

- ◆ Provide stem cell replacement
  - Autologous and allogeneic
- ◆ Destroy malignancy
  - Potentially lethal chemotherapy/radiation
  - Immunotherapy



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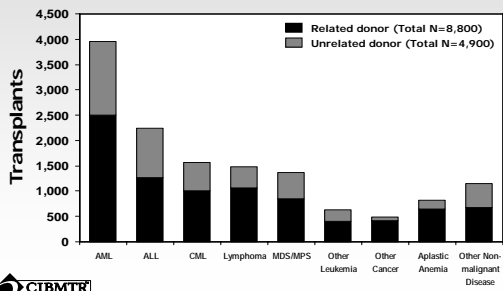
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## Indications for Allogeneic Hematopoietic Stem Cell Transplants, 2003 – Worldwide



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## Pre-TED AML

Select most specific WHO classification:

**ACUTE LEUKEMIAS**

Acute Myelogenous Leukemia (AML)

AML, with recurrent genetic abnormalities

AML, with t(8;21)(q22;q22) [AML t(8;21)] (n)

AML, with abnormal EML promyelocyte and inv(16)(p13q22) or t(16;16)(p13;q22) [CBFβ/PLZF] (n)

APL, with t(15;17)(q22;q21) [PML/RARα] and variants (M3) (n)

AML, with t(11q23) [MLL] abnormalities (n)

AML, with multilineage dysplasia (n)

AML, not otherwise categorized (NOS) (n)

AML, minimally differentiated (M0) (n)

AML, without maturation (M1) (n)

AML, with maturation (M2) (n)

Acute Myelomonocytic Leukemia (M4) (n)

Acute Monoblastic/Acute Monocytic Leukemia (M5) (n)

Acute Erythroid Leukemia [erythroid/myeloid and pure erythroleukemia] (M6) (n)

Acute Megakaryoblastic Leukemia (M7) (n)

Acute Basophilic Leukemia (n)

Acute Pancytopenia with Myelofibrosis (n)

Myeloid Sarcoma (n)

AML, NOS (n)

Acute Lymphoblastic Leukemia (ALL)

Precursor B-cell ALL B (L1, L2) (n)

t(9;22)(q34;q11) [BCR/ABL] (n)

t(11q23); MLL rearranged (n)

t(1;19)(q21;p13) [E2A/PBX1] (n)

t(12;21)(p13;q22) [ETV6/CFP1] (n)

Precursor T-cell ALL (n)

ALL, NOS (n)

Acute Leukemias of ambiguous lineage

Acute undifferentiated leukemia (n)

Biphenotypic, bilineage or hybrid leukemia (n)

Acute mast cell leukemia (n)

Other acute leukemia, (n) specify \_\_\_\_\_



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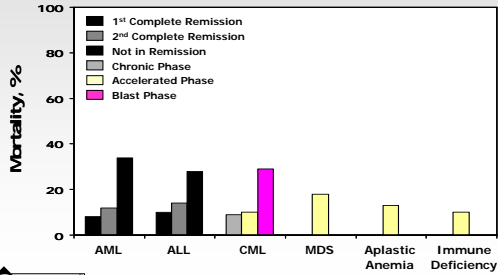
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## 100-day Mortality after HLA-identical Sibling Myeloablative Transplants, 2002-2003



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## Acute Leukemia section

States at Transplantation:

Unrelated

Primary Induction Failure (PIF)

Complete Remission (CR) -  1<sup>st</sup>  2<sup>nd</sup>  3<sup>rd</sup> or higher

Relapse

For Hematologic CR:

In bone

Cytogenetic remission

Molecular remission



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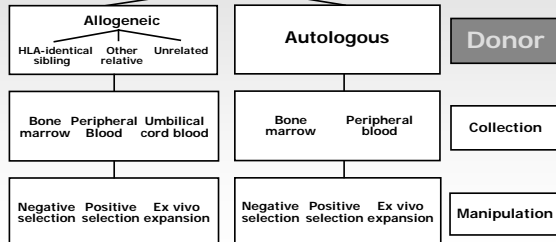
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## Hematopoietic Stem Cell Transplantation



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## Basics of HLA

- ◆ HLA = human leukocyte antigens
- ◆ Proteins on cell surfaces that are key players in immune response



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## HLA

- ◆ Class 1 = HLA- A, B, C
- ◆ Class 2 = HLA- DR, DP, DQ
- ◆ Differ in types of organisms they recognize and cells on which they are found



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## HLA Compatible Donor

- ◆ Varies among HSCT centers
- ◆ Varies among protocols
- ◆ Current acceptable donor
  - A, B – serologic match?
  - DRB1 – allele match



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## Antigen vs Allele

- ♦ Antigen = protein on surface of cells (serology)
- ♦ Allele = gene (DNA)



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## What is a "Match" ?

P:	A1, , DR1 B7, B8, DR3	A*0101, A*0201, DRB1*0101 B*0702, B*0801, DRB1*0301
D:	A1, , DR1 B7, B8, DR3	A*0101, A*0301, DRB1*0101 B*0702, B*0803, DRB1*0304
Serology	DNA-Based	



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## Pre-TED Donor Type

**Donor Type:**

Autologous (self)     Multiple donors (check all that apply)

**Allogeneic:**

Syngeneic (monozygotic twin)

HLA-identical sibling (not monozygotic twin)

HLA-matched other relative

HLA-mismatched relative/haploidentical

Degree of allele mismatch:	Allele	Match	Mismatch	Not done
	HLA-A	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	HLA-B	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	HLA-C	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	HLA-DR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

HLA-matched unrelated donor (MUD)

Registry, specify:

\_\_\_\_\_ Other, specify: \_\_\_\_\_

\_\_\_\_\_ Other, specify: \_\_\_\_\_

HLA-mismatched unrelated donor



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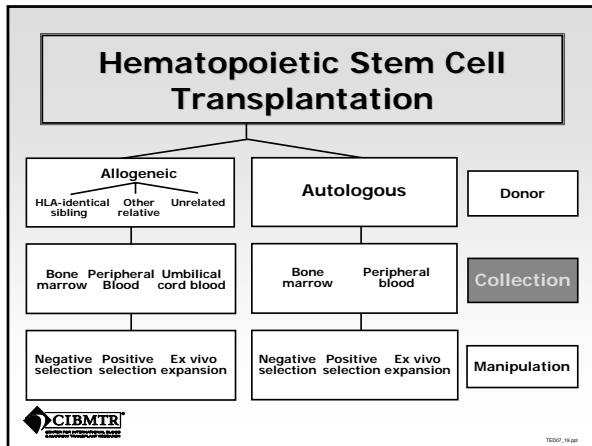
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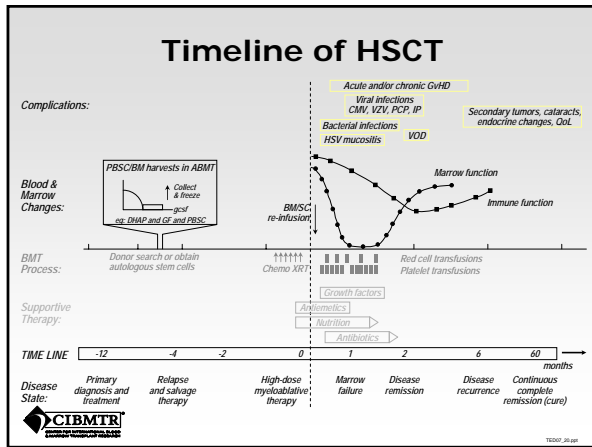
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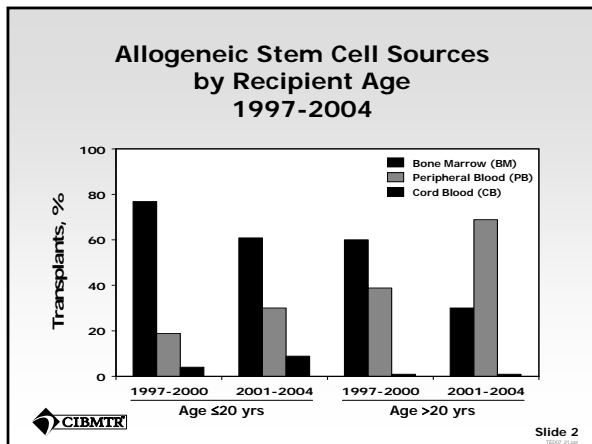
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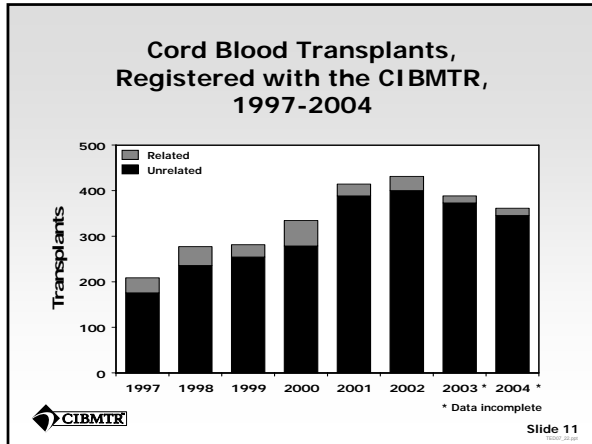
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### Cell Source section

Cell source for this HSCT (check all that apply):

Bone marrow     Peripheral blood     Cord blood

Other: \_\_\_\_\_

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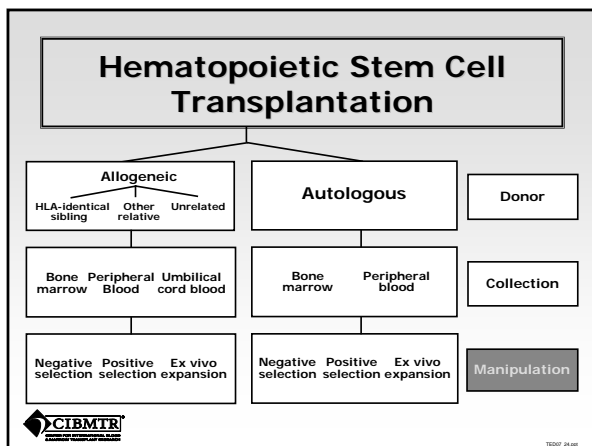
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## Pre-TED Graft Manipulation

Was there Ex vivo Graft Manipulation other than for RBC removal or volume reduction?  Yes  No  
 (Check all that apply) Optional for non-U.S. Centers

- T-cell depletion
- Tumor purging
- Other negative selection, specify: \_\_\_\_\_
- CD34 selection
- ex vivo expansion
- Other, specify: \_\_\_\_\_



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## Most Commonly Used Preparative Regimen Agents

	HLA-ident sib BMT-malignancy	Unrelated Donor BMT-malignancy	Auto-HSCT Lymphoma
TBI	52%	85%	25%
Cytoxan	87%	91%	85%
Busulfan	48%	17%	10%
Etoposide	24%	19%	73%
Ara-C	5%	10%	25%
Thiotepa	4%	14%	8%
Platinum*	<1%	<1%	7%
Nitrosourea**	1%	<1%	53%



\* cis-Platinum / carboplatin \*\* BCNU / CCNU

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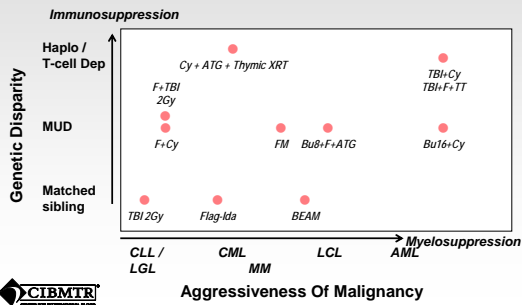
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## A Continuum of Non-myeloablative/Reduced Intensity Prep Regimens



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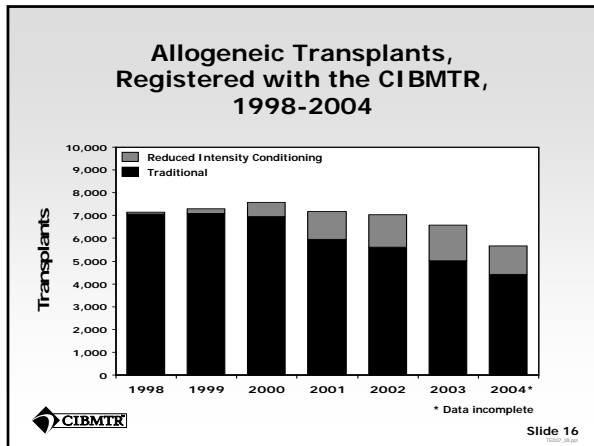
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### Pre-TED Preparative Regimen

(For all transplants) Donor Sex:  Male  Female

Pretransplant Conditioning:  Yes  No

Agents to be used for conditioning (check all that apply):

- None
- Total Body Irradiation (TBI)
- Total Lymphoid/Nodeal Radiation
- Other radiation, specify: \_\_\_\_\_
- ALL/ALKALOID(S)
- Anthracycline
- Bleomycin
- Busulfan  Oral  IV
- Carboplatin
- Cisplatin
- Contraceptives
- Cyclophosphamide
- Cytarabine (Ara-C)
- Etoposide (E-10)
- Flutamide
- Gleevec (STG71, imatinib mesylate)
- Hydroxyurea
- Ifosfamide
- Melphalan (L-PM)
- Mitoxantrone
- Monoclonal antibody, specify: \_\_\_\_\_
- Radioiodinated monoclonal antibody, specify: \_\_\_\_\_
- Nitrosourea (BCNU, CCNU)
- Paclitaxel (Taxol)
- Teniposide (VM26)
- Thiopurine
- Other drug, specify: \_\_\_\_\_

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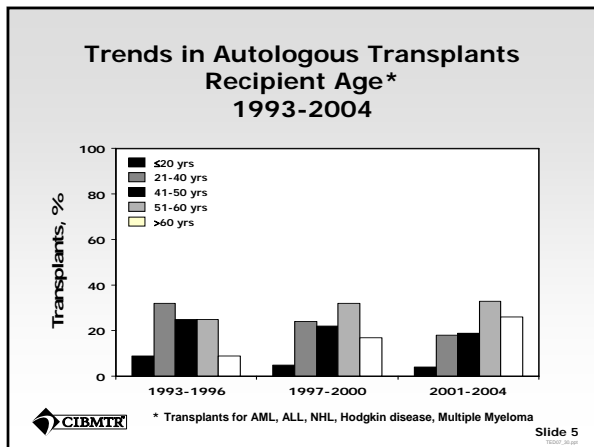
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## Enhance/Monitor Recovery

- ◆ Administer growth factors
  - G-CSF, GM-CSF
- ◆ Monitor hematopoietic recovery
  - Cell number and type (granulocytes, platelets, etc.)
  - Marrow cellularity
  - Chimerism (X/Y, VNTR, HLA)



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## ANC recovery (not engraftment)

- ◆ Report first of three consecutive days of ANC greater than 500
- ◆ Usually not before 8-10 days for myeloablative HSCT
- ◆ May never become neutropenic for reduced-intensity



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## Post-TED ANC Recovery

AFTER HSCT

Initial ANC recovery (Neutrophils  $\geq 0.5 \times 10^9/L$ )?

Yes, date Neutrophils  $\geq 0.5 \times 10^9/L$ :    YY YY    MM    DD

No, date of last assessment:    YY YY    MM    DD

Never below     Previously reported     Unknown

Did graft failure occur?     Yes     No



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## Complications

- ◆ Graft rejection
- ◆ Graft vs host disease
- ◆ Relapse of disease
- ◆ Infection
- ◆ Regimen-related toxicity



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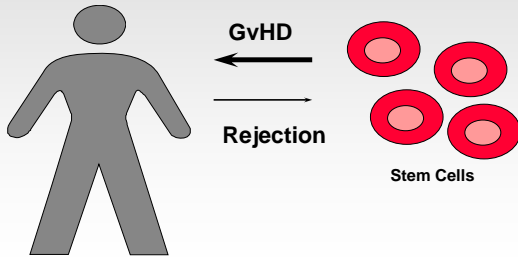
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## Graft vs Host Disease/Graft Rejection

HLA differences stimulate detrimental immune responses



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## Factors Influencing Risk Of GVHD

- |                            |                                  |
|----------------------------|----------------------------------|
| <b>Donor/Graft-related</b> | <b>Recipient-related</b>         |
| ◆ HLA-disparity            | ◆ Older age                      |
| ◆ Female → Male            | ◆ Prior viral infection/exposure |
| ◆ Parity                   | ◆ Other microbial infection      |
| ◆ Older age                |                                  |
| ◆ T-cell dose              |                                  |
| ◆ AGVHD (for CGVHD)        |                                  |

- Treatment-related**
- ◆ Conditioning regimen
  - ◆ Inadequate immune suppression



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### Acute GVHD Glucksberg Staging (organs) Criteria

Stage	Skin	Liver (Bilirubin)	Intestinal tract* (Diarrhea)
Stage 0	No rash	<2.0 mg/dL or <35 mmol/L	None or <500 ml/day or <280 ml/m <sup>2</sup> /day
Stage 1	Maculopapular rash, <25% of body surface	2.0-3.0 mg/dL or 35-52 mmol/L	>500 but <1000 ml/day or 280-555 ml/m <sup>2</sup> /day
Stage 2	Maculopapular rash, 25-50% of body surface	3.1-6.0 mg/dL or 53-103 mmol/L	>1000 but <1500 ml/day or 556-833 ml/m <sup>2</sup> /day
Stage 3	Generalized erythroderma	6.1-15.0 mg/dL or 104-236 mmol/L	>1500 ml/day or >833 ml/m <sup>2</sup> /day
Stage 4	Generalized erythroderma with bullae formation and desquamation	>15.0 mg/dL or >356 mmol/L	Severe abdominal pain, with or without ileus

\* use ml/day for adult patients and ml/m<sup>2</sup>/day for pediatric patients



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### Overall Grade

- Grade I Stage 1 to 2 skin rash; no gut involvement; no liver involvement; no decrease in clinical performance
- Grade II Stage 1 to 3 skin rash; Stage 1 gut involvement or liver involvement (or both); mild decrease in clinical performance
- Grade III Stage 2 to 3 rash; Stage 2 to 3 gut involvement or Stage 2 to 4 liver involvement (or both); marked decrease in clinical performance
- Grade IV Similar to Grade II with Stage 2 to 4 organ involvement and extreme decrease in clinical performance

Thomas ED - *N Engl J Med* - 1975 Apr 24; 292(17):895-902



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### Chronic GVHD

- ◆ Poorly understood late manifestation
  - Both alloimmune and autoimmune features
  - In part a failure of thymus function
- ◆ Incidence
  - ~1/3 of matched sibs
  - 60-70% of matched unrelated
  - Higher with mismatched
- ◆ Risk factors
  - HLA disparity, patient age, prior aGvHD, graft source



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## Chronic GVHD Classification (old but it's what we've got)

- ◆ Limited
  - Either or both
    - Localized skin involvement
    - Hepatic dysfunction due to cGVHD



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## Chronic GVHD Classification continued

- ◆ Extensive
  - Generalized skin involvement, or
  - Localized skin involvement and/or hepatic dysfunction due to chronic GvHD
  - OR
    - Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis, or
    - Eye involvement (Schirmer test <5mm wet), or
    - Involvement of minor salivary glands/oral mucosa
    - Involvement of any other organ



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## Manifestations Of Chronic GVHD (I)

Organ System	Definite manifestations of Chronic GVHD	Possible manifestations of Chronic GVHD
Skin	Scleroderma (superficial or fasciitis), lichen planus, vitiligo, scarring alopecia, hyperkeratosis pilaris, contractures from skin immobility, nail bed dysplasia	Eczematoid rash, dry skin, maculopapular rash, hyperpigmentation, hair loss
Mucous membranes	Lichen planus, non-infectious ulcers, corneal erosions/non-infectious conjunctivitis	Xerostomia, keratoconjunctivitis sicca
GI tract	Esophageal strictures, steatorrhea	Anorexia, malabsorption, weight loss, diarrhea, abdominal pain
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubineamia



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## Manifestations Of Chronic GVHD (II)

Organ System	Definite manifestations of Chronic GVHD	Possible manifestations of Chronic GVHD
Liver	None	Elevation of alkaline phosphatase, transaminitis, cholangitis, hyperbilirubineamia
GU	Vaginal stricture, lichen planus	Non-infectious vaginitis, vaginal atrophy
Musculoskeletal/Serosa	Non-septic arthritis, myositis, myasthenia, polyserositis, contractures from joint immobilization	Arthralgia
Hematologic	None	Thrombocytopenia, eosinophilia, autoimmune cytopenias
Lung	Bronchiolitis obliterans	Bronchiolitis obliterans with organizing pneumonia, interstitial pneumonitis



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## Post-TED GVHD

**GVHD (Allo only)**

Maximum Grade of Acute Graft Versus Host Disease (GVHD):  0  I  II  III  IV  Unknown

Maximum extent of Chronic GVHD:  None  Limited  Extensive  Unknown

Date of diagnosis of chronic GVHD:  Continued from last report

\_\_\_\_ - \_\_\_\_ - \_\_\_\_



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## Evaluating Post-HSCT Disease Status

- ◆ Most frequent cause of treatment failure
- ◆ Vigilance may affect rapidity of diagnosis
- ◆ Method of detection really does matter



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## Method of Detection of Disease

- ◆ Molecular (most sensitive)
  - Blood or marrow
  - Bcr/abl, bcl-2
- ◆ Cytogenetic (mod. sensitive)
  - Blood or marrow
  - t(9:22), t(14:18)
- ◆ Hematologic (least sensitive)
  - Blood or marrow appearance



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## Post-TED Disease Assessment

Was a CR ever achieved in response to HSCT (including any therapy administered as of Day 0, not including any change in therapy in response to assessment)?

Recipient already in CR at start of preparative regimen (N/Ap)

Yes, post-HSCT CR achieved, date: \_\_\_\_\_

First CR date reported previously

No, never in CR from HSCT

Did the patient *first* experience a relapse or progression as detected by any of the following methods during this period (complete all questions)?

Done	Not Done	Method	Relapse or Progression detected?	
			Yes	No
<input type="checkbox"/>	<input type="checkbox"/>	Molecular*	<input type="checkbox"/>	<input type="checkbox"/>
		Date 1 <sup>st</sup> detected: _____	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Cytogenetic	<input type="checkbox"/>	<input type="checkbox"/>
		Date 1 <sup>st</sup> detected: _____	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>	Clinical/Hematologic	<input type="checkbox"/>	<input type="checkbox"/>
		Date 1 <sup>st</sup> detected: _____	<input type="checkbox"/>	<input type="checkbox"/>



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## Indications for DCI

- ◆ Relapse prophylaxis ("planned")
- ◆ Treatment of relapse: CML, AML
- ◆ Treatment of PTLD, EBV-Lym
- ◆ Treatment of GVHD
- ◆ Treatment of Viral Infections
- ◆ Chimerism
  - Stable or declining donor cells
- ◆ Other emerging indications



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## Post-TED DCI

**DONOR CELLULAR INFUSION (DCI)**  
*For HSCT Anniversary answer since last report*

Was DCI given?  No  Yes Total # in 26 days: \_\_\_\_\_

Date of first DCI: \_\_\_\_/\_\_\_\_/\_\_\_\_

Type of cell(s) (check all that apply):  
 Lymphocytes  Fibroblasts  Dendritic cells  
 Mesenchymal  Other, specify: \_\_\_\_\_

Indication:  
 Planned  Chimerism  Stable/Mixed  
 Treat disease  Loss/Decreased  
 Treat PTLD, EBV-Lym  Other, specify: \_\_\_\_\_  
 Treat viral

Maximum Grade of Acute Graft Versus Host Disease (GVHD):  0  I  II  III  IV  Unknown

If another DCI was received in this reporting period, disease status before next DCI:  CR  Not in CR  Not assessed



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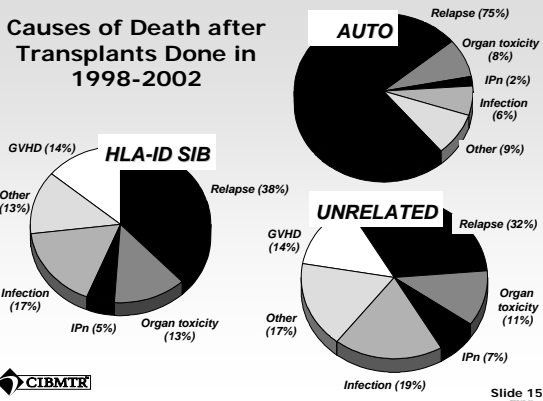
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## Causes of Death after Transplants Done in 1998-2002



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## Post-TED Survival

**SURVIVAL**

Survival status at latest follow-up:  
 Alive  Dead  LTF

Latest follow-up: \_\_\_\_/\_\_\_\_/\_\_\_\_ Last known date alive: \_\_\_\_/\_\_\_\_/\_\_\_\_  
 Date estimated

Main cause of death (check only one main cause):  
 Relapse/Progression/Persistent disease  
 HSCT related causes (check as many as appropriate):  
 GVHD  Pulmonary toxicity  
 Cardiac toxicity  Rejection/Poor graft function  
 Infection  VOD  
 Other: \_\_\_\_\_

New malignancy  
 Other: \_\_\_\_\_  
 Unknown



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## Late Complications of BMT

- ◆ Regimen-related toxicity
  - Cataracts
  - Neurologic
  - Gonadal
  - Endocrine
  - Growth & development
- ◆ Infection
- ◆ Chronic GVHD
- ◆ Relapse of malignancy/New-2<sup>nd</sup> cancers



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## Post-TED Second Cancer

**DID A NEW MALIGNANCY, LYMPHOBLASTIC OR MYELOPROLIFERATIVE DISORDER OCCUR?**  
Different from the disease for which HSCT performed (not recurrence or transformation).

Yes  No  Unknown, if yes:

Date of diagnosis: \_\_\_\_/\_\_\_\_/\_\_\_\_

Acute myeloid leukemia (AML, ANLL)

Other leukemia (including ALL), specify: \_\_\_\_\_

Breast cancer

Central nervous system (CNS) malignancy (glioblastoma, astrocytoma)

Clonal cytogenetic abnormality without leukemia or MDS

Gastrointestinal malignancy (colon, rectum, stomach, pancreas, intestine)

Genitourinary malignancy (kidney, bladder, ovary, testicle, genitalia, uterus, cervix)

Hodgkin disease

Lung cancer

Lymphoma or lymphoproliferative disease

Is the tumor EBV positive?  Yes  No  Unknown

Melanoma

Other skin malignancy (basal cell, squamous)

Myelodysplasia (MDS)/myeloproliferative (MPD) disorder

Oropharyngeal cancer (tongue, buccal mucosa)

Sarcoma

Thyroid cancer

Other malignancy, specify: \_\_\_\_\_

Copy of pathology report/documentation attached?  Yes  No



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## Factors Affecting HSCT Success

- ◆ Diagnosis and stage of disease
- ◆ Time from diagnosis to HSCT
- ◆ Quality of HLA match
- ◆ Ages of recipient/donor
- ◆ Prior CMV exposure
- ◆ Disease treatment
- ◆ HSCT protocol



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## Observational Database

**I**nformation on persons treated under ordinary circumstances, with treatments selected by the recipients, by clinical judgements of physicians, or by nature rather than by experimental design.



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