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Conditioning regimens before allogeneic stem cell transplantation

BHS Educational Course
16/03/2024

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1. Introduction: Conditioning regimen

- Preparative regimen administered prior to HSCT
  - *'preparing the patient to recieve the transplant'*
- Chemotherapy / Radiation / Antibodies
- Two key components:
  - Myelodepletion – targets host stem cells
    - Busulfan, Melfalan, TBI
  - Lymfodepletion – targets host lymphoid system
    - Fludarabine, Cyclofosfamide

1. **Introduction:** Goals of conditioning regimen

Eradicate hematologic malignancy
In case of malignant indication
Myelodepletion (e.g. BU – MEL – TBI)

Supress host immunity
Ensure engraftment
Prevent graft rejection

Provide stem cell niches
Eradicate host hematopoiesis

→ **AND limit toxicity and TRM**

1. Introduction: Conditioning Intensity

- Myeloablative
  - Regimen causing irreversible pancytopenia in ‘almost all’ patients
  - Classical regimens:
    - CY/TBI (IV Cyclofosfamide 60 mg/kg 2d – 12 Gy TBI)
    - BU/CY (IV Cyclofosfamide 60 mg/kg 2d - 4 mg/kg 4d Busulfan PO)
  - Limited to younger patients in good medical conditioin
    - <55 sibling donors / <50 in unrelated donors
    - Transplant related toxicity (Non Relapse Mortality)
- Reduced Toxicity
  - Reducing toxicity without compromising SCT efficacy
  - e.g. Fludarabine with myeloablative doses of busulfan or treosulfan
  - Flu/Bu4
- Reduced intensity
  - Older patients
  - Patients with comorbidities
  - Heavily pre-treated patients
- Non Myeloablative

1. Introduction: Conditioning Intensity

- Common toxicities of standard MAC regimens
  - Prolonged aplasia
    - Irreversible
    - Risk of infection
  - GI toxicity
    - Mucositis
    - Nausea/vomiting
  - Organ toxicities
    - VOD/SOS
    - Pnuemonitis
  - Cytokine storm
    - Ridk of acute GvHd
  - Long-term toxicities
    - Infertility
    - Gonadal dysfunction - Iatrogenic menopauze/andropauze
    - Secondary malignancies

1. Introduction: Conditioning Intensity

Standard Myeloablative Conditioning

MYELOABLATION

>

Reduced Intensity Conditioing

IMMUNOABLATION

↓ **TOXICITY**

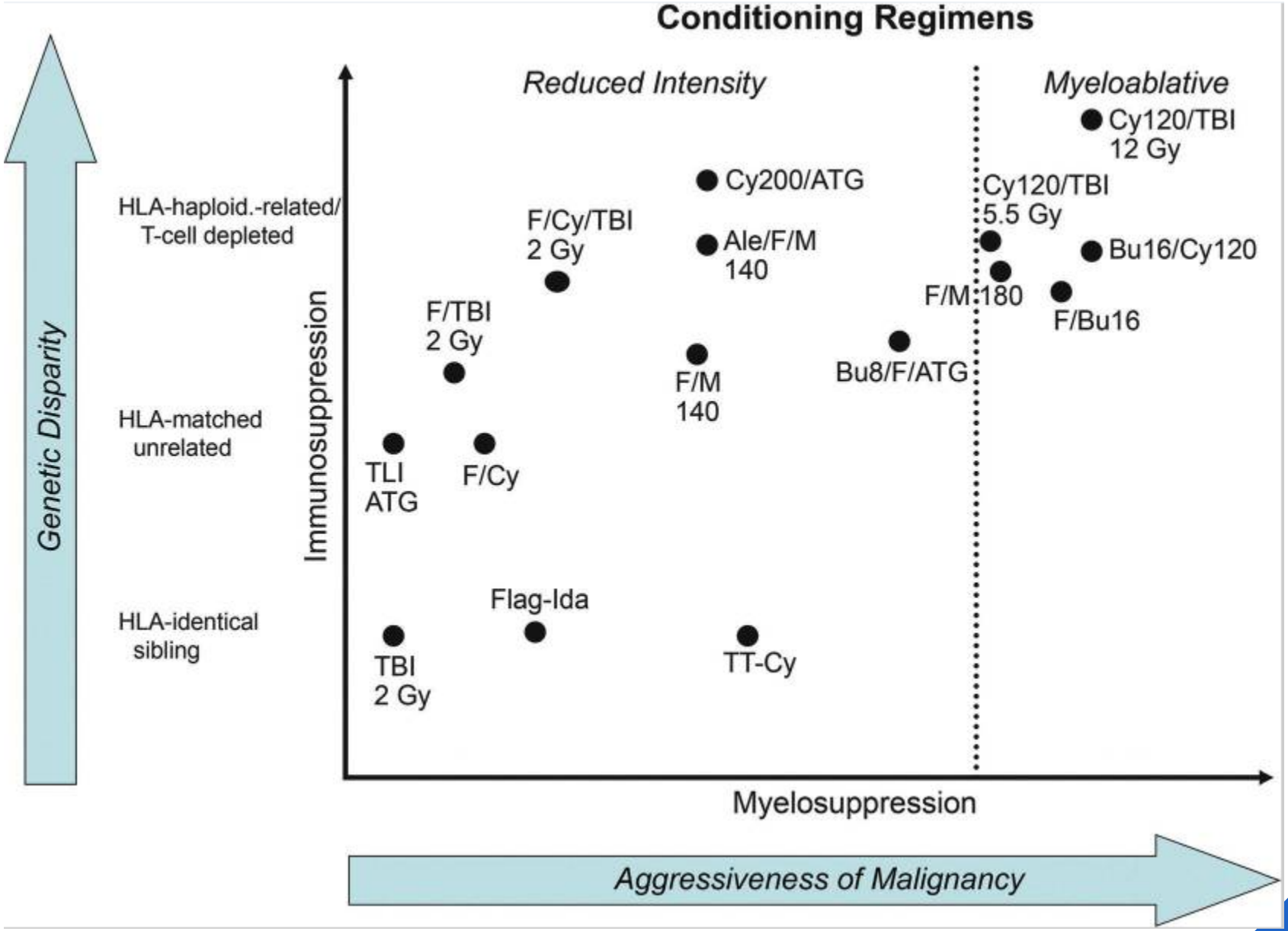
GRAFT IMMUNE EFFECTS

Disease control > graft vs. tumor

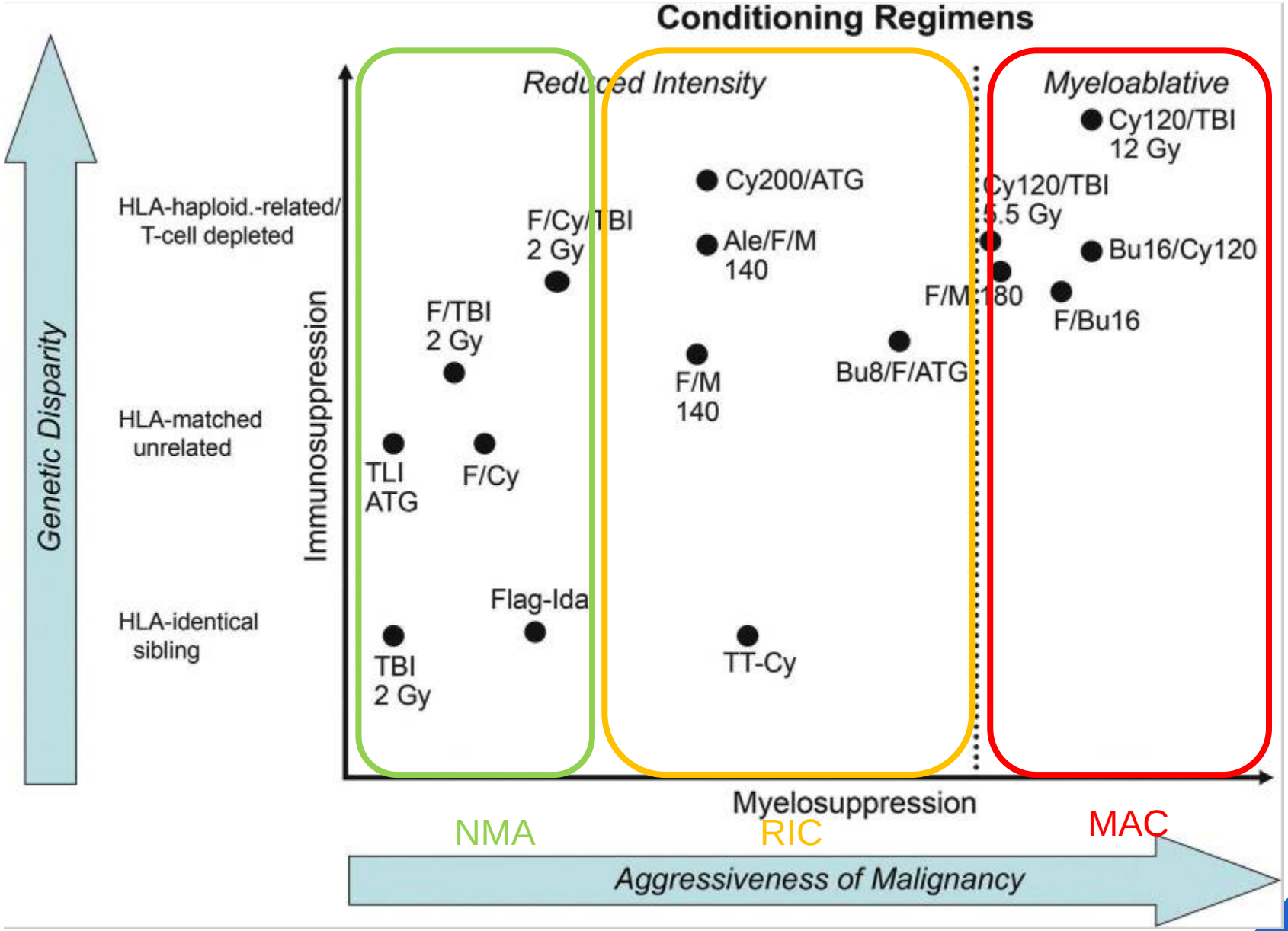
Engraftment > graft vs. hematopoiesis

1. Introduction: Conditioning Intensity

Myeloablative (MA)	Nonmyeloablative (NMA)
TBI ≥5 Gy single dose or ≥8 Gy fractionated	TBI ≤ 2 Gy± purine analog
Bu > 8 mg/kg PO or IV equivalent	Flu + Cy ± ATG
	Flu +AraC + Ida
	Cladribine + AraC
	Total Lymphoid Irradiation + ATG



From: EBMT Handobook 2019; Chapter 1: Historical Perspective, Storb R.



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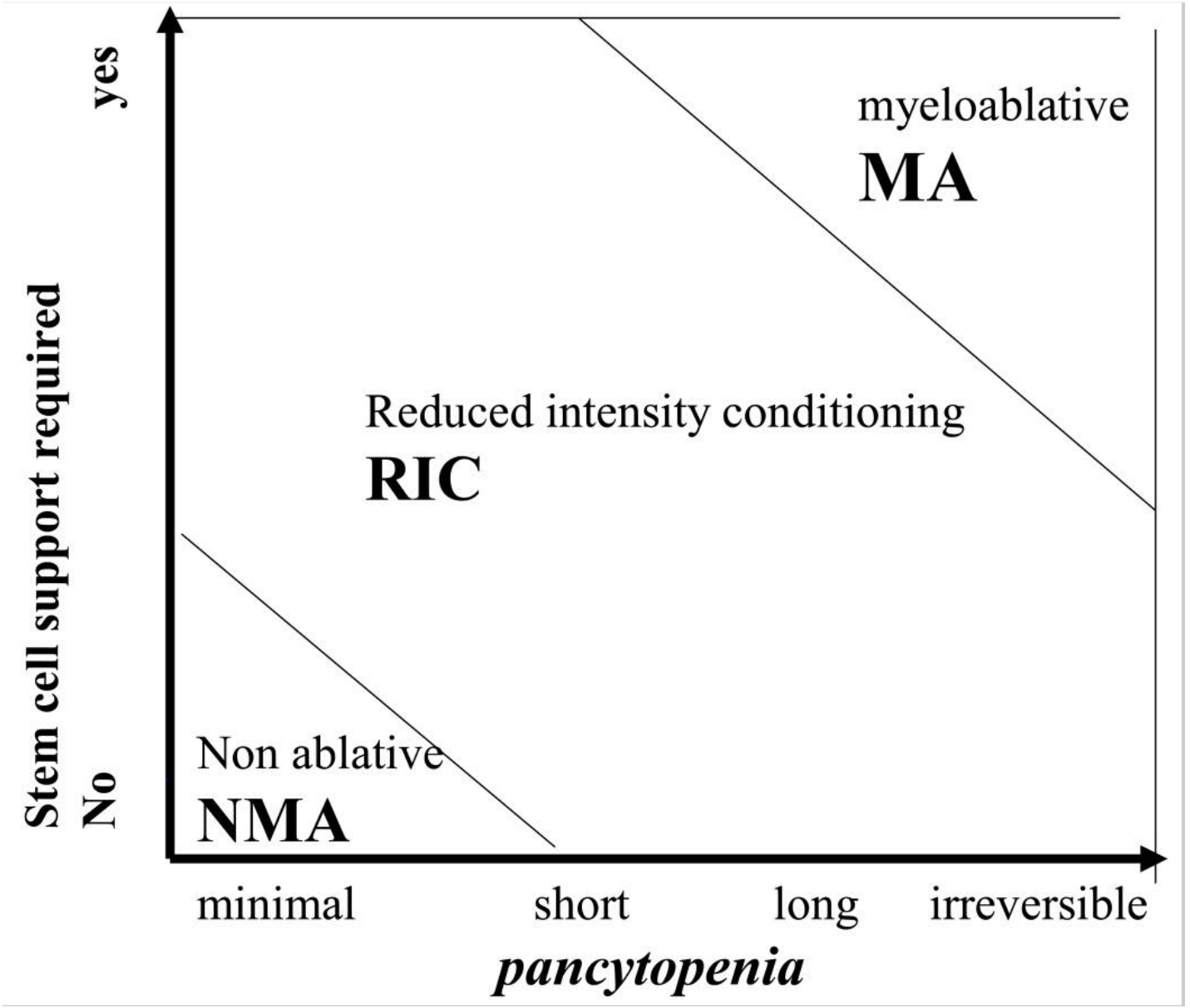


Bacigalupo et. al BBMT 2009; 15(12):1628-33

1. Introduction: Commonly used drugs

Total Body Irradation	
Antitumor effect	**Yes**
Myeloablation	**Yes** - Myeloablative if ≥5 Gy single dose ≥8 Gy fractionated
Immunosupression	**Yes**
Toxicity	Common toxicities of MAC Parotitis Thyroid damage Cataract

Cyclofosfamide	
Antitumor effect	Limited
Myeloablation	Limited
Immunosupression	**Yes**
Toxicity	Hemorrhagic cystitis ➔ hyperhydration + Mesna (if Cy dose > 1 g/m²) Cardiotoxicity (high dose) SIADH Pneumonitis (rare)

Busulfan / Melphalan	
Antitumor effect	**Yes**
Myeloablation	**Yes** – Myeloablative if: Bu ≥ 8mg/kg (or IV equivalent) Mel ≥ 150mg/m²
Immunosupression	Limited
Toxicity	High dose: common toxicities of MAC Busulfan: Sinusoidal obstructive syndrome Pneumonitis (rare) Seizure Skin rash, melanodermia Metabolic disturbances: hyperglycemia, hyperuricemia, hypoK/Mg/PO4 Melphalan: Severe mucositis Pneumonitis (rare)

1. Introduction: Commonly used drugs

Fludarabine	
Antitumor effect	Limited
Myeloablation	Limited
Immunosupression	Yes
Toxicity	Cholestasis Polyneuropathy Seizure, coma, toxic leukencephalopathy (rare) Pemphigus

Thiotepa	
Antitumor effect	Yes
Myeloablation	Yes
Immunosupression	Yes
Toxicity	High dose: common toxicities of MAC GI trouble, colitis Secondary neoplasms Leuco-encephalopathy

2. Choice of optimal conditioing regimen

Risk of toxicity
Age, PS, comorbidities, previous treatments

Patient related factors
Age, PS, comorbidities

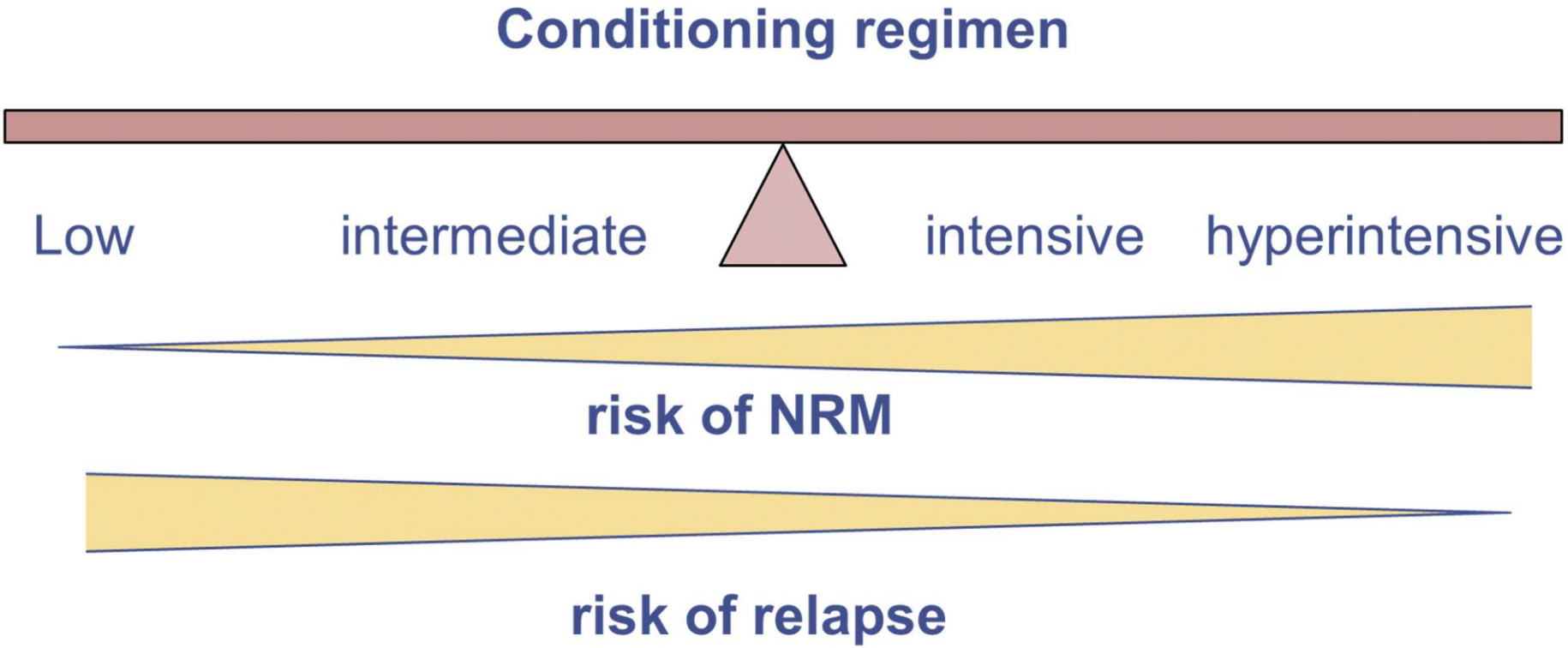
Risk of disease relapse
Remission status, susceptibility to GvL effect, pevious treatments, graft source

Disease related factors
Type of disease, remission status, previous treatments, DRI

Risk of graft rejection
graft source
Donor type

Graft related factors
Graft source
Donor type
HLA match

Choice of conditioing



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2. Choice of optimal conditioing regimen

- Risk assesment of alloHSCT
  - Fit for HSCT vs. not fit for HSCT
  - Fit for MAC vs. fit for RIC/NMA
- Evaluate patients according to a pre-established work plan
  - Analyse individual risk factors for HSCT
  - Institution based assessment plan
- Impact of several pre-transplant variables on the results of AlloHSCT
  - No one factor individually is sufficient to predict results
- Predictive models
- **Patients with high risk of NRM should be considered for RIC or NMA**

2. Choice of optimal conditioing regimen

- No one factor individually is sufficient to predict results
- Variables that have prognostic value in ALL predictive models
  - Age
  - General condition
    - Karnofsky <80%
  - Disease
    - not in remission
  - Type of donor
    - HLA identical sibling
    - Other
  - HLA compatibility
    - HLA-A, HLA-B- HLA-C and DRB1 difference
  - CMV serology
    - mismatch between donor/recipient
  - Donor
    - Donor age >35-40
    - Female donor for male recipient (> multiparous female)
  - Comobidities → HCT-CI
  - Presence of iron overload
  - Expierience of the center

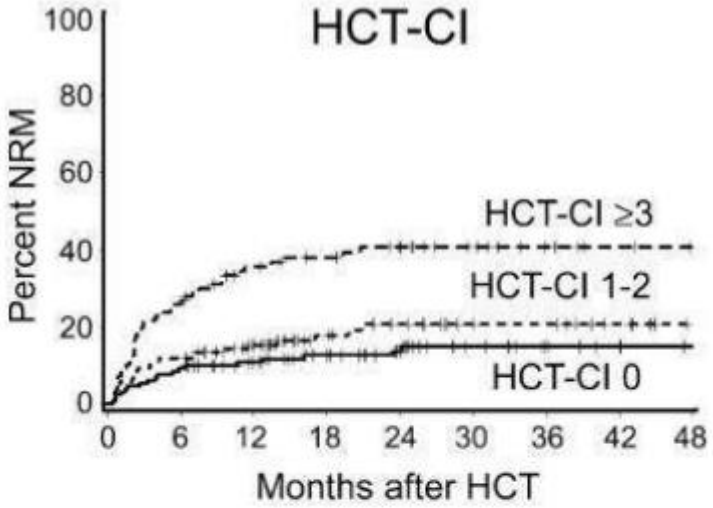
2. Choice of optimal conditioing regimen - **Patient**

- Use of **predictive models**
  - **HCT-CI**
  - **EBMT Risk Score**
  - **Disease Risk Index**
  - EBMT machine learning algorithm
  - All have a limited predictive value
  - No one model stands out
- Allow for realistic approach and assessment of risks
  - Help guide choice ‘fitness’ for transplant
  - Help guide choice for RIC vs. MAC conditioning
  - Adapt transplant procedure to patient needs

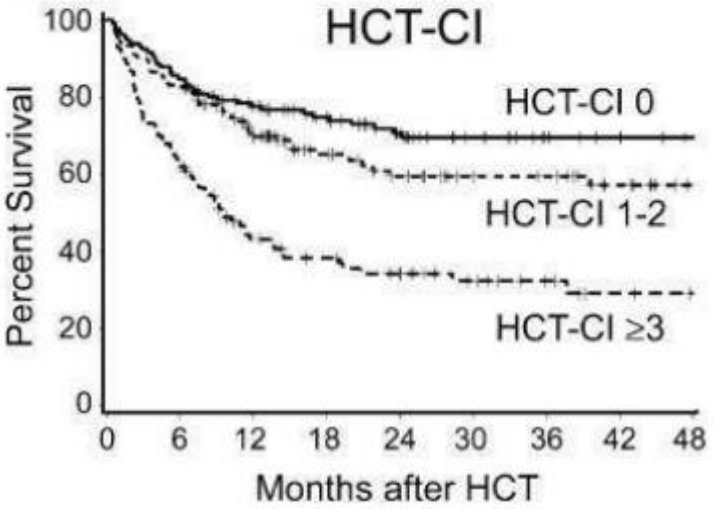
2. Choice of optimal conditioing regimen - Patient

- **Hematopoietic stem cell transplantation-comorbidity index (HCT-CI)**
- Predict NRM and OS post HSCT
- Stratifying patients into 3 specific risk groups corelated with 2 year NRM and OS
  - low (0 points)
  - interlmediate (1-2)
  - High (>3)
- Tool to measure organ dysfunction prior to HSCT
- Capture magnitude of organ damage
- Assesses the presence and degree of 17 comobidities
- Tool for decision making in clinical practice (conditioing, graft source) and clinical studies

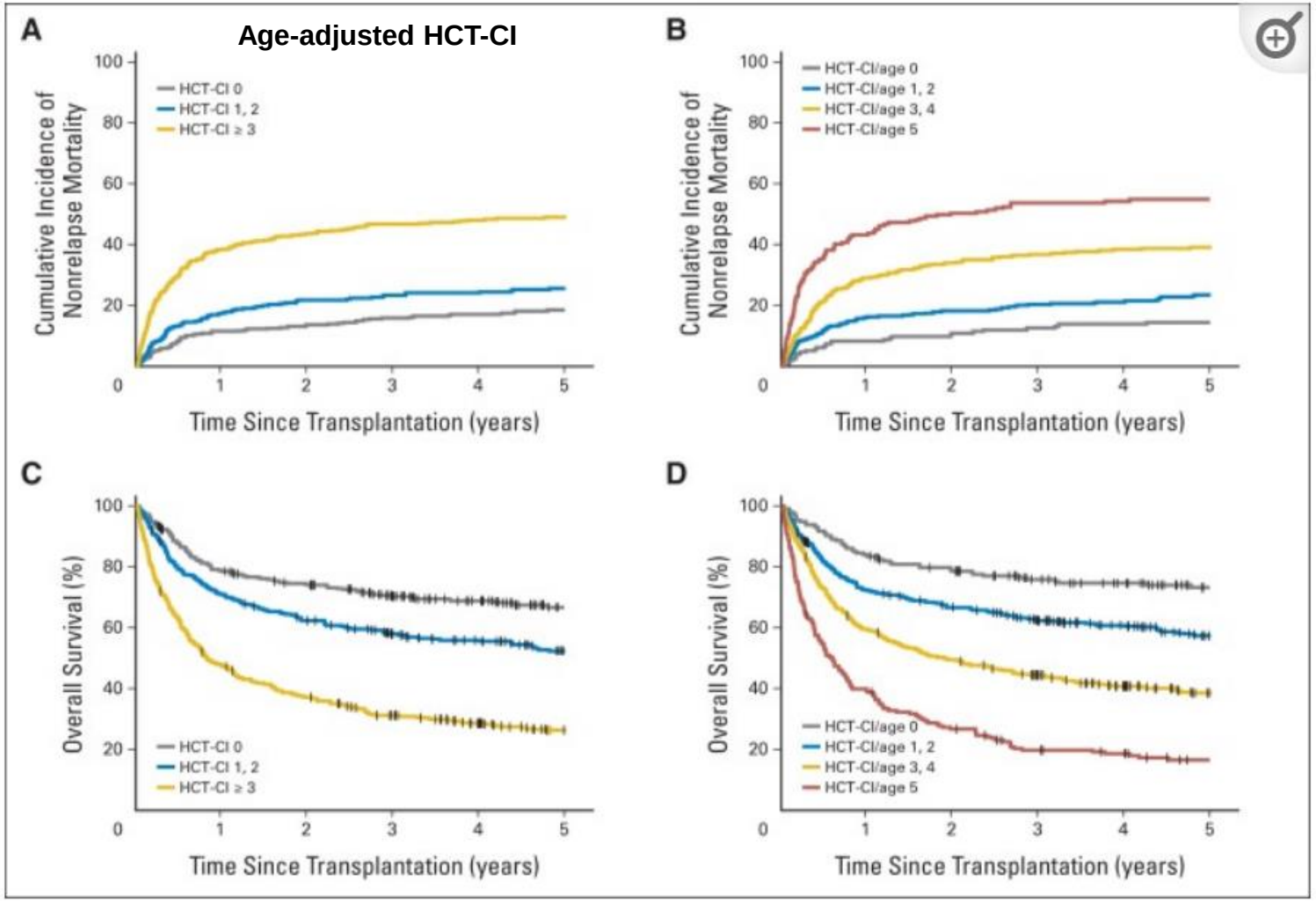
- Age-adjusted HCT-CI
  - +1 point for patients ≥ 40 yr
  - significantly improves predictive capacity



If HCT-CI ≥3 → RIC or NMA
(or not fit for HSCT)



Sorror M. et al. Blood 2005; 106:2912-2919



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Sorror et al. JCO 2014; 32(29):3249-56

Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) ☆

Predicts survival after HCT in patients with hematologic malignancies, including optional age adjustment.

INSTRUCTIONS

Entering age to obtain age-adjusted HCT-CI is optional. The original HCT-CI (without age adjustment) is still considered the standard.

When to Use ⌄ | Pearls/Pitfalls ⌄ | Why Use ⌄

History of arrhythmia	**None**	0
	Afib/flutter, <abbr title='Sick sinus syndrome'>SSS</abbr>, or ventricular arrhythmias	+1
Cardiac disease CAD = ≥1 vessel coronary stenosis requiring medical tx, stent, or CABG	**None**	0
	CAD, CHF, MI, or EF ≤50%	+1
	Valvular disease (except mitral prolapse)	+3
Inflammatory bowel disease	**None**	0
	Crohn disease or ulcerative colitis	+1
Diabetes	**None or diet-controlled**	0
	Treated w/insulin or oral hypoglycemics	+1

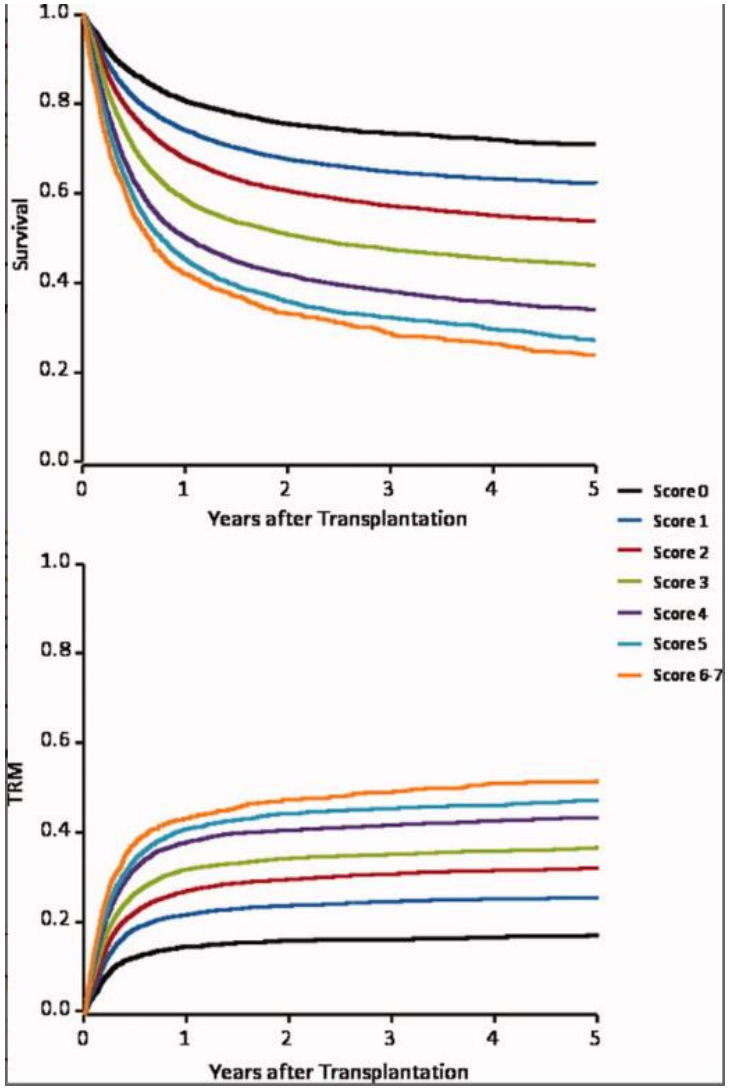
2. Choice of optimal conditioing regimen - **Patient**

- **EBMT risk score** (score 0-7)
- Predict 5-year probability of OS and TRM in most disease categories
- Based on five factors
  - Age of patient
  - Stage of the disease
  - Time from diagnosis
  - Donor type
  - Donor recipient gender combination
- Also useful in 2nd AlloSCT

Table 2. European Group for Blood and Marrow Transplantation Risk Score Definition

Risk Factor	Score Point
Age of the patient, y	
<20	0
20-40	1
>40	2
Disease stage*	
Early	0
Intermediate	1
Late	2
Time interval from diagnosis to transplant, mo†	
<12	0
>12	1
Donor type	
HLA-identical sibling donor	0
Unrelated donor	1
Donor-recipient sex combination	
All other	0
Donor female, male recipient	1

HLA indicates human leukocyte antigen.
*See text for the definitions according to main disease category; does not apply for patients with severe aplastic anemia (score 0).
†Does not apply for patients transplanted in first complete remission (score 0).



Gratwohl et al. Cancer 2009;115(20):4715-26.

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Table 11.3 Probability (%) of TRM at 5 years applying the EBMT risk score

Points	0	1	2	3	4	5	6–7
AML	14	20	25	30	36	40	41
ALL	15	23	24	30	40	47	53
CML	15	22	30	38	45	52	55
AA	18	26	40	49	52		
MDS	25	28	30	35	38	46	50
MM			29	35	40	42	52
NHL	15	24	28	30	34	36	38

Extracted from Gratwohl (2009)

Table 11.4 Probability (%) of OS at 5 years applying the EBMT risk score

Points	0	1	2	3	4	5	6–7
AML	68	59	52	38	30	23	18
ALL	66	52	43	38	22	16	14
CML	76	72	60	51	39	26	14
AA	81	72	60	49	45		
MDS	56	52	46	40	35	28	25
MM			48	40	36	22	17
NHL	75	59	50	48	43	40	38

Extracted from Gratwohl (2009)

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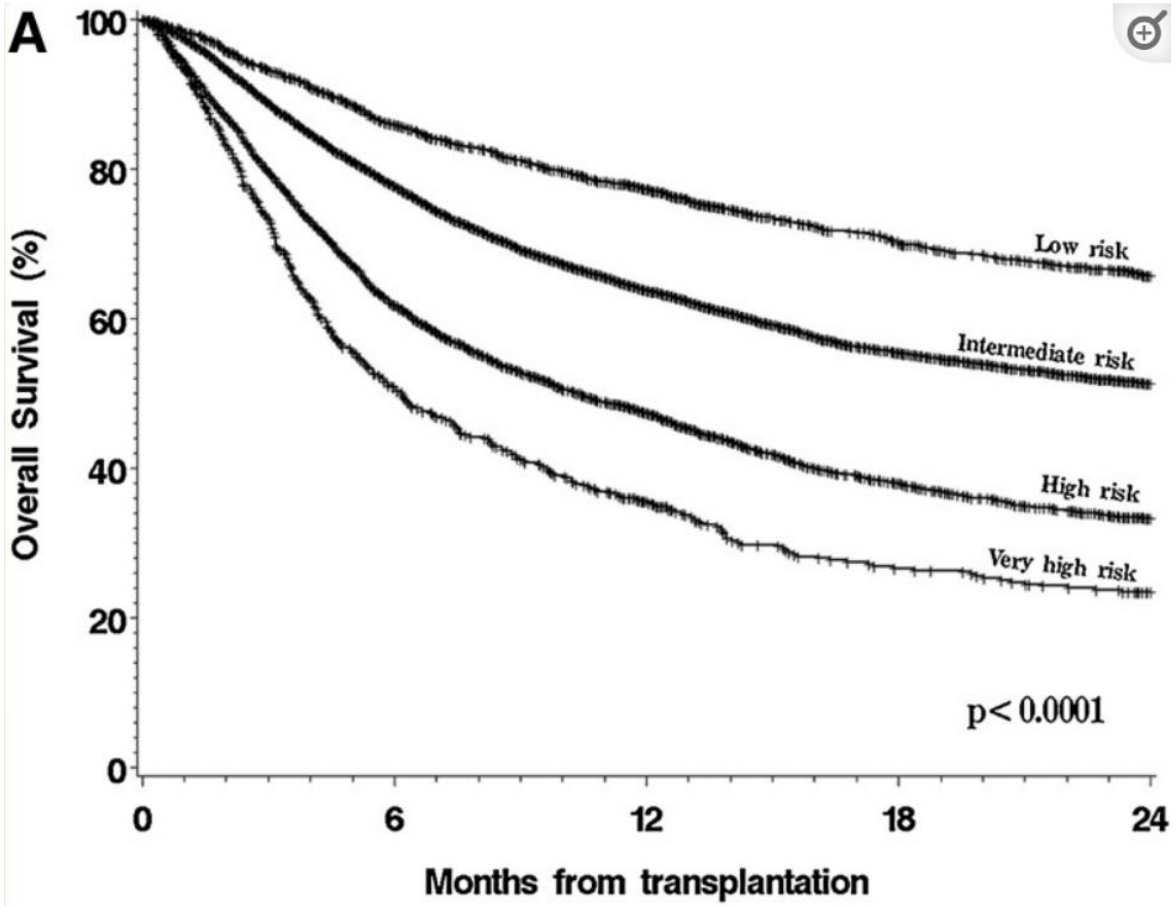
From: EBMT Handbook 2019; Chapter 11: Evaluation and Counseling of Candidates; Enric Carreras.

2. Choice of optimal conditioing regimen - **Patient**

- **Disease Risk Index (DRI)**
- Based on disease and disease status
- Stratification into 4 groups
  - Low
  - Intermediate
  - high
  - very high
- Significantly different OS and PFS
- based on differences in relapse risk
- INDEPENDANT of HCT-CI and conditioning intensity



OS stratified by DRI

2 year OS
- Low risk 64%
- Intermediate risk 51%
- High risk 34%
- Very high risk 24%

(Armand et al. 2014)

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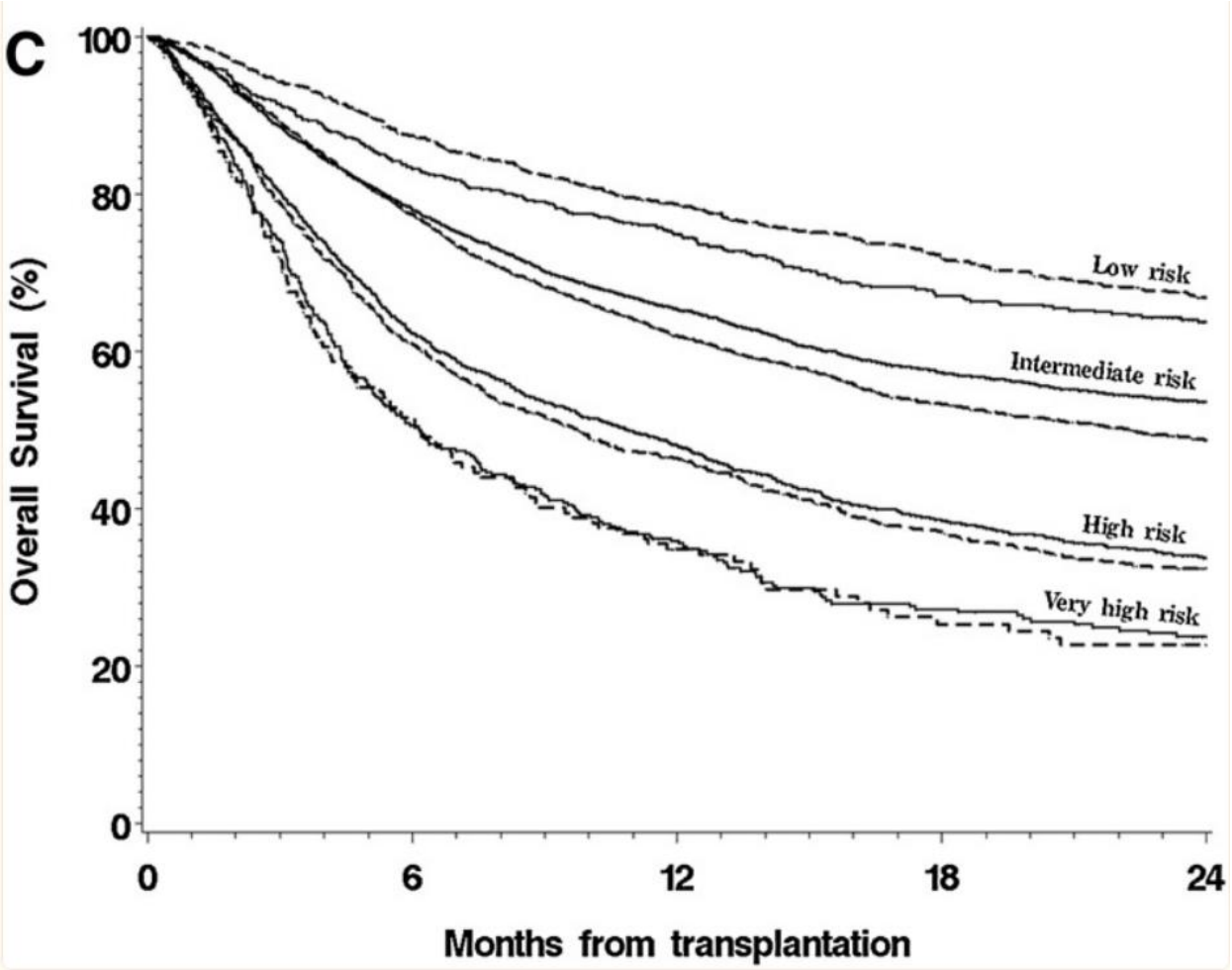

OS stratified by DRI and conditioing intensity

(Armand et al. 2014)

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Table 11.1 Disease risk index (Armand 2012, 2014)

Risk	Disease		
Low	AML with favorable cyt., CLL, CML, indolent B-cell NHL		
Intermediate	AML intermediate cyt., MDS intermediate cyt., myeloproliferative neoplasms, MM, HL, DLBCL/ transformed indolent B-NHL, MCL, T-cell lymphoma nodal		
High	AML adverse cyt, MDS adverse cyt, T-cell lymphoma extranodal		
Risk	Stage		
Low	CR1, CR≥2, PR1, untreated, CML CP, PR≥2 (if RIC)		
High	PR≥2 (if MAC), induction failure, active relapse, CML AP or BP		
Disease risk	Stage risk	Overall risk	OS at 4 years
Low	Low	Low	64% (56–70%)
Low	High	Intermediate	46% (42–50%)
Intermediate	Low		
Intermediate	High	High	26% (21–31%)
High	Low		
High	High	Very high	6 (0–21%)

Adapted from Armand (2012). *Cyt.* cytogenetics

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From: EBMT Handbook 2019; Chapter 11: Evaluation and Counseling of Candidates; Enric Carreras.

Disease Risk Index (DRI) Assignment Tool

About the Disease Risk Index (DRI)

The Disease Risk Index (DRI) is a validated tool to categorize groups of patients undergoing allogeneic stem cell transplantation (HCT) for **hematologic malignancy** by disease risk. It is intended for research purposes to stratify patients in broad disease risk categories for retrospective or prospective studies.

View Publication Details

The DRI considers only disease-related parameters (i.e., disease, stage and, for

It does not consider patient-related variables such as age and co-

The DRI was developed using data in

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https://cibmtr.org/CIBMTR/Resources/Research-Tools-Calculators/Disease-Risk-Index-DRI-Assignment-Tool

2. Choice of optimal conditioing regimen - **Disease**

- **GVT effect : graft vs. tumor**
- Susceptibility of disease to graft immune effect is variable

Highly sensitive	CML CLL Low-grade lymphoma Mantle cell lymphoma
Intermediate sensitivity	AML Intermediate-grade lymphoma Hodgkin's lymphoma Plasma cell myeloma
Relatively insensitive	ALL High-grade lymphoma

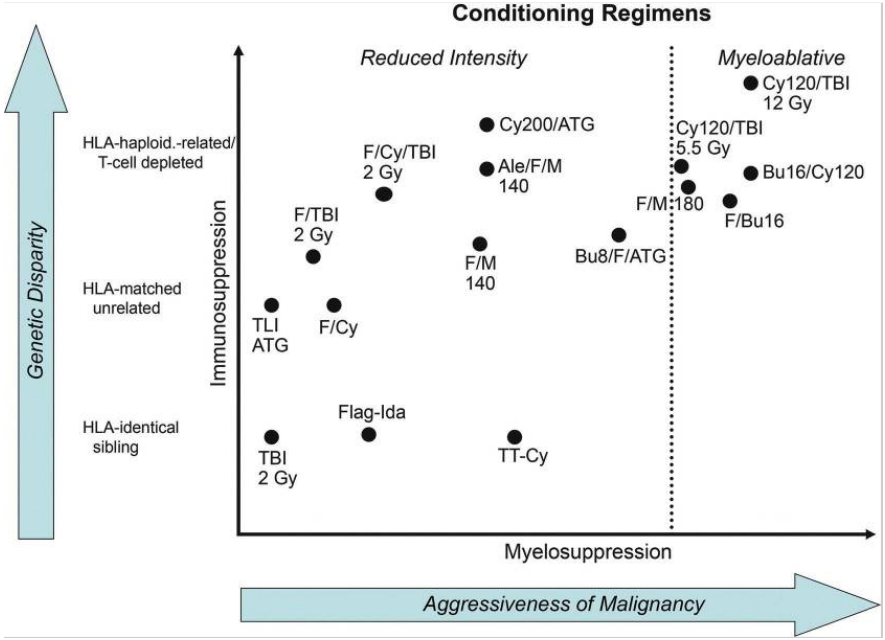
Pingali SR, Champlin RE BMT 2015;50(9):1157-67

2. Choice of optimal conditioing regimen - **Disease**

- **RIC vs. MAC in specific disease?**
- When does MAC imporve PFS/OS?
  - Data is limited and heterogeneic
  - Still to be decided
  - Review: Gagelmann et al. Haematologica 2021
- General concepts:
  - Indolent disease – highly sensitive to GvT effects
    - RIC
  - Agressive disease, disease not in CR
    - MAC
- Alternative strategies?
  - Use of sequential conditioning regimens
    - FLAMSA-RIC (chemo or TBI based)
  - Use of post HSCT interventions
    - Maintenance
    - DLI

2. Choice of optimal conditioing regimen - **Donor**

- **Alternative donor source: MMUD / Haplo / MMUD**
- high incidence of **non-engraftment / graft rejection**
- high TRM
  - major improvement with use of novel conditioing regimens
  - need for **specific protocols**
  - high degree of **immunosupression / immunoablation**



3. Commonly used MAC regimens

MAC	Drug	Dose(total)	Schedule(d)
Traditional			
Cy/TBI	Cy	120 mg/kg	– 6, – 5
	f-TBI	12 ~ 14 Gy	– 3 ~ – 1 or -6 ~ -1
Bu/Cy	Bu	16 mg/kg(po)or 12.8/kg(iv)	–7 ~ – 4
	Cy	120 mg/kg	– 3, – 2

Cy: cyclophosphamide
F-TBI: fractionated total body irradiation (6 fractions of 2Gy; 1 or 2 fractions per day)
Bu: Busulfan

3. Commonly used MAC regimens

- TBI vs. Busumfan based MAC
  - Lymphoid malignancies (eg ALL) : **preference for TBI-based** MAC
    - Penetrance to sanctuary sites – SNC, testis
  - Myeloid malignancies: **≈ similar results** with both regimens (**IV Busulfan**)
    - IV Busulfan not available in Belgium at this time (no commercialisation > imported from abroad with aditional costs)
    - Oral Bu: **variable bioavailability** (important inter- en intra-patient variability of AUCs)
    - variability in tumor response and toxicity (SOS/VOD)
    - PK monitoring for dose adjustment

3. Commonly used MAC regimens

- TBI vs. Bu based MAC
  - Lymphoid malignancies (eg ALL) : **preference for TBI-based** MAC
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    - Oral Bu: **variable bioavailability** (important inter- en intra-patient variability of AUCs)
    - variability in tumor response and toxicity (SOS/VOD)
    - PK monitoring for dose adjustment

3. Commonly used RIC/NMA regimens

Conditioning regimen	Drug	Dose (total)	Schedule(d)
International regimen			
Flu/Mel	Flu	150 mg/m^2	– 7 ~ – 3
	Mel	100 - 140 mg/m^2	– 2, – 1
Flu/Bu *«Slavin regimen»*	Flu	150 mg/m^2	– 9 ~ – 5
	Bu	8~ 10 mg/kg (po)	– 6 ~ – 4
Flu/TBI *«Seattle regimen»*	Flu	90 mg/m^2	- 4 ≈ - 2
	TBI	2 – 4 Gy	0

Flu: Fludarabine; Mel: Melphalan; Bu: Busulfan; TBI: total body irradiation

3. Commonly used RIC/NMA regimens

- Flu/Bu vs. Flu/Mel?
  - No consensus
  - Recent data suggest benefit for Flu/Mel in AML and MDS
  - Meta-analysis: Jain et al. BBMT 2019; 25(4):728-733
    - OS and PFS were not statistically significantly different
    - OS was better with FM in subgroup analysis of AML/MDS studies
    - Nonrelapse mortality was lower with Flu/Bu
    - Relapse was lower with Flu/Mel

4. Use of Immunotherapy

- **Anti-T cell globulin (ATG)**
  - Most widely used strategy for GvHD prevention in Europe
  - Added to standard profylaxis with CNI and MTX or MMF
  - 'In vivo' T-cel depletion
  - Immunosupression
- Rabbit ATG:
  - Inoculation of rabbits with human thymocytes or human Jurkat cell line
    - Thymogobulin® (Sanofi) - derived from rabbit vaccination with human thymocytes
    - Anti-T-lymphocyte globulin® (Neovii) - derived from human Jurkat T-cell line
    - Different doses per specialty
    - No large studies comparing ATG-T vs. ATG-F > observed data cannot be automatically extended to the other formulation
- Reacts against host and donor lymphocytes
  - reduction of the risk of GvHD
  - prevention of graft failure
- Associated with delayed immune reconstitution
  - Potential increased risk of infections and relapse

Meta-analysis

6 RCTs

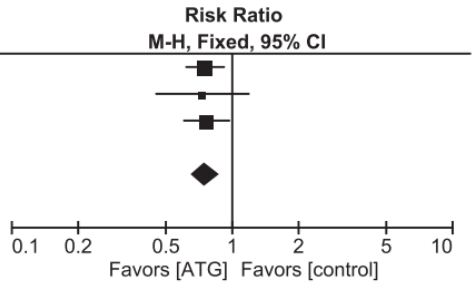
845 patients

(a) acute GVHD (all grade)

Study or Subgroup	ATG Events	ATG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Finke 2009, Socie 2011	58	103	74	99	45.0%	0.75 [0.61, 0.92]	2011
Kroger 2016	21	86	25	75	15.9%	0.73 [0.45, 1.20]	2016
Walker 2016	50	101	66	102	39.1%	0.77 [0.60, 0.98]	2016
Total (95% CI)		**290**		**276**	**100.0%**	**0.75 [0.65, 0.88]**	
Total events	129		165				

Heterogeneity: Chi² = 0.03, df = 2 (P = 0.99); I² = 0%

Test for overall effect: Z = 3.59 (P = 0.0003)

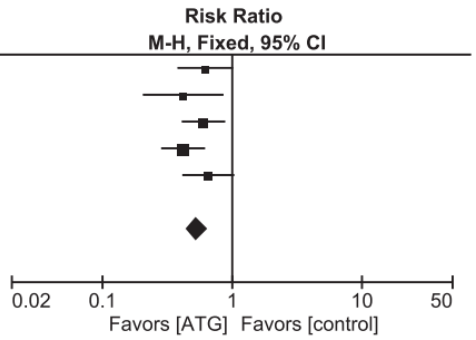


(b) chronic GVHD (all grade)

Study or Subgroup	ATG Events	ATG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Bacigalupo 2006	14	38	22	37	13.0%	0.62 [0.38, 1.02]	2006
Bacigalupo 2010	9	84	22	86	12.7%	0.42 [0.20, 0.86]	2010
Finke 2009, Socie 2011	27	90	40	80	24.7%	0.60 [0.41, 0.88]	2011
Kroger 2016	23	86	48	75	29.9%	0.42 [0.28, 0.62]	2016
Walker 2016	22	101	34	102	19.7%	0.65 [0.41, 1.04]	2016
Total (95% CI)		**399**		**380**	**100.0%**	**0.54 [0.44, 0.66]**	
Total events	95		166				

Heterogeneity: Chi² = 3.41, df = 4 (P = 0.49); I² = 0%

Test for overall effect: Z = 5.98 (P < 0.00001)



Arai et al. Leuk Lymphoma 2017;58(8):1840-1848

Meta-analysis

6 RCTs

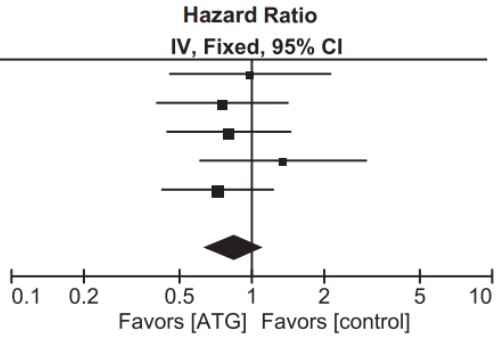
845 patients

(a) OS

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Year
Bacigalupo 2006	-0.0161	0.3957	13.9%	0.98 [0.45, 2.14]	2006
Bacigalupo 2010	-0.2827	0.323	20.9%	0.75 [0.40, 1.42]	2010
Finke 2009, Socie 2011	-0.2193	0.3049	23.4%	0.80 [0.44, 1.46]	2011
Kroger 2016	0.3001	0.4087	13.0%	1.35 [0.61, 3.01]	2016
Walker 2016	-0.3285	0.275	28.8%	0.72 [0.42, 1.23]	2016
Total (95% CI)			**100.0%**	**0.85 [0.63, 1.13]**	

Heterogeneity: Chi² = 1.95, df = 4 (P = 0.74); I² = 0%

Test for overall effect: Z = 1.14 (P = 0.25)

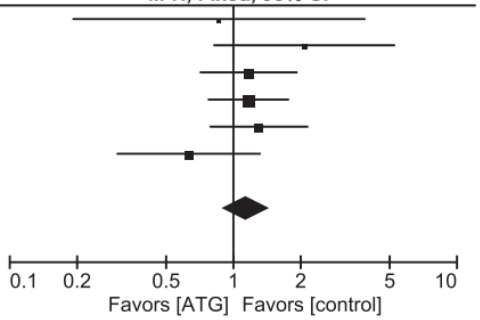


(b) Relapse

Study or Subgroup	ATG Events	ATG Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Bacigalupo 2001A	3	29	3	25	3.5%	0.86 [0.19, 3.90]	2001A
Bacigalupo 2001B	10	27	5	28	5.3%	2.07 [0.81, 5.28]	2001B
Bacigalupo 2010	24	84	21	86	22.4%	1.17 [0.71, 1.93]	2010
Finke 2009, Socie 2011	34	103	28	99	30.8%	1.17 [0.77, 1.77]	2011
Kroger 2016	27	83	18	72	20.8%	1.30 [0.78, 2.16]	2016
Walker 2016	10	101	16	102	17.2%	0.63 [0.30, 1.32]	2016
Total (95% CI)		**427**		**412**	**100.0%**	**1.14 [0.90, 1.45]**	
Total events	108		91				

Heterogeneity: Chi² = 4.44, df = 5 (P = 0.49); I² = 0%

Test for overall effect: Z = 1.07 (P = 0.28)



Arai et al. Leuk Lymphoma 2017;58(8):1840-1848

Expert recommendations

Table 2 Final recommendations.

Conditioning regimen	Stem cell source	Donor	Recommendation	Agreement among experts
MALIGNANT DISEASES				
Myeloablative	Bone marrow/ peripheral blood	Unrelated	Recommended	Full
Myeloablative	Peripheral blood	HLA-identical sibling	Recommended	Partial
RIC/NMA	Bone marrow/ peripheral blood	HLA-identical sibling/matched or mismatched unrelated	Partially recommended	Partial
Any conditioning plus post-transplant cyclophosphamide	Bone marrow/ peripheral blood	Haploidentical	Undecidable	Full
Any conditioning without post-transplant cyclophosphamide)	Bone marrow/ peripheral blood	Haploidentical	Advised to follow the conditioning published protocols	Full
Any conditioning	Cord blood transplant	Cord blood	Undecidable	Full
NON-MALIGNANT DISEASES				
Any conditioning	Any stem cell source		Recommended	Full

RIC reduced intensity conditioning, *NMA* nonmyeloablative conditioning.

Bonifazi et al. BMT 2020; 55:1093-1102

4. Use of Immunotherapy

- **Anti-T cell globulin (ATG)**

ATG	
Antitumor effect	No
Myeloablation	No
Immunosupression	Yes
Toxicity	Infusion reaction: Fever, chills, pruritus, rash, bronchospasm, hypotension, anaphylaxis Late: serum sickness Pancytopenia Hemolysis

4. Use of Immunotherapy

- **Alemtuzumab**
- Humanised anti-CD52 IgG1 mAB
  - CD52 - expressed by lymphoctes, monocytes, dendritic cells...
  - T- cell depletion
- Durable engraftment
- Decreased risk of chronic GvHd
- Decreased TRM
- Increased disease relapse due to impaired GvM effect
  - Decreased PFS
- Slower immune reconstitution
  - Risk of opportunistic infections

5. Haplo-Identical HSCT

- Major HLA-mismatched setting
  - Risk of GvHd ⬆
  - Risk of graft rejection / non engraftment ⬆
- Challenges:
  - Primary prevention and treatment of GvHD
  - Prevention of graft rejection
- Use of novel conditioning regimens and transplant aproaches
  - Ex-vivo T cel depletion
  - Unmanipulated graft transplantation
    - ATG based
    - PTCy based
    - (ATG + PTCy based)

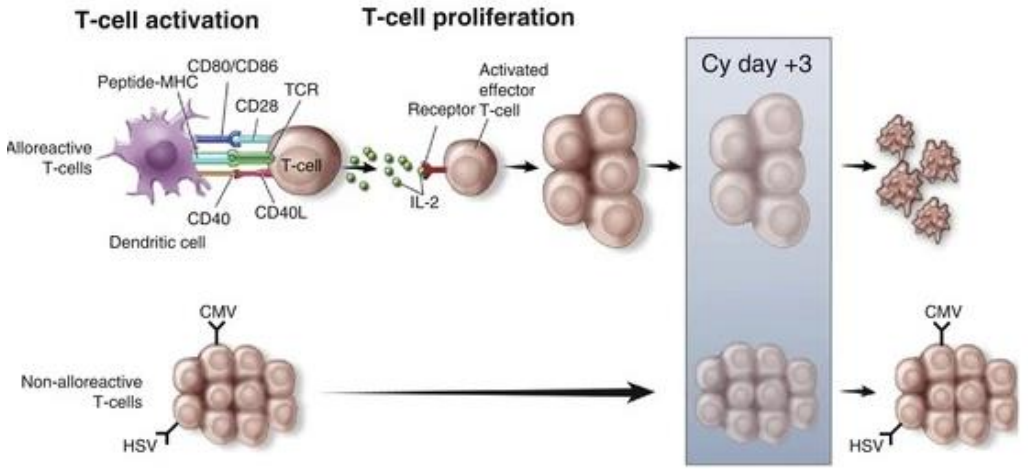
5. Haplo-Identical HSCT

- **Post-transplant Cyclophosphamide**
- Selective depletion of ‘alloreactive’ host and donor T-cells
  - Activated by HLA molecules on the surface of donor and recipient antigen-presenting cells
  - Prevention of graft rejection and GvHD
- Delay in Cy administration allows host and donor cells to react to foreign HLA
- Non-alloreactive Tcells relatively quiescent
  - Predominance of effector memory Tcells
  - Persistence of FoxP3+ regulatory T-cells
- Intra-thymic clonal deletion (dendritic cells)

5. Haplo-Identical HSCT

Post-transplant Cyclophosphamide

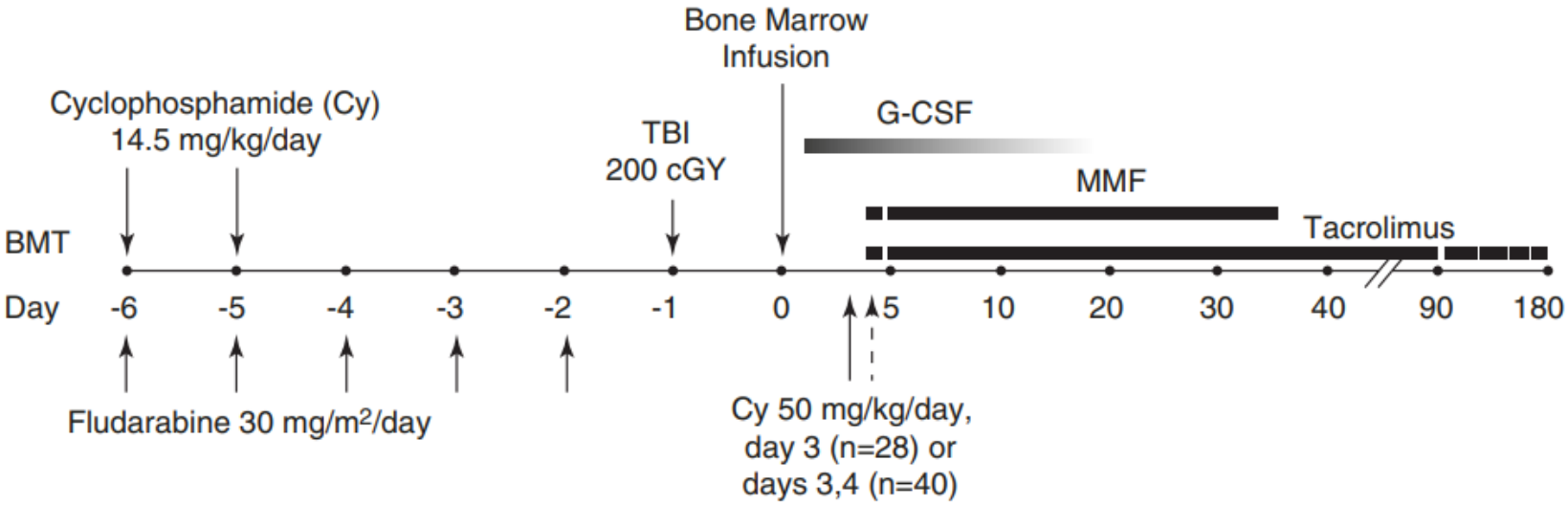
- Alloreactive T-cells activated by HLA-molecules of donor and recipient APCs
  - Proliferation leads to sensitivity to Cyclofosfamide
  - Selective depletion of alloreactive Tcells
- Non-alloreactive T-cells relatively quiescent
  - Relatively resistant to Cyclofosfamide
  - Survive to establish periferal Tcell pool / immune reconstitution



Haploidentical Transplantation 2018, chapter 7, Post-transplant Cyclophosphamide in Haploidentical Transplantation.

5. Haplo-Identical HSCT

- **Post-transplant Cyclophosphamide**
- Initial approach RIC with BM grafts
  - Pioneered by the Baltimore group
  - Flu/Cy/TBI + PTCy
- Introduction of MAC and PB in time

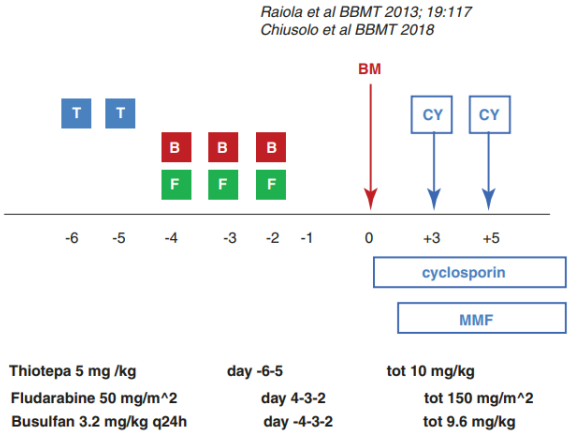


From: EBMT Handbook 2019; Chapter 65: Haploidentical HSCT.

5. Haplo-Identical HSCT

MAC Regimens

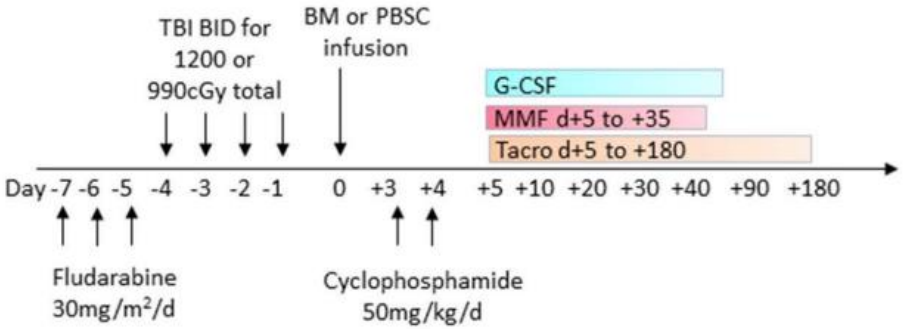
TBF (Thiotepa/Busulfan/Flu + PTCy)



From: EBMT Handbook 2019; Chapter 65: Haploidentical HSCT.

Hopkins protocol

MAC PTCy
Hopkins protocol
(Solomon BBMT 2015)



Baumeister H Front Immunol. 2020;14:11:191

5. Haplo-Identical HSCT

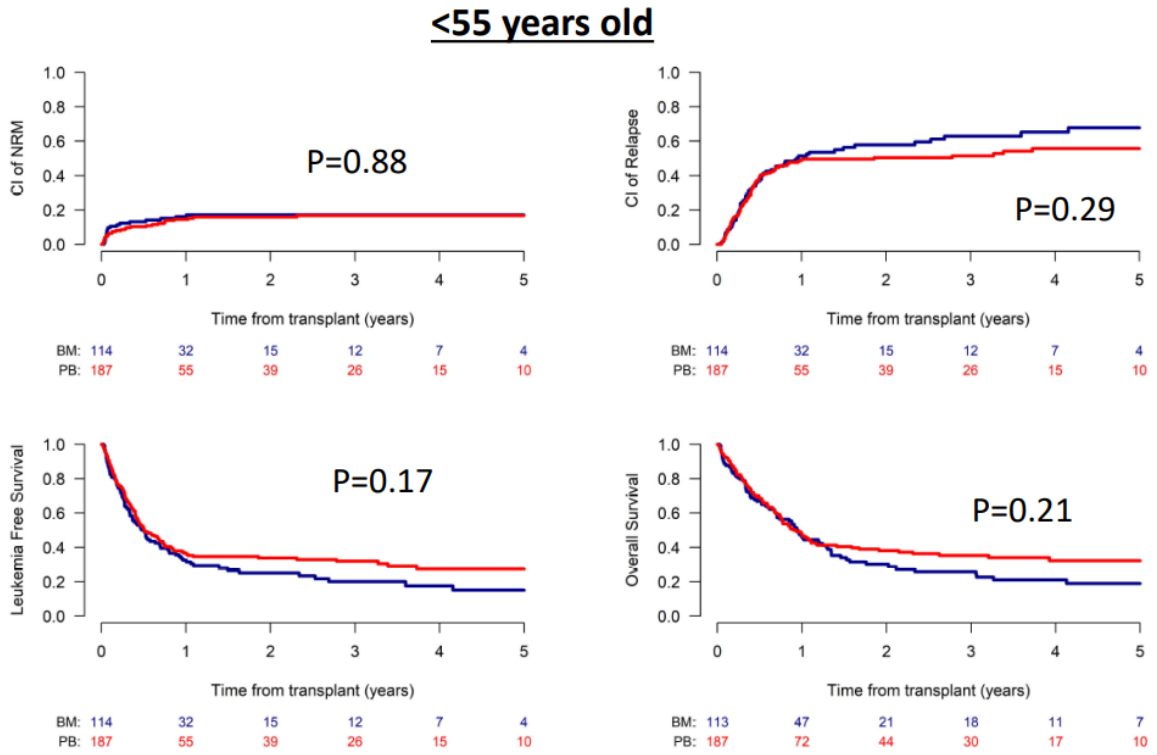
- **PTCy vs. ATG**
  - Comparison in AML patients (Ruggeri et al. Haematologica 2017;102(2): 401–410.)
  - Less grade 3-4 acute graft-versus-host disease
  - Comparable rates of cGvHd
  - Lower non relapse mortality
  - No difference in relapse incidence
  - better GRFS and LFS, trend for higher OS

5. Haplo-Identical HSCT

- **PBSC vs. BM**
  - EBMT registry study (Ruggeri et al. 2018)
    - Increased acute GvHD II–IV and III–IV
    - Same chronic GvHD, same relapse, and same 2-year OS
  - CIBMTR registry study (Bashey et al. 2017)
    - Increased GvHD II–IV, but not III–IV
    - increased chronic GvHD
    - reduced relapse
    - Similar 2y OS
  - EBMT registry study in R/R AML (Baron et al. 2020)
    - Higher incidence of grade II–IV and grade III–IV acute GVHD
    - Patients <55 years: comparable LFS
    - Patients ≥55 years of age
      - Higher non-relapse mortality
      - Lower LFS
      - Lower overall survival

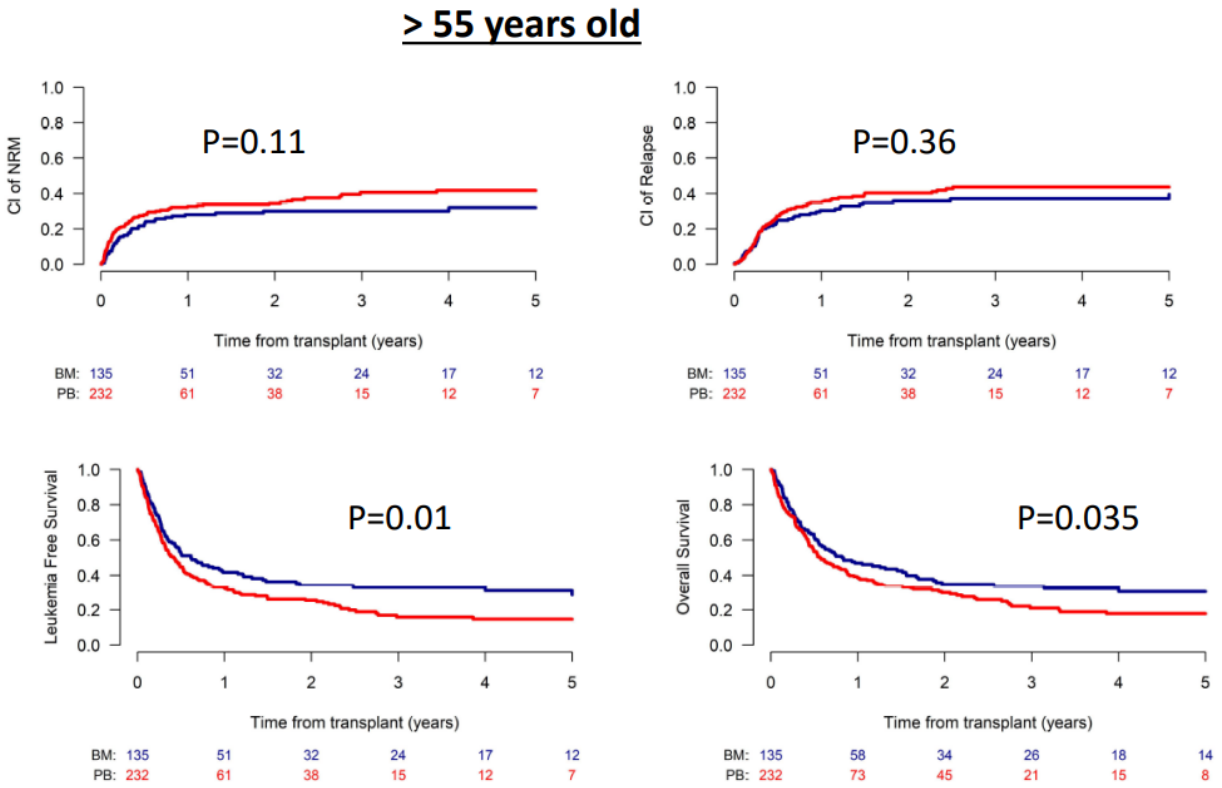
5. Haplo-Identical HSCT

- **PBSC vs. BM**
  - Baron et al 2020
  - Patients <55 yr, R/R AML



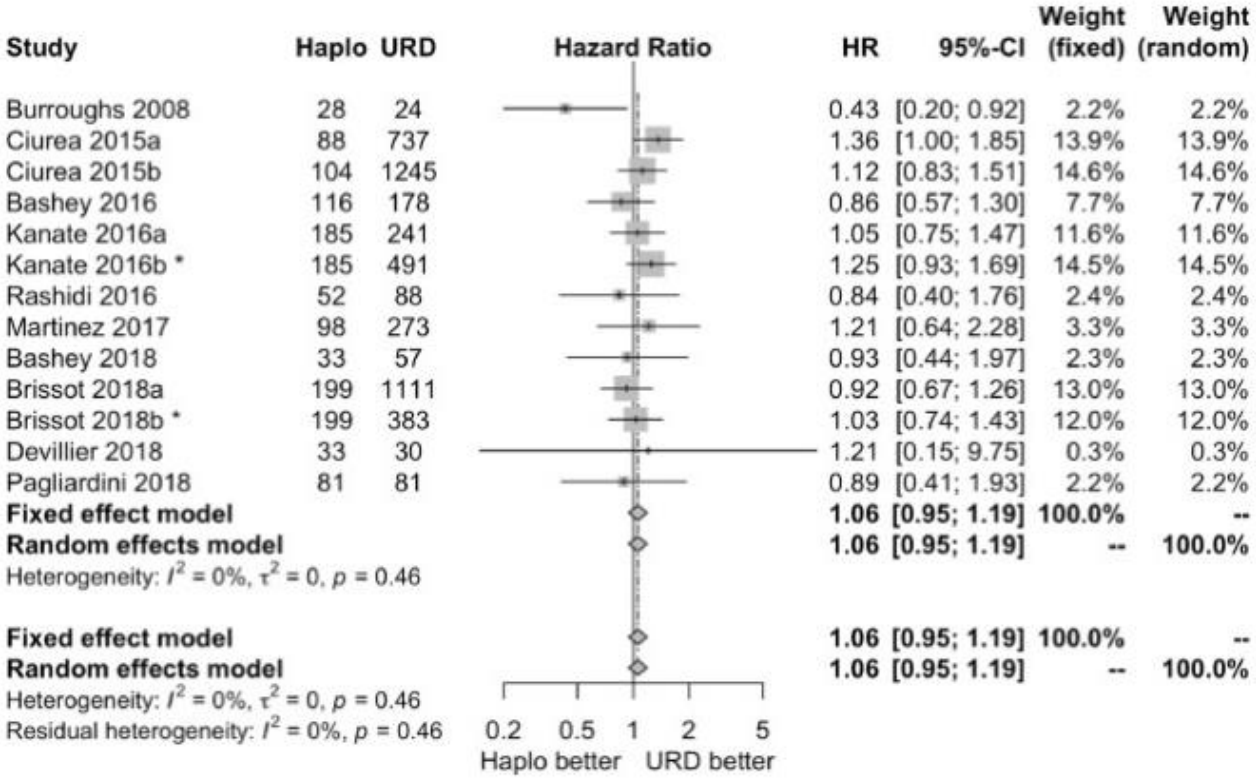
5. Haplo-Identical HSCT

- **PBSC vs. BM**
  - Baron et al 2020
  - Patients ≥55 yr R/R AML



5. Haplo-Identical HSCT

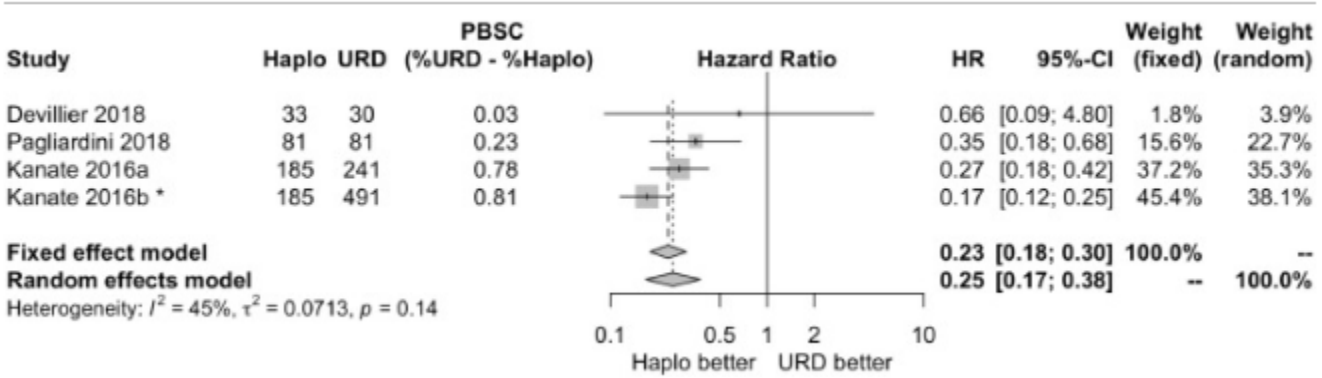
- **Haplo vs. MUD**
  - Meta-analysis 20 observational studies (1783 Haplo / 6077 MUD)
  - **OS**



Arcuri et al. BBMT 2019; 25(12):2422-2430

5. Haplo-Identical HSCT

- **Haplo vs. MUD**
  - Meta-analysis 20 observational studies (1783 Haplo / 6077 MUD)
  - **cGvHD**



Arcuri et al. BBMT 2019; 25(12):2422-2430

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