Fragility in Fanconi Anemia

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No Financial Disclosure

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Objectives

- Relate the clinical features of Fanconi Anemia (FA) patients to unique pharmacotherapy strategies to optimize outcomes
- Outline the recommendations for the optimal time to proceed to hematopoietic cell transplant (HCT)
- Describe the progression of treatment options to current day strategies in the setting of HCT
- Explain the importance of an inter-disciplinary team for long term follow up care.

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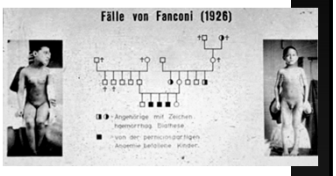
Dr. Guido Fanconi



- 1927 – first described
  - 3 siblings with bone marrow failure and congenital anomalies between ages of 5 – 7.
- 1964 – published hypothesis as cause by chromosomal translocations
  - 1960's – No translocation found but several research groups showed **chromosomal instability**

Lopitz S, et al. Nature. 2006;893-898

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Fanconi Anemia

- Most frequent inherited bone marrow failure syndrome – >2000 cases reported in total
  - Incidence: 1:100,000 to 1:200,000
  - Carrier: 1:181
- Primarily autosomal recessive
  - Except for the very rare X linked FANCB
- Peak diagnosis around 7 years of age
  - Range: in utero to > 50 years
- Death:
  - 1980-90's: median 19 years
  - 2000 – median 30 years

Shimamura A, et al. Blood Rev 2010;24:101-22

Phenotype Extremely Variable

1982 – Dr. Glanz and Dr. Fraser compared probands

TABLE *Characteristics in Fanconi anaemia in probands and non-probands.*

	Present in probands (%) (n = 94)	Non-probands (%) (n = 44)
Growth retardation	77	48*
Skin hyperpigmentation	73	57†
Combined radial ray deformities	66	39†
Radial ray reduction	55	36†
Hypogenitalia	51	18†
Malformed thumb	39	27
Microcephaly	37	25
Renal malformation	32	23
Mental retardation	29	20
Cardiac murmur	29	16
Absent thumb	22	13
Supernumerary thumb	16	5†
Microphthalmia	14	7
Hypoplastic/absent radius	13	9
Hearing loss	13	5
Hypospadias	11	4
Ear malformation	11	11
Congenital hip dislocation	9	5
Cryptorchidism	7	19
Male	59	63
No malformations	—	25

*$p<0.001$ using χ^2 test.
†$p<0.05$.

- The range and frequency of the various associated anomalies are diverse
- 25% of affected sibs had no dysmorphic features.
- No one feature is exclusive to FA
- FA diagnosis by chromosomal breakage should be confirmed even in the absence of clinical features

Glanz A, et al. Journal of Medical Genetics. 1992; 19:412-416

Clinical Features of FA

- Endocrine
- Skin
- Renal
- Skeletal
- Cardiac
- Ocular
- Auditory
- GI
- Reproductive malformations

Important to Remember:
Approximately 1 out of 3 patients will have no clinical features!

Endocrine Risks – 80%

- Growth hormone -40%
  - short stature
  - In-utero growth retardation
- Hypothyroidism
- Abnormal glucose/insulin metabolism
- Obesity
- Dyslipidemia
- Decreased fertility

Special Considerations:

Monitor Glucoses closely

Petite stature

< 10 kg – convert chemotherapy dosing

Monitor metabolic risks long-term

Counsel on fertility & pregnancy risks

Shimamura A, et al. Blood Rev 2010;24:101-22

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Skin – 71%

Café-au-lait spots

Hyperpigmentation

Hypopigmentation

Special Considerations:

Very High risk for secondary malignancy for squamous cell carcinoma

Counsel to use sunscreen

Avoid exposure to sun

Avoid voriconazole

Wagner et al. Hematopoietic Cell Transplantation for Fanconi's Anemia. In: Thomas' Hematopoietic Cell Transplantation; Fourth Edition 2009: chapter 79.

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Renal – 57%

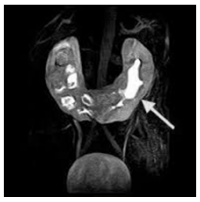
Ectopic kidney

Pelvic kidney

Horseshoe kidney

Hypoplastic kidney

Hydronephrosis



Special Considerations:

Nuclear Medicine GFR

Avoid nephrotoxins when possible

Continuous CSA infusions

Renal Dosing Adjustments

Wagner et al. Hematopoietic Cell Transplantation for Fanconi's Anemia. In: Thomas' Hematopoietic Cell Transplantation; Fourth Edition 2009: chapter 79.

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Skeletal – 50%

- Upper Limbs – 60%
  - Thumb abnormalities
  - Radial ray defects
  - Hypoplastic thenar eminence
  - Dysplastic ulna
- Lower Limbs
- Microcephaly
- Micrognathia
- Triangular face

Wagner et al. Hematopoietic Cell Transplantation for Fanconi's Anemia. In: Thomas' Hematopoietic Cell Transplantation; Fourth Edition 2009: chapter 79.

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Others:

Deafness /Ear deformity 11%
GI anomalies – 7%
Eyes/Vision – 20%
  small /close set eyes
  strabismus
  cataracts
Gonades
  Males: 25%
  Females: 2%

Genitalia:
Males: 50%
Females: 2%
  Important with education regarding fertility

Important to Remember: Approximately 1 out of 3 patients will have none!

Wagner et al. Hematopoietic Cell Transplantation for Fanconi's Anemia. In: Thomas' Hematopoietic Cell Transplantation; Fourth Edition 2009: chapter 79.

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Others:

•Cardiac Risks – 6%
- Various Congenital Heart Defects
- Cardiology Consult
  - Antihypertensive Agents of Choice

•Other considerations:
- Iron overload from past transfusions
- Discontinue androgen therapy & thorough evaluation for liver adenomas
- ID consult for extensive evaluation
  - Prophylaxis with anti mold agent

Wagner et al. Hematopoietic Cell Transplantation for Fanconi's Anemia. In: Thomas' Hematopoietic Cell Transplantation; Fourth Edition 2009: chapter 79.

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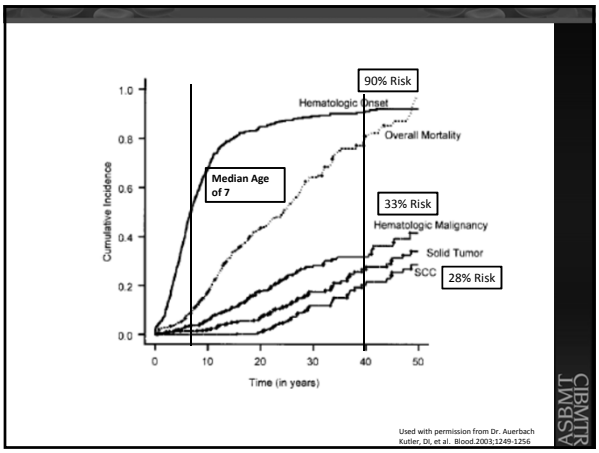

Used with permission from Dr. Auerbach
Kutler, DI, et al.. Blood.2003;1249-1256

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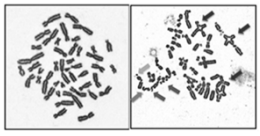
Diagnosis

Confirm Chromosomal Breakage



Culture peripheral blood, bone marrow, skin fibroblasts & fetal cells with a DNA crosslinking agent

- Diepoxybutane (DEB)
- Mitomycin C (MMC)

- Cytogenetic lab will count number of DNA breakages
- Very sensitive!

Zeirhut, et al. J Genet Counsel. 2014; 910-921

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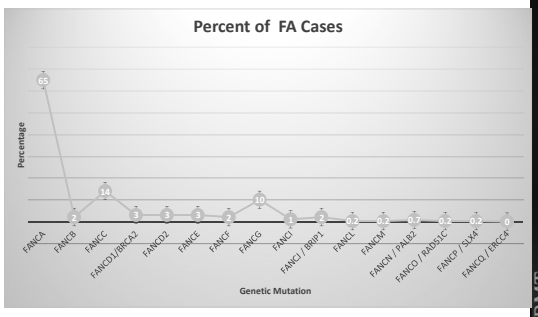
Known FA Genes



Adapted from Zeirhut, et al. J Genet Counsel. 2014; 910-921

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BRCA2/FANCD1 Biallelic Mutations

- 97% risk of developing a malignancy by 5.2 years
  - solid tumor
    - Wilm's Tumor, medulloblastoma, retinoblastoma & even reports of neuroblastoma
    - Rare in FA except with BRCA2/FANCD1 mutations
      - 26 years median age for general FA population
      - 60 years median age for general population
  - leukemia – AML, MDS, unique T-Cell lineage
- Much less risk for bone marrow failure & MDS
- Concern for FA diagnosis in a very young child with solid tumor diagnosis

Malric, et al. Pediatri Blood Cancer. 2014;9999:1-8.
Alter, et al. J. Med. Genet. 2007;44:1-9

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ARS Questions

SK is a 9-year-old girl who was recently diagnosed with Fanconi Anemia by confirmation of DEB testing. Genetic testing revealed FANCA mutation. SK meets indications for HCT. Which of the following are important to consider in her pre transplant pharmacy evaluation?

a. Nuclear Medicine GFR
b. Infectious Disease History
c. Weight
d. All of the above

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Importance of Genetic Testing

- May help identify risk for developing bone marrow failure
- May predict cancer risks
- May identify lymphocyte mosaicism
- Reproductive planning
- Family Member Counseling
  - All siblings should be tested
- Research

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Treatments Options for FA

- Supportive Care:
  - Androgens – Usually avoided for risk of SE
  - Prednisone - no proven benefits
  - Growth Factors for supportive care
  - Antioxidants
  - Treat complications
- HCT – only cure to date for hematologic issues

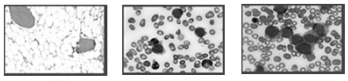
Guardiola, et al. Blood. 2000;422-420

Recommendations for Time to Transplant

Individualized timing based on patient progression to bone marrow failure

- Standard Risk usually considered:
  - Hgb < 8 g/dL
  - ANC < 500/uL
  - Plt < 20,000/uL

- Monitor CBC q3months & Annual BM biopsy
- Indications for HCT are consistent regardless of the donor source



MacMillan et al. British Journal of Hematology. 2010; 14-21

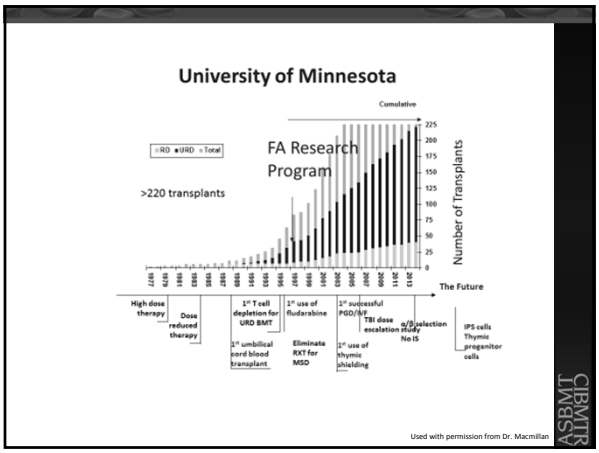
ARS #2

Prior to your evaluation with SK and her family, you review lab results.

Hgb: 7 g/dL ANC : 400/uL Plt: 12,000/uL
Bone marrow results suggest aplastic anemia

True or False:

SK meets criteria for transplant only because she has a matched sibling donor.



What does a pharmacist need to know?

1. Understand the risks associated with clinical features of FA
   - Renal
   - Endocrine
2. DNA Repair Defect
   - Chemotherapy sensitivity
   - Radiation sensitivity
3. HCT issues for FA
   - Graft Failure
   - GVHD
   - Long Term Risks

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Why is dosing of Cy so important?

•First 5 transplants in FA children:
- Excessive regimen related toxicity (RRT) with signs of severe cyclophosphamide toxicity
- Severe Acute GVHD (aGVHD)
- Poor Survival with 1 survival after 3 years
- In vitro lab studies confirmed hypersensitivity to Cy

•Gluckman et al proposed dose reduction
- 200 mg/kg to 20 mg/kg + TAI 500 cGy
- Favorable outcomes in 8 patients transplanted
- No deaths after 330 days post HCT

Gluckman, et al. British Journal of Hematology. 1980 ; 557-564 Berger et al.British Journal of Haematology. 1980: 565-568
Auerbach, et al. Cancer Genetics and Cytogenetics. 1983; 25-36. Gluckman et al. British Journal of Haematology. 1983; 431-44

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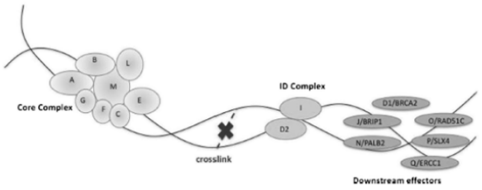
Why the peculiar sensitivity to FA Cells?

FA Proteins Repair DNA!



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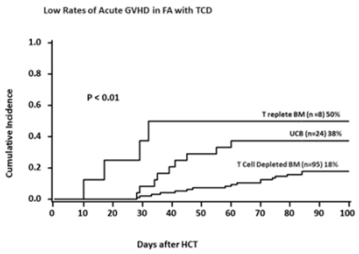
T Cell Depletion



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HLA identical sibling donor HCT with Radiation

	Regimen	GVHD px	# of Cases	Median recipient age	Sustained Engraftment	Acute GVHD	Outcome
Dufour et al. 2001	Cy 20 /kg TAI 5-6 Gy (12) Cy 20-80 mg/kg TBI 3-6 Gy (10) Cy 100-200 /kg (5)	CSA CSA+MTX MTX	27	9 years	23/25	2/25	81% alive at 3 yrs
Farzin et al. 2007	Cy 20 /kg TAI 4 Gy	CSA+MP+ATG	30	7.6 years	27/30	2/30	90% alive at 10 years

Adapted from Macmillan et al. British Journal of Haematology. 2010;14-21
Dufour et al. British Journal of Haematology. 2001; 796-805
Farzin et al. British Journal of Haematology. 2007; 633-640

HLA identical sibling donor HCT without Radiation

	Conditioning	# of cases	Engrafted	Outcome (range)
Ebell 2002	Flu 75-180/m2 + ATG + OKT3	7	5	5/7 alive
Tan et al. 2006	Flu 125 /m2 + Cy 20 /kg + ATG	11	10	100% alive at 2 years
Torjemane et al. 2006	Cy 40 /kg + Bu 6 /kg +/- ALG	17	14	72% alive (median 16 mos)
Ayas et al. 2008	Cy 60 mg/kg + ATG	34	34	33 alive (median 33.7 mos)
Ertem et al 2009	Bu 6 mg/kg + Cy 40/kg or Flu 150 mg/kg + Cy 20 mg/kg + ATG	8	8	7 alive (median 2.5 years)

Adapted from Macmillan et al. British Journal of Haematology. 2010;14-21

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TBI vs No TBI in HLA identical sibling donor

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,[2] Arleen D. Auerbach, MD,[3] Todd E. DeFor, MS,[4,5] Arne Slungaard, MD,[6] and Margaret L. MacMillan, MD[1,5]

- First study to show that the addition of fludarabine could eliminate radiation for MSD HCT
- To date:
  - 100% neutrophil engraftment
  - 3% aGVHD 0% cGVHD
  - 0% Grade 3 RRT
  - Long term follow-up still needed

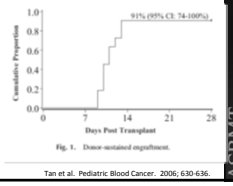

Fig. 1. Donor-sustained engraftment.

Tan et al. Pediatric Blood Cancer. 2006; 630-636.

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TBI vs No TBI in Matched Sibling Donor

HLA-Matched Sibling Hematopoietic Stem Cell Transplantation for Fanconi Anemia: Comparison of Irradiation and Nonirradiation Containing Conditioning Regimens

Ricardo Pasquini,[1] Jeanette Carreras,[2] Marcelo C. Pasquini,[2] Bruce M. Camitta,[3] Anders L. Fasth,[4] Gregory A. Hale,[5] Richard E. Harris,[6] Judith C. Marsh,[7] Anibal J. Robinson,[8] Ma-Jie Zhang,[2] Mary Eapen,[2] John E. Wagner[9]

- 148 patients
- Compared irradiation & nonirradiation regimen
- Proved no significance in hematopoietic recovery, aGVHD or cGVHD, and 5 year OS
- Longer follow-up is needed for impact on cancer risk

Pasquini et al. Biol of Blood and Marrow Transplantation. 2008;1141-1147.

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In Summary:

- HLA Identical Sibling Donor
  - Generally associated with excellent outcomes
    - IF performed prior to MDS or leukemia
    - Prior to androgen therapy
    - Prior to any blood transfusions
    - Fludarabine + TCD marrow based regimen preferred for engraftment
    - Irradiation sparing regimen to reduce late effects
      - Longer follow up needed to confirm

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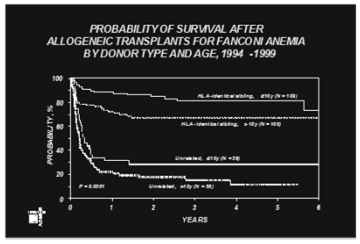
Challenges for Unrelated Donor HCT



- **Donor availability**
- **Regimen related toxicity**
- **High risk of graft failure**
- **High risk of GVHD**
- **High risk of opportunistic infection**
- **Advanced stage of the disease at time of transplant**

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Unrelated Donor HCT

	Conditioning	GVHD px	# of cases	Age (range)	Engraftment	Acute GVHD	Survival
Guardiola et al. 2000	Varied	Varied	69	10.8 (4-37.4)	83%	34%	33% alive at 3 years
Wagner et al. 2007	Varied	Varied	98	12 (0.8-33)	89% Flu 69% no Flu	21% - TCD 70% - no TCD	52% Flu 13% No Flu at 3 years
Gluckman et al. 2007	Varied	Varied	93	8.6 (1-45)	60% +/-5%	32% +/- 5%	74% +/- 13% with 6/6 HLA (n = 12) 48% +/- 9% with HLA 5/6 (n=35) 25% +/- 7% with HLA 3-4/6 (n=45)
Chaudhury et al. 2008	Cy 40/kg +TBI 450cGy + rATG 10/kg	TCD	21	21/21			14/21 alive
MacMillan et al. 2009	Cy 40/kg + TBI 300/150 with thymic shielding + Flu 140 /m2 + ATG 150 mg/kg	TCD + CSA	24	8.8 (4-21.2)	22/22 with TBI 300 cGy 0/2 with TBI 150 cGy	3/22 0/2	19/22 alive 2/2 alive

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Addition of Fludarabine

The Saudi Experience in Fludarabine-Based Conditioning Regimens in Patients with Fanconi Anemia Undergoing Stem Cell Transplantation: Excellent Outcome in Recipients of Matched Related Stem Cells but Not in Recipients of Unrelated Cord Blood Stem Cells

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

Bone Marrow Transplantation for Fanconi Anemia Using Fludarabine-Based Conditioning

Excellent outcome of allogeneic bone marrow transplantation for Fanconi anemia using fludarabine-based reduced-intensity conditioning regimen

- Concept to reduce secondary malignancies and reduce toxicity
- Proven to improve OS with low rejection
- Decreased the risk of graft failure

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Unrelated Donor: Impact on Mortality

Results of multivariable analysis for predictors of early mortality

Variables	N1/N2	RR (95% CI)	P
Conditioning regimen			< .001[2]
FLU-containing regimen	11/46	1.00	
Non-FLU-containing regimen, T-cell–depleted grafts	17/26	4.19 (1.88-9.39)	< .001
Non-FLU-containing regimen, non-T-cell–depleted grafts	15/24	5.11 (2.21-11.84)	< .001
Age at transplantation			
10 years or younger	12/37	1.00	
Older than 10 years	31/59	2.07 (1.03-4.15)	.041
Donor-recipient CMV status			.006[2]
Donor negative/recipient negative	10/45	1.00	
Donor positive/recipient negative	5/18	1.11 (0.40-3.09)	.839
Donor negative/recipient positive	13/24	2.20 (1.07-4.52)	.032
Donor positive/recipient positive	6/9	4.91 (1.83-13.19)	.002

N1 indicates number of early deaths; N2, number of evaluable patients; FLU, fludarabine.

Results of multivariable analysis for predictors of overall mortality

Variables	N1/N2	RR (95% CI)	P
Conditioning regimen			< .001[2]
FLU-containing regimen	21/46	1.00	
Non-FLU-containing regimen, T-cell–depleted grafts	24/26	3.44 (1.72-6.91)	< .001
Non-FLU-containing regimen, non-T-cell–depleted grafts	19/24	3.57 (1.80-7.08)	< .001
Prior red blood cell transfusions			
20 or less	28/40	1.00	
More than 20	22/24	2.49 (1.34-4.66)	.004
Donor-recipient CMV status			.007[2]
Donor negative/recipient negative	10/45	1.00	
Donor positive/recipient negative	11/18	1.09 (0.53-2.26)	.817
Donor negative/recipient positive	15/24	1.29 (0.68-2.44)	.437
Donor positive/recipient positive	8/9	4.52 (1.90-10.74)	< .001

N1 indicates number of deaths; N2, number of evaluable patients; and FLU, fludarabine.

[2]Two-degree freedom test.
[3]Three-degree freedom test.

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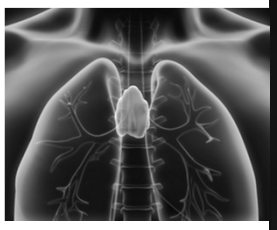
Thymic Shielding

Decreased risk of opportunistic infections without affecting hematopoietic recovery

Standard of Care for radiation containing regimens



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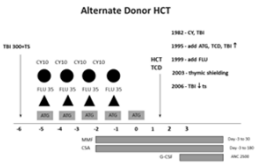
Decrease in TBI



- 300 cGy with 50 patients
  - Neutrophil engraftment: 98%
  - Acute GVHD: 11%
  - Chronic GVHD: 4%
  - 1 year OS: 94%

Personal communication with Dr. MacMillan

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In Summary:

•Alternative Donor for HCT

- Addition of Fludarabine has overcome graft failure
- With improved outcomes, indication for alternative donor are increasingly similar to sibling donor
- Risks include prior exposure to androgens, absence of fludarabine and >/= 3 malformations
- CY-FLU with TBI 300 cGy with thymic shielding is new standard of care.
- Emphasis is now being placed on risk of infection, quality of life and late effects

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HCT in the setting of leukemia or MDS

- 21 FA patients with acute leukemia or advanced MDS underwent HCT
- 6 patients has biallelic BRCA2 mutations
- 8 patients received pre tx cytoreduction
  - 3 achieved complete remission
- 2 MSD & 19 alternative

Results:

Neutrophil engraftment: 95%

aGVHD 19%

5 year OS: 33%

Relapse Rate: 24%

Similar OS in patients with biallelic BRCA2 mutations

Mitchell, et al. British Journal of Haematology 2014. 164; 384-395.

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HCT in the setting of leukemia or MDS

- No standard treatment options
- Considered Very HIGH RISK
- Long term survival is possible

MacMillan et al. British Journal of Haematology. 2010; 14-21.
Mehta et al. Pediatric Blood Cancer. 2007; 668-672.

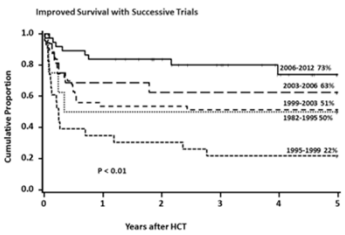
•1980 - Cy Dose Reduction with TBI

•1995 T-Cell Depletion to decrease GVHD

•1999 - Addition of Fludarabine to improve engraftment

•2003 -Thymic Shielding to improve neutrophil recovery

•2006 – Dose reduction of TBI



•Today - Improve Quality of Life & Reduce Late Effects
  •Reduce toxic therapies or eliminate allo-HCT

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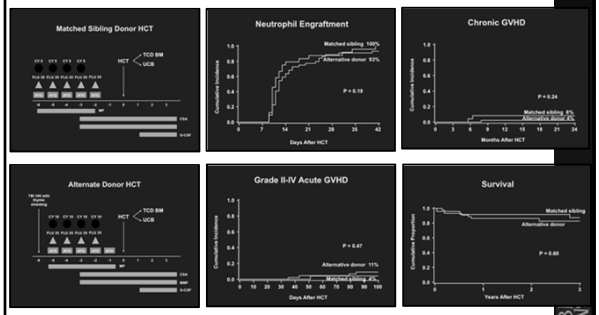
Outcomes by Donor Source



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ARS Question #3

Which of the following statements has not improved outcomes in FA therapies?

a. Fludarabine based conditioning regimens
b. Decreasing the cyclophosphamide dosing
c. Using Graft T cell depletion
d. Androgen therapy

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Solid Tumors

Risk is extraordinary high!!

Differing reports but estimations:

- 50 fold higher for all solid tumors
- 100-1000 fold higher
  - Head and neck
  - Esophagus
  - Liver
  - Vulva and Cervix
- Risks even higher post BMT
  - cGVHD and aGVHD
  - Older Age
  - Radiation

Kutler et al. Blood. 2003; 1249-1256
Roenberg et al. Blood. 2003; 822-826
Guardiola et al. Blood. 2004; 73-88

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Pharmacist Monitoring

- Avoid use of voriconazole in all FA patients
  - Independent risk factor the development of cutaneous malignancy in lung transplant pts
  - Unknown mechanism but proposed to involve VNO metabolite
- Avoid medications that increase chance of DNA breakage
  - Methotrexate
  - Azathioprine
  - Any toxic medications that involve DNA repair

Williams et al. Reviews of anti-infective Agents. 2014: 58; 997-1002

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Fanconi Anemia Comprehensive Program

- BMT Team
  - Providers, Nurse Coordinators, Nurses, Research Coordinators, Dietician, Social Workers, Pharmacists
- Genetics
- Radiology
- Dermatology
- Gynecology
- Nephrology
- Infectious Disease
- Gastroenterology
- Surgery
- Lab Medicine
- Pharmacology
- Neuropsychology
- Audiology
- Ophthalmology
- Cardiology
- Pulmonology

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ARS Question #4

SK is now five years from transplant, fully engrafted and recently started high school. Unfortunately, SK developed CRF & requires three times weekly dialysis therapy. She is awaiting a match for an URD kidney transplant. Which of the following medications would you not recommend for her immunosuppression?

a. Cyclosporine
b. Azathioprine
c. Tacrolimus
d. Mycophenolate

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What's Next?

- Haploidentical
  - Several case series reporting successful results
  - Typically reserved for patients with limited donor options
- Gene Therapy
  - Self-Correcting Mutations?
  - Mosaicism?
  - Lentiviral vector
  - Integration free-induced pluripotent stem cells (iPSC's)

Tolar, et al. Pediatric Blood and Marrow Transplantation. 2011; 1193-1198.

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Conclusion

- Appropriate chemotherapy doses are essential in this population.
- Pharmacists must be aware of pre-existing organ dysfunction and DNA repair defect when considering medications.
- Addition of fludarabine significantly increased engraftment in MSD & URD donor.
- Progression of treatment strategies have significantly improved outcomes.
- Takes a team specialized in treating FA

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Any questions?

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