THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Stem Cell Transplantation for Myelodysplastic Syndrome

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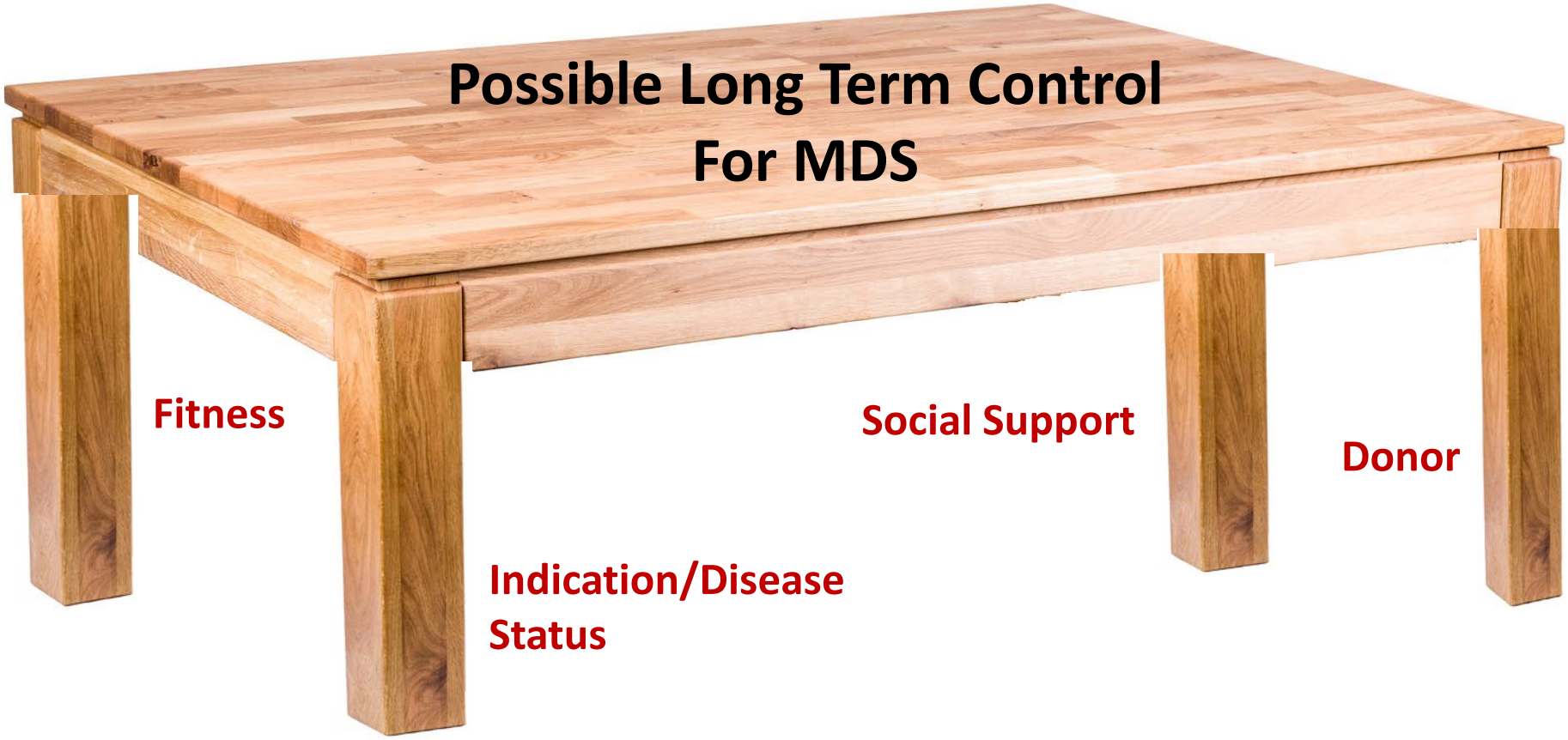
LEARNING OBJECTIVES

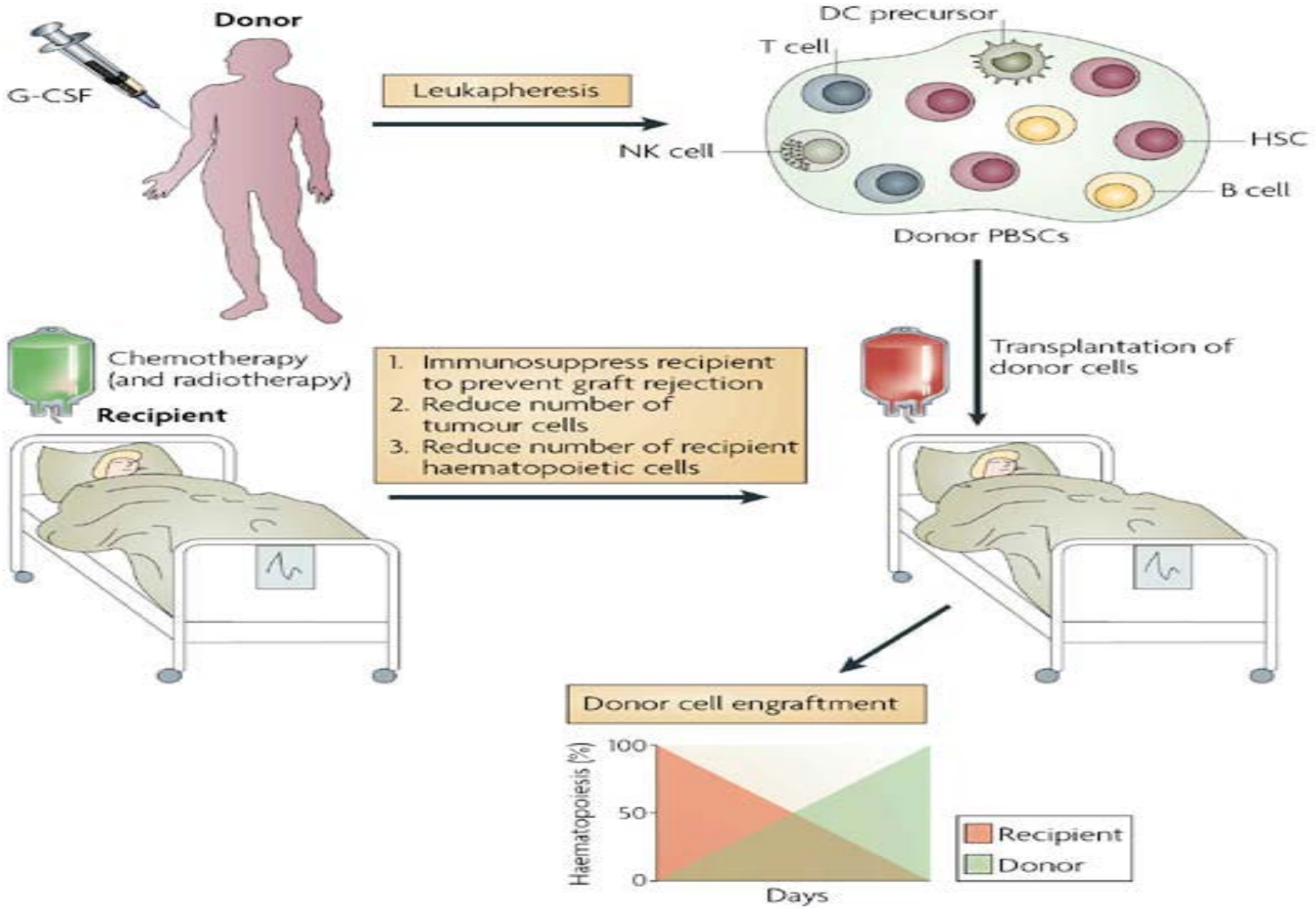
- **Indications for Transplantation in MDS**
- **Which patients?**
- **When?**
- **How?**

Possible Long Term Control For MDS



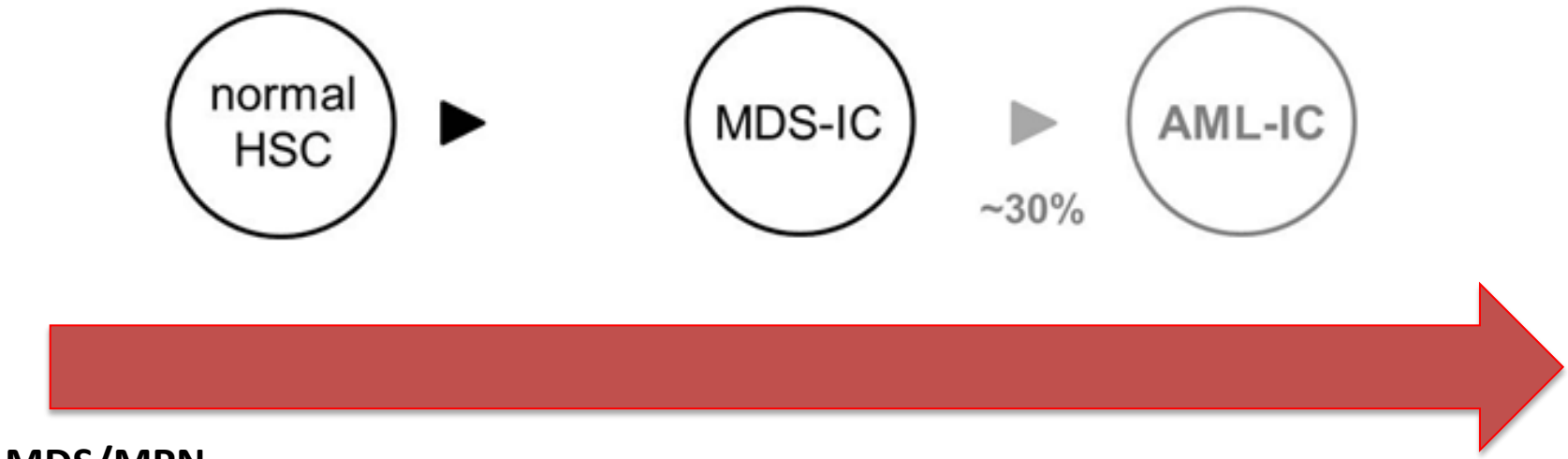
Exciting Time for Cancer Therapy

Allogeneic Stem Cell Transplantation is the original "immunotherapy"



Schlomick, Nature Reviews Immunology 2007)

Myeloid Disease on a Continuum

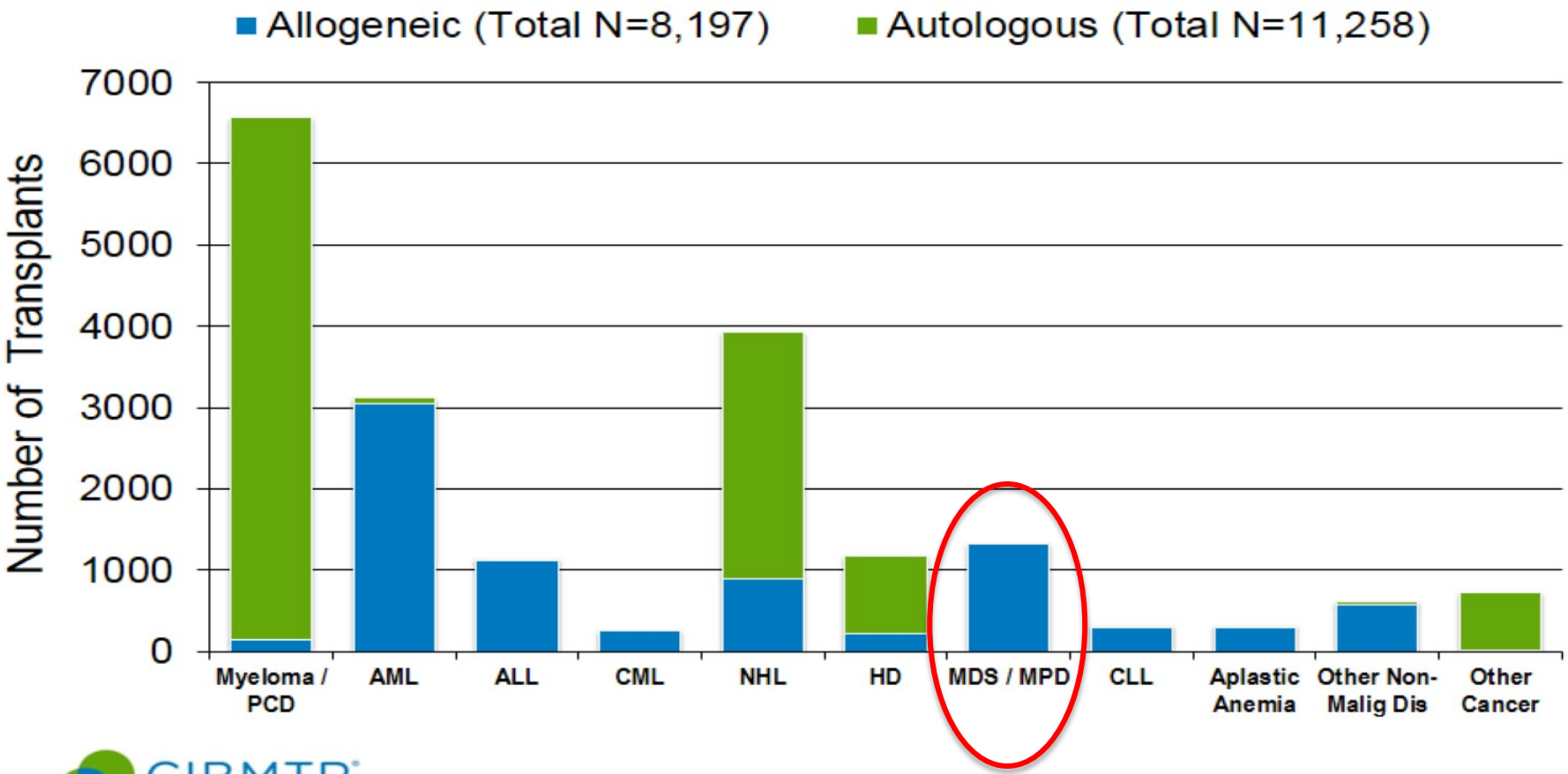


- **Risk**
- **Evolution**

When To Consider Transplant

Zhou et al. Int. J. Mol. Sci. 2015

Indications for Hematopoietic Stem Cell Transplants in the US, 2013



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Balancing Act

- **Efficacy of Allogeneic Transplantation (Intensity and GVL)**

vs…

- **Transplant Related Complications (GVHD, Infections etc.)**

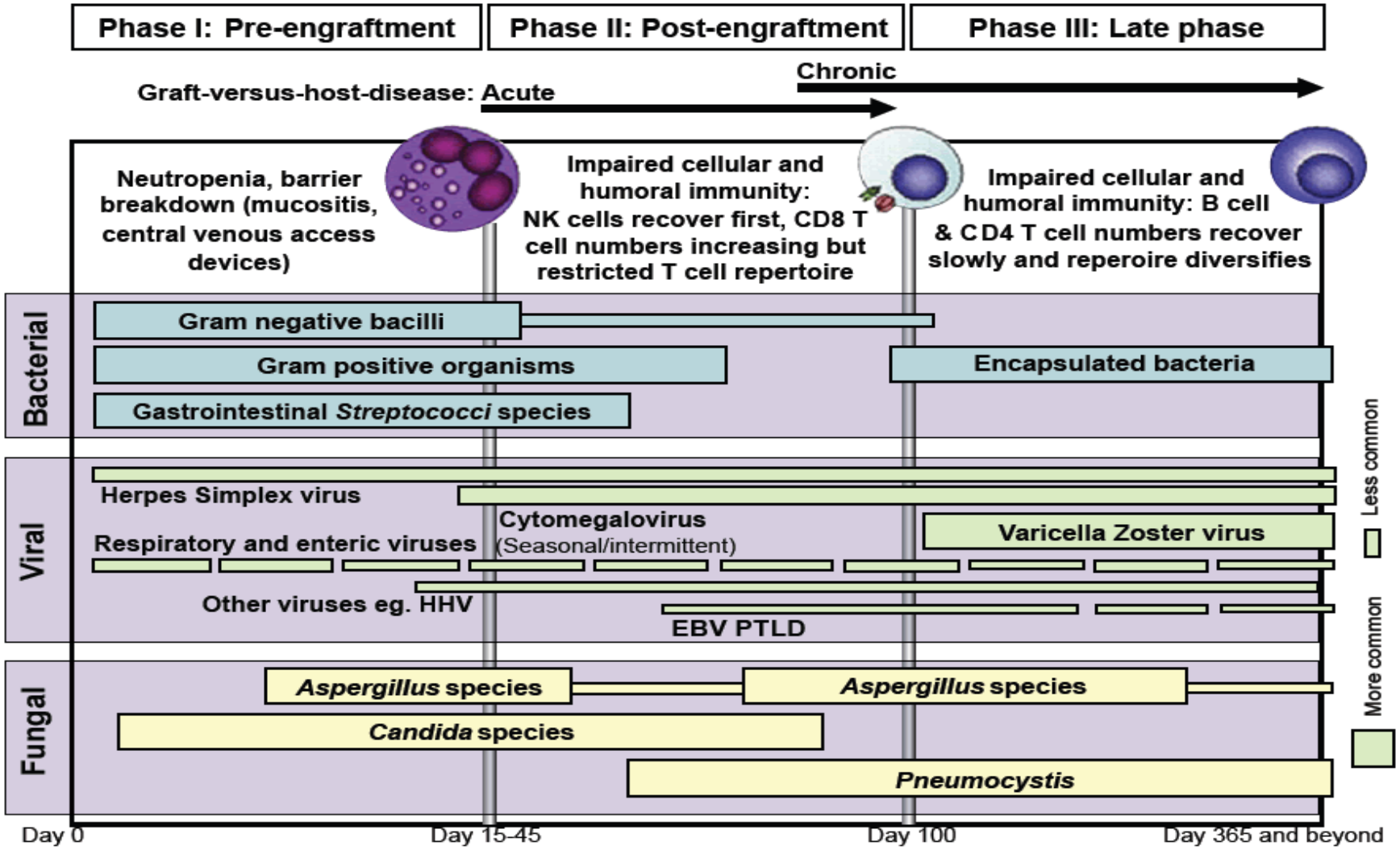
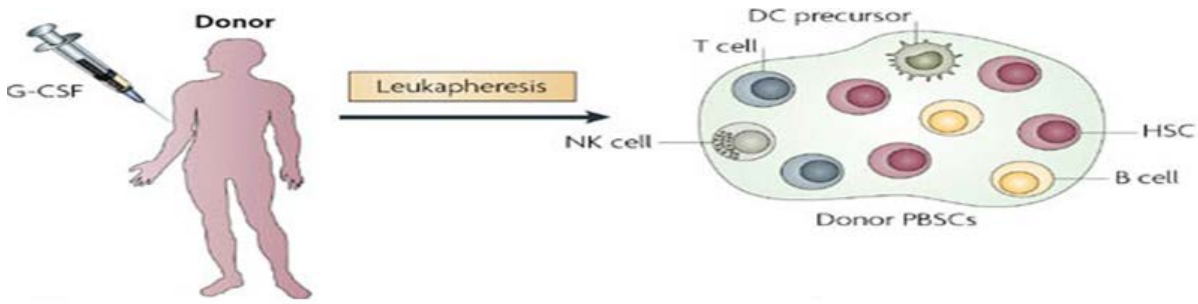


Figure 1: Phases of opportunistic infections among allogeneic HSCT recipients.

Kedia et al 2013

Balancing Risks



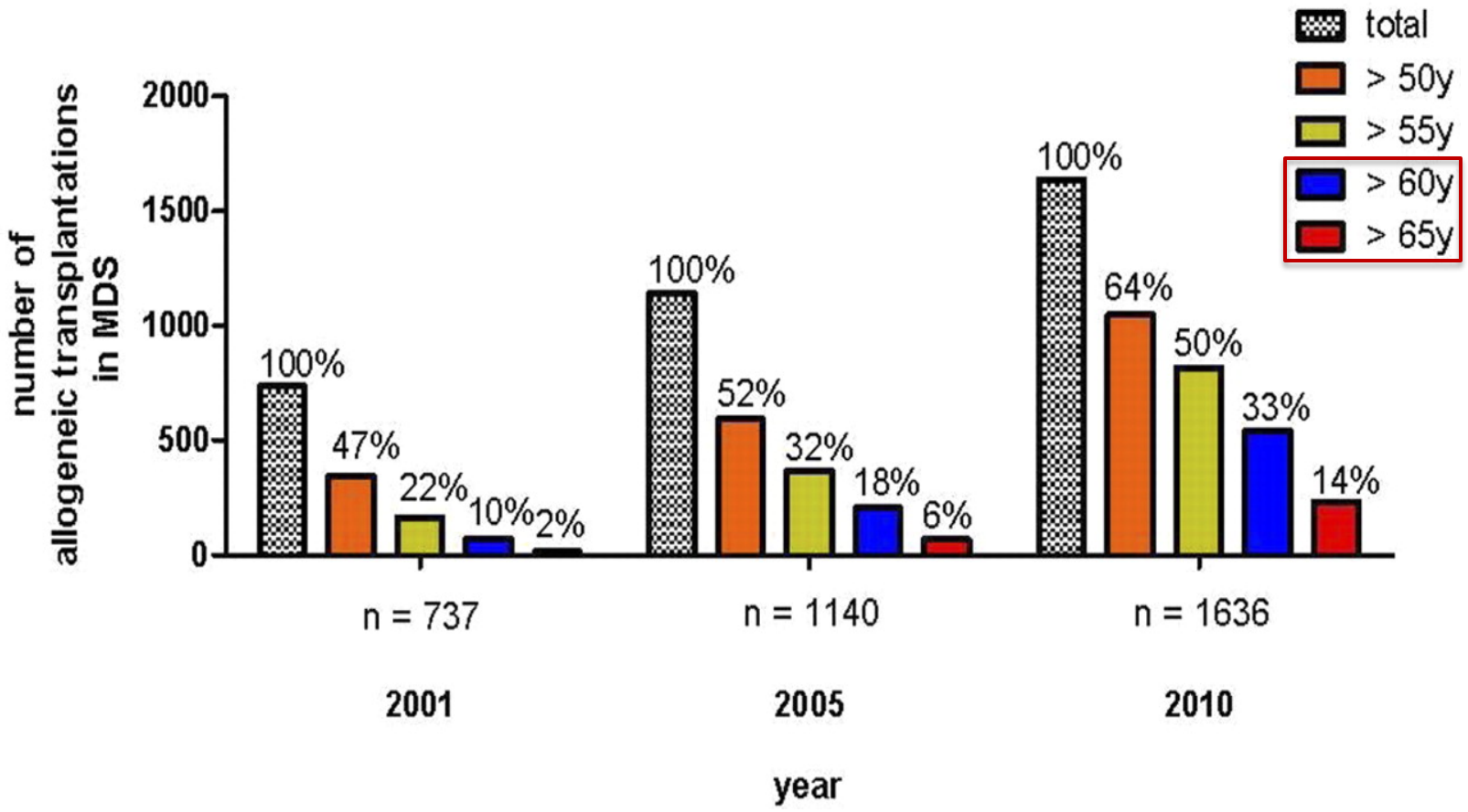
GVL
(Graft vs Tumor)

GVHD
(Graft vs Host Disease)

Barriers

- **Transplant is an important part of the treatment paradigm for certain MDS**
- **Optimal Transplant Referral & Evaluation**
- **Barriers to Referral**
  - **Historic negative perceptions about risks**
  - **Efficacy and toxicity especially in advanced age group patients**

MDS & Transplant



Kroger Blood 2012

Able To Offer Transplant To More

1980-1990's- >50 - Transplant

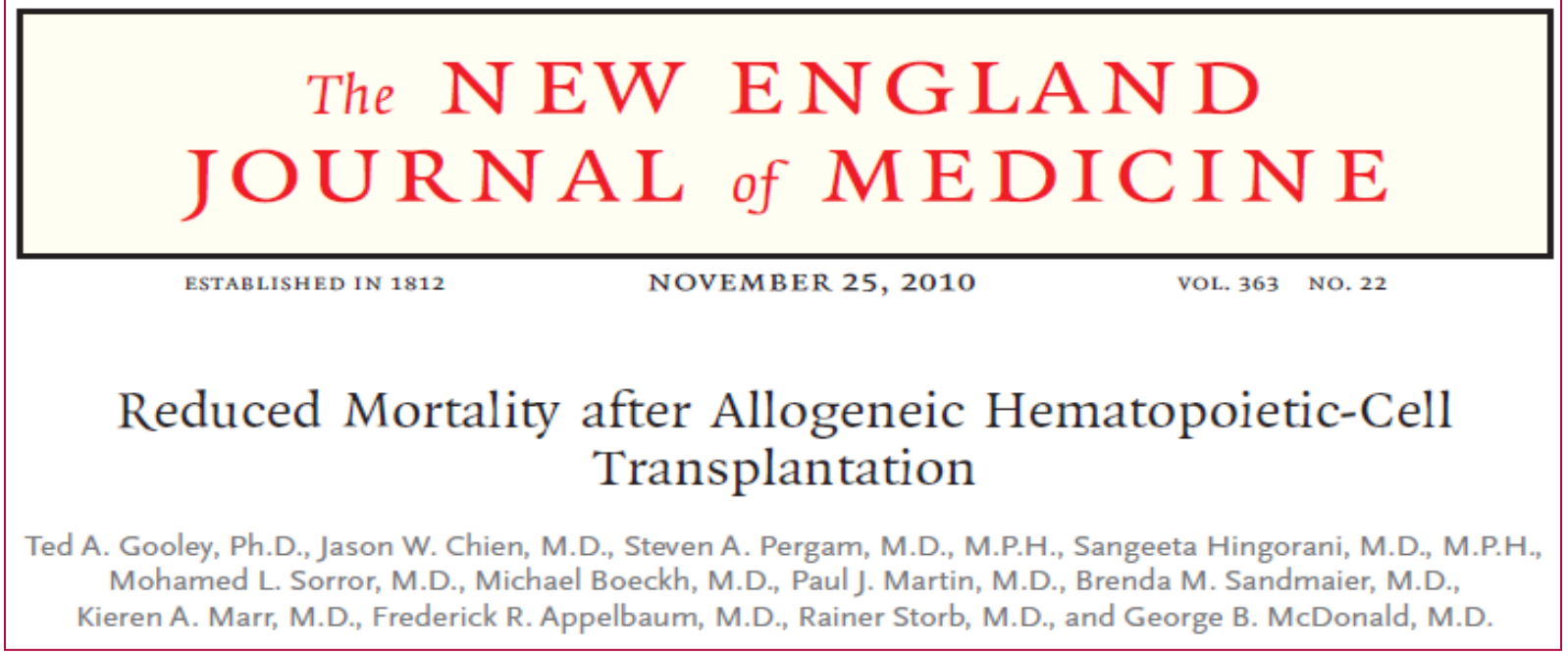
1990-2000's- >60 - Transplant

Early 2000's- >70 – Transplant

Current - >70 - Transplant

Yuichiro Miura

Especially Pertinent to MDS Patients



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 25, 2010 VOL. 363 NO. 22

Reduced Mortality after Allogeneic Hematopoietic-Cell Transplantation

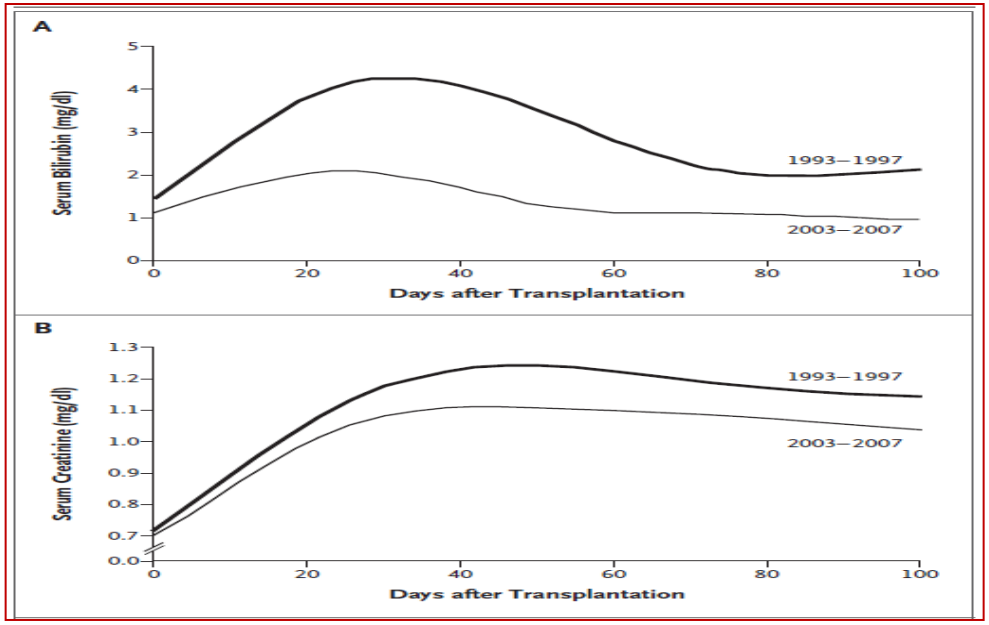
Ted A. Gooley, Ph.D., Jason W. Chien, M.D., Steven A. Pergam, M.D., M.P.H., Sangeeta Hingorani, M.D., M.P.H., Mohamed L. Sorror, M.D., Michael Boeckh, M.D., Paul J. Martin, M.D., Brenda M. Sandmaier, M.D., Kieren A. Marr, M.D., Frederick R. Appelbaum, M.D., Rainer Storb, M.D., and George B. McDonald, M.D.

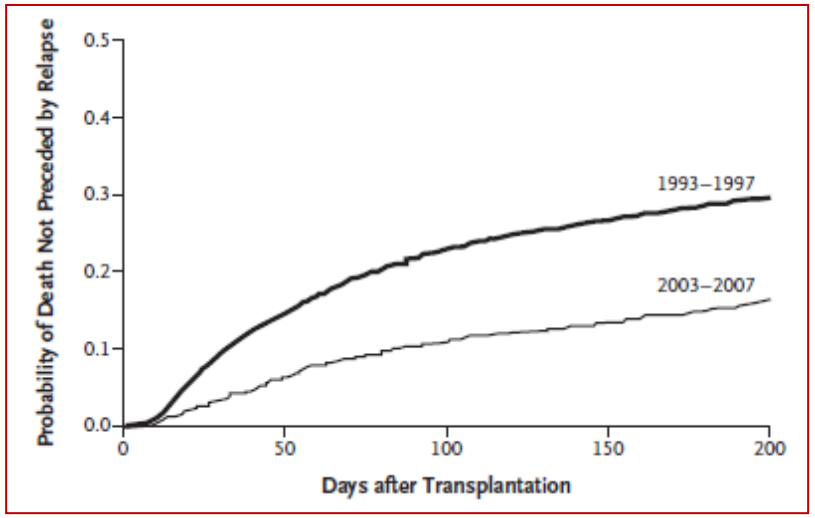
- **1400 pts (1993-1997) vs. 1200 pts (2003-2007)**
- **First Allogeneic Transplantation**
- **Survival, Relapse, Transplant Related Mortality (GVHD, Infection, Organ Damage)**

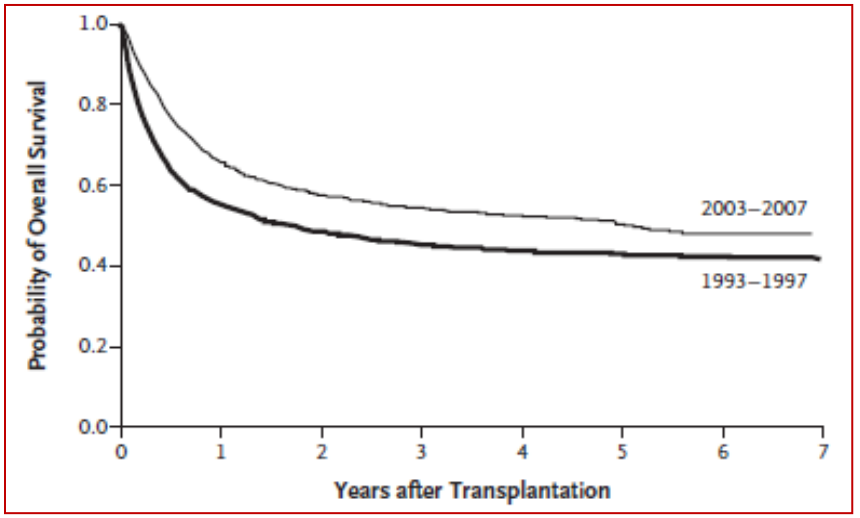
Table 1. Characteristics of Transplant Recipients According to Time Period.*

Variable	1993–1997 (N = 1418)	2003–2007 (N = 1148)	P Value†
Age — yr			<0.001
Median	37.4	47.2	
Range	0.6–67.8	0.4–78.9	
Diagnosis — no. (%)			<0.001
Aplastic anemia	46 (3)	39 (3)	
Acute lymphocytic leukemia	188 (13)	166 (14)	
Acute myeloid leukemia	352 (25)	459 (40)	
Chronic lymphocytic leukemia	15 (1)	32 (3)	
Chronic myeloid leukemia	463 (33)	104 (9)	
Hodgkin's lymphoma	18 (1)	3 (<1)	
Myelodysplastic syndrome	174 (12)	230 (20)	
Multiple myeloma	56 (4)	3 (<1)	
Non-Hodgkin's lymphoma	71 (5)	60 (5)	
Other	35 (2)	52 (5)	
Disease severity — no. (%)§			<0.001
Low	433 (31)	174 (15)	
Intermediate	427 (30)	622 (54)	
High	558 (39)	352 (31)	
Transplant donor — no. (%)			<0.001
HLA-identical sibling	625 (44)	443 (39)	
Mismatched sibling or relative who was not a sibling	200 (14)	29 (3)	
Unrelated donor	593 (42)	676 (59)	
Stem-cell source — no. (%)			<0.001
Bone marrow	1240 (87)	227 (20)	
Peripheral-blood hematopoietic cells	158 (11)	871 (76)	
Bone marrow and peripheral-blood hematopoietic cells	11 (1)	1 (<1)	
Cord blood	9 (1)	49 (4)	
Conditioning regimen — no. (%)			<0.001
Reduced intensity	1 (<1)	257 (22)	
Myeloablative‡	427 (30)	774 (67)	
High-dose myeloablative¶	990 (70)	117 (10)	
GVHD prophylaxis — no. (%)			<0.001
Calcineurin inhibitor plus methotrexate or trimetrexate	1258 (89)	643 (56)	
Calcineurin inhibitor plus mycophenolate mofetil	1 (<1)	242 (21)	
Calcineurin inhibitor alone	64 (5)	46 (4)	
Other	95 (7)	217 (19)	

Gooley et al NEJM 2010







Gooley et al. NEJM 2010

PROGRESS

– **Old issues like GVHD still remain a veritable “Thorn in the side”**

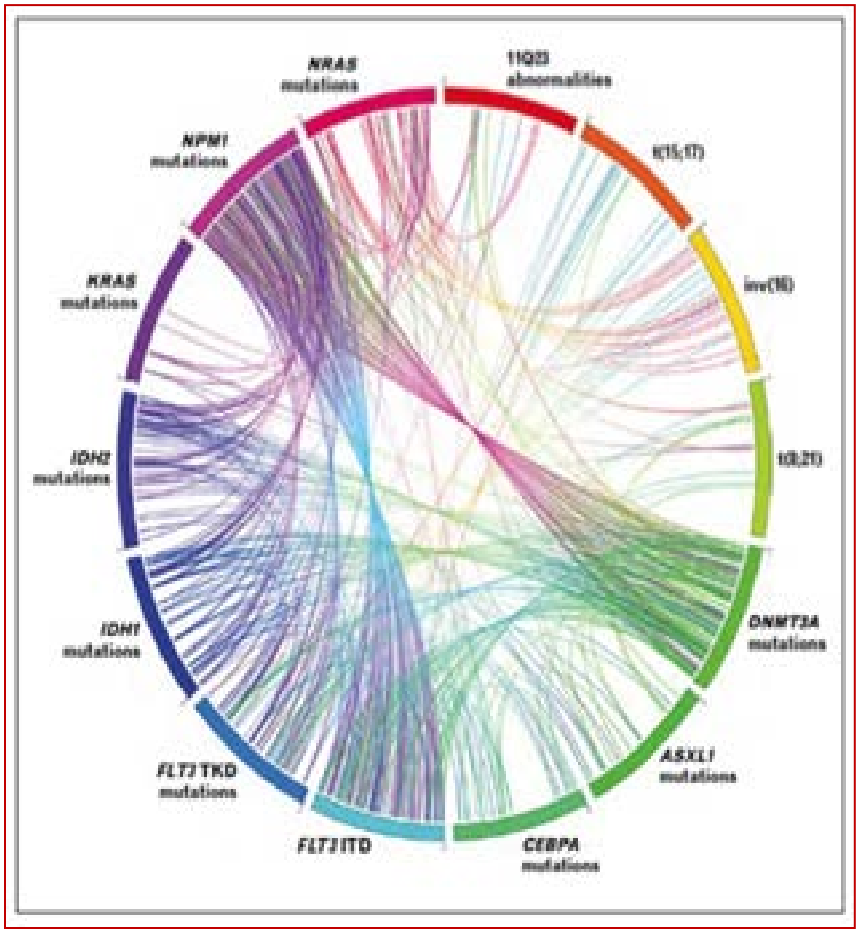
- **Refinement in patient selection**
- **Timing of transplantation**
- **Conditioning regimen selection**
- **New drugs**
- **Improvements in supportive care**
- **More inclusive for advanced age patients**

EVOLUTION IN MDS

Risk Stratification:

Benefits vs. Risk

- Risk assessment of AML/MDS was morphology and cytogenetics. Cytogenetics – essential but supplemented with analyses of molecular abnormalities.
- Whole-genome sequencing has identified additional repetitively mutated genes in AML/MDS that are starting to be considered in disease risk assessment
- Disease Based Risk & Patient Based Risk



Chakraborty, Oncology 2013

IPSS- Most Widely Used Disease Stratification

DISEASE BASED

- **WHO classification-based prognostic scoring system (WPSS)**
- **International Prognostic Scoring System – diagnosis**
  - **widely in clinical decision-making**
  - **clinical trials**
  - **FDA and EMA in their approval of novel drugs for MDS.**

International Prognostic Scoring System (IPSS) Risk Stratification

Scores	0	0.5	1.0	1.5	2.0
BM blasts	< 5%	5%–10%		11%–20%	21%–30%
Karyotype	Good nl, -y, 5q-, 20q-	Inter			
Cytopenias Hgb < 10 g/dL or ANC < 1,800/μL or plt < 100 × 10^9/L	0/1	2/3			
Risk Groups	**Low**	**Int-1**	**Int-2**	**High**	
IPSS	0	0.5–1.0	1.5–2.0	2.5–3.5	

Greenberg et al Blood 1997

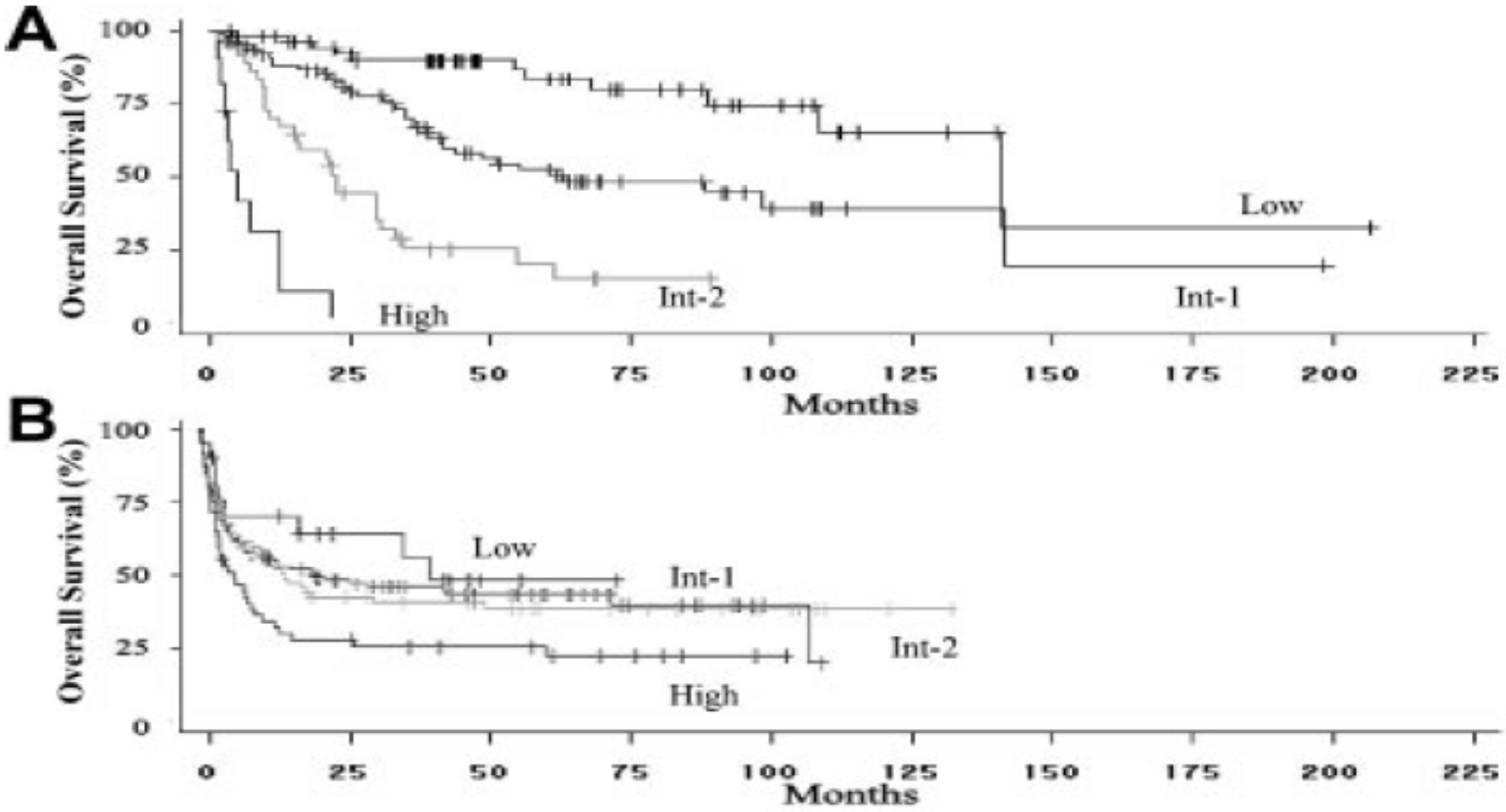
A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome

Corey S. Cutler, Stephanie J. Lee, Peter Greenberg, H. Joachim Deeg, Waleska S. Pérez, Claudio Anasetti, Brian J. Bolwell, Mitchell S. Cairo, Robert Peter Gale, John P. Klein, Hillard M. Lazarus, Jane L. Liesveld, Philip L. McCarthy, Gustavo A. Milone, J. Douglas Rizzo, Kirk R. Schultz, Michael E. Trigg, Armand Keating, Daniel J. Weisdorf, Joseph H. Antin, and Mary M. Horowitz

Blood 2004

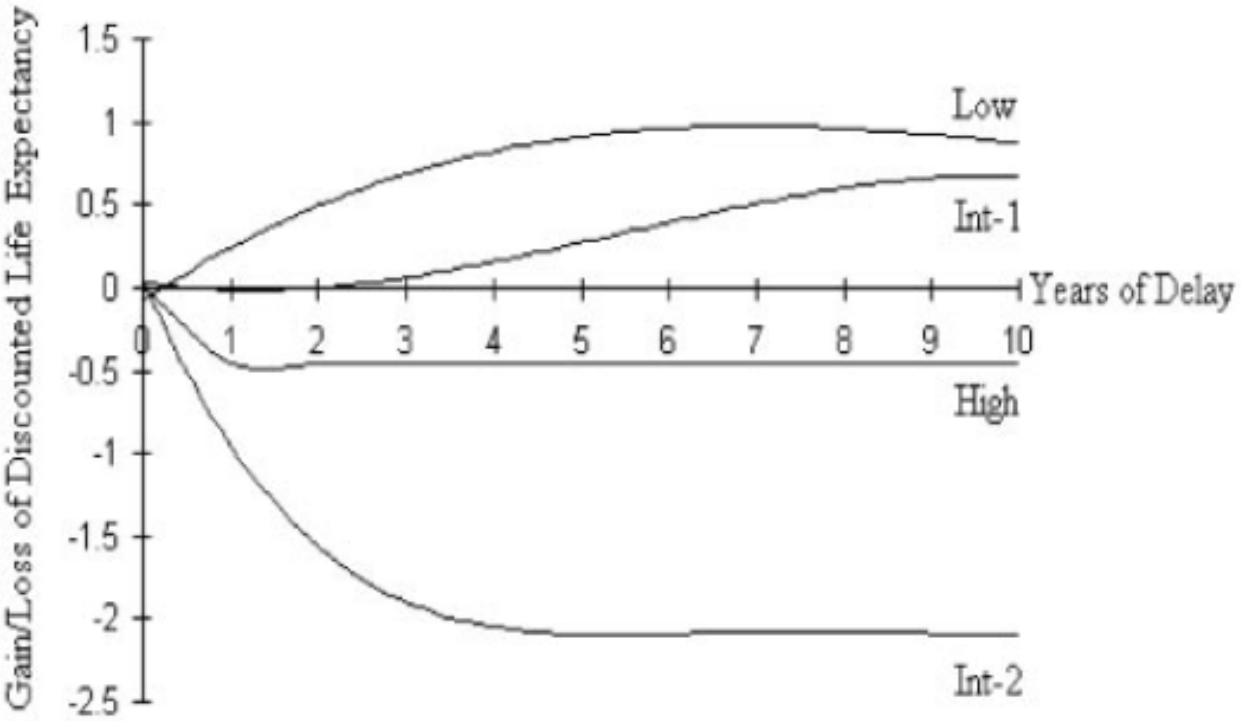
- **Establish which patients with MDS benefit from an allogeneic stem cell transplant**
- **All patients had newly diagnosed MDS**
- **Utilized the IPSS as the risk stratification method at diagnosis**

Transplant Benefits Int-2 & High Risk MDS



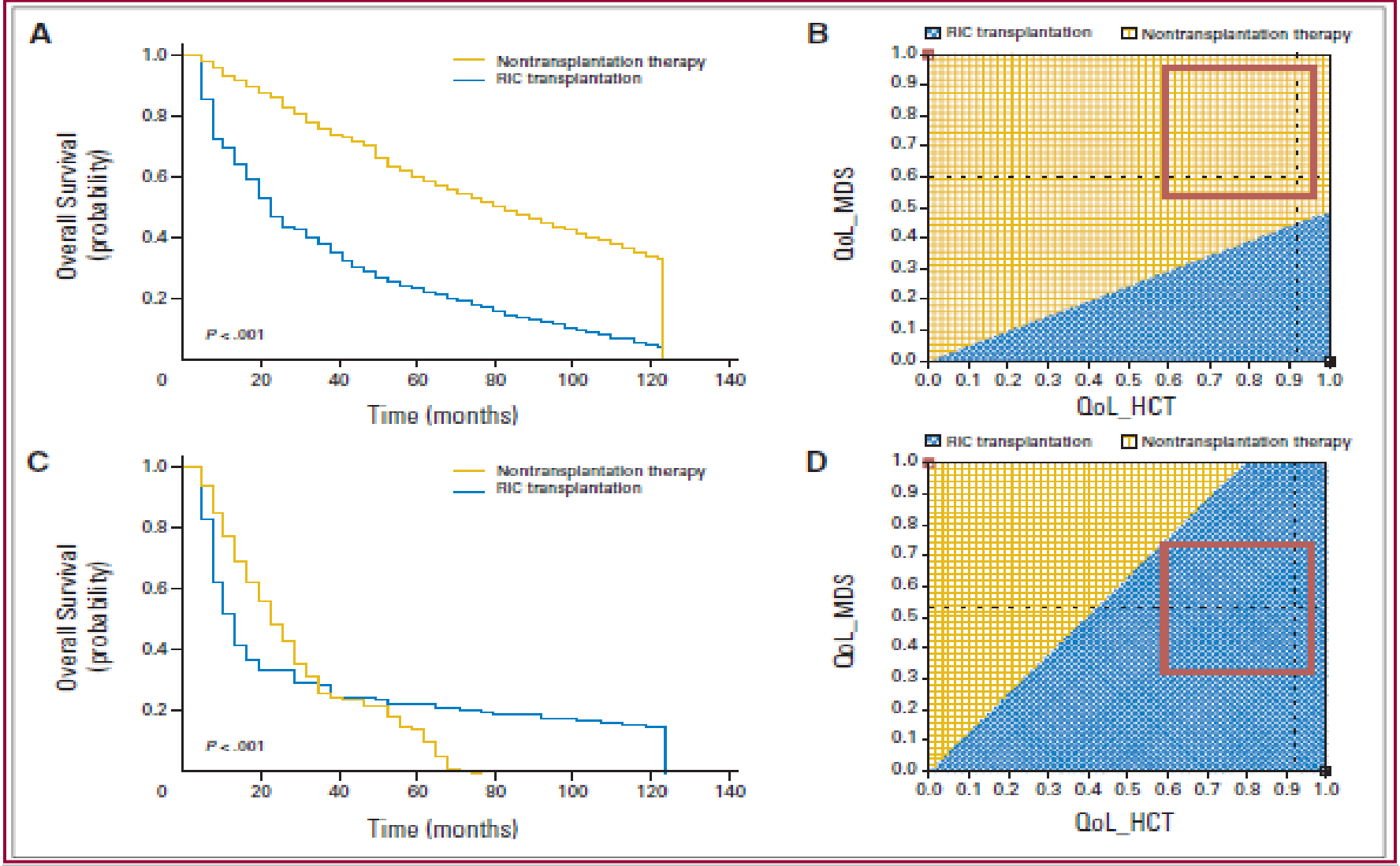
Cutler et al Blood 2004

Delaying Transplant Hurts Int-2 and High Risk MDS



Cutler et al Blood 2004

MDS RISK & TRANSPLANT



Koreth JCO 2013

MDS RISK & TRANSPLANT

Table 3. Markov Analysis: Transplantation and Nontransplantation Strategy Outcomes

Variable	Early RIC Transplantation Survival (months)	Nontransplantation Survival (months)
Patients with low/intermediate-1 IPSS MDS*		
LE		
Base case	38	**77**
Modeling discounted survival	35	**68**
Modeling "plateau in RIC transplantation survival"	48	**77**
All RIC *v* BSC (time from MDS diagnosis)	57	**80**
All RIC *v* all nontransplantation therapies (time from MDS diagnosis)	57	**80**
RIC within 12 months *v* BSC (time from MDS diagnosis)	49	**80**
RIC within 12 months *v* all nontransplantation therapies (time from MDS diagnosis)	49	**80**
RIC within 12 months *v* ESA therapy (time from treatment)	42	**67**
QALE		
Base case	35	**47**
Modeling discounted survival	32	**41**
Modeling "plateau in RIC transplantation survival"	44	**46**
Assuming worst QoL with HSCT (chronic GVHD)	23	—
Assuming best QoL with MDS (transfusion independent)	—	**65**
Patients with intermediate-2/high IPSS MDS†		
LE		
Base case	**36**	28
Modeling discounted survival	**32**	27
Modeling "plateau in RIC transplantation survival"	**38**	28
RIC within 12 months *v* hypomethylating agents (GFM/Nordic data set—time from treatment)	**36**	28
QALE		
Base case	**33**	15
Modeling discounted survival	**30**	14
Modeling "plateau in RIC transplantation survival"	**35**	15
Assuming worst QoL with HSCT (chronic GVHD)	**22**	—
Assuming Best QoL with advanced MDS (estimated)	—	21

Koreth JCO 2013

Who Is Considered For Allo Transplant ???

IPSS (international prognostic scoring system) for MDS

IPSS Int-2-and High-risk MDS

- Allogeneic SCT is first choice, unless clear co-morbidity or **refractory disease!**
- Transplantation soon after the diagnosis confers the best prognosis, since the rate of transformation to acute leukemia is high, with most patients progressing within the first year.

IPSS Low-risk/Int-1 MDS

- prognosis of low- and int-1–risk patients with supportive measures alone is excellent, with a median survival that ranges from 5 yrs to a decade in the low-risk IPSS group, it seems reasonable to avoid the immediate risks of transplantation
- Consider allogeneic SCT in case of prognostic adverse factors, including high transfusion need not responding to erythropoietin and/or lenalidomide,adverse cytogenetic characteristics, signs of progression (blasts and/or marrow failure)

Refined IPSS

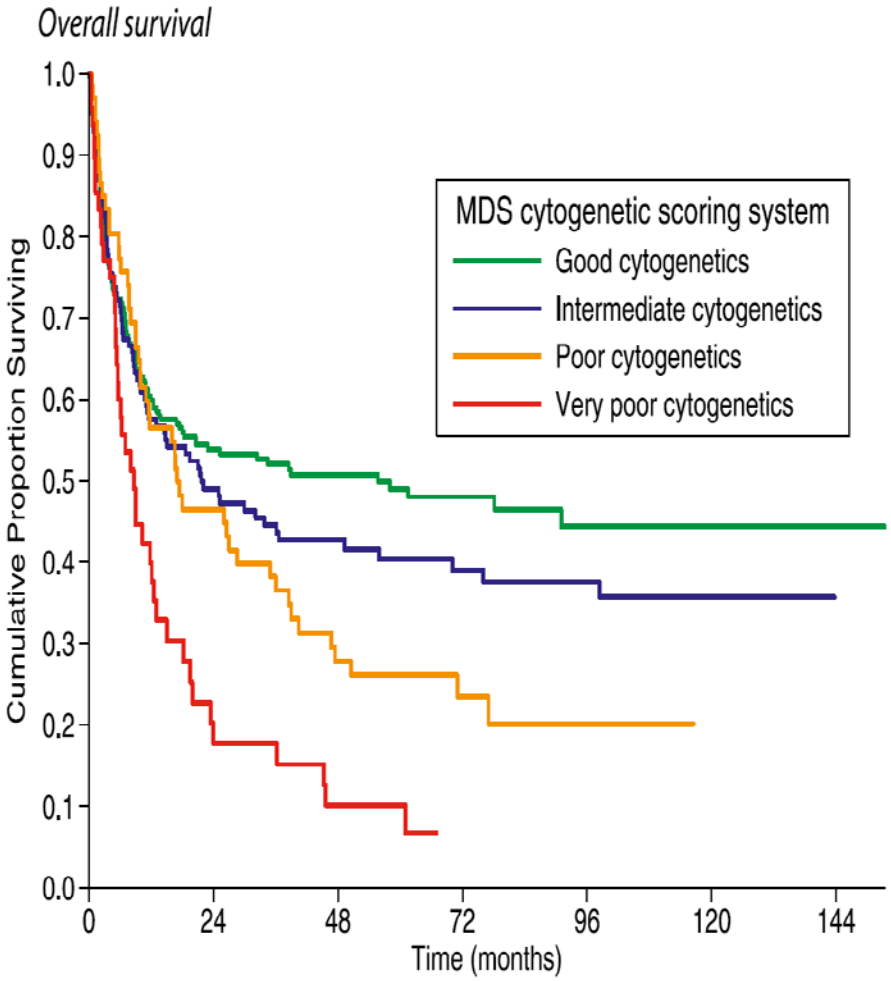
- **Designed for - diagnosis - diseases can evolve with time**
- **IPSS- R is a more refined strategy**

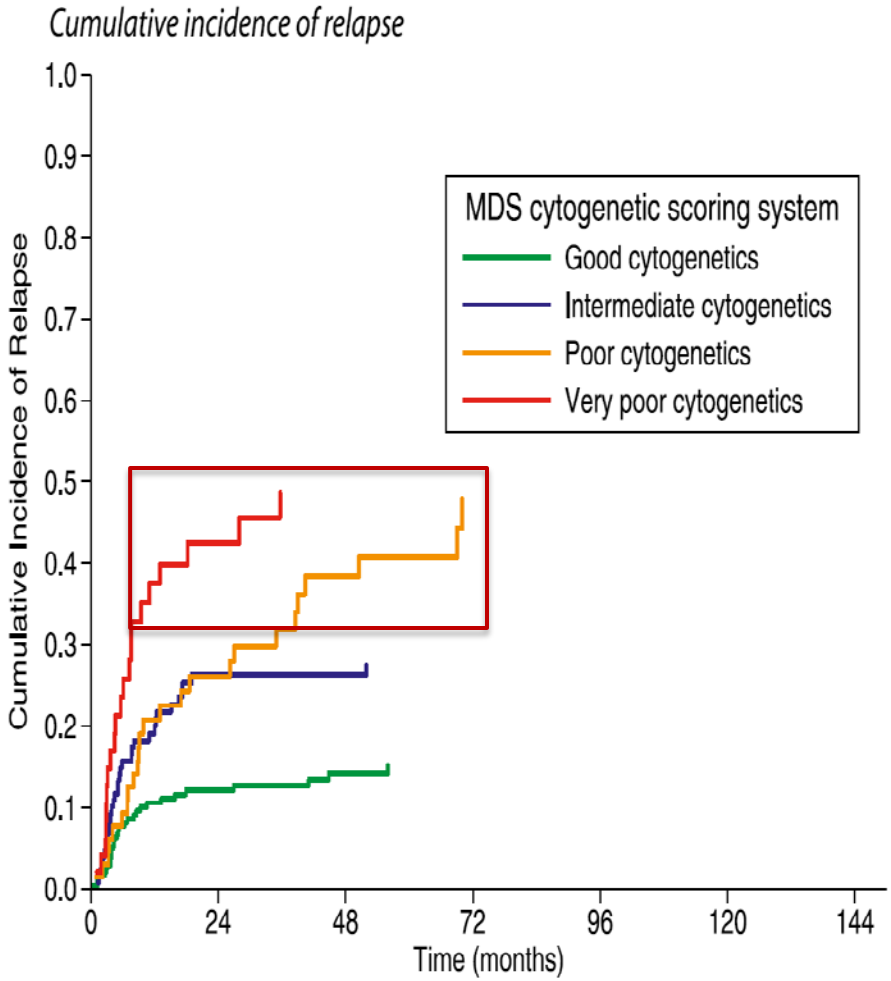
Revised international prognosis scoring system

	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM blast (%)	≦2		>2–<5		5–10	>10	
Hb (g/dl)	≧10		8–<10	<8			
Plt ($\times 10^4/\mu l$)	≧10	5–<10	<5				
ANC ($/\mu l$)	≧800	<800					

	≦1.5 (0–1.5)	>1.5–3 (2–3)	>3–4.5 (3.5–4.5)	>4.5–6 (5–6)	>6 (7–10)
Risk group	Very Low	Low	Intermediate	High	Very High
Median survival (yrs)					
Median time to 25% AML evolution (yrs)	NR	10.8	3.2	1.4	0.73

Greenberg et al Blood 2012





Della Porta et al, Blood 2014

Post Transplant

Relapse is still the number 1 reason for failure of transplant

Pre-tx status
Cytogenetic/Molecular

High Risk

HMA's
Clinical Trials

www.clinicaltrials.gov identifier NCT00887068.

Relapsed

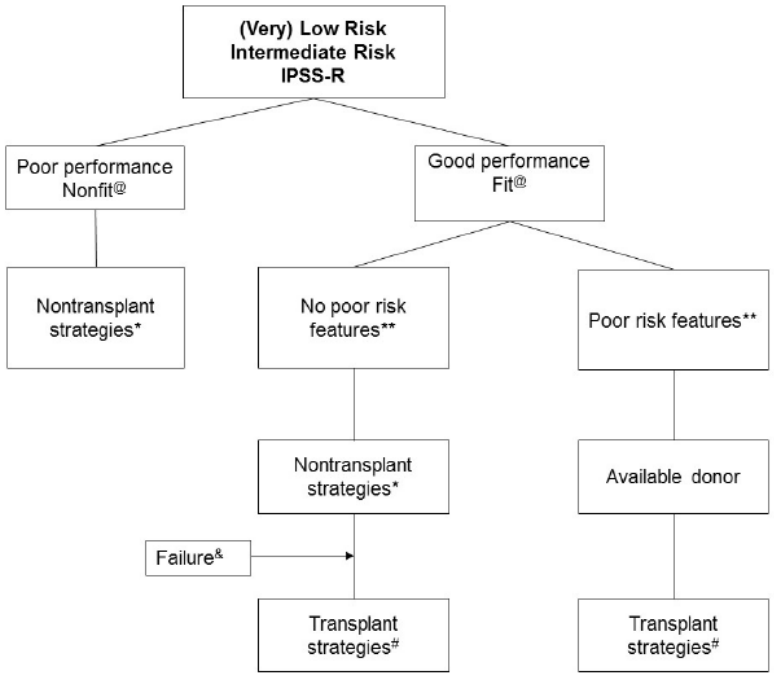
IS Withdrawal
HMA's
DLI
Chemo - Toxicity
2nd Transplant- Toxicity not successful

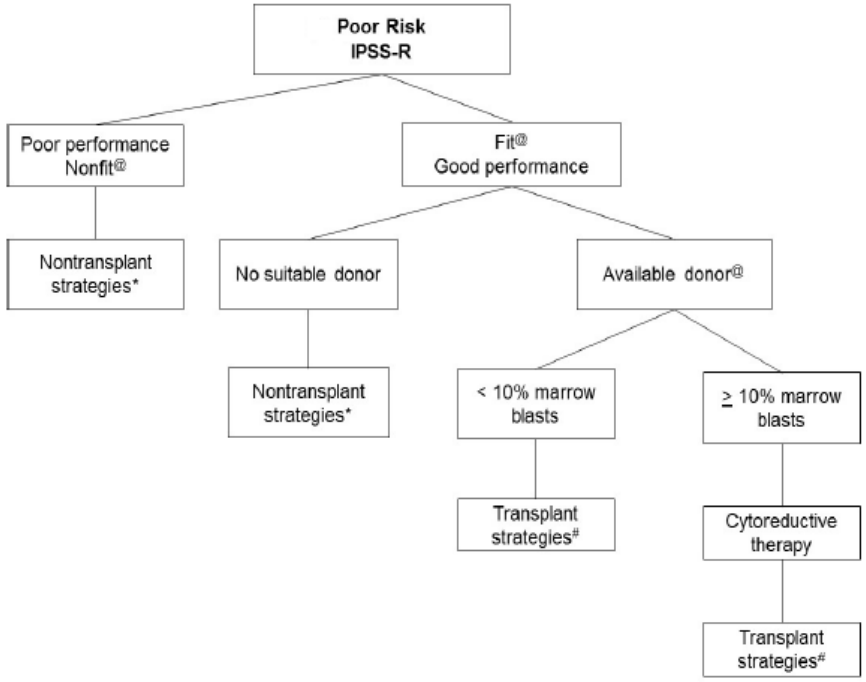
Risk Stratification According To Patient

Comorbidities	Definitions	HCT-CI Weighted Scores
Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, and ventricular arrhythmias	1
Cardiac	Coronary artery disease,* congestive heart failure, myocardial infarction, or ejection fraction ≤ 50%	1
Inflammatory bowel disease	Crohn's disease or ulcerative colitis	1
Diabetes†	Requiring treatment with insulin or oral hypoglycemic, but not diet alone	1
Cerebro-vascular disease	Transient ischemic attack or cerebro-vascular accident	1
Psychiatric disturbance†	Depression/anxiety requiring psychiatric consult or treatment	1
Hepatic, mild†	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN	1
Obesity†	Patients with a BMI of > 35 for adults or with BMI-for-age ≥ 95th percentile for children	1
Infection†	Documented infection or fever of unknown etiology requiring anti-microbial treatment before, during, and after the start of conditioning regimen	1
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	2
Peptic ulcer	Requiring treatment	2
Moderate/ severe renal†	Serum creatinine > 2 mg/dL, on dialysis, or prior renal transplantation	2
Moderate pulmonary†	DLco and/or FEV_1 > 65%–80% or Dyspnea on slight activity	2
Prior solid tumor	Treated at any time in the patient's past history, excluding nonmelanoma skin cancer	3
Heart valve disease†	Except mitral valve prolapse	3
Severe pulmonary†	DLco and/or FEV_1 ≤ 65% or Dyspnea at rest or requiring oxygen	3
Moderate/ severe hepatic†	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN	3

Sorror et al

Incorporate Both





High risk- consider post transplant strategies

DeWitt et al

SIO

- **High Ferritin Levels are associated with increased risk of transplant related complications**
- **The reasons for this observation remain, at least in part, not very well defined.**
- **Limitation of serum ferritin measurement, including its association with variables important for transplantation outcome such as comorbidities**
- **Approaches to prevent severe iron overload are reasonable and warranted. It is recommended to use iron chelation before HCT in selected patients with SIO, although no definitive cutoff for ferritin or liver iron has been systematically defined. – Platzbecker et al.**

Take Home Points

- **When deciding if transplant can benefit an MDS patient, in addition to IPSS-R scores, take into consideration the behavior of the disease and patient fitness**
  - **IPSS intermediate 2, high risk, transfusion dependency, high risk cytogenetics**
  - **Individual Case assessment for lower risk disease**
  - **Disease Assessment along with Patient Assessment (HCT-CI)**

- **Risks of the underlying disease have to be balanced against comorbidities, hazards of the allogeneic, procedure, patient's preferences, and therapeutic alternatives**

For Future:

- **Additional attention should be drawn to the monitoring and treatment of MRD and MDS-specific interventions prevent relapse**
- **Once deficiencies in patient health identified what can we do to minimize risk?- Dr. Artz**

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

Thank You

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Treatment of Murine Leukaemia with X-Rays and Homologous Bone Marrow: II*

D.W.H. BARNES and J.F. LOUTIT

Lethal Radiation to treat mice with Leukemia

Bone Marrow Stem Cells

Syngeneic → **Did Well Past 100 days**

Allogeneic → **2-3 weeks later didn't do well**