Fragility in Fanconi Anemia

Melissa K. Stricherz, PharmD, BCOP
University of Minnesota Masonic Children’s Hospital
Clinical Pediatric Blood & Marrow Transplant/Hematology/Oncology Pharmacist
No Financial Disclosure

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.

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

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

Phenotype Extremely Variable

1982 – Dr. Glanz and Dr. Fraser compared probands

- 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

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

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

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

Skeletal – 50%

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

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!

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
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!

Known FA Genes

Adapted from Zeirhut, et al. J Genet Counsel. 2014; 23: 910-921
**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

**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

**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
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

Recommendations for Time to Transplant

- Standard Risk usually considered:
  - Hgb < 8 g/dL
  - ANC < 500/uL
  - Plt < 20,000/uL
- Indications for HCT are consistent regardless of the donor source
  - Monitor CBC q3months & Annual BM biopsy

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

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
Why the peculiar sensitivity to FA Cells?
FA Proteins Repair DNA!

T Cell Depletion

HLA identical sibling donor HCT with Radiation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GVHD</th>
<th># of Cases</th>
<th>Median recipient age</th>
<th>Sustained engraftment</th>
<th>Acute GVHD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dufour et al., 2001</td>
<td>CSA</td>
<td>27</td>
<td>9 years</td>
<td>23/25</td>
<td>2/25</td>
<td>81% alive at 3 yrs</td>
</tr>
<tr>
<td></td>
<td>TAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-6 Gy (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cy 20-80/mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cy 100-200/mg/kg</td>
<td></td>
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<tr>
<td></td>
<td>MTX</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>CSA+MP+A</td>
<td></td>
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<tr>
<td></td>
<td>TSG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farzin et al., 2007</td>
<td>CSA+</td>
<td>30</td>
<td>7.6 years</td>
<td>27/30</td>
<td>2/30</td>
<td>90% alive at 10 years</td>
</tr>
<tr>
<td></td>
<td>TAI</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 Gy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Macmillan et al. British Journal of Haematology. 2010;147(2) 256-263
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**

<table>
<thead>
<tr>
<th>Conditioning</th>
<th># of cases</th>
<th>Engrafted</th>
<th>Outcome (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tbell 2002</td>
<td>7</td>
<td>5</td>
<td>57 alive</td>
</tr>
<tr>
<td>Tan et al. 2006</td>
<td>31</td>
<td>30</td>
<td>100% alive at 2 years</td>
</tr>
<tr>
<td>Torjesen et al. 2006</td>
<td>17</td>
<td>14</td>
<td>72% alive (median 16 mos)</td>
</tr>
<tr>
<td>Aysa et al. 2006</td>
<td>34</td>
<td>34</td>
<td>33 alive (median 33.7 mos)</td>
</tr>
<tr>
<td>Etem et al. 2009</td>
<td>8</td>
<td>8</td>
<td>7 alive (median 2.5 years)</td>
</tr>
</tbody>
</table>

Adapted from Ebell et al., British Journal of Haematology, 2010;140:21.

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**TBI vs No TBI in HLA identical sibling donor**

- 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

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**TBI vs No TBI in Matched Sibling Donor**

- 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
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

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

Unrelated Donor HCT

<table>
<thead>
<tr>
<th>Conditioning</th>
<th>GVHD ph</th>
<th># of cases</th>
<th>Age (range)</th>
<th>Engraftment</th>
<th>Acute GVHD</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guardiola et al. 2000</td>
<td>Varied</td>
<td>59</td>
<td>0.8-27 (16)</td>
<td>66%</td>
<td>14%</td>
<td>33% alive at 3 years</td>
</tr>
<tr>
<td>Wagner et al. 2007</td>
<td>Varied</td>
<td>58</td>
<td>0.2-27 (16)</td>
<td>66%</td>
<td>34% no TBI, 21% TCD 70% no TBI, 12% TBI</td>
<td>34% alive at 3 years</td>
</tr>
<tr>
<td>Shukeman et al. 2007</td>
<td>Varied</td>
<td>93</td>
<td>8.6 (2-45)</td>
<td>66% +/-5%</td>
<td>12% +/-5%</td>
<td>27% +/-18% with/without 5/6 HLA, 34% +/-18% with/without 6/6 HLA, 21% +/-18% with/without 4/6 HLA</td>
</tr>
<tr>
<td>Chaudhary et al. 2008</td>
<td>Cy 40mg/kg + TBI 450cGy + rATG 10/kg TCD</td>
<td>21</td>
<td>2/21</td>
<td>3/22</td>
<td>2/22</td>
<td>52/22 alive</td>
</tr>
<tr>
<td>Marcelli et al. 2009</td>
<td>Cy 40mg/kg + TBI 450cGy + rATG 10/kg TCD + CSA</td>
<td>24</td>
<td>4/21 (2-21)</td>
<td>100% with/without TBI at 60 days, 1/2 alive</td>
<td>1/2 alive</td>
<td>1/2 alive</td>
</tr>
</tbody>
</table>
Addition of Fludarabine

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

Unrelated Donor: Impact on Mortality

Thymic Shielding

Decreased risk of opportunistic infections without affecting hematopoietic recovery

Standard of Care for radiation containing regimens
Decrease in TBI

Alternate Donor HCT

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

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

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
HCT in the setting of leukemia or MDS

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

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

Outcomes by Donor Source

Used with permission from Dr. MacMillan
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

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

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
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

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

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)

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

Any questions?