Hematopoietic Cell Transplantation in Bone Marrow Failure Syndromes

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- Bone marrow failure is defined as a quantitative or qualitative abnormality in >=1 of the erythroid, megakaryocytic, or granulocyte/monocyte lineages
- Historically, BMF syndromes were poorly understood and invariably fatal but over the last 20 years research has improved our understanding of these disorders leading to improved therapy and better clinical outcomes

Overview

- These syndromes are a heterogeneous group of disorders characterized by bone marrow failure usually in association with one or more somatic abnormality
- The bone marrow failure often presents in childhood but may not do so until adulthood in some cases
- Some patients initially labeled as having “idiopathic aplastic anemia” actually have cryptic presentations of these genetic syndromes

DNA repair

- Fanconi anemia is perhaps the first BMF syndrome to be characterized as a distinct entity
- >18 genes that cause FA have been identified: DNA repair
- BMF can progress to malignancy, in particular the relationship of FA mutations to acute myeloid leukemia, and to breast, head and neck, and genitourinary tumors

Ribosomopathies

- Cellular metabolism
- BMF that affect the function of ribosomes are Diamond Blackfan anemia (DBA), Shwachman-Diamond syndrome
- (SDS), and dyskeratosis congenita (DC)
- They are all associated with perturbed ribosomal function that leads to specific clinical disorders.
- DBA, SDS, and DC patients have a greatly increased predisposition to malignancy

Telomeropathies

- Patients with DC have mutations in the genes associated with the telomerase complex
- Predisposition to cancer
- Germ-line mutations seen in telomerase genes can also lead to lung and liver disease that may be masked by AA and complicate treatment
- More complete understanding of the role of telomerase dysfunction in the clinical spectrum in AA and its associated disorders

Fanconi

- Usually inherited as an autosomal recessive trait
- Clinically heterogeneous
- Progressive development of bone marrow failure and an increased predisposition to malignancy
- Affected individuals may also have one or more developmental abnormality including skin, skeletal, genitourinary, gastrointestinal and neurological anomalies
- Approximately 30% of patients with Fanconi anemia have no overt somatic abnormalities
- The majority of patients present towards the end of the first decade of life

Fanconi

- Fanconi anemia cells display a high frequency of spontaneous chromosomal breakage and hypersensitivity to DNA cross-linking agents such as Diepoxybutane
- This genomic instability led to the development of a diagnostic test over two decades ago

Fanconi

- The proteins encoded by the FA genes participate in a complicated network important in DNA repair

Fanconi

- The FA pathway is composed of several genes (A, B, C, D1, D2, E, F,G, I, K, L, M, N, O, P, and Q)
- The encoded proteins can be subdivided within the FA pathway into 3 groups:
  - Proteins that make up the core complex
  - The FANCI and FANCD2 proteins, which compose the ID2 complex
  - Downstream effector proteins that possess a DNA repair function

Fanconi

- Unraveling of the downstream proteins, namely, BRCA2/FANCD1, BACH1/FANCJ, PALB2/FANCN, RAD51C/FANCO, SLX4/FANCP, and XPF/FANCQ, reveals an intimate link to DNA repair and mainstream cancer biology, including breast cancer

Dyskeratosis Congenita

- There is no consensus for the naming of telomere diseases (telomeropathies, telomere syndromes, impaired telomere maintenance spectrum disorder, dyskeratosis congenita)

Dyskeratosis Congenita

- Classical dyskeratosis congenita is an inherited bone marrow failure syndrome characterized by the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy and mucosal leucoplakia
- A variety of other (dental, gastrointestinal, genitourinary, neurological, ophthalmic, pulmonary and skeletal) abnormalities have also been reported
- Bone marrow failure is the major cause of mortality with patients having an additional predisposition to malignancy and fatal pulmonary complications
- X-linked recessive, autosomal dominant and autosomal recessive subtypes of DC are recognized

Treatment

Supportive care

- Judicious use of blood products
- Given the multisystem nature of such diseases, patients may be managed in conjunction with, or with consultation of, pediatricians, hematologists, dermatologists, dentists and oncologists
- Patients and their families will need to be seen by a medical geneticist for confirmation of a diagnosis, identification of mutations and appropriate counseling

Treatment

Androgens:

- Even in the current era of HCT; particularly when a suitable donor is not readily available or when the patient is not a HCT candidate
- Use of androgen in DC per se is less common than in Fanconi anemia but there are data to suggest that DC patients are particularly sensitive to androgen

Treatment

Steroids:

- There are no other diseases for which patients receive potentially life-long steroid therapy beginning in infancy other than Blackfan Diamond syndrome
- Transient improvement in FA has been reported

Treatment

Growth factors:

- Results have generally been disappointing in other constitutional marrow failures
- If the decision is made to treat with growth factors, it is strongly recommended to monitor patients for clonal aberrations prior to and during long-term treatment

Treatment

Hematopoietic cell transplantation (HCT):

- The only curative modality, (up until now) for bone marrow failure patients is allogeneic HCT
- Despite many similarities, the heterogeneity of the bone marrow failure syndromes precludes the implementation of general rules and guidelines when deciding about the process of HCT

Treatment

HCT in Fanconi anemia:

- Hypersensitivity to alkylating agents
- Hypersensitivity to radiation therapy
- Higher incidence of chemo-related toxicity such as mucositis, hemorrhagic cystitis
- Lower doses chemotherapy
- Higher incidence of GVHD

Treatment

HCT in Fanconi anemia:

- When is the right time to transplant an FA patient
  - Before or after the development of cytopenia
  - Myelodysplasia, clonality and leukemic transformation

Treatment

HCT in Fanconi anemia:

- What is the best conditioning regimen
- The role of radiation therapy is not clear
- Effect of radiation therapy? Carcinogenic
- FA patients have an increased risk of GVHD
- Addition of ATG to the conditioning/GVHD prophylaxis regimen
  - the role and dose of ATG are not well determined

Treatment

HCT in Fanconi anemia:

- FA patients who present with myelodysplasia or clonal abnormalities, should they receive special conditioning
- Best approach to patients who fail their first SCT

HCT in Fanconi anemia

- A review of our data at KFSH&RC from 1993 to 2011 identified 94 FA

Details of the Conditioning Regimens

Conditioning Regimen	Time Period when Regimen Was Used	Patients, n
CY (20 mg/kg), ATG, TAI	1995-1999	22
CY (60 mg/kg), ATG	2000-2007	40
CY (20 mg/kg), flu, ATG	2008-2011	21*
CY (20 mg/kg), ATG, TBI	In patients with MDS, regardless of time of HCT	11

Ayas et al, Biol Blood Marrow Transplant 2014

HCT in Fanconi anemia (matched related)

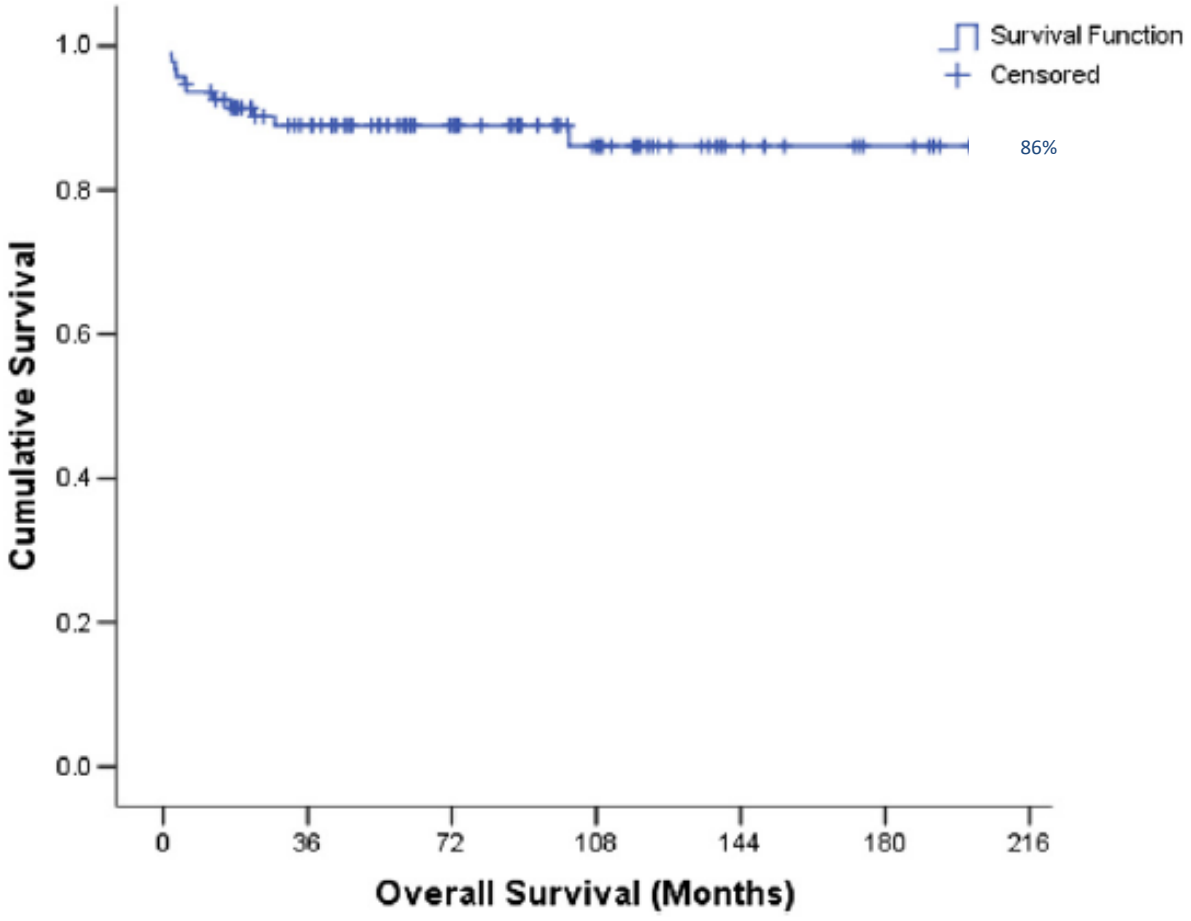


Figure 1. Overall survival of all patients.

Ayas et al, Biol Blood Marrow Transplant 2014

HCT in Fanconi anemia (matched related):

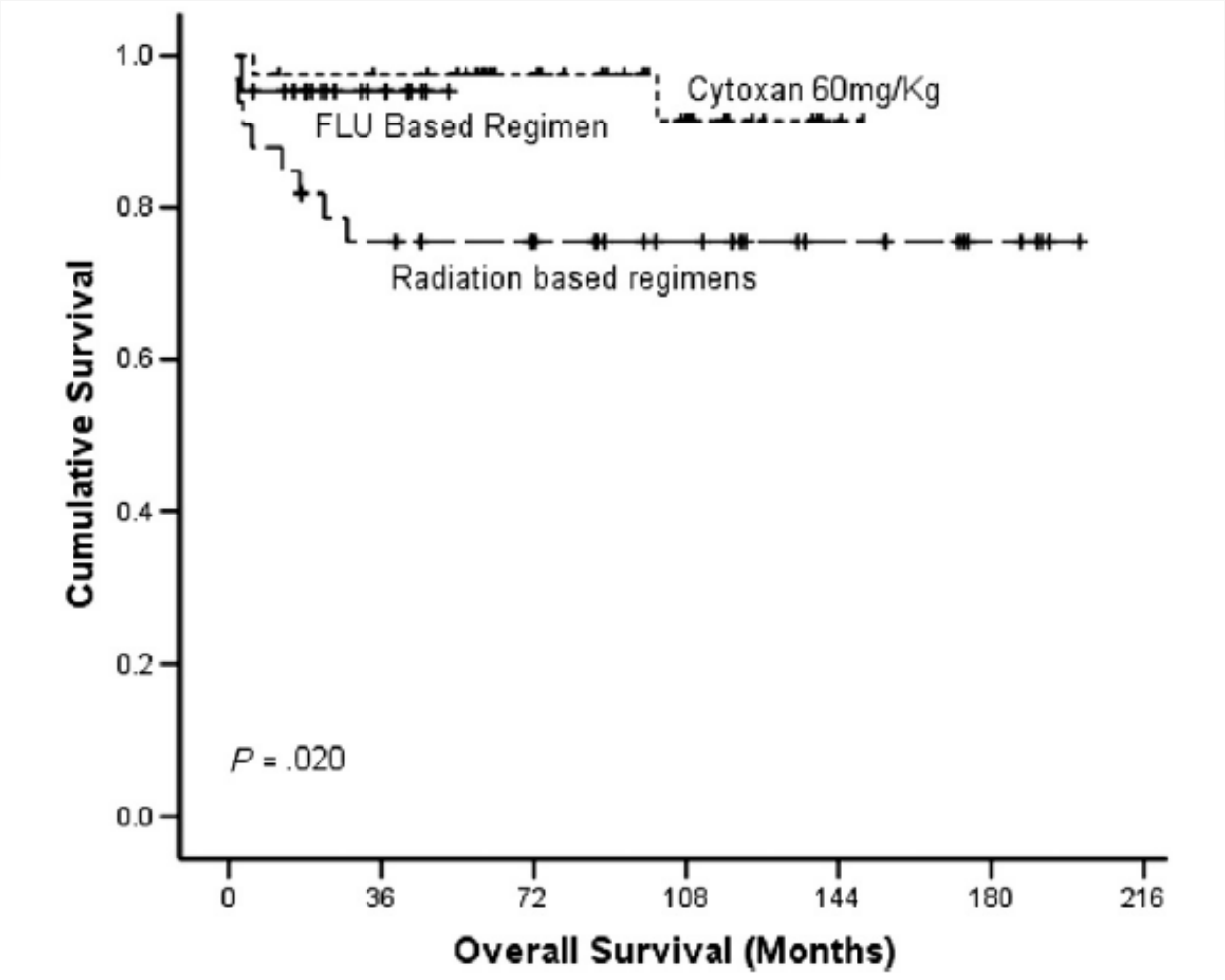


Figure 2. Overall survival according to the conditioning regimen.

Ayas et al, Biol Blood Marrow Transplant 2014

MUD/Unrelated cord blood HCT in Fanconi anemia

- 130 FA patients (median age, 9.0 years) underwent alternative donor HCT at the University of Minnesota between 1995 and 2012
- All patients received CY, single fraction TBI, and ATG with or without fludarabine (FLU), followed by T-cell–depleted bone marrow or unmanipulated umbilical cord blood transplantation
- The addition of FLU enhanced engraftment 3-fold

Macmillan et al, Blood. 2015;125:3798-804

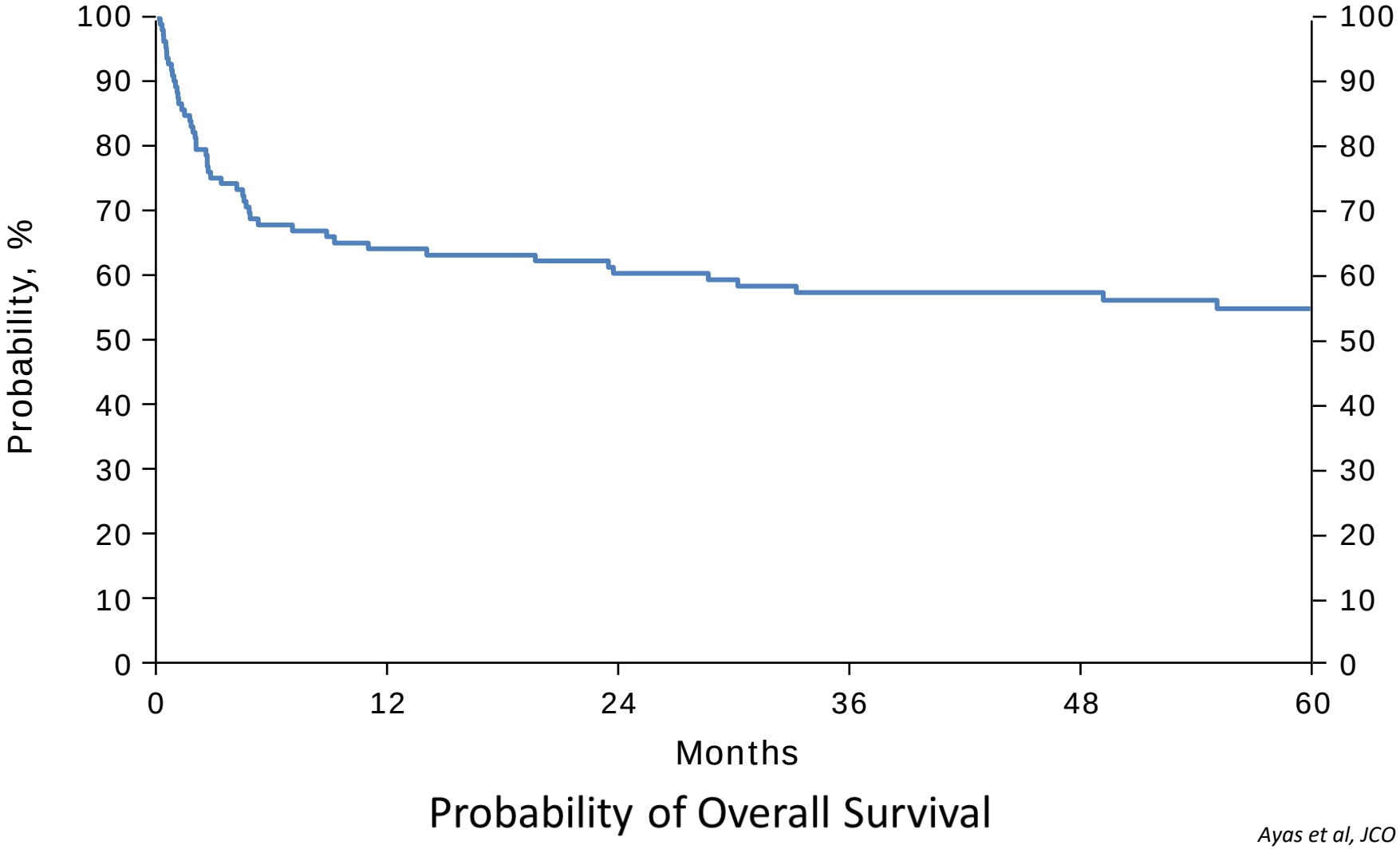
MUD/Unrelated cord blood HCT in Fanconi anemia

- The incidence of grades 2-4 aGVHD/cGVHD was 20% and 10%, respectively
- Severe toxicity was highest in patients >10 years of age or those with a history of opportunistic infections or transfusions before HCT
- Mortality was lowest in patients without a history of opportunistic infection or transfusions and who received conditioning with TBI 300 cGy, CY, FLU, and ATG
- These patients had a probability of survival of 94% at 5 years

HCT in Fanconi anemia with MDS/leukemia:

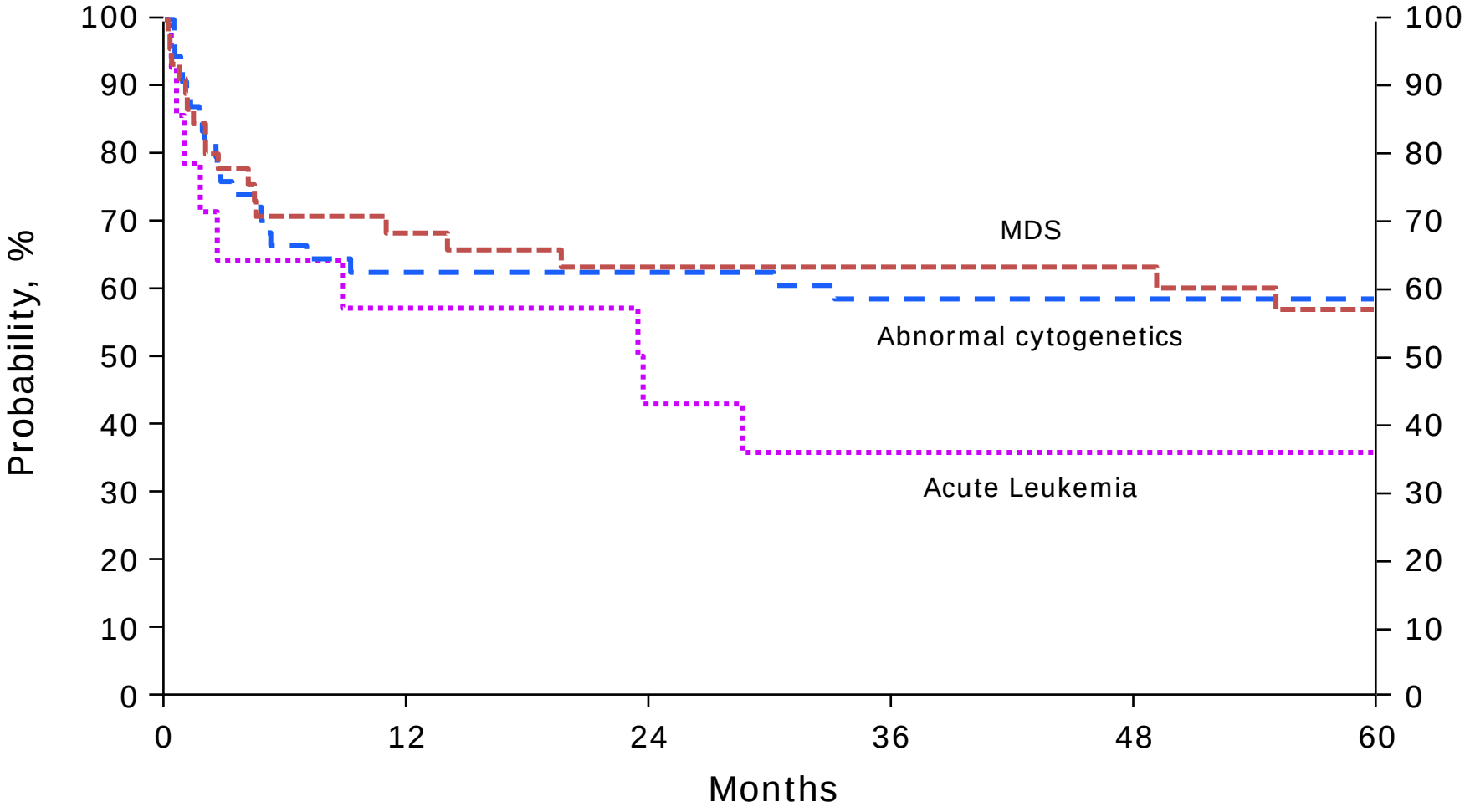
- CIBMTR data between 1985 and 2007
- 113 FA patients who had evidence of clonal abnormalities, MDS, or acute leukemia before HCT
- The primary outcome studied was survival

HCT in Fanconi anemia with MDS/leukemia:



Ayas et al, JCO 2014

HCT in Fanconi anemia with MDS/leukemia:



Probability of Overall Survival by Clonal Disease

Ayas et al, JCO 2014

HCT in Fanconi anemia with MDS/leukemia

Variable	N eval	Prob (95% CI)	P-value
Patient Age at transplant			0.001
≤14 years	59	69 (57-80)	
> 14 years	54	39 (26-53)	
Clonal disease prior to HCT			0.46
Acute leukemia/MDS	59	51 (38-64)	
Abnormal cytogenetics	54	58 (45-71)	

Ayas et al, JCO 2014

HCT in Fanconi anemia with MDS/leukemia

Variable	N eval	Prob (95% CI)	P-value
Patient Age at transplant			.00006
≤14 years	38	78 (64-90)	
> 14 years	44	34 (20-50)	
Clonal disease prior to HCT			0.03
Acute leukemia/MDS	44	43 (27-59)	
Abnormal cytogenetics	38	67 (52-81)	

Ayas et al, JCO 2014

Haplo-identical HCT in Fanconi anemia

- Haploidentical HCT provides an opportunity for patients to benefit from transplant when an HLA genotypically matched sibling is not available
- In non-FA pts, several reports documented high rates of stable engraftment/low risk of graft-versus-host disease (GVHD) using unmanipulated HLA-mismatched stem cells from related donors and post HCT high-dose cyclophosphamide (PT-CY) for GVHD prophylaxis

Haplo-identical HCT in Fanconi anemia

- In FA patients, concerns are raised that high dose alkylating agents in FA are associated with increased toxicity and mortality and that lower doses of PT-CY may lead to increased GVHD
- The optimal dose for PT-CY in FA patients is therefore undetermined

Haplo-identical HCT in Fanconi anemia

- 30 FA patients used fludarabine 150 mg/m2 + TBI 200 to 300 cGy ± CY 10 mg/kg without or with ATG 4 to 5 mg/kg PT-CY at 25 mg/kg/day on days +3 and +5, CSA and mycophenolate mofetil (MMF) were given to all patients
- All engrafted in the subgroup of patients who did not receive ATG (n = 14), but their transplant course was complicated by high rates of acute and chronic GVHD; only 8 patients are alive

Biol Blood and marrow transplant. 2016 Nov [Epub ahead of print]

Haplo-identical HCT in Fanconi anemia

- In the subgroup that received ATG (n = 16), 14 patients had sustained engraftment, severe GVHD rates were lower, and 13 patients are alive
- Hemorrhagic cystitis occurred in 50% of patients, whereas cytomegalovirus reactivation occurred in 75%
- One-year overall survival for the entire cohort was 73%, and all surviving patients achieved full donor chimerism

Biol Blood and marrow transplant. 2016 Nov [Epub ahead of print]

Haplo-identical HCT in Fanconi anemia

KFSHRC experience

- We are using:
  - fludarabine 30mg/m2/day x 5
  - Anti-Thymocyte globulins 5mg/kg/day x 4
  - Total body irradiation (TBI; 200 cGy) x 1
- GVHD prophylaxis with cyclosporine and mycophenolate and PT-CY 25 mg/kg on days +3, and +5

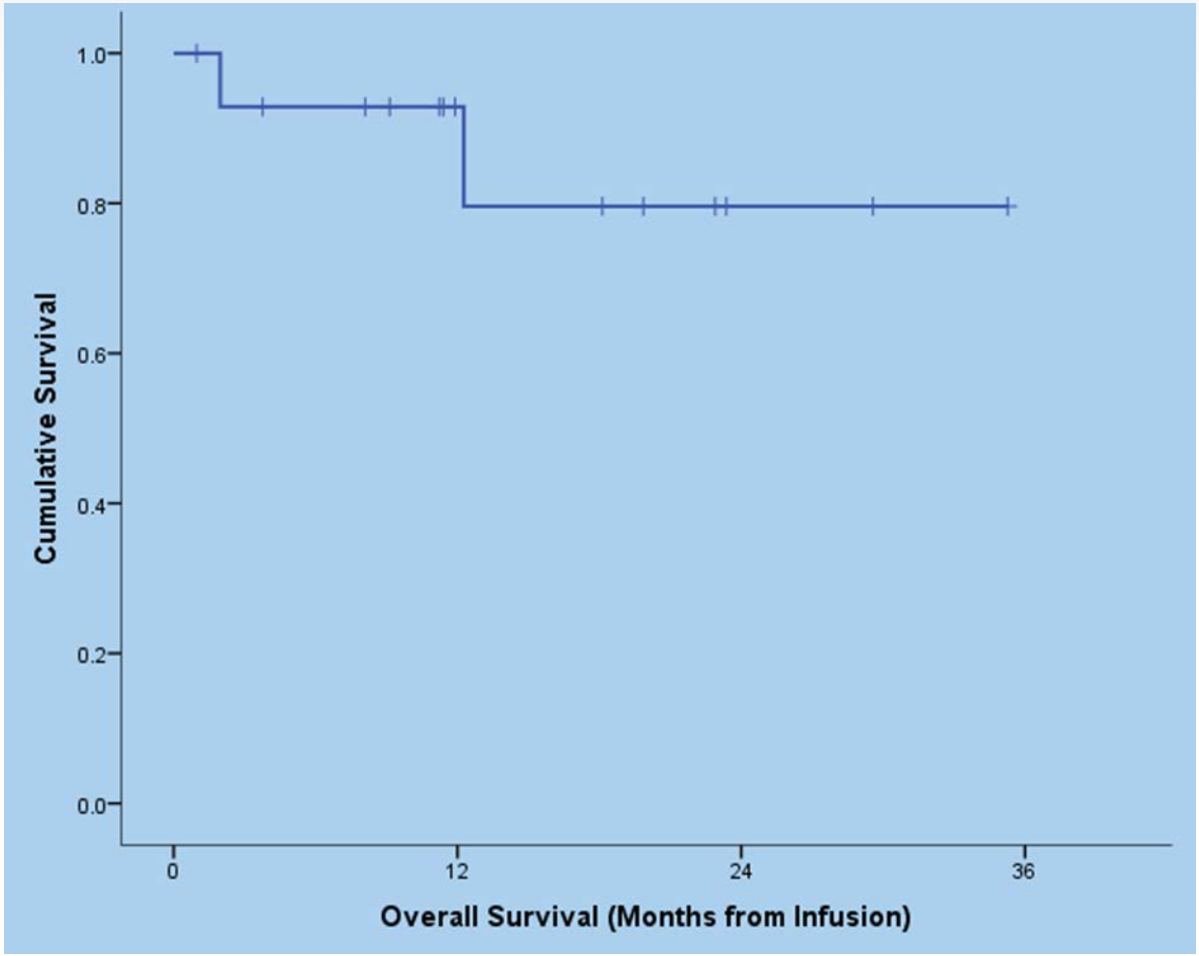
Haplo-identical HCT in Fanconi anemia

- Absolute neutrophil count (ANC) recovery occurred in all patients, median of 13 days (11-15)
- Platelet-transfusion independence occurred in 12, median of 20.5 days (16-112)
- Severe mucositis (Grade III and above) developed in 5 pts and hemorrhagic cystitis in 2
- Grade I-II aGVHD of skin occurred in 2 pts and grade III-IV GVHD of skin/liver/gut in 3 (1 patient expired)

Haplo-identical HCT in Fanconi anemia

- Thirteen (86.7%) patients are now alive with normal hematopoiesis; all have 100% donor chimerism both myeloid and lymphoid
- Primary causes of death included severe GVHD in one and relapsed leukemia in the other
- At a median follow-up of 18.1 months (95%CI: 6.7-29.6), the three year probability of overall survival for this cohort is 0.796±0.136

Haplo-identical HCT in Fanconi anemia



HCT in Dyskeratosis congenita

- In patients with DC the evidence supporting the use of reduced intensity conditioning (RIC) transplants is lacking
- However, many series reported increased pulmonary and hepatic toxicities with conventional intensity regimens
- It has been proposed that the use of RIC may induce milder toxicity and better survival

HCT in Dyskeratosis congenita

- An analysis from EMBMT of 9 DC patients who underwent an HCT from HLA-matched, morphologically normal-related donors revealed that 7 patients were alive and transfusion independent at a median follow-up of 61 (0.8-212) months
- RIC was used in eight patients
- GVHD prophylaxis consisted of CSA with MTX or MMF

Ayas et al, Bone marrow transplant. 2013; 48(9): 1168-1172.

HCT in Dyskeratosis congenita

- ATG was administered at various doses in four cases
- Median time to ANC engraftment was 21 (17-27) days
- In one case, late graft failure was noted at 10.4 months
- One patient developed grade II acute GVHD, and 5 had Chronic GVHD
- One death was due to metastatic gastric adenocarcinoma and another to graft failure

Ayas et al, Bone marrow transplant. 2013; 48(9): 1168-1172.

HCT in Dyskeratosis congenita

- 34 DC patients after HCT, over 3 decades, was reported by CIBMTR
- 10-year probability of survival of 30% with 14 patients alive at last follow-up
- The median age at HCT was 13 years (range, 2 to 35)
- Approximately 50% of transplantations were from related donors
- The day-100 probability of grade II to IV acute GVHD and the 3-year probability of chronic GVHD were 24% and 37%

Gadalla et al, Biol Blood Marrow Transplant. 2013; 19: 1238-*1243*.

HCT in Dyskeratosis congenita

- 10 deaths occurred within 4 months from transplantation due to graft failure (or other HCT-related complications; 9 of these patients had undergone HCT from mismatched related or from unrelated donors
- 10 deaths occurred after 4 months; 6 of them occurred more than 5 years after HCT, and 4 of these were attributed to pulmonary failure suggesting that regimen intensity and HCT from mismatched related or unrelated donors were associated with early mortality

Gadalla et al, Biol Blood Marrow Transplant. 2013; 19: 1238-*1243*.

HCT in Dyskeratosis congenita

- Transplantation of grafts from HLA-matched siblings with CY-containing nonradiation regimens was associated with early low toxicity
- Late mortality was attributed mainly to pulmonary complications

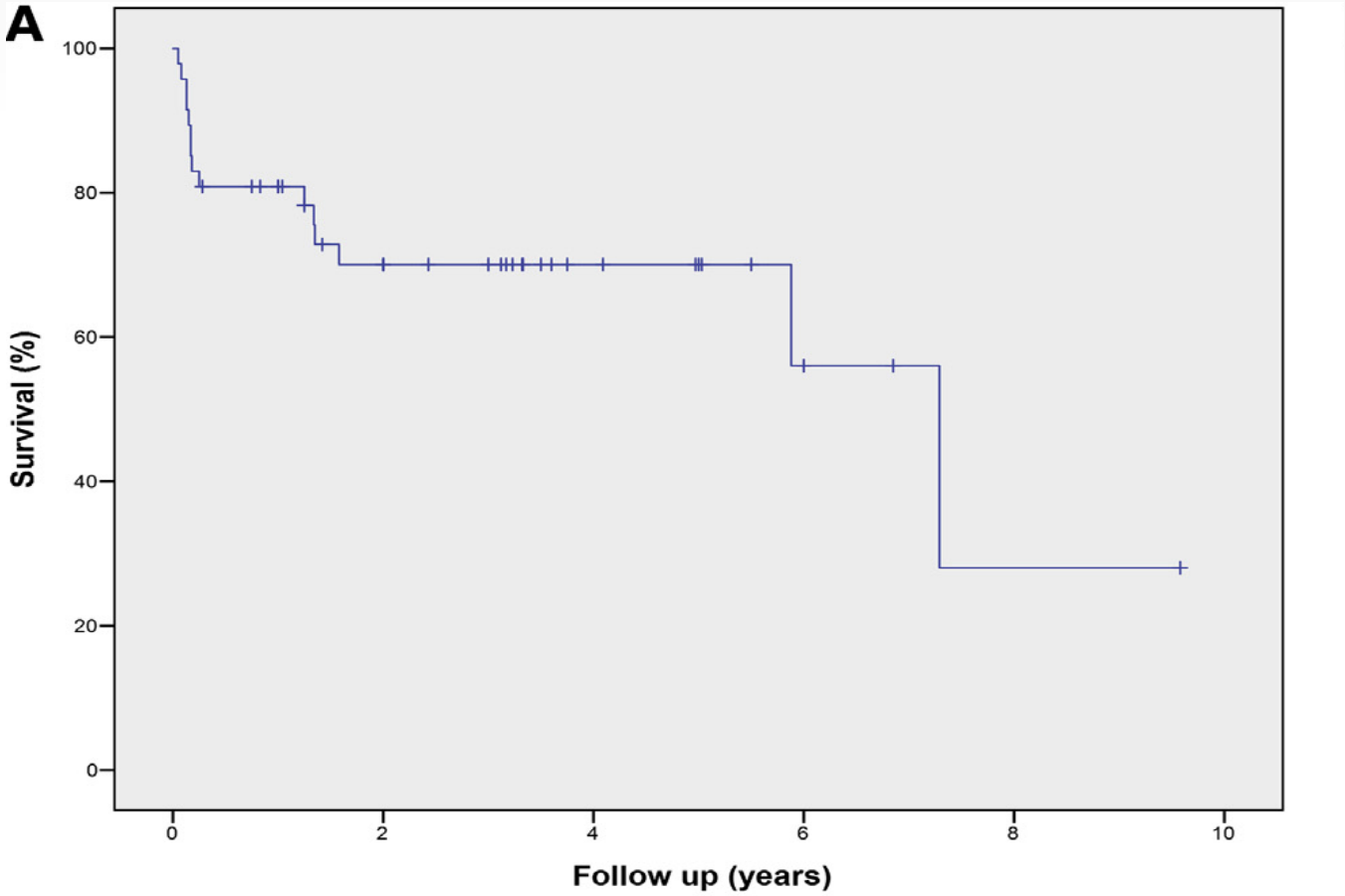
Gadalla et al, Biol Blood Marrow Transplant. 2013; 19: 1238-*1243*.

HCT in Dyskeratosis congenita

- 54/109 patients (50%) were alive at last reported
- follow-up
- Predicted 5-year overall survival rate for the entire cohort was 57%
- There was a continual decline in survival with 10-year survival estimates of only 23%
- The most common causes of deaths reported were infection (24%), pulmonary disease (20%), and nonengraftment (17%)

P. Barbaro et al. Biol Blood Marrow Transplant 22 (2016)

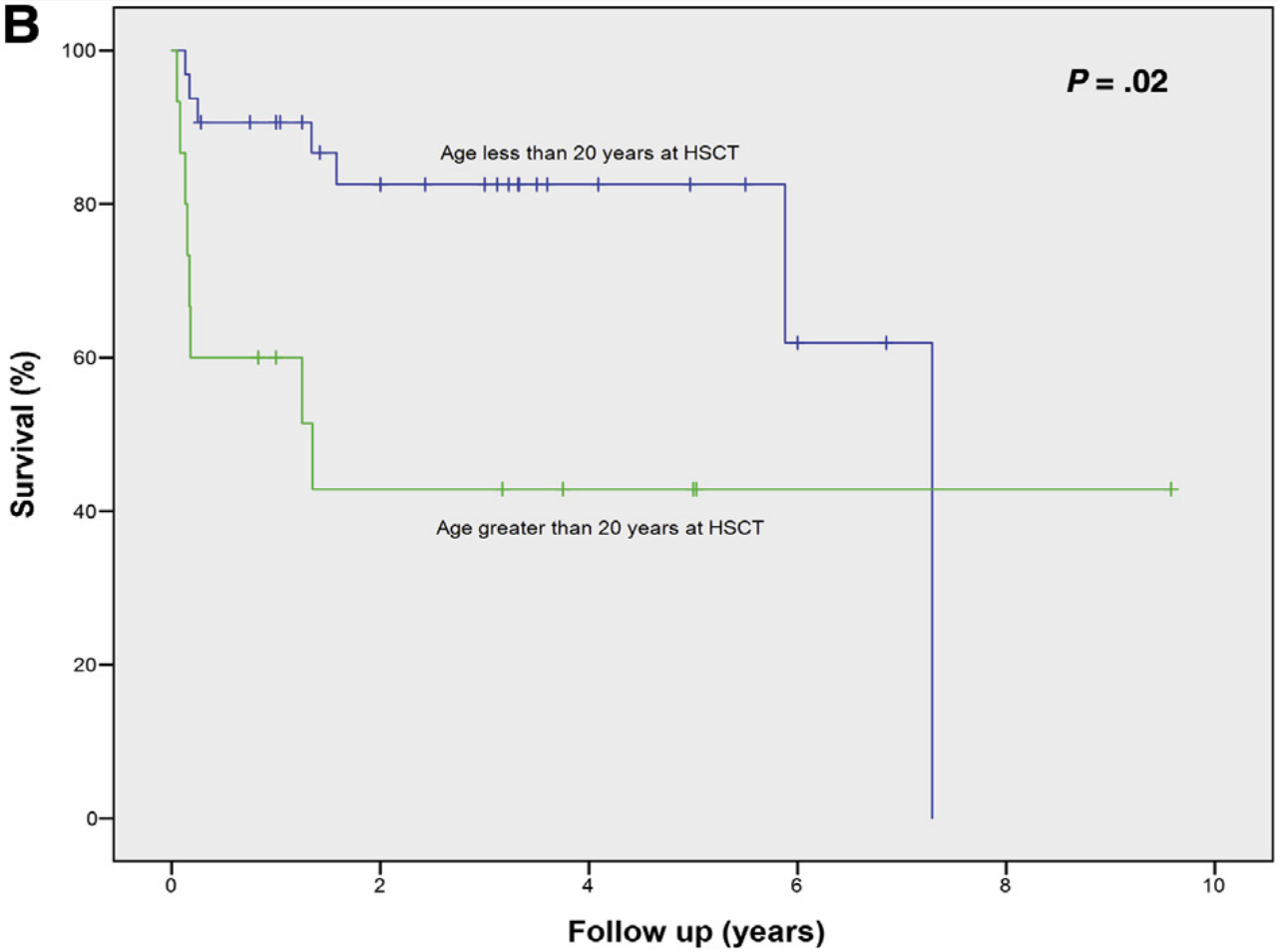
HCT in Dyskeratosis congenita



Overall survival for the entire cohort analyzed from the literature search

P. Barbaro et al. Biol Blood Marrow Transplant 22 (2016)

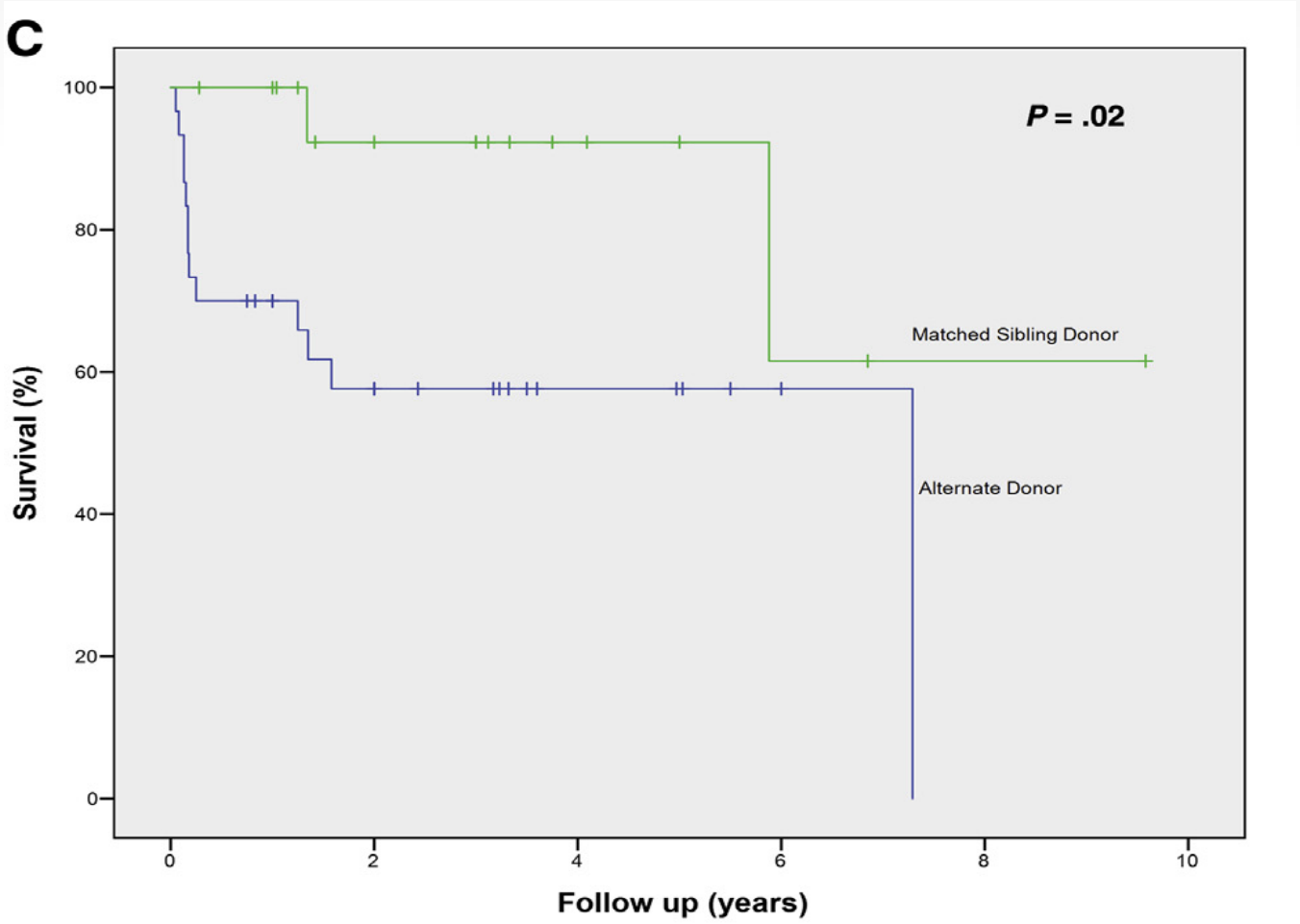
HCT in Dyskeratosis congenita



Survival by age group at transplant (above and below 20 years

P. Barbaro et al. Biol Blood Marrow Transplant 22 (2016)

HCT in Dyskeratosis congenita



Survival based on donor source (MSD versus alternate donor)

P. Barbaro et al. Biol Blood Marrow Transplant 22 (2016)

HCT in Dyskeratosis congenita

- Should the carrier status be determined in related donors for DC patients undergoing related HCT?
- Possibility of future hematological deterioration even in carriers
  - One report indicates that one silent carrier has subsequently developed mild thrombocytopenia and a hypocellular marrow
- Silent carriers should be avoided as donors
  - Some families have unknown gene mutations, it is strongly recommended that lymphocyte telomere length in the donor be determined before donation

Conslusions

- The major strides that have been made towards understanding the cause and finding a cure for bone marrow failure syndromes not only helped improve outcome in patients with BMF but also led to major discoveries in cancer biology
- Matched related donor HCT in FA is associated with excellent outcomes
- Alternative donor stem cell transplant is now a reality and is associated with extremely favorable outcomes in FA

Conslusions

- Bone marrow failure is a curable aspect of FA
- Solid tumors remain a leading cause of death in FA patients: Education and early detection remain the key to survive these malignancies

Conslusions

- In patients with DC, the data are less clear as to the best HCT approach
- It is recommended to avoid carriers as donors
- Use of reduced intensity conditioning is probably better