
بسم الله الرحمن الرحیم

دوازدهمین کنگره سالیانه
پزشکی و پرستاری
پیوند سلولهای بنیادی خونساز

Hematopoietic Stem Cell Transplantation in Inherited Bone Marrow Failure Syndromes:

Special Considerations & Challenges

Azadeh Kiumarsi

Assistant Professor of Pediatric Hematology, Oncology, Stem Cell Transplantation

Tehran University of Medical Sciences

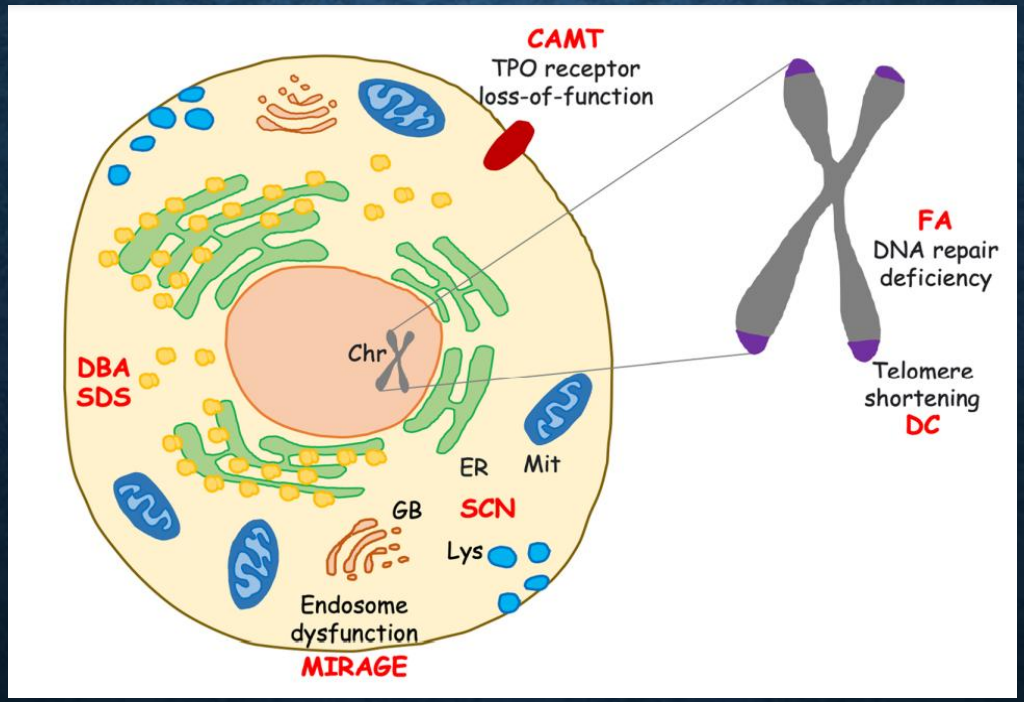
- Inherited bone marrow failure syndromes (IBMFS) account for **10–20%** of all childhood BMFs.
  - varying degrees of bone marrow failure
  - predisposition to hematologic malignancies & solid tumors
  - a range of congenital abnormalities

In a single-center study from Mashhad, out of 312 suspected individuals, 84 patients (26.9%) were positive for FA.

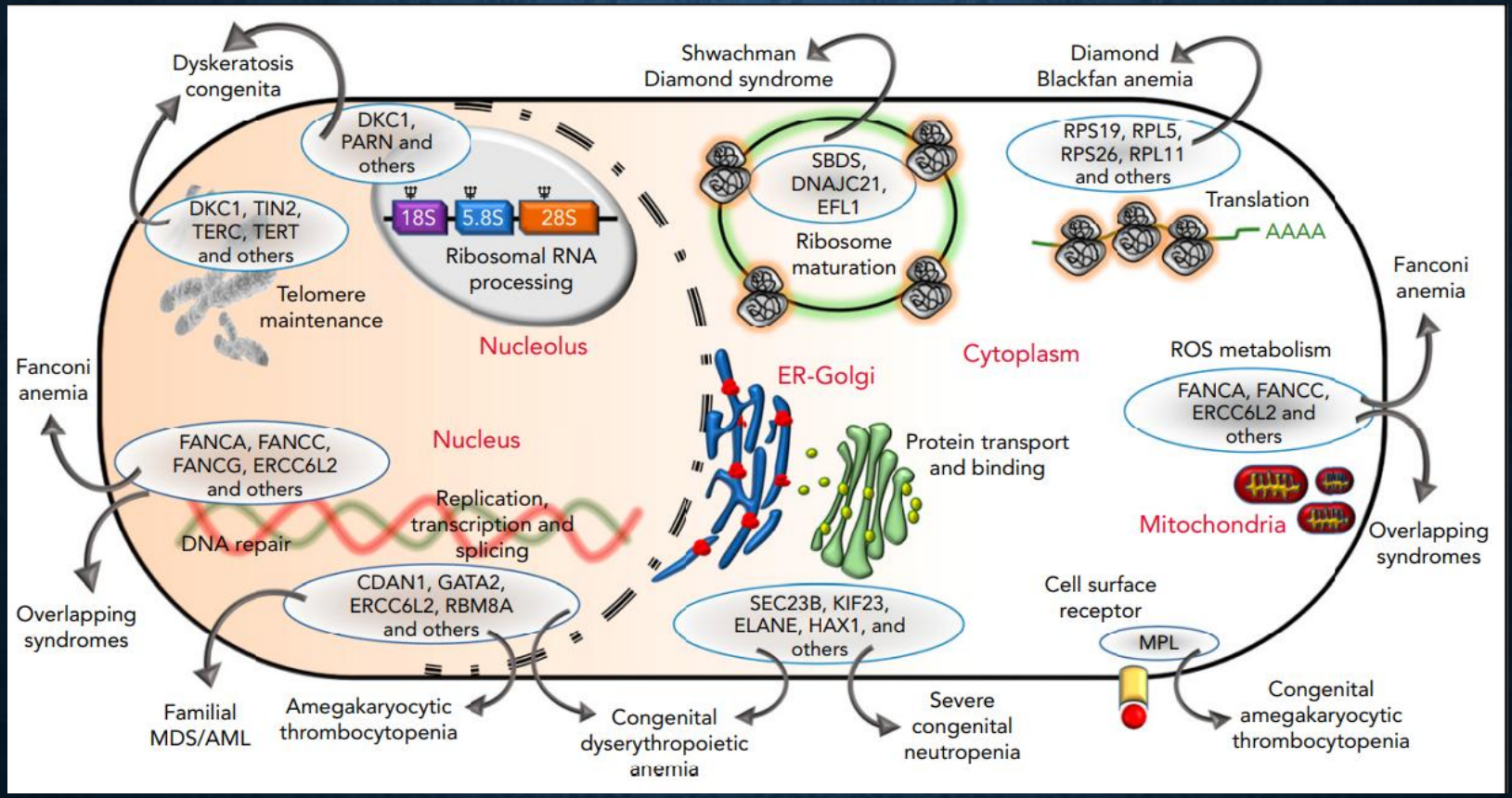
Shakeri S, et al. Evaluation of Prevalence and Characteristics of Patients with Fanconi Anemia: A Study in Northeast of Iran. Medical Laboratory Journal. 2023 Jan 10;17(1):42-6.

Classical IBMFSs include

Fanconi anemia	Dyskeratosis congenita	Diamond–Blackfan anemia
Impaired DNA damage repair	Telomere maintenance dysfunction	Aberrant ribosomal protein biosynthesis



Sakaguchi H, Yoshida N. Recent advances in hematopoietic cell transplantation for inherited bone marrow failure syndromes. International Journal of Hematology. 2022 Jul;116(1):16-27.


Dyskeratosis congenita
DKC1, PARN and others
DKC1, TIN2, TERC, TERT and others
Telomere maintenance
18S
5.8S
28S
Ribosomal RNA processing
Nucleolus
Shwachman Diamond syndrome
SBDS, DNAJC21, EFL1
Ribosome maturation
Diamond Blackfan anemia
RPS19, RPL5, RPS26, RPL11 and others
Translation
AAAA
Fanconi anemia
Cytoplasm
ROS metabolism
FANCA, FANCC, ERCC6L2 and others
Mitochondria
Overlapping syndromes
Fanconi anemia
FANCA, FANCC, FANCG, ERCC6L2 and others
DNA repair
Nucleus
Replication, transcription and splicing
ER-Golgi
Protein transport and binding
Overlapping syndromes
CDAN1, GATA2, ERCC6L2, RBM8A and others
SEC23B, KIF23, ELANE, HAX1, and others
Cell surface receptor
MPL
Familial MDS/AML
Amegakaryocytic thrombocytopenia
Congenital dyserythropoietic anemia
Severe congenital neutropenia
Congenital amegakaryocytic thrombocytopenia

Allogeneic HSCT can **cure** **hematologic aspects**

but it does not correct and **may exacerbate** the non-hematologic manifestations, such as organ dysfunction, cancer risk, or somatic abnormalities

The potential for cure with HSCT
must be balanced
against the natural history of the condition
and the short-term and long-term toxicities of transplantation

Indications for HSCT IN IBMFS
EBMT 2019

Transfusion dependent FA with a suitable donor
in the phase of **moderate cytopenia**
with no poor-risk clonal abnormalities and no MDS/AML

DC and other telomeropaties
pre-transplant organ damage (lung and liver) assessment
is requiremed for HSCT eligibility

Children with DBA having an MSD
if they do not respond to steroids
If MSD not available, HSCT from a MUD in experienced centres

Bone Marrow Transplantation (2019) 54:1525–1552
https://doi.org/10.1038/s41409-019-0516-2

- Earlier transplantation reduces complications from cytopenias (eg, infections from neutropenia, iron overload), lessens the likelihood of malignant transformation, and may avert other complications of the underlying disorder (eg, liver or lung dysfunction).
  - International Fanconi Anemia Registry report → by age 40, cytopenias from progressive bone marrow failure were present in 90 to 98 percent of patients and occurred at a median age of 7 years.
- In a large registry study, compared with HSCT at **age <10 years**, risk for death was increased in patients transplanted at age 10 to 20 years (HR 1.39; 95% CI 1.07 to 1.80).

Kutler DI, et al. A 20-year perspective on the International Fanconi Anemia Registry (IFAR). Blood 2003; 101:1249.

- FA physicians have agreed on consensus treatment guidelines for severe BMF or transformation: persistent hemoglobin <8 g/dL, platelets <30,000/mm3, absolute neutrophil count <500/mm3, overt leukemia with at least 20 % blasts in the marrow, or morphologic MDS.
- When an MRD is available, the optimal timing for HSCT besides clonal evolution is when severe isolated cytopenia or severe BMF occurs, ideally before the need for transfusion.

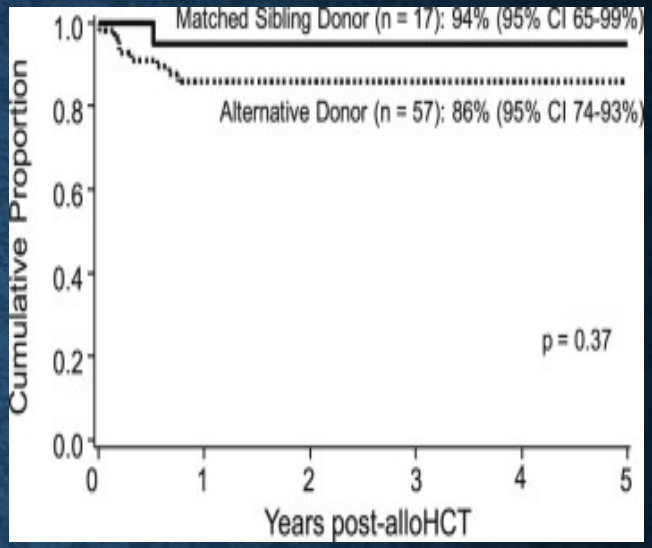
Pre-HSCT Considerations

- In an experienced medical center
- By a multidisciplinary team
- FH & DH
- Ferritin & T2* MRI
- Brain MRI & MRA
- BMA
- Lifestyle
- Fertility

DONOR SELECTION

- **Best → MSD**
- But evaluation to R/O the disease is necessary:
  - Mutation testing / Chromosomal breakage analysis
- **If MSD is unavailable → search for an alternative donor**
- In some cases, pre-implantation genetic diagnosis has been used to select an embryo from in vitro fertilization to provide an MSD graft.
  - A survey of North American FA support group members reported that only one-third of families were aware of this option.

- American group: in 74 FA patients, 5-year OS not statistically different between the 2 groups (94% [95% CI, 65%-99%] for MSD-HCT recipients and 86% [95% CI, 74%-93%] for AD-HCT recipients; P = .37)

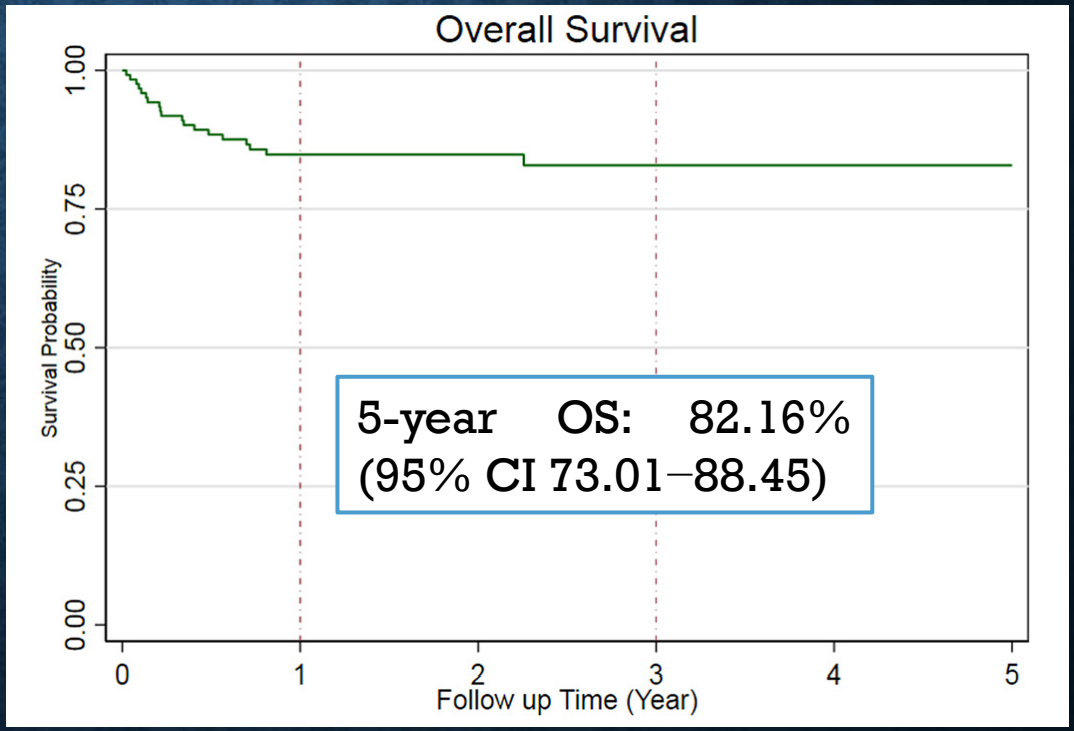


- Spanish Working Group for Bone Marrow Transplantation in Children: in 34 FA patients, 5-year OS of 73%, with no differences between MSD and MUD transplants.

Ebens CL, et al. Biology of Blood and Marrow Transplantation. 2018 Apr 1;24(4):765-71.
Murillo-Sanjuán L, et al. Bone Marrow Transplantation. 2021 May;56(5):1213-6.

- A total of 122 patients (median age: 8 years)
- 5-year OS in HSCT from MUD was lower than MSDs and MRDs, donor type had no statistically significant association with OS (MUD: HR 1.6, 95% CI 0.4–5.6; MRD: HR 0.9, 95% CI 0.3–2.6, p:0.69 compared with the MSD reference group).

Grade 3–4 acute GvHD was more likely in MUD than MRD and MSD (p:0.009).



Rostami T, et al. Experimental Hematology. 2022 May 1;109:27-34.

- The total number of patients with FA and other disorder who received haploidentical transplants were n=340.
- Cumulative Overall survival reported was 79.1%. Cumulative acute GVHD was seen in 38.2%, while cumulative chronic GVHD was seen in 18.6% of patients.

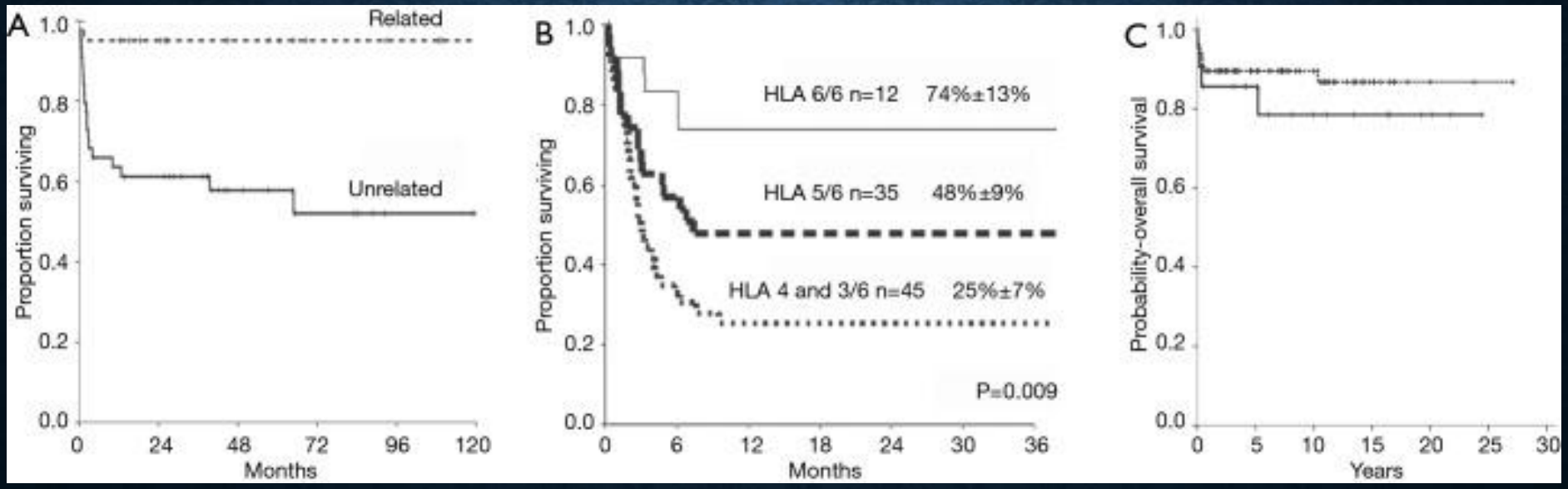
Shah Z, et al. Outcomes of Haploidentical Stem Cell Transplantation in Patients with Fanconi Anemia; A Systematic Review. Blood. 2021 Nov 23;138:4308.

SOURCE

- Either bone marrow or peripheral blood are acceptable with comparable survival.
- GVHD has been associated with increased incidence of secondary cancers in patients with FA and DC. In transplantation for acquired aplastic anemia in children, bone marrow has been associated with less GVHD than PBSPC. However, for HCT with IBMFS, there is no consistent difference in survival, GVHD, or cancer incidence according to the graft source.
  - In a registry study that included 795 patients transplanted for FA, compared with marrow grafts, PBSPC grafts were associated with more secondary cancers (hazard ratio [HR] 3.29; 95% CI 1.30-8.35). Graft source was not independently associated with OS, incidence of GVHD, NRM, or engraftment.

Peffault de Latour R, et al. Blood 2013; 122:4279.

- Gluckman et al. 2007, 93 FA, Single and double UCBT → 2-year OS 40% with 32% grade II–IV aGVHD; 16% cGVHD
- MacMillan et al. 2015; 130 FA, Single and double UCBT → 1-year OS 63%, 20% grade II–IV aGVHD; 10% cGVHD
- Pagliuca et al. 2017; 48 FA; N=2 SDS; N=3 DC;
- N=5 CAT; N=27 DBA; N=4 CN; → 7-year OS: 87.9%, 14%: II–IV aGVHD; 14.5% cGVHD



In the absence of a suitable BM donor, CBT is an option, especially if a sibling CB donor is used.

A better selection of the CB units (more than 4×10^7 nucleated cells/kg) and an adaptation of the conditioning regimens can be able to overcome the risk of rejection.

For patients with FA and other inherited BMF only 1 CB is recommended with no more than one mismatch.

Donor specific antibody screening should be performed in every patient to minimize the risk of rejection.

Ex-vivo CB expanding strategies aiming to better engraftment are under investigation.

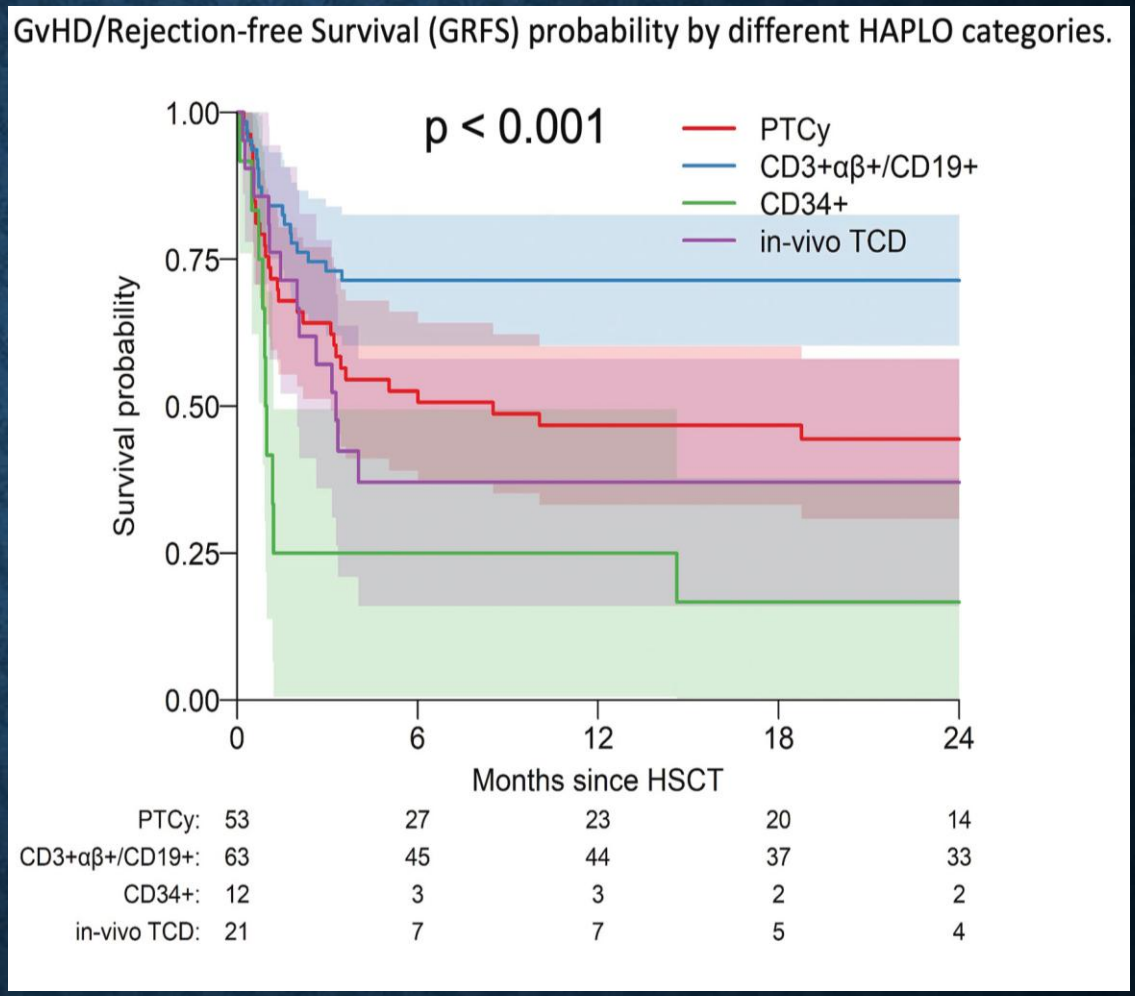
Retrospective evidence suggests to reduce chemotherapy and radiation doses, and integrating Flu, especially in FA patients.

Pagliuca S, et al. Cord blood transplantation for bone marrow failure syndromes: state of art. Stem Cell Investigation. 2019;6.

T CELL DEPLETION

- T cell depletion can reduce the incidence of GVHD with all donor types, but it is typically avoided for UCB grafts and when the patient has developed MDS or leukemia prior to HCT.
  - Ex vivo T cell depletion – Ex vivo CD34+ enrichment depletes most T cells, while permitting limited add-back of T cells. TCR alpha/beta depletion retains TCR-gamma-delta cells, which may enhance engraftment and GVL effects.
  - In vivo T cell depletion – In vivo T cell depletion strategies include ATG and alemtuzumab. PTCy (to selectively target rapidly dividing alloreactive T cells) has been employed for in vivo T cell depletion in non-IBMFS settings. However, a benefit of PTCy has not been proven for FA and there is concern about increased risk of alkylating agents in these patients.
- Transplantation for FA using T cell-depleted MSD grafts was associated with <5 percent grade ≥3 GVHD.

- Data from 162 patients affected by I-BMFs undergoing HAPLO with 4 different TCD approaches in 56 centers:
  - PGF: 10% [5-14%]), SGF: 8% [3-12%]
  - 100-day grade II-IV acute GvHD: 29 % (22-36)
  - 24-month chronic GvHD: 11% (6-16%) & extensive form: 4% (1-7%)
  - After a median follow-up of 43.4 months, the 2-year OS and GRFS: 67% (60-74%) & 53% (45-61%)
  - TCR CD3+ab+/CD19+ depletion group showed the best OS (79%) & GRFS (71%)



Blood (2022) 140 (Supplement 1): 5813–5815.
https://doi.org/10.1182/blood-2022-163219

CONDITIONING REGIMEN

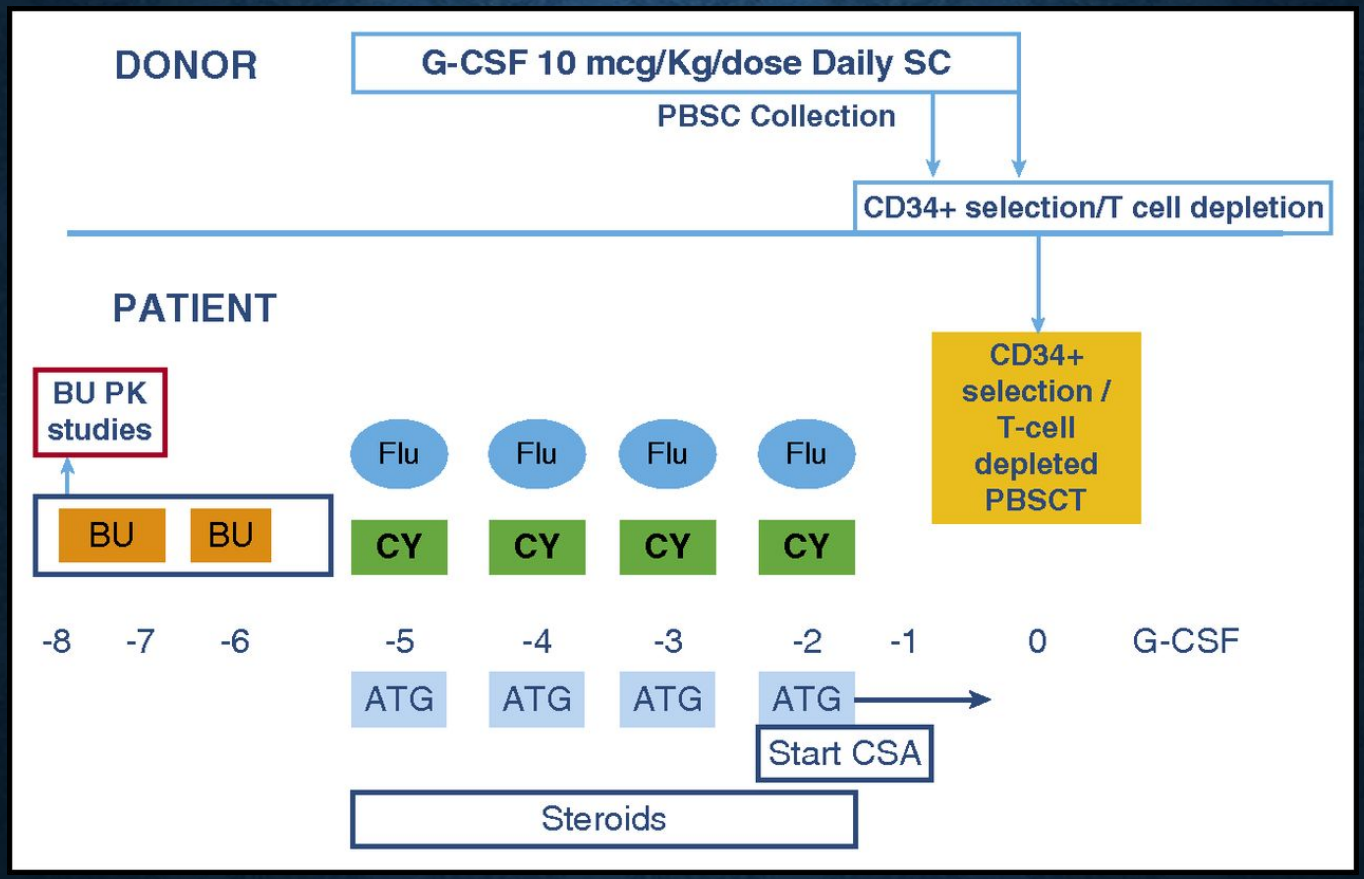
- TBI should be avoided or dose-adjusted to reduce long-term adverse effects.
- For patients with FA and DC, **fludarabine-based conditioning**, rather than cyclophosphamide- or radiation-based regimens are suggested.
  - 8-year OS was 86% with fludarabine versus 59% with non-fludarabine-based conditioning
  - A study of 98 patients with FA who underwent alternative donor transplantation → fludarabine was associated with superior 3-year adjusted OS (52 versus 13 percent), lower day 100 mortality (24 versus 65 percent), and improved recovery of neutrophils and platelets.
- It should be noted that for FA and DC, which are associated with defects in DNA repair, fludarabine-based conditioning functions as myeloablative conditioning, even though it would be considered RIC in other transplantation settings.

Locatelli F, et al. Haematologica 2007; 92:1381.
Wagner JE, et al. Blood 2007; 109:2256.

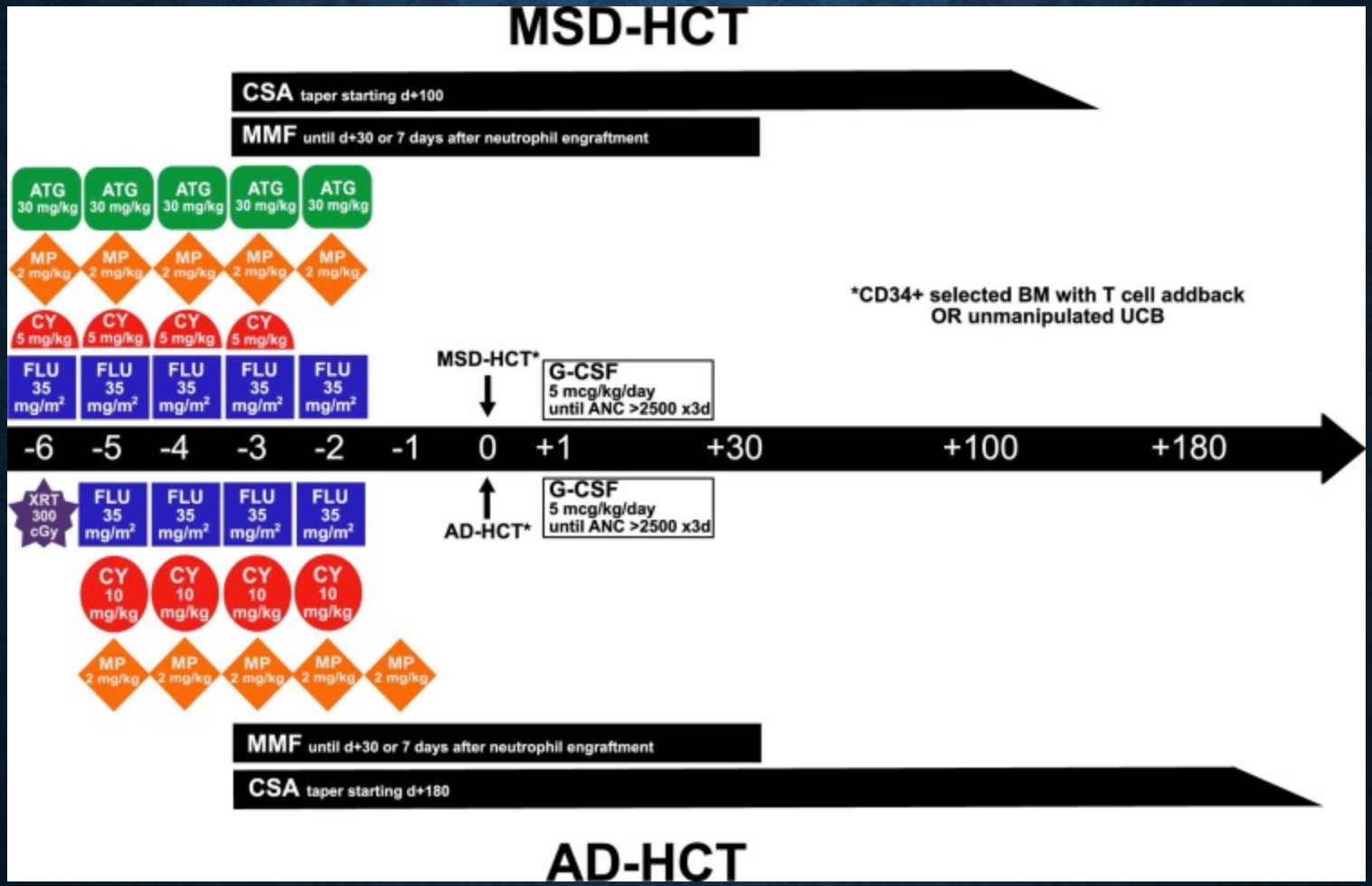
Fanconi anemia	
MRD	FLU 30 mg/m^2 × 3 (D-4 to D-2), CY 10 mg/kg × 4 (D-5 to D-2)
	Postgraft immune suppression associates CsA (3 mg/kg D-1) and mycophenolate (D+1 to D+45).
MUD‡	FLU 30 mg/m^2 × 4 (D-6 to D-3), CY 10 mg/kg × 4 (D-6 to D-3) and ATG 2.5 mg/kg × 2 (D-4 to D-3) and TBI 2 Gy (D-1)
	Postgraft immune suppression associates CsA (3 mg/kg D-1) and mycophenolate (D+1 to D+45)
Dyskeratosis congenita	
MRD§	FLU 30 mg/m^2 × 5 (D-7 to D-3), CY 60 mg/kg × 2 (D-3 to D-2) and alemtuzumab 0.3 mg/kg × 3 (D-6 to D-4) (FCC regimen, pediatric)
	Postgraft immune suppression with CsA alone (3 mg/kg D-1)

- A single injection of rituximab (150-200 mg/m2) is recommended per day +5.

Killick SB, Bown N, Cavenagh J, et al; British Society for Standards in Haematology. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172(2):187-207.

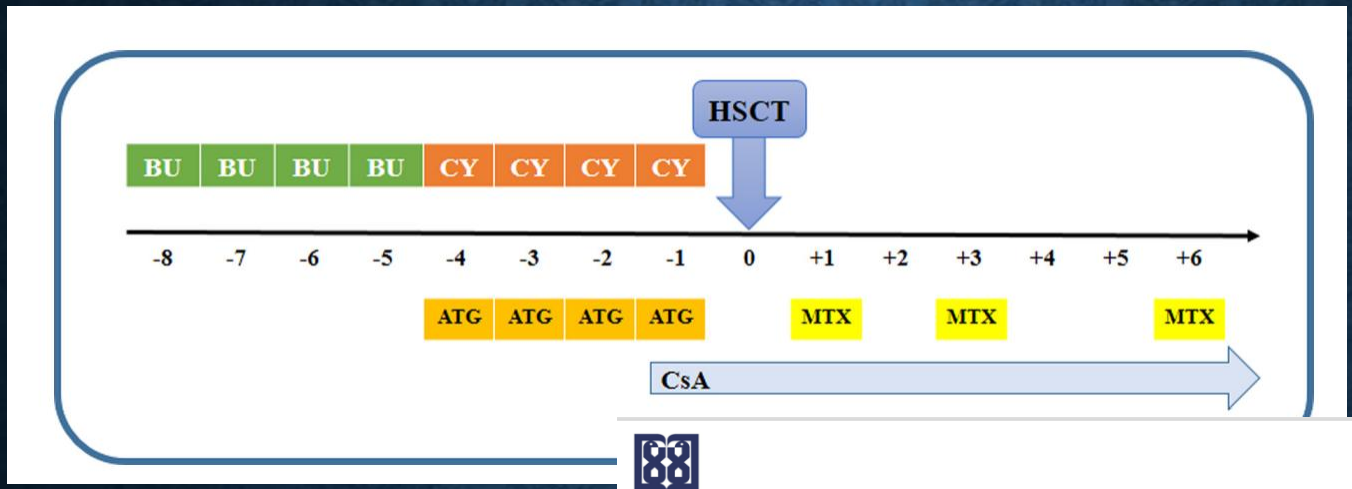


Mehta PA, et al. Radiation-free, alternative-donor HCT for Fanconi anemia patients: results from a prospective multi-institutional study. Blood, The Journal of the American Society of Hematology. 2017 Apr 20;129(16):2308-15.



Ebens CL, et al. Comparable outcomes after HLA-matched sibling and alternative donor hematopoietic cell transplantation for children with Fanconi anemia and severe aplastic anemia. Biology of Blood and Marrow Transplantation. 2018 Apr 1;24(4):765-71.

- All patients underwent a conditioning regimen containing intravenous busulfan (a total dose of 0.8 mg/kg/day according to patients' ideal body weight, from days −9 to −6) and cyclophosphamide (15 mg/kg/day from days −5 to −2), along with mesna.



Fanconi anemia
MAC*(Bu-Flu-Cy) for MSD†

Patient name:				Diagnosis:					AIBW:				
Body weight:				Height:					BSA:				
Days	Date	Conditioning	Levebel	TMP-SMX	Alp	Acy	Itra	UDCA	CsA	Mesna	MP	MTX	LCV
-9			X	X	X	X	X	X					
-8		Bu+Flu	X	X	X	X	X	X					
-7		Bu+Flu	X	X	X	X	X	X					
-6		Bu+Flu	X	X	X	X	X	X					
-5		Bu+Flu	X	X	X	X	X	X					
-4		Rest	X	X	X	X	X	X					
-3		Cy+ATG		X	X	X	X	X	X	X	X		
-2		Cy+ATG		X	X	X	X	X	X	X	X		
-1		ATG		X	X	X	X	X	X	X	X		
0		HSCT							X		X		

Rostami T, et al. Experimental Hematology. 2022 May 1;109:27-34.

RIC regimens are preferred for SDS, rather than MAC because of lower rates of TRM, successful engraftment, little or no GVHD, and long-term survival.

Most experience has been with MAC, which is associated with high rates of engraftment and low rates of GVHD in patients with DBA.

Burroughs LM, et al. Biol Blood Marrow Transplant 2017; 23:1669.
Peffault de Latour R, et al. Bone Marrow Transplant 2015; 50:1168.

JOURNAL OF BONE MARROW TRANSPLANTATION AND CELLULAR THERAPY **JBMTCT**

DOI: 10.46765/2675-374X.2021v4n1p39-43

HSCT FOR INHERITED BONE MARROW FAILURE SYNDROMES

Luiz Guilherme Darrigo Junior [1], Phillip Scheinberg [2], Elias Hallack Atta [3], and Carmem Bonfim [4,5,6]

FANCONI ANEMIA

Recommendation:
Indications for transplant include marrow failure or clonal evolution (myelodysplastic syndrome - MDS or acute myeloid leukemia - AML). In an ideal scenario, HSCT should be performed before blood transfusions, serious infections, or the development of clonal disease [6,12,13].

Conditioning:

Patient in aplasia with an identical related donor (14)
• Cy 60 mg / kg (divided into 4 days: D -6, -5, -4, -3);

• Mesna, 160% of the Cy dose, divided into five doses (0, 3, 6, 9, and 12 hours after Cy);

• Rabbit ATG at a dose of 5 mg/kg (divided into three days: D-3, D-2, and D-1), in patients aged 11 years and older, to reduce the incidence and severity of GVHD.

Patient in aplasia with unrelated matched donor (6,13,15)
• Cy 60 mg / kg (divided into four days: D -6, D-5, D-4, D-3);

• Mesna, 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Fludarabine 150 mg / m^2 (divided into 5 days: D -6, D-5, D-4, D-3 D-2);

• Rabbit ATG 5 mg / kg (divided into three days: D -3, D-2 and D-1).

TELOMERE BIOLOGY DISEASE

Recommendation:
The indication for transplant includes patients in aplastic phase, myelodysplasia, or acute leukemia. In the ideal scenario, HSCT should be performed before transfusions, serious infections, or clonal evolution [13]. The prototype of telomeric biology disease (TBD) is DKC; however, we recommend that transplant also be performed in patients with severe aplasia and very short telomeres (<1%), even in the absence of classic symptoms of DKC.

Conditioning:
Patients with matched related or unrelated donors [13,17]

• Cy 60 mg / kg (divided into 4 days: D -6, D-5, D-4, D-3);

• Mesna, 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Fludarabine 150 mg / m^2 (divided into 5 days: D -6, D-5, D-4, D-3 D-2);

• Rabbit ATG 5 mg / kg (divided into three days: D -3, D-2 and D-1).

BLACKFAN-DIAMOND ANEMIA

Recommendation [13,18]:
• Non-response to steroids, steroid dependency at a dose of ≥ 0.3 mg/kg/day, unacceptable steroid toxicity

de São Paulo - Ribeirão Preto - 2 - Hospital A Beneficên- CA - 4 - Hospital de Clínicas da Universidade Federal do Senhora das Gracas

SHWACHMAN-DIAMOND SYNDROME

Recommendation [13,22]:
• Progressive cytopenias or pancytopenia.
• Dependence on blood transfusions.
• Progression to MDS / LMA.

Conditioning:
Patients with matched related or unrelated donors [13,22]
• Cy 120 mg / kg + Fludarabine 150 mg/m^2;

• Mesna, 160% of the Cy dose, divided into 5 doses (0, 3, 6, 9 and 12 hours after Cy);

• Rabbit ATG 5 mg/kg (divided into three days: D-3, D-2 and D-1).

Comments:
The best results are obtained in patients receiving a reduced-intensity conditioning regimen using a matched related or unrelated donor [13,22]

Congenital Amegakaryocytic Thrombocytopenic Purpura

Recommendation [23,24]
• Severe thrombocytopenia and transfusion-dependent patients.
• Pancytopenia or evolution to MDS / AML.

Conditioning:
Patients with matched related or unrelated donors [24,25]:
• Busulfan 16 - 20 mg/kg EV + Fludarabine 160 mg/m^2.
• Rabbit ATG 5 mg/kg (divided into three days: D -3, D -2 and D -1).
The busulfan dose should be myeloablative and based on the patient's weight and preferrable with pharmacokinetics, as mentioned before.

CONCLUSION

• HSCT is currently the only curative option for the hematological complications related to the different IBMFS [1,10,26]

• All family donors should be screened before considered as potential donors.

• Patients and their families should be informed that HSCT corrects only the hematological manifestations of the disease

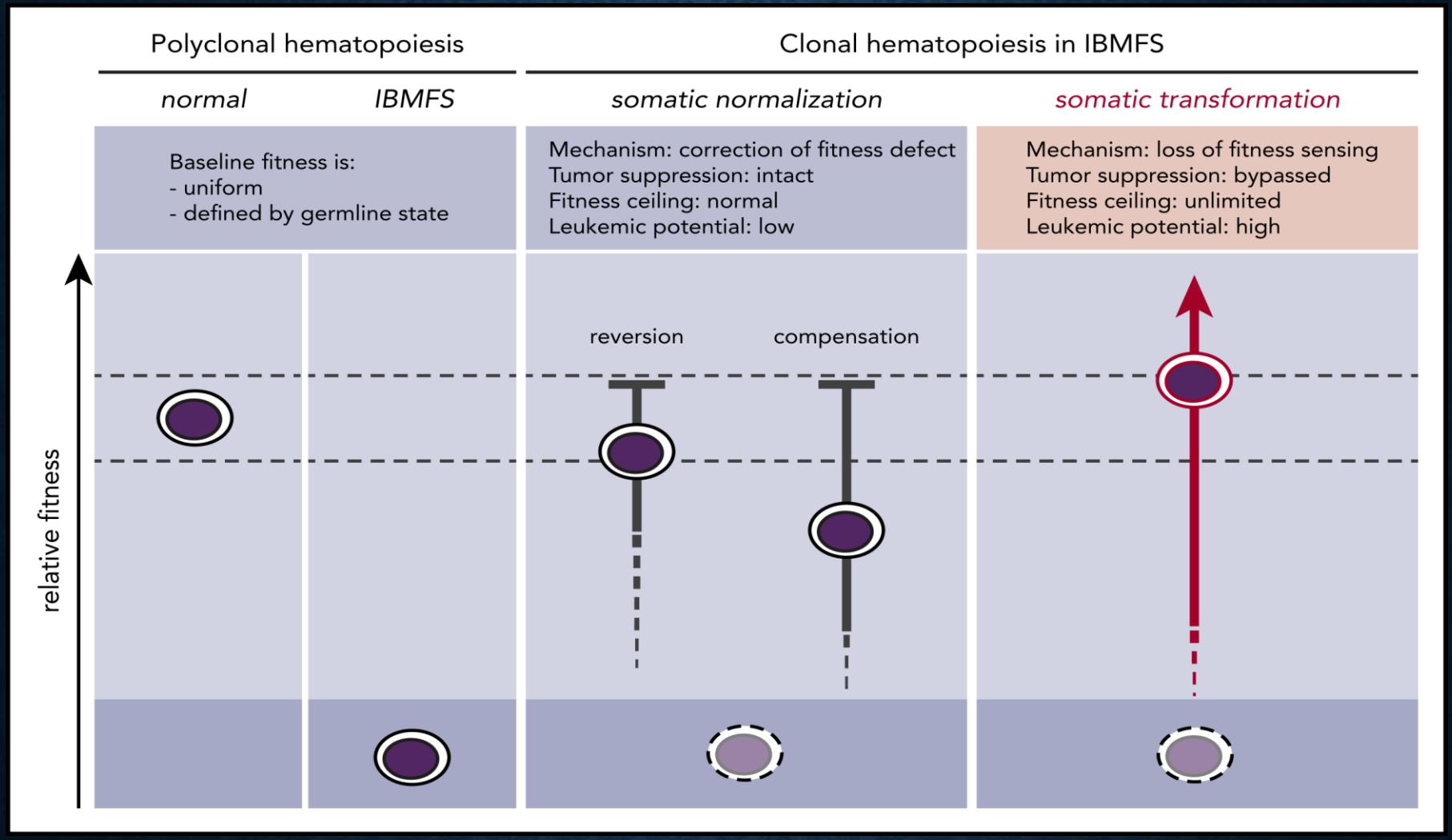
• We advise that all transplant patients be followed up for a lifetime with the aim of preventing or detecting early changes resulting not only from HSCT but also from the underlying genetic disorder [5]

• Particular attention should be paid to the appearance of hematological and non-hematological malignancies [4,5]

CLONAL HEMATOPOIESIS in IBMFS

- In IBMFSs, the germline deficiencies establish a qualitatively impaired functional state at baseline.
- Somatic alterations can promote clonal hematopoiesis by improving the competitive fitness of specific hematopoietic stem cell clones.
  - Some somatic alterations relieve baseline fitness constraints by normalizing the underlying germline deficit through direct reversion or indirect compensation, whereas others do so by subverting senescence or tumor-suppressor pathways.
  - Clones with normalizing somatic mutations may have limited transformation potential that is due to retention of functionally intact fitness-sensing and tumor-suppressor pathways, whereas those with mutations that impair cellular elimination may have increased risk for malignant transformation that is due to subversion of tumor-suppressor pathways.
- Because clonal hematopoiesis is not deterministic of malignant transformation, rational surveillance strategies will depend on the ability to prospectively identify specific clones with increased leukemic potential.

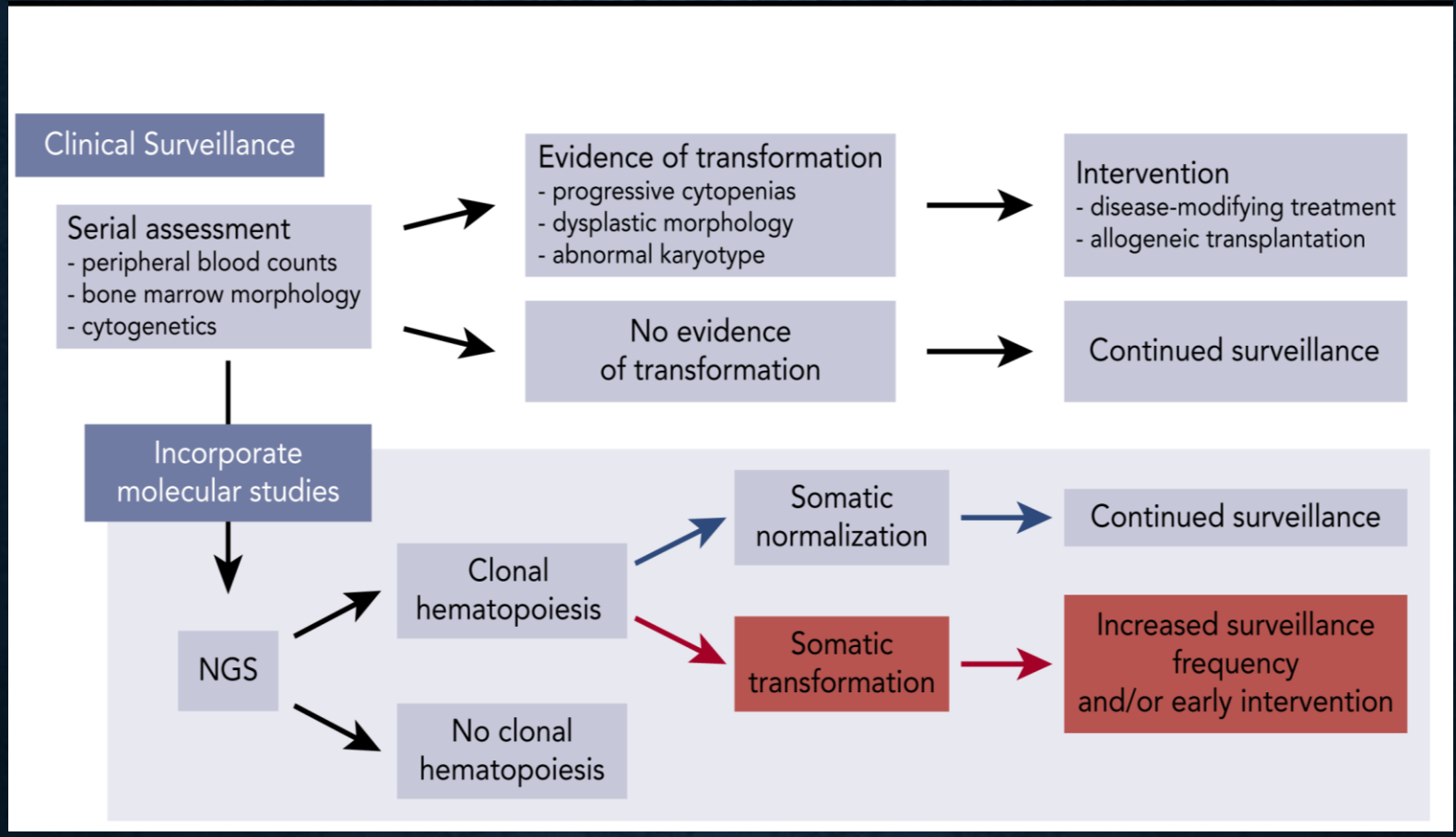
Tsai FD, Lindsley RC. Blood. 2020 Oct 1;136(14):1615-22.



HSPCs in IBMFSs have impaired baseline global fitness compared with normal HSPCs. Somatic mutations can lead to the development of CH by improving fitness over the germline state.

In contrast, somatic transformation occurs through loss of fitness sensing, with bypass of tumor-suppressor pathways and leukemic potential is high.

- CH itself does not indicate impending myeloid transformation. Thus, rational surveillance strategies depend on the ability to prospectively identify specific clones with increased leukemic potential.



MALIGNANT TRANSFORMATION

- Transplantation prior to malignant transformation is especially important for patients with FA, DC, and SDS, because these syndromes are associated with treatment-resistant AML and excessive toxicity from remission induction therapy.
- Among 795 patients transplanted for FA, 58 underwent HCT after progression to MDS or AML. For the entire cohort, 20-year OS was 49 percent. Compared with patients transplanted for bone marrow failure, those transplanted with MDS/AML had increased risk for graft failure (HR 3.17; 95% CI 1.60-6.28) and death (HR 2.10; 95% CI 1.41-3.11).
- Other small series have reported 33 to 80 percent OS at three to five years for patients transplanted after clonal progression, with most deaths due to relapse or opportunistic infection.

IBMFS WITH AML

- Most experts would not treat for chromosomal, immunophenotypic, or molecular findings of clonality alone (ie, without evidence of malignant transformation) to avoid the risk of exacerbating or prolonging cytopenias.
- The most commonly reported remission induction regimens for AML developing from IBMFS are **moderate-dose or low-dose FLAG** but no studies have directly compared induction regimens. Patients in remission after treatment for AML have better survival than those transplanted with active disease, but pretransplant chemotherapy may cause excessive toxicity and prolonged aplasia, especially in patients with FA, DC, and SDS.
    - In a small series, sequential induction with FLAG followed by HCT (cyclophosphamide 10 mg/kg for 4 days, fludarabine 30 mg/m2 for 4 days, ATG 3.75 mg/kg, and TBI [2 Gy]) reported that all patients engrafted (median 21 days) and were alive in CR without clonal evolution after median follow-up of 28 months.

Talbot A, et al. Haematologica 2014; 99:e199.

POSTTRANSPLANT EVALUATION OF PATIENTS WITH IBMFS

- **Maintain healthy diet, regular exercise, good oral hygiene, and sunscreen use.**
- **Recommend complete abstinence from alcohol and smoking (including vaping).**
- **Ensure HPV vaccination for all patients.**
- **Organize regional/national family meetings as this may help patients, increase disease awareness, and improve research**
- **Attention to neurocognitive issues, especially in patients with development delays**
- **Psychologic evaluation and psychologic support**
- **Address visual and hearing problems as they may impact the learning process and decrease academic achievements and quality of life**
- **Annual liver, kidney, and gastrointestinal evaluation. Cardiac and pulmonary evaluation every other year, except for DC patients**
- **Annual endocrine evaluation: growth assessment, glucose, lipid metabolism. Assess gonadal function and bone mineral density**

Bonfim C. Special pre-and posttransplant considerations in inherited bone marrow failure and hematopoietic malignancy predisposition syndromes. American Society of Hematology Education Program Book. 2020 Dec 4;2020(1):107-14.

POSTTRANSPLANT EVALUATION OF PATIENTS WITH IBMFS

For postpubertal female patients: annual gynecologic evaluation. Discuss fertility options.

For male patients: gonadal function and spermogram

Iron overload: Check ferritin levels within 6 mo to 1 y of transplantation. Consider T2* MRI to determine liver iron overload. Phlebotomy is the first choice of treatment; second is desferasirox

GVHD increases the risk of cancer after HCT for all patients with IBMFS. Treatment of GVHD with steroids may be associated with metabolic syndrome, diabetes, avascular necrosis, and adrenal insufficiency.

Aggressive cancer surveillance. Cancer risk increases as patients get older and in the presence of GVHD

Dermatologic evaluation: skin cancer screening every 6-12 mo

Oral examination performed by a dentist every 6-12 mo. Encourage monthly oral self-examination

DISEASE-SPECIFIC POSTTRANSPLANT COMPLICATIONS

FA	DC	DBA
Endocrinologic problems including thyroid dysfunction, fertility, hypogonadism, and GH deficiency	**Pulmonary and liver complications**	**Iron overload and LTFU problems include diabetes, delayed puberty, and hypothyroidism**
Short stature can be treated with GH after 6 mo of HCT, if GH deficiency is confirmed.	**Perform annual PFTs and check SpO_2 and signs of pulmonary and/or liver fibrosis and arteriovenous malformations (lung, liver, and gastrointestinal tract) after HCT**	**Other problems include those related to chronic steroid use and fertility issues.**
Cancer risk		
Skin SCC and BCC Head and neck and anorectal and vulvar SCC Esophagus, breast, and brain cancer	Skin SCC and BCC Head and neck and anorectal SCC Esophagus, stomach, and lung cancer	Colorectal carcinoma Osteogenic sarcoma

FUTURE DIRECTIONS

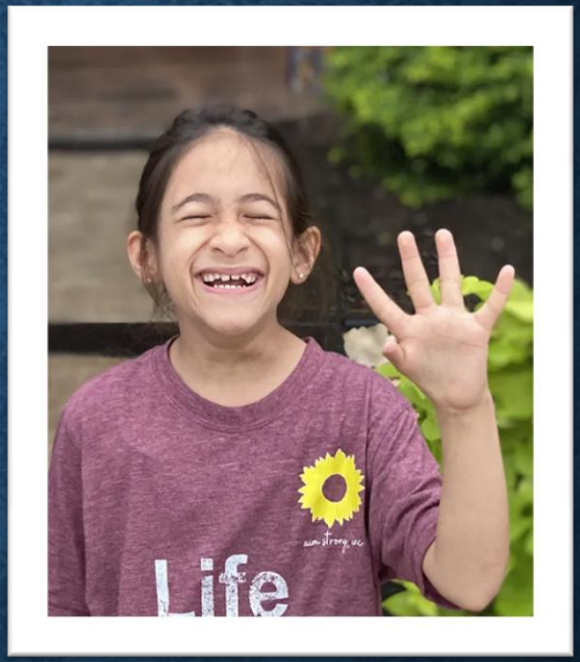
Ongoing clinical trials addressing gene therapies →

hematopoietic stem cells are harvested, genetically corrected by lentiviral transduction, and reinfused to the patient.

Patient-specific induced pluripotent stem (iPS) cells have been derived from cases with DC, FA, and DBA mimicking the deficient hematopoietic phenotype.

An unbiased drug screen platform using iPS cells found a molecule that induces autophagy and increased erythropoiesis in a DBA model.

The combination of patient-specific iPS cells, new genome editing strategies, and gene therapy may have a major impact on the treatment of patients with inherited bone marrow failure syndromes in the future.



Thank You!

03.03.2023
Azadeh Kiumarsi
Akiumarsi@sina.tums.ac.ir