Hematopoietic cell transplantation in bone marrow failures

Menachem Bitan, M.D., Ph.D.

Pediatric Blood and Marrow Transplantation & Immunotherapy Program
Department of Pediatric Hematology/Oncology
Danna-Dwek Children's Hospital
Tel-Aviv Sourasky Medical Center
Tel-Aviv, Israel

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Introduction

Regarding –

"How to build a transplant program":

- **Principles, not numbers.**
- **Compare bone marrow failure (BMF) to leukemia.**
- **Taking Fanconi's anemia as a leading example.**
- **Point-out a "Take-home message".**
- **In Africa the median age is younger –**
  - More children with children's problems.

Bone marrow failure

- Group of disorders that can be either inherited or acquired.

- Disorders of the hematopoietic stem cell that can involve either one cell line or all of the cell lines.

- Lymphocytes are usually spared.

- Most common of inherited (referred also as syndromes):
  Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Bodian Diamond syndrome, Amegakaryocytic thrombocytopenia, Severe congenital neutropenia.

- Most common of acquired is aplastic anemia.

- Other diseases with presentation that be mimic acquired are:
  myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria, and large granular lymphocytic leukemia.

Fanconi's anemia

- Inherited as an autosomal recessive or X-linked disease.
- Bone marrow failure with the need for allogeneic transplant.
- Non-malignant disease BUT with high susceptibility for cancer, with both hematological and solid tumors.
- Relatively specific physical findings in ~75% of affected persons including: Café au lait spots, short stature, abnormal thumbs, infertility, abnormal kidneys, etc.
- Laboratory findings include:
  - aplastic anemia
  - increased chromosome breakage in cells grown in the presence of a chemical which damages DNA.
  - mutations in genes responsible for the repair of DNA damage: 15 separate genes have been identified - known as "complementation groups". One of these genes (FANCD1) is the breast/ovarian susceptibility gene (BRCA2).

First transplant for fanconi – Prof. Gluckman

British Journal of Haematology, 1980, 45, 351–364

Bone Marrow Transplantation in Fanconi Anaemia

E. GLUCKMAN, A. DEVERGIE, C. SOLIMANDO, A. BUSSEL, B. BRAHIM, J. SOULIER* AND J. HERNIGOU

U.E.R. d'Hématologie, Institut de Recherches sur les Leucémies et les Maladies du Sang, Hôpital Saint-Louis, Paris, and *Service de Dermatologie (P. Degrange), Hôpital Saint-Louis, Paris

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Summary. Five patients with Fanconi anaemia have been treated by bone marrow transplantation from HLA identical donors. Only one patient survived for more than 3 years. She is now perfectly healthy with complete haematological reconstitution, with chimaerism and disposition of chromosomal abnormalities. In contrast, four patients died of acute severe GVHD soon after grafting. In addition, all had signs of severe cyclophosphamide toxicity. This evolution could be explained by a special sensitivity of FA cells to alkylating agents and may indicate the need to modify the conditioning regimen in FA patients.

Fanconi anaemia (FA) is an autosomal recessive inherited condition in which congenital malformations are associated with bone marrow failure. The most common abnormalities are skin pigmentation, microcephaly, short stature, skeletal defects particularly of the lateral aspect of the forearm and hand, kidney and cardiac malformations (Fanconi, 1967; Brand, 1976). Multiple abnormalities of peripheral blood lymphocyte chromosomes are almost always present. In its natural course the evolution of FA is always fatal, with death by progressive marrow aplasia (Brand, 1976) or less frequently by development of acute leukaemia (Passweg in Hill, 1977; Heath, 1976).

This article describes our experience of bone marrow transplantation (BMT) in five cases of FA. The unexpected problems we encountered could provide insight into the nature of the disease.

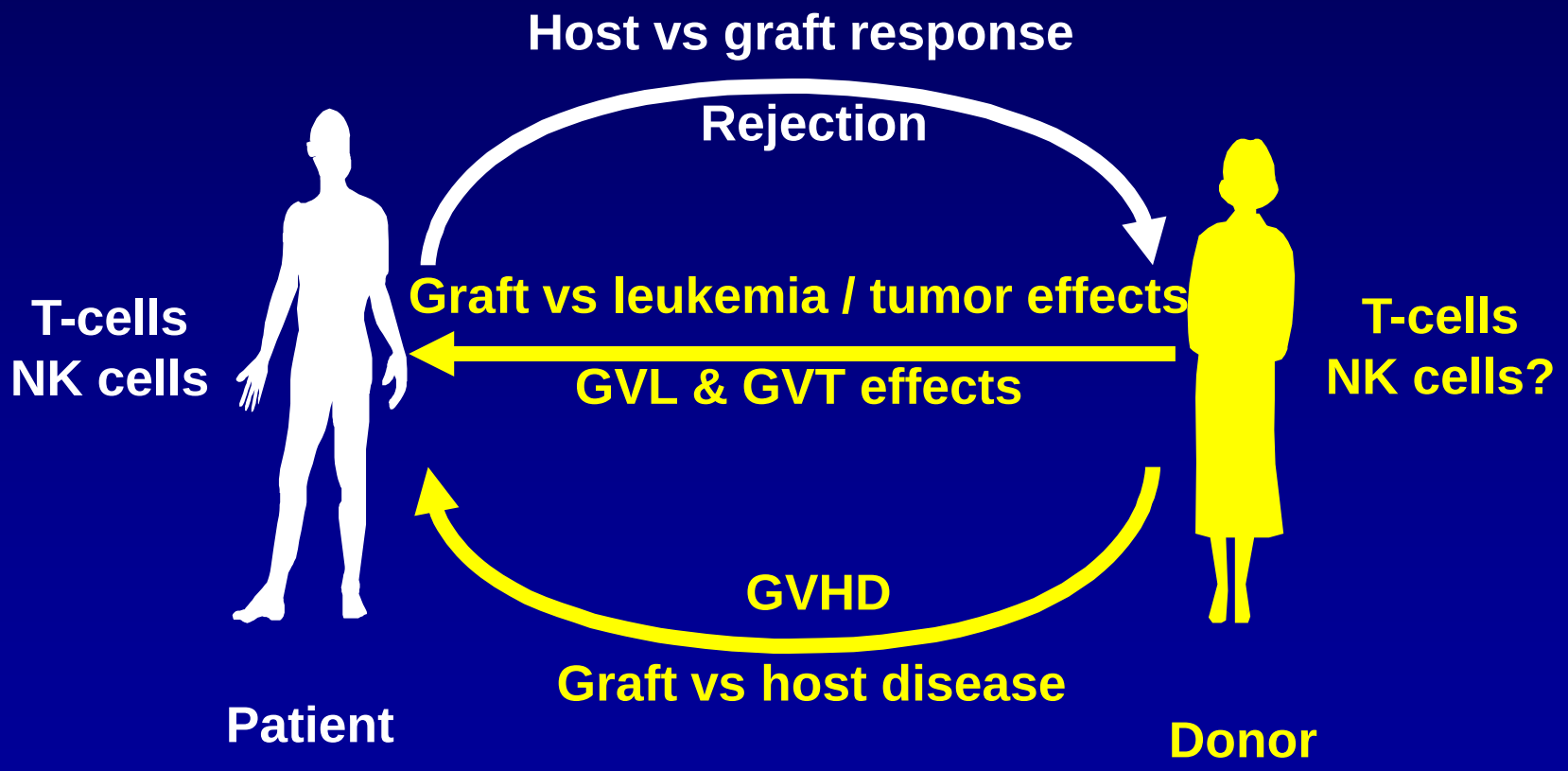
METHODS

All the patients were transplanted in the Hospital Saint-Louis Bone Marrow Transplant Unit. The technique of BMT has been described elsewhere (Thierry et al, 1975). Briefly, the patient were in reverse isolation rooms. They were decontaminated with chlorhexidine solution (in mouth and skin, with oral non-absorbable antibiotics (for gut. They received a sterile gluteal-free diet. Physicians and nurses wore sterile gowns, masks and gloves. On admission, a central venous catheter was inserted and used for all infusions (including i.v. hyperalimentation) and for the collection of blood samples for laboratory tests. Prophylactic oral cell and platelet transf-

Correspondence: Pr. Dr. E. Gluckman, Unité de Greffe de Moelle, Centre Hayem, Hôpital Saint-Louis, 1 place du Docteur A. Fournier, 75010 Paris, France.

Immunological pathways in allogeneic BMT

Obstacles and benefits




Malignancy
Non-malignancy

Pre-transplant

- conditioning regimens

Transplant

- graft composition

Post-transplant

- immuno-suppression/GVHD

Purpose of transplant

- **Restore function and prevent malignancy.**

- **Cures only the hematological problem of the syndrome.**

  In malignancy:

  Cure by means of chemotherapy and allogeneic effect.

What do we do with a BMF patient that already developed malignancy ?

Conditioning regiments

Myeloablative ⟷ **Reduced intensity**

Myeloablative ⟷ **Immunosuppression**

Caution regarding specific chemotherapy agents

- Lung fibrosis
- Immunosuppression

Leukemia (2013) **27**, 829–835

www.nature.com/leu

ORIGINAL ARTICLE

Secondary malignancies after allogeneic stem-cell transplantation in the era of reduced-intensity conditioning; the incidence is not reduced

A Shimoni[1], N Shem-Tov[1], A Chetrit[2], Y Volchek[1], E Tallis[1], A Avigdor[1], S Sadetzki[2], R Yerushalmi[1] and A Nagler[1]

Graft composition and matching

Do we need allogeneic effect?

Malignant dis. → **YES**

Non-malignant dis. → **NO**

Matching degree

- **Source of graft**
- **Degree of immunosuppression**
- **Transplant-related morbidity & mortality**

Post - Transplant

- Side effects -  blood 2005 105: 67-73 doi:10.1182/blood-2004-04-1652 originally published online August 26, 2004 gnancy but not
- No need for (Risk of head and neck squamous cell cancer and death in patients with Fanconi anemia who did and did not receive transplants Philip S. Rosenberg, Gerard Socié, Blanche P. Alter and Eliane Gluckman st GVHD.
- No need for 100% donor chimerism. Do need stable chimerism.
- Greater risk for rejection due to competent immune system at the beginning.

Development in concepts of transplant

1980's	Myeloablative, TBI, MSD.
1990's	RIC protocols, Fludarabine, MUD.
2000's	Less TBI, PGD.
2010's	Haplo., Gene therapy (?).

Summary

- Thirteen year old boy
- Presented with AML
- Received BFM full protocol
  - long duration to recovery
  - dysmorphic teeths
- Diagnosis of Dyskeratosis congenita
- Went into CR
- Relapse
- FLAG-Ida
  - recovery with blasts.

?

Thank you !

bjh research paper

Fludarabine-based cytoreductive regimen and T-cell-depleted grafts from alternative donors for the treatment of high-risk patients with Fanconi anaemia

Sonali Chaudhury,[1] Arleen D. Auerbach,[2] Nancy A. Kernan,[1] Trudy N. Small,[1] Susan E. Prockop,[1] Andromachi Scaradavou,[1] Glenn Heller,[3] Suzanne Wolden,[4] Richard J. O'Reilly[1] and Farid Boulad[1]

Summary

Eighteen consecutive patients aged 5·5–24 years with Fanconi anaemia and diagnoses of aplastic anaemia ($n = 8$), myelodysplastic syndrome ($n = 4$), acute myeloid leukaemia ($n = 6$), received allogeneic haematopoietic stem cell transplants from alternative donors. All patients had been transfused, 13

British Journal of Haematology 2000, **109**, 121–129

Haematopoietic cell transplantation in patients with Fanconi anaemia using alternate donors: results of a total body irradiation dose escalation trial

M. L. MacMillan, A. D. Auerbach, S. M. Davies, T. E. DeFor, A. Gillio, R. Giller, R. Harris, M. Cairo, K. Dusenbery, B. Hirsch, N. K. C. Ramsay, D. J. Weisdorf and J. E. Wagner *Departments of Paediatrics, Medicine, Biostatistics, Therapeutic Radiology, Laboratory Medicine and Pathology, Blood and Marrow Transplant Program, University of Minnesota, Minneapolis, MN, USA, Laboratory of Human Genetics and Hematology, The Rockefeller University, New York, NY, USA, Hackensack University Medical Center, Hackensack, NJ, USA, University of Colorado, Denver, CO, USA, Children's Hospital Medical Center, Cincinnati, OH, USA, and Children's Hospital of Orange County, Orange County, CA, USA*

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blood 2001 97: 2957-2961
doi:10.1182/blood.V97.10.2957

Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leukocyte antigen–matched unrelated donor bone marrow: results of a matched-pair analysis

Juliet N. Barker, Stella M. Davies, Todd DeFor, Norma K. C. Ramsay, Daniel J. Weisdorf and John E. Wagner

blood 2004 103: 1147-1151
doi:10.1182/blood-2003-02-0587 originally published online September 22, 2003

Successful hematopoietic stem cell transplantation for Fanconi anemia from an unaffected HLA-genotype–identical sibling selected using preimplantation genetic diagnosis

Satkiran S. Grewal, Jeffrey P. Kahn, Margaret L. MacMillan, Norma K. C. Ramsay and John E. Wagner

Biology of Blood and Marrow Transplantation 12:712-718 (2006)

1083-8791/06/1207-0003$32.00/0
doi:10.1016/j.bbmt.2006.03.002

Fludarabine-Based Reduced Intensity Conditioning for Stem Cell Transplantation of Fanconi Anemia Patients from Fully Matched Related and Unrelated Donors

M. Bitan,[1] R. Or,[1] M. Y. Shapira,[1] M. Aker,[2] I. B. Resnick,[1] A. Ackerstein,[1] S. Samuel,[1] S. Elad,[1] S. Slavin[1]

Pediatr Blood Cancer 2006;46:630–636

Successful Engraftment Without Radiation After Fludarabine-Based Regimen in Fanconi Anemia Patients Undergoing Genotypically Identical Donor Hematopoietic Cell Transplantation

Poh-Lin Tan, MBBS,[1] John E. Wagner, MD,[1] Arleen D. Auerbach, MD,[2] Todd E. DeFor, MS,[1,3] Arne Slungaard, MD,[4] and Margaret L. MacMillan, MD[1]*

Biol Blood Marrow Transplant 20 (2014) 571–576

HLA-Haploidentical T Cell–Depleted Allogeneic Hematopoietic Stem Cell Transplantation in Children with Fanconi Anemia

Marco Zecca [1], Luisa Strocchio [1], Daria Pagliara [2], Patrizia Comoli [1], Alice Bertaina [2], Giovanna Giorgiani [1], Cesare Perotti [3], Franco Corbella [4], Letizia Brescia [2], Franco Locatelli [2,5,*]

[1] *Oncoematologia Pediatrica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[2] *Dipartimento di Oncoematologia Pediatrica, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy*
[3] *Servizio di Immunoematologia e Medicina Trasfusionale, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[4] *Struttura Complessa di Radioterapia Oncologica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[5] *Department of Pediatric Science, Università degli Studi di Pavia, Italy*

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DOI: 10.3109/08880018.2012.708708

informa
healthcare

HEMATOLOGY/TRANSPLANT

Cyclophosphamide-Based In Vivo T-Cell Depletion for HLA-Haploidentical Transplantation in Fanconi Anemia

M.S. Thakar,[1] C. Bonfim,[2] B.M. Sandmaier,[3] P. O'Donnell,[3] L. Ribeiro,[2] T. Gooley,[3] H.J. Deeg,[3] M.E. Flowers,[3] R. Pasquini,[2] R. Storb,[3] A.E. Woolfrey,[3] and H.P. Kiem[3]

Stem Cell Gene Therapy for Fanconi Anemia: Report from the 1st International Fanconi Anemia Gene Therapy Working Group Meeting

Jakub Tolar[1], Jennifer E Adair[2], Michael Antoniou[3], Cynthia C Bartholomae[4], Pamela S Becker[5], Bruce R Blazar[1], Juan Bueren[6], Thomas Carroll[7], Marina Cavazzana-Calvo[8], D Wade Clapp[9], Robert Dalgleish[10], Anne Galy[11], H Bobby Gaspar[12,13], Helmut Hanenberg[14,15], Christof Von Kalle[4], Hans-Peter Kiem[2,5], Dirk Lindeman[15,16], Luigi Naldini[17], Susana Navarro[6], Raffaele Renella[18], Paula Rio[6], Julián Sevilla[6,19], Manfred Schmidt[4], Els Verhoeyen[20], John E Wagner[1], David A Williams[18] and Adrian J Thrasher[12,13]

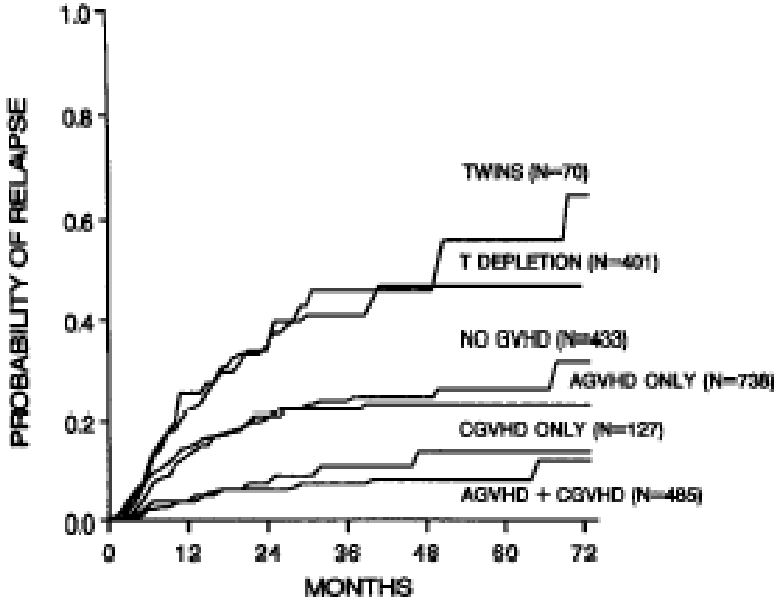
- compare to Tx for malignancies
- % of allo-SCT from total. Europe/USA, Peds/Adults

- purposes of allogeneic SCT – restore function and prevent malignancy.
- cures only the hematological problem of the syndrome.
- in malignancy – destroy malignant cells by means of allogeneic effect (GVL/GVT/GVM)
- side effects – price to pay may be agreed for that (GVHD)
- no need for GVL ---> aggressive treatment against GVHD.
- no need for 100% donor chimerism. Do need stable chimerism.
- greater risk for rejection due to competent immune system at the beginning.
- conflict with the need to give RIC because of syndrome-derived susceptibility.
- Fanconi anemia as an example.
- graph of immune system along the Tx course.

concept

Historically: As autologous → "chemo can cure cancer"

Relapse rates post allo-SCT:



MM Horowitz, et al. **Graft-versus-leukemia reactions after bone marrow Transplantation**. Blood, Feb 1990; 75: 555 - 562.

- **Same conditioning regimen**
- **Same patient disease**
- **Same status of disease**
- **Same donor origin**
- **Same source of graft**

Demonstrated Different eradication capabilities

“The allogeneic effect”