Hematopoietic Cell Transplantation for Marrow Failure: Options and Decisons

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Marrow Failure

- Acquired
  - Aplastic anemia
  - PNH
  - Myelodysplastic Syndrome
  - Marrow Fibrosis
  - Pure Red Cell Aplasia
  - Infiltrating/Metastatic Disease
  - other
- Congenital
  - Fanconi Anemia

How do we decide about treatment ?

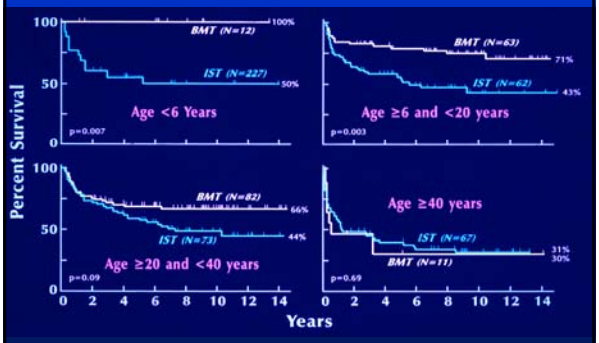
- How severe is the disease?
  - Duration
  - Prognosis
- Do we understand the disease mechanisms?
- What are the options?
  - Treatment Related Morbidity/Mortality
  - Donor Availability
- How old is the patient?
- Does the patient have other medical problems?
- Are there socio-economic issues?

Aplastic Anemia

- What is the mechanism of the disease ?
  - Immunologically mediated
  - Microenvironmental defect
  - Hematopoietic stem cell failure
    - Mutations (e.g.DKC)

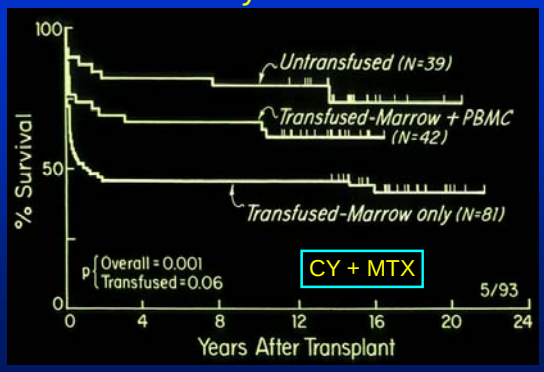
Related Donors

Immunosuppression or HCT ?



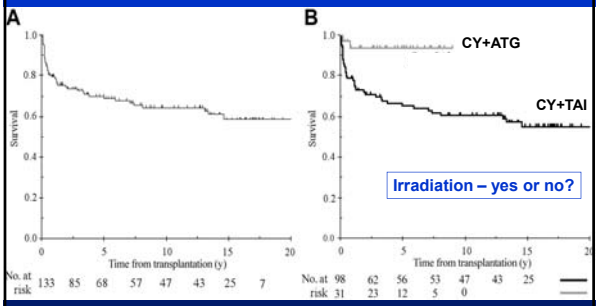
Doney et al, Ann.Int.Med.

Early Results



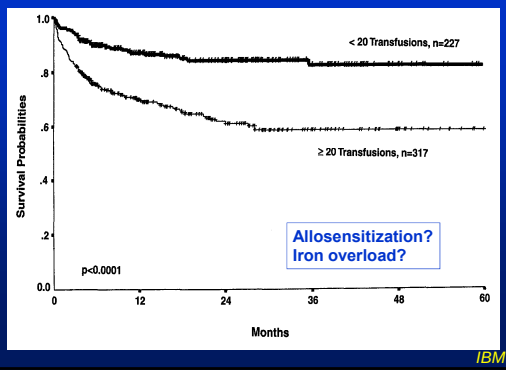
Blood 60: 524, 1982.

Effect of Conditioning Regimens



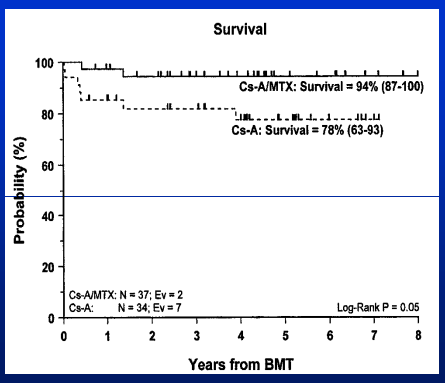
Ades, L. et al. Blood 2004;103:2490-2497

Effect of Pre-Transplant Transfusions

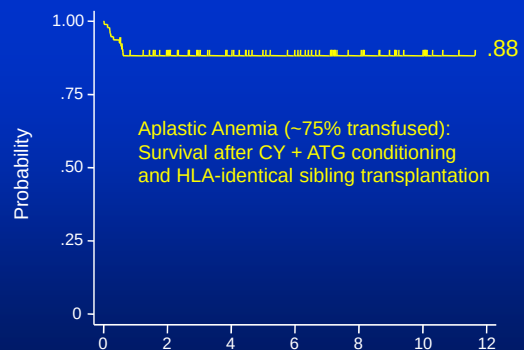


Allosensitization?
Iron overload?

IBMTR

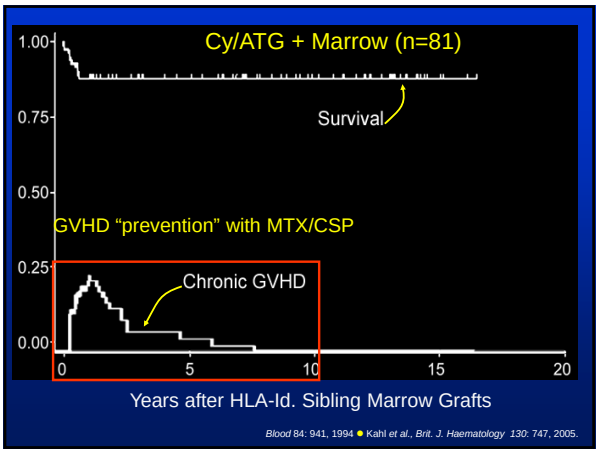


Locatelli, et al., 2000



Aplastic Anemia (~75% transfused):
Survival after CY + ATG conditioning
and HLA-identical sibling transplantation

Storb et al, BBMT

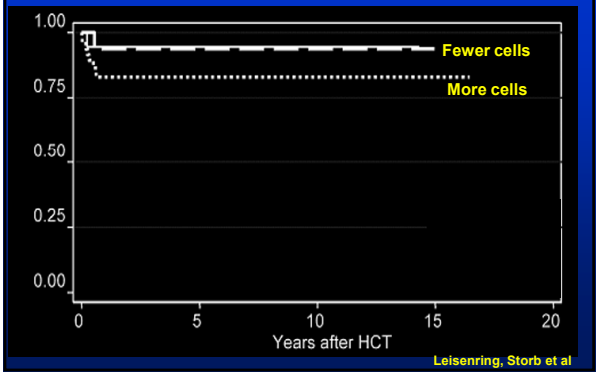


Would less be more?
Cell Dose and Chronic GVHD

Variable	n	Mean	S.D.	Quartiles Min	.25	Median	.75	Max
No chronic GVHD								
Cell dose	57	3.02	1.88	0.94	1.90	2.51	3.50	10.75
Chronic GVHD								
Cell dose	20	3.72	1.49	2.19	2.52	3.20	4.77	8.07

W. Leisenring et al

Marrow Cell Dose and Survival



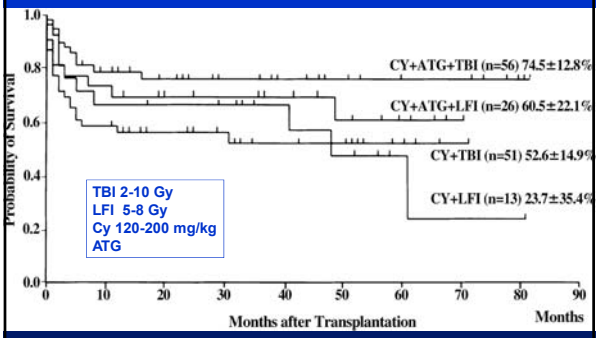
Leisenring, Storb et al

Current Protocol
(HLA Identical Siblings)

- Cyclophosphamide, 4 x 50 mg/kg
- ATG, 3 x 30 mg/kg
- *2.0 - 2.5 x 10^8 BM cells/kg*
- MTX + CSP
- Patients ≤ 65 ys

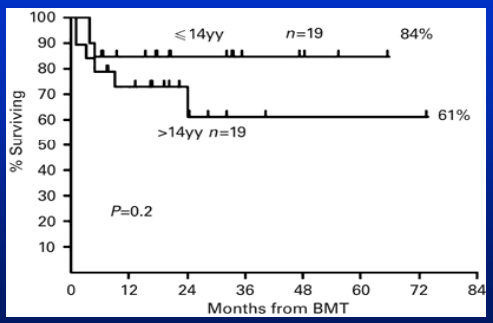
Unrelated Donors

CY + Irradiation ± ATG



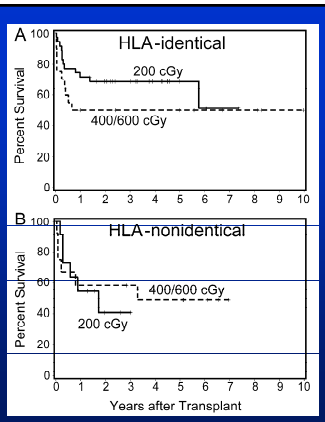
Kojima et al , Blood, 2002

Unrelated Transplants for AA (Flu+Cy+ATG)



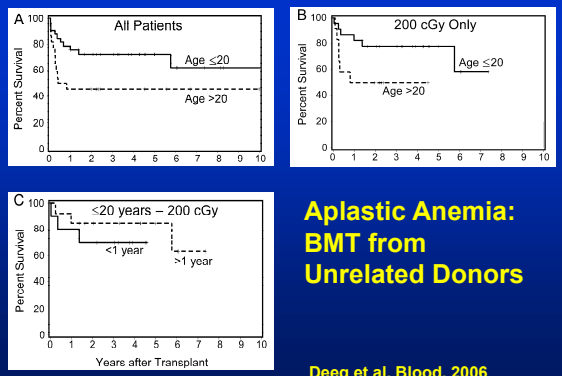
Bacigalupo et al, BMT, 36:947, 2005

Aplastic Anemia: Unrelated Donors



Deeg et al, Blood, 2006

Aplastic Anemia: BMT from Unrelated Donors



Deeg et al, Blood, 2006

Other Considerations

- Sex match versus mismatch
- Sensitization of the Donor
- CMV
- Other viruses ?
- Other sources of stem cells

Current CTN Trial for Unrelated Donor Transplants for AA

- Goal:
  Further reduce toxicity and GVHD
- Strategy:
  Maintain ATG and 200 cGy TBI
- Add Fludarabine (4x30)
  Stepwise decrease cyclophosphamide →

Anderlini et al

PNH

Transplantation for PNH at FHCRC

- Indications
  - Aplastic phase n=12
  - Hemolysis, thrombosis n=16

Transplant Characteristics

- Donors:
  - HLA-ID sibling 15
  - HLA non-identical related 4
  - Syngeneic 2
  - Unrelated 5
  - Cord blood 2
- Conditioning
  - TBI based (200-1350) 5
  - BU/CY +/- 16
  - CY +/- 5
  - None 2

Survival from Transplant

- Aplastic phase presentation
  - HLA-ID Sibling 7/7
  - Other donor 4/5

  } 11/12
- Hemolytic, thrombotic presentation
  - HLA-ID sibling 4/8
  - Other donor 5/8

  } 9/16

Transplantation for PNH (IBMTR)

• PNH	39
• PNH to AA	16
• AA to PNH	2
Total	57

Saso R Br. J. Haem. 104:392-396 (1999)

Transplantation for PNH (IBMTR)

- Conditioning Regimens
  - BUCY
  - CY TBI
  - CY LFI
  - CY
  - None

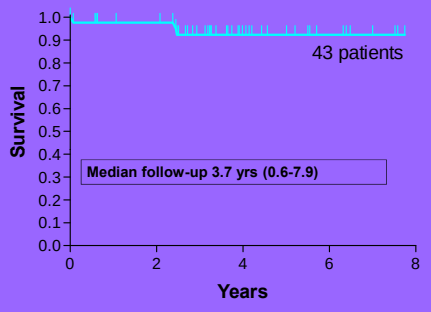
Transplantation for PNH (IBMTR)

Survival by Donor Type

- Donor Type
  - HLA-ID sib 48
  - Syngeneic 2
  - URD 6
  - Haploidentical 1
- Survival
  - 27 (at 2 yr)
  - 2 (8 and 12 yr)
  - 1 (5 yr)
  - 0

Fanconi Anemia

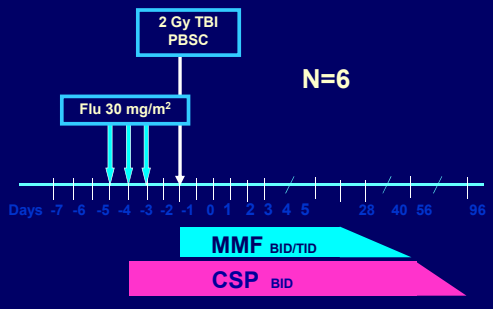
FA patients conditioned with CY 60 mg/kg - *HLA-identical siblings*



Bonfim et al, BBMT, 2007 ;13(12):1455-60.

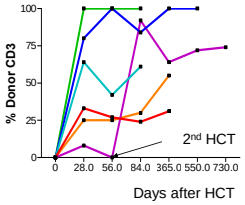
Transplantation for FA from *URD:*

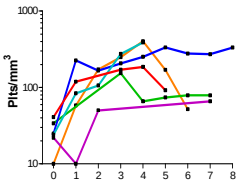
Low intensity conditioning



M.Thakar et a, unpubl.

Mixed chimerism is sufficient to restore hematopoiesis





Acute GVHD n=3 (grade II=2, III=1)
cGVHD n=3
TRM n=3 (cGVHD)

Thakar et al, unpublished

Summary

- HCT provides effective therapy and cure for patients with marrow failure from aplastic anemia and other causes
- The success rate has increased progressively in recent years with both related and unrelated donor transplants
- GVHD, particularly in its chronic form, remains a problem

Questions

- **Best time for transplantation?**
- **Best conditioning regimen?**
- **Should we use marrow peripheral blood "stem cells"?**
- **Do cord blood cells offer an advantage?**
- **Should patients with aplastic anemia for whom a donor is available, be given repeat courses of immunosuppression?**

Thank you!