STEM CELL TRANSPLANTATION IN MYELOFIBROSIS

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Critical Issues

- Decision
- Risk communication (how and what)
- Prognostic factors
- Pre-transplant splenectomy/spleen reduction
- Conditioning regimen (myeloablative vs non-mieloablative; high-toxicity vs low-toxicity)
- Immunosuppressive regimen
- Monitoring after transplant

Allogeneic Stem Cell Transplant in Myelofibrosis

Who and when to transplant

Deciding transplant

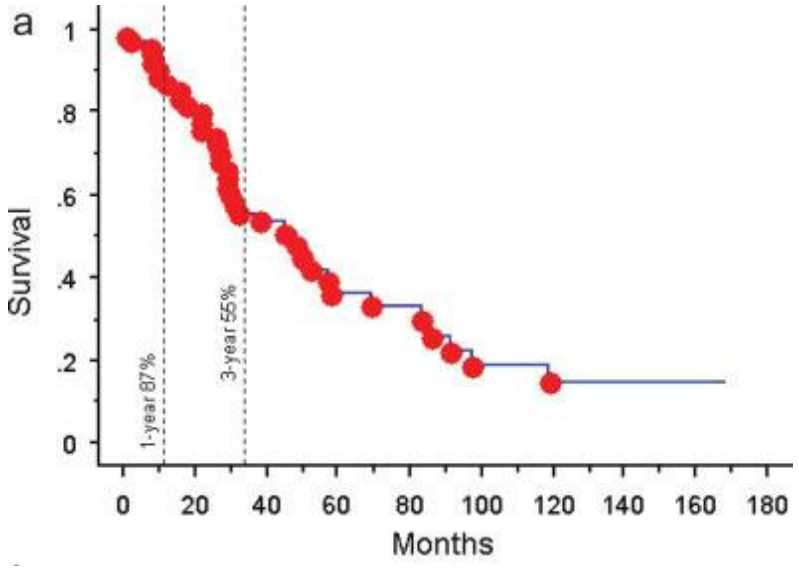
1. Evidence-based decision (clinical trials)

- No clinical controlled trials in myelofibrosis
- Theoretically feasible (genetic allocation/randomization)
- Genetic randomization in chronic diseases difficult
- No projects (to my knowledge)

Deciding transplant

1. Evidence-based decision (clinical trials)
2. Inductive reasoning (compare the outcomes of transplant vs. non transplant in comparable populations of subjects)

Overall survival of 65 young patients (age < 60 years) with primary myelofibrosis and high-or intermediate-risk disease category at Mayo Clinic



The 1- and 3-year survival rates were 87% and 55% respectively

Siragusa et al, Am J Hematol 2009

Reference	N. of patients	Median age (years)	Intermediate/high risk	Survival
Myeloablative conditioning				
Guardiola et al	55	42	76%	31% at 5 y
Deeg et al	56	43	53%	58% at 3 y
Kerbauy et al.	104	49		61% at 7 y
Reduced-intensitiy conditioning				
Rondelli et al.	21	54	100%	85% at 2.5 y
Bacigalupo et al.	46	51	91%	45% at 5 y
Kroeger et al.	103	55	88%	67% at 5y
Various conditioning				
Patriarca et al.	52	53	89%	54%
Gupta et al.	46	47-54	84.7%	48-68% at 3 y
Ballen et al.	289	45	67%	39% at 5 y

Comparison of survival rates with HSCT and medical therapy in patients with high-intermediate-risk myelofibrosis

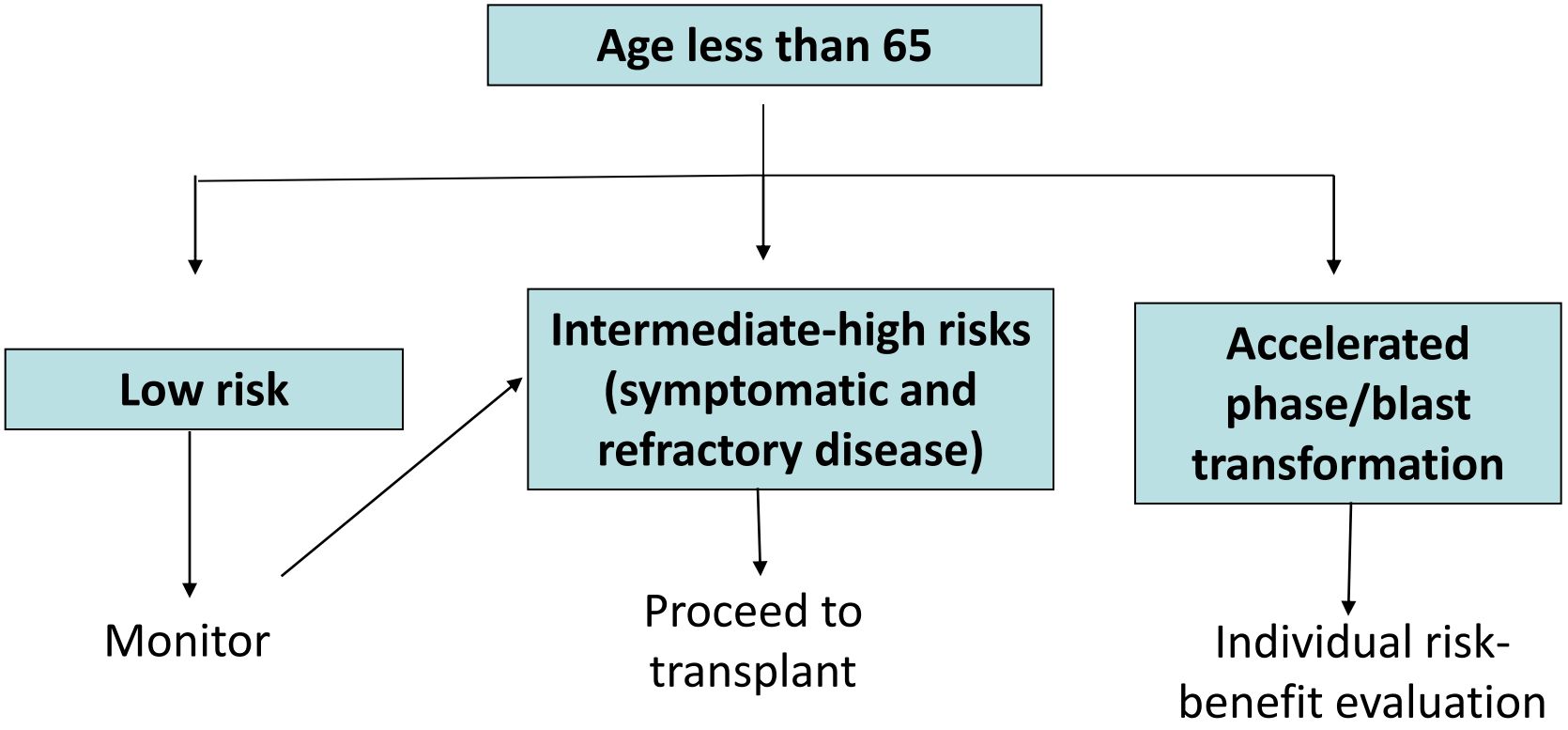
- The survival rates with HSCT differ among the studies.
- The most numerous study (Ballen, 2010) reports 5-year overall survival rates from 30 to 40%
- The more optimistic is the European study from Kroeger (2010) that reports 5-year survival rate of 67%
- The survival rates with HSCT do not appear to be substantially different than those obtained of patients with myelofibrosis who did not receive HSCT (55% at 3 years)

Philadelphia–Negative Classical Myeloproliferative Neoplasms: Critical Concepts and Management Recommendations from European LeukemiaNet

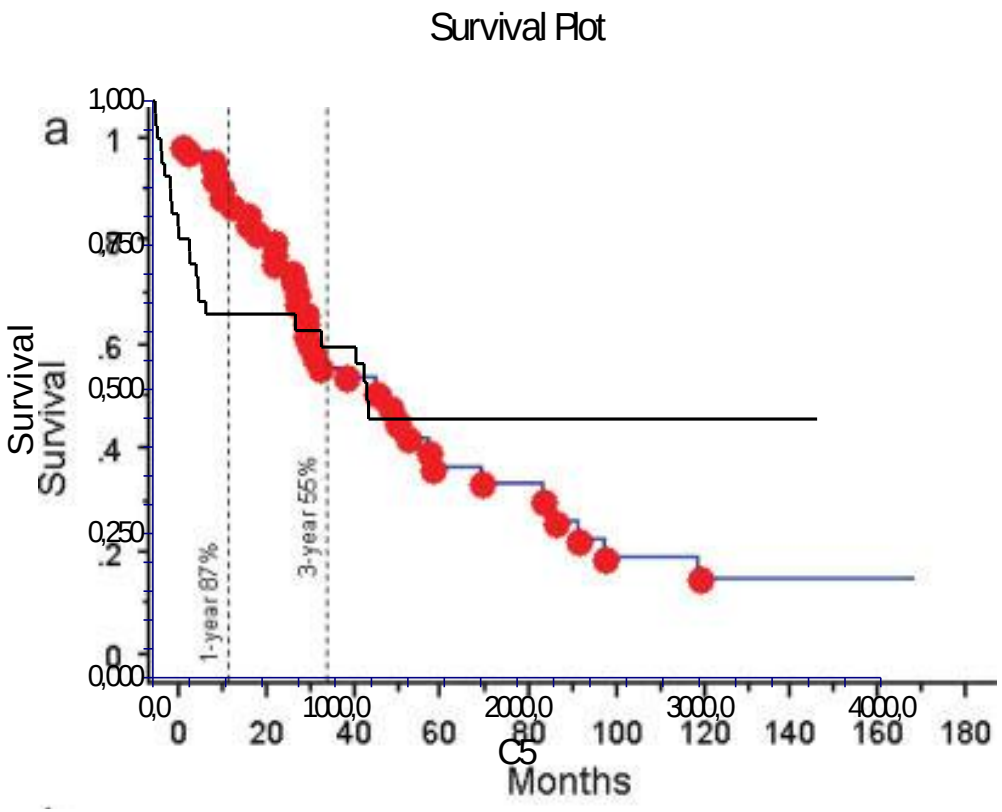
Barbui et al. JCO 2011

"It is reasonable to justify the risk of allo-SCT-related complications in otherwise transplant-eligible patients whose median survival is expected to be less than 5 years. This would include IPSS high (median survival ~27 months) or intermediate-2 (median survival ~48 months) risk patients as well as those with either red blood cell transfusion-need (median survival ~20 months) or unfavorable cytogenetic abnormalities (median survival ~40 months). "

Deciding Allo-SCT in Myelofibrosis by inductive reasoning



Criticism to decision by inductive reasoning



Comparing the survival plots of transplant vs non-transplant patients with PMF

Criticism to decision by inductive reasoning

It neglects:

1. Early-immediate death due to transplant

2. The individual chance of survival (disease stage-independent)

3. The quality of life after transplant

Deciding transplant

1. Evidence-based decision (clinical trials)
2. Inductive reasoning (compare the outcomes of transplant vs. non transplant in comparable populations of subjects)
3. An analytical approach (decision analysis model that takes into account the disvalue of early death, the quality of life after transplant, and the individual survival chance)

Valuing early death

Reference	N. of patients	Median age (years)	Transplant-related mortality
Myeloablative conditioning			
Guardiola et al	55	42	27% at 1 y
Deeg et al	56	43	20% at 1 y
Kerbauy et al.	104	49	34% at 5 y
Reduced-intensitiy conditioning			
Rondelli et al.	21	54	10% at 1 y
Bacigalupo et al	46	51	24% at 5 y
Kroeger et al.	103	55	16% at 1 y
Various conditioning			
Patriarca et al	52	53	30% at 1 y
Gupta et al	40	47-54	23-39%
Ballen et al	289	45	22% at day 100

Early death for transplant in myelofibrosis

Early transplant related mortality:

- 10 to 16% with reduced intensity conditioning
- 20 to 30% with myeloablative conditioning

Risk aversion and time-discounting

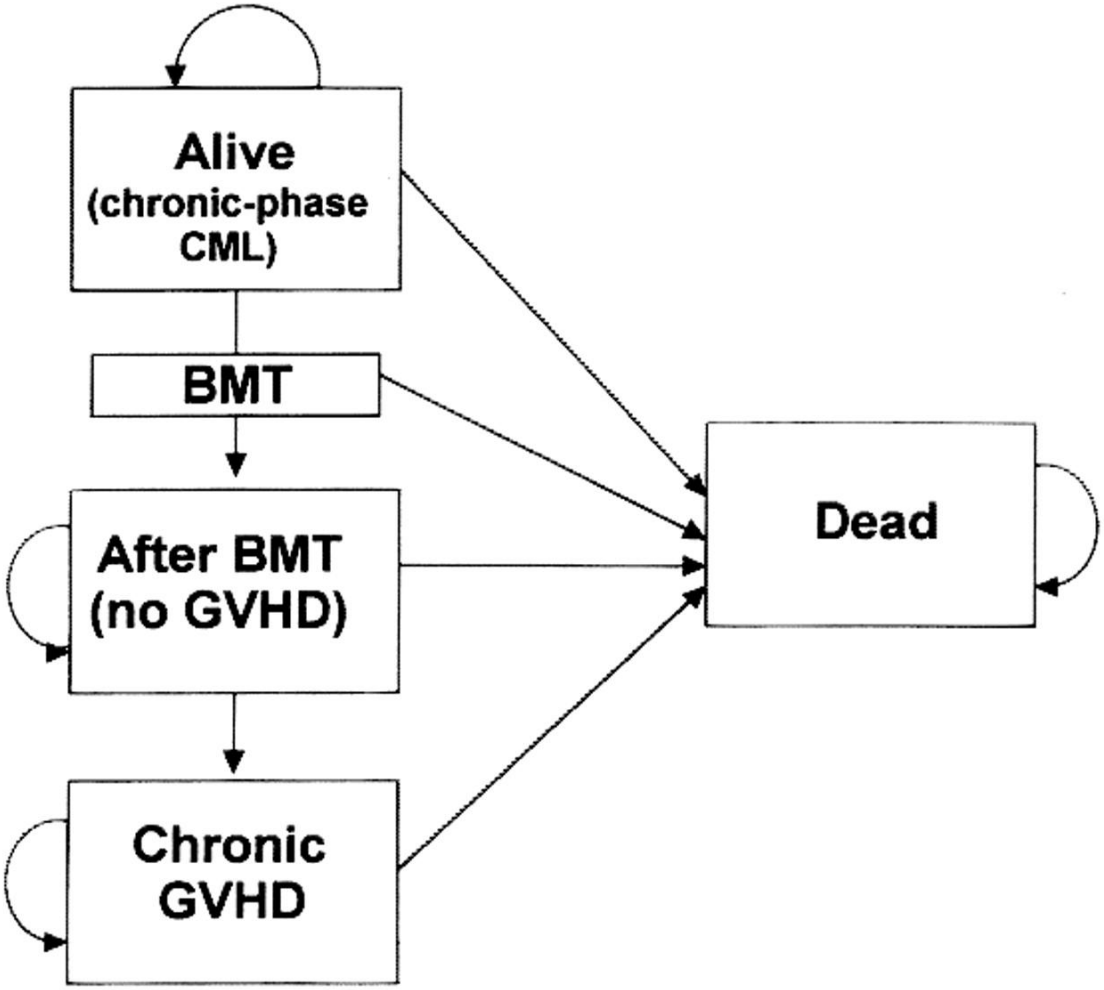
- Time preferences for life-years assumes that persons value present time more than they do distant time.
- Decision analysis models these concepts by a **declining exponential function of life years**. For example, at a 10% annual time discount rate, 1 year of life now is equivalent to 0.90 years of life next year, which is equivalent to 0.81 years of life 2 years from now
- Rates from near zero to more than 200% have been found in literature

Unrelated Donor Bone Marrow Transplantation for Chronic Myelogenous Leukemia: A Decision Analysis

Stephanie J. Lee, MD, MPH; Karen M. Kuntz, ScD; Mary M. Horowitz, MD, MS; Philip B. McGlave, MD;
John M. Goldman, DM; Kathleen A. Sobocinski, MS; Janet Hegland, BS; Craig Kollman, PhD;
Susan K Parsons, MD, MRP; Milton C. Weinstein, PhD; Jane C. Weeks, MD, MS; and Joseph H. Antin, MD

Annals of Internal Medicine, 1997

Structure of the Markov model.



Lee S J et al. Ann Intern Med 1997;127:1080-1088

Annals of Internal Medicine

Unrelated Donor Bone Marrow Transplantation for Chronic Myelogenous Leukemia: A Decision Analysis

(Lee SH et al. Ann Intern Med, 1997)

- Transplantation within the first year after diagnosis maximizes quality adjusted, discounted life expectancy.
- When the annual discount rate is greater than 21% (1 year of life now is equivalent to 0.87 years of life next year, which is equivalent to 0.76 years of life, 2 years from now), the model predicted that quality adjusted life survival is maximized by no transplantation

Quality of life with transplant

Quality of life and Transplant

- Studies on quality of life post-transplant have indicated GVHD as the main determinant of morbidity
- Although chronic GVHD often resolves in practice, most patients with this complication have ongoing compromised quality of life

Reference	N. of patients	Median age (years)	Chronic GVH-grade
Myeloablative conditioning			
Ballen et al	289	45	23-40%
Guardiola et al.	55	42	Limited 40.7% Extensive: 59.3%
Deeg et al	56	43	Limited: 5.5% Extensive: 51.8%
Kerbauy et al.	104	49	
Reduced-intensitiy conditioning			
Rondelli et al.	21	54	Limited: 28% Extensive:44%
Bacigalupo et al.	46	51	21-37%
Kroeger et al.	103	55	Limited: 24%; extensive: 24%
Patriarca et al.	52	53	Limited: 35% Extensive: 15%

GVHD in transplant for myelofibrosis

Extensive, chronic GVHD occurs in:

- 52-59% of patients transplanted with myeloablative conditioning
- 15-44% of patients with reduced-intensity conditioning

Transplant- and disease-specific prognostic factors

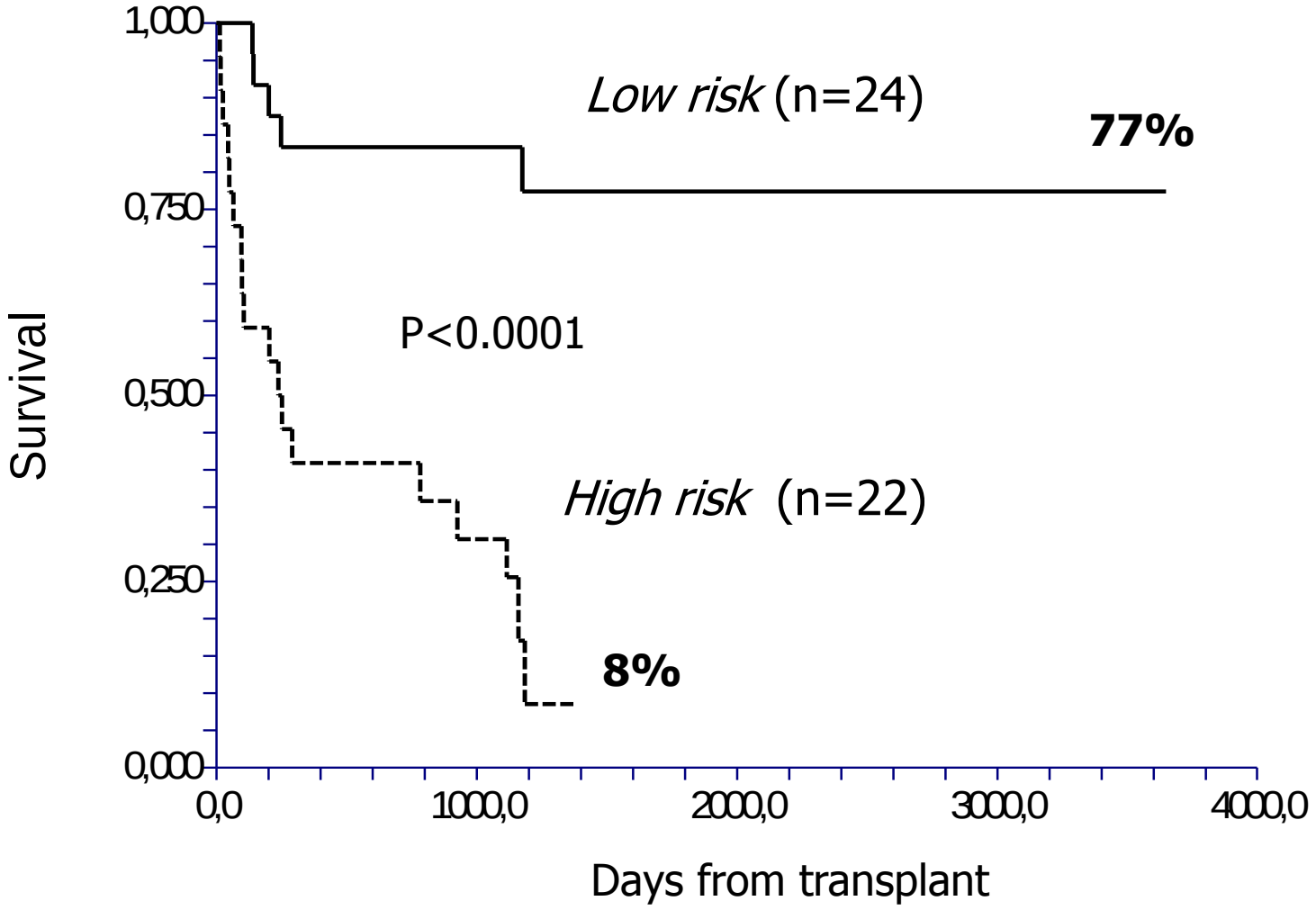
A Disease Specific Prognostic Score

Center: Genua; N= 40; Conditioning: RIC with Thiotepa and Cyclo

Variable	Univariate	Multivariate	
	P value	P value	RR
Peripheral blasts >1%	0.04		
BM blasts >5%	0.04		
AML-like chemotherapy	0.08		
Interval Dx/Tx >1013 d.	0.4		
Transfusions =>20	0.01	0.007	5.2
Spleen > 22 cm	0.02	0.01	3.8
Splenectomy yes/no	0.4		
Lille Score	0.9		
Donor HLA (id./unrelated)	0.1		
Donor age	0.9		
Patient age	0.8		

Spleen >22 cm: score 1
Transfusions >20: score 1
Alternative donor: score 1

Low risk= score 0-1
High risk =score 2-3



Best results for allo TX

- With favourable cytogenetics
- With short interval Dx TX
- Untransfused
- Low grade fibrosis
- With moderate, small splenomegaly
- JAK2 V617F positive

Conclusion

- Today we can only use inductive reasoning for deciding transplant in myelofibrosis
- Patients preferences about risk aversion, the impact of quality of life after transplant and the individual prognostic factors against transplant should be considered.
- A decision analysis model would help in revealing the most sensitive factors in the decision.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