Comorbidities before Allogeneic Hematopoietic Cell Transplantation (HCT)

The HCT-specific Comorbidity Index (HCT-CI)

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Outline

- Pretransplant Essential data
- Why comorbidities are important?
  - For patients with cancer
  - For patients given allogeneic HCT
- What is the HCT-CI?
- How to collect comorbidities per the HCT-CI?
- How the HCT-CI scores could be utilized?
  - Outcome prediction
  - Comparing trials at different institutions
  - Causes of death
  - Other pretransplant risk factors

Pre-Transplant Essential Data

Were there clinically significant co-existing disease or organ impairment at time of patient assessment prior to preparative regimen?
❑ Yes ❑ No
(Check all that apply:)

Yes	Comorbidity	Definitions
❑	Arrhythmia	Atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias
❑	Cardiac	Coronary artery disease §, congestive heart failure, myocardial infarction, or EF ≤ 50%
❑	Cerebrovascular disease	Transient ischemic attack or cerebrovascular accident
❑	Diabetes	Requiring treatment with insulin or oral hypoglycemics but not diet alone
❑	Heart valve disease	Except mitral valve prolapse
❑	Hepatic, mild	Chronic hepatitis, bilirubin > ULN to 1.5 × ULN, or AST/ALT > ULN to 2.5 × ULN
❑	Hepatic, moderate/severe	Liver cirrhosis, bilirubin > 1.5 × ULN, or AST/ALT > 2.5 × ULN
❑	Infection	Requiring continuation of antimicrobial treatment after day 0
❑	Inflammatory bowel disease	Crohn disease or ulcerative colitis
❑	Obesity	Patients with a body mass index > 35 kg/m²
❑	Peptic ulcer	Requiring treatment
❑	Psychiatric disturbance	Depression or anxiety requiring psychiatric consult or treatment
❑	Pulmonary, moderate	DLco and/or FEV_1 66-80% or dyspnea on slight activity
❑	Pulmonary, severe	DLco and/or FEV_1 ≤ 65% or dyspnea at rest or requiring oxygen
❑	Renal, moderate/severe	Serum creatinine > 2 mg/dl, or >177 µmol/L, on dialysis, or prior renal transplantation
❑	Rheumatologic	SLE, RA, polymyositis, mixed CTD, or polymyalgia rheumatica
❑	Solid tumor, prior	Treated at any time point in the patient's past history, excluding nonmelanoma skin cancer

§ One or more vessel-coronary artery stenosis requiring medical treatment, stent, or bypass graft.
EF indicates ejection fraction; ULN, upper limit of normal; SLE, systemic lupus erythmatosis; RA, rheumatoid arthritis; CTD, connective tissue disease; DLco, diffusion capacity of carbon monoxide.

Source: Blood, 15 October 2005 · Volume 106, Number 8

CIBMTR/EBMT/FACT Transplant Essential Data — Pre-TED (11/06v2) Page 2 of 10

Why comorbidities are important?

For patients with cancer

Background
Comorbidity

- Any distinct additional clinical entity that has existed or may occur during the clinical course of a patient with an index disease. (Feinstein. J Chronic Dis. 1970; 23:455)
- Relevant in the prognosis of cancer patients.
- Physiological burden of chronic disease and its interaction with cancer and cancer treatment
- Increased severity of comorbidities leads to increased risks of toxicities to specific therapies

Comorbidities and Cancer

Clinical impacts

- Prognosis
- Quality of care
  - Choice of therapy
  - Tolerability to therapy
  - Mortality
- Quality of life (QOL)

Statistical impact

- Confounder
- Effect modifier
- Predictor of study outcome
- One comprehensive measure

de Groot V. J. Clin. Epidemiol., 2003

Comorbidities and Cancer
Solid Tumors ± Lymphoma

- Major predictors of quality of life
  - Age
  - Comorbidities (scores or numbers)
  - Cancer site
  - ± Symptom severity

- Age did not constitute a difference (<45, 45-65, >65)
- Comorbidities caused age-related differences

Greimel ER. British J Cancer, 1997

Comorbidities and Hematological Malignancies
Lymphoma
Leukemia

- Impact survival
  - Death from comorbidities
  - Contraindications to specific therapy
  - Reduction of specific-therapy dose
  - Treatment-related complications

Lymphoma: van Spronsen DL. Euro. J Cancer, 2005

Leukemia: Pinto A. Critical Reviews, 2001

Why comorbidities are important?

For patients given allogeneic HCT

Allogeneic HCT for hematological malignancies

- Myeloablative conditioning regimens:
  - High-dose chemotherapy and/or radiotherapy
  - Potentially curative treatment
  - Relatively high NRM
  - Young healthy patients with limited prior treatment history
- Nonmyeloablative or reduced-intensity conditioning regimens:
  - Milder regimen-related toxicity and mortality
  - Enroll older patients
  - Enroll more patients with comorbidities

Allogeneic HCT for hematological malignancies

- Available literature focuses on studying individual comorbidities
- No data on the impact of increasing number and severity of comorbidities on HCT outcomes
- No comorbidity objective measures are available to determine which patients:
  - Could tolerate myeloablative conditioning
  - Would benefit from nonmyeloablative conditioning
  - Would not benefit from either kind of conditioning

Initial experiences with comorbidity indices in allogeneic HCT

The Charlson Comorbidity Index (CCI)

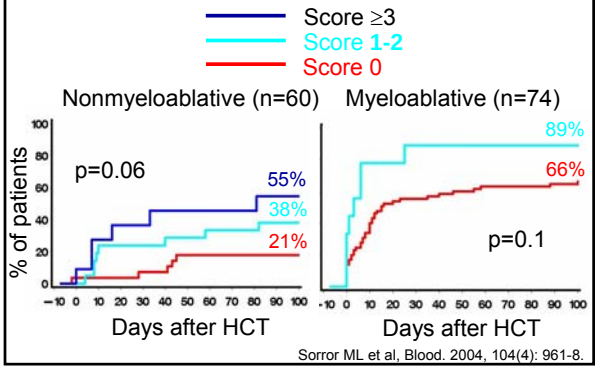
The CCI

- Developed from
  - Number and severity of comorbid diseases
  - An inception cohort of 604 medical patients
  - Admitted for a 1 month period at NY hospital
  - One-year follow up data
- Comorbidity weighted index (training population):
  - Relative risks of each comorbidity for 1-year mortality
  - Adjusted for
    - All other comorbidities
    - Illness severity
    - Reason for admission
  - Employed as weights for different comorbidities

Charlson et al, J Chronic Dis., 1987;104:961-968

Seattle experience

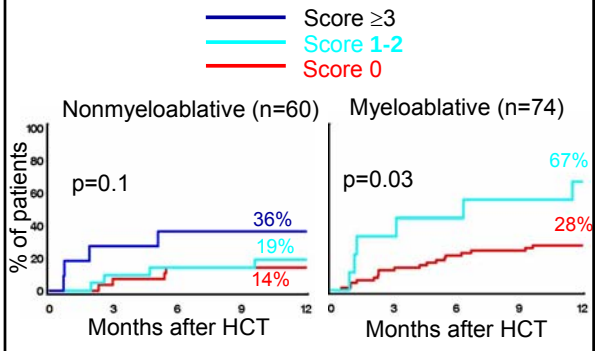
CCI scores and grade IV toxicity: URD



Sorror ML et al, Blood. 2004, 104(4): 961-8.

Seattle experience

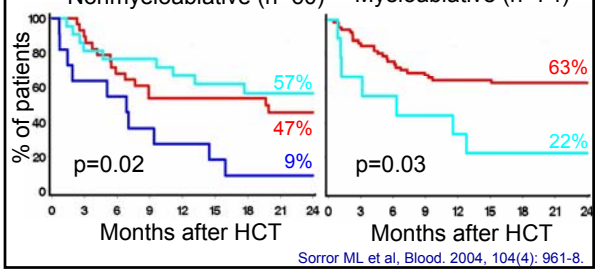
CCI scores and NRM: URD



Sorror ML et al, Blood. 2004, 104(4): 961-8.

Seattle experience

CCI scores and survival: URD



Sorror ML et al, Blood. 2004, 104(4): 961-8.

Houston experience

CCI scores and outcomes: AML/MDS

Outcomes for all patients	Scores 0-2 (n = 28)	Scores >2 (n = 50)	*P*
% OS @ 2yrs.	83	53	0.001
% EFS @ 2yrs.	76	38	0.0004
% NRM Day100	3	14	0.02
% NRM Day360	4	26	0.02

Giralt S et al, Tandem BMT Meeting 2004

The HCT-CI

Sorror et al, Blood. 2005, 106(8): 2912-9

Limitations of the CCI for HCT

- Some CCI comorbidities were rarely identified among HCT patients
  - Pulmonary and hepatic comorbidities
- Some comorbidities were not represented in the CCI
  - Infections and depression
- Lack of sensitivity
  - Scores ≥1 in 35% of patients
    - Particularly low in myeloablative patients (12%)

Aims

- Better define comorbidities using laboratory data
  - Pulmonary, hepatic, cardiac, and renal comorbidities
- Investigate additional comorbidities among HCT patients
  - All new comorbidities
- Establish comorbidity scores suited for HCT
  - Other comorbidities as originally defined

Design: 1055 patients

- Nonmyeloablative = 294
- Myeloablative = 761
- Transplanted between
  - 1997- 2003 for related recipients
  - 2000-2003 for unrelated recipients
- Malignant or non-malignant hematological diseases
- Database pre-HCT lab values
  - Bilirubin, AST, ALT, creatinine, EF, DLco, FEV_1
- Retrospective chart review

Developing the new HCT-CI

- All patients were randomly divided into two populations
  - Training set (n=708)
  - Validation set (n=347)

Refining some comorbidity definitions

Comorbidity	Old definition CCI	Added definition HCT-CI
Pulmonary:		
Mild	Dyspnea grade II	DLco/ FEV1 >80%
Moderate	Dyspnea grade III	DLco/ FEV1 66-80%
Severe	Dyspnea grade IV	DLco/ FEV1 ≤65%
Cardiac	Heart failure & myocardial infarction	EF ≤50%

Refining some comorbidity definitions

Comorbidity	Old definition CCI	Added definition HCT-CI
Hepatic:		
Mild	Hepatitis or cirrhosis	Hepatitis, bilirubin (1.5 ULN), or AST/ALT (2.5 ULN)
Moderate/severe	Portal hypertension ± bleeding varices	Cirrhosis, bilirubin (>1.5 ULN), or AST/ALT (>2.5 ULN)
Renal:		
Mild	Creatinine 2-3 mg/dl	Creatinine >1.2-2 mg/dl
Moderate/severe	Creatinine >3 mg/dl, renal dialysis/transplant	Creatinine >2mg/dl

The added new comorbidities

New comorbidity	Prevalence
Bleeding	1%
Migraine/headache	4%
Osteoarthritis	1%
Osteoprosis	1%
Depression/anxiety	9%
Obesity	2%
Infection	4%

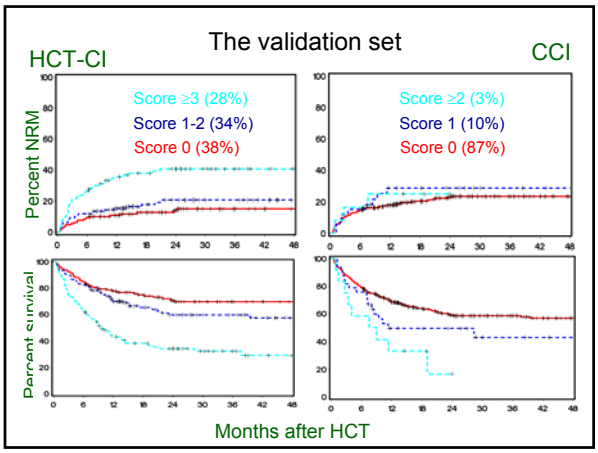
Development of the scores Training set

- 28 comorbidities
- Calculation of unadjusted HR of each comorbidity for
  - NRM
    At 2-years
- Adjustment of HRs for
  - All other comorbidities
  - Disease risk
  - Type of conditioning
  - Age
- Adjusted HR were employed as weights:
  - HR ≤1.2 = score 0
  - HR 1.3-2.0 = score 1
  - HR 2.1-3.0 = score 2
  - HR 3.1-3.9 = score 3

New scores and prediction of NRM

Scores	Training set (n = 708)			Validation set (n = 346)		
	# Pts, %	NRM, %	HR*	# Pts, %	NRM, %	HR*
0	38	9	1	38	14	1
1	17	14	1.66	18	22	1.57
2	17	27	3.48	17	19	1.26
3	17	41	6.09	15	41	3.95
≥ 4	11	43	6.93	13	40	3.05

*Adjusted for age, disease risk and type of conditioning



HCT-CI

Scoring comorbidities

Cardiovascular

- Arrhythmia:
  - Atrial fibrillation (AF)
  - Atrial flutter
  - Ventricular arrhythmias (Tachycardia or fibrillation)
  - Sick sinus syndrome
- Cardiac problems:
  - Coronary artery disease
  - Myocardial infarction
  - Congestive heart failure
  - Ejection fraction (EF) ≤50%
- Valvular disease
  - Any proven valve stenosis or malfunction with the exception of asymptomatic mitral valve prolapse
  - Prosthetic aortic or mitral valves

Gastrointestinal

- Inflammatory bowel disease
  - Ulcerative colitis
  - Crohn's disease
- Peptic ulcer
  - Previously required treatment
  - Previously bled from ulcer

Endocrine

- Diabetes
  - Type I
  - Type II
    - requiring treatment with oral hypoglycemic drugs or insulin

Neurology

- Cerebro-vascular disease
  - History of transient ischemic attacks
  - History of a cerebro-vascular accident

- Obesity
  - Patients with body mass index of >35 (weight in kg/ height x height in m)
- Infection
  - Documented or suspected and requiring treatment before, during, and after start of conditioning regimen

- Psychiatric disturbances
  - Depression
  - Anxiety
    - Previously diagnosed and receiving specific treatment
    - Diagnosed and started treatment at the time of HCT

- Renal
  - Serum creatinine >2 mg/dl
  - On dialysis
  - Had prior renal transplantation
- Preceding solid malignancy
  - Requiring treatment
  - Excluding non-melanoma skin cancer

- Rheumatologic
  - Systemic lupus erythmatosis (SLE)
  - Rheumatoid arthritis (RA)
  - Polymyositis
  - Mixed connective tissue disease
  - Polymyalgia rheumatica

Hepatic

- Mild
  - Chronic hepatitis
  - Bilirubin >upper limit of normal (ULN)-1.5 x ULN
  - AST or ALT >ULN-2.5 x ULN

Or

- Moderate-severe
  - Cirrhosis or fibrosis proved by liver biopsy
  - Bilirubin >1.5 x ULN
  - AST or ALT >2.5 x ULN

Pulmonary

- Moderate
  - Diffusion capacity of CO (DLco) 80%-66%
  - FEV1 80%-66%
  - Shortness of breath on exertion

Or

- Severe
  - DLco ≤65%
  - FEV1 ≤65%
  - Shortness of breath at rest
  - Requiring supplemental oxygen

Current and future applications of the HCT-CI

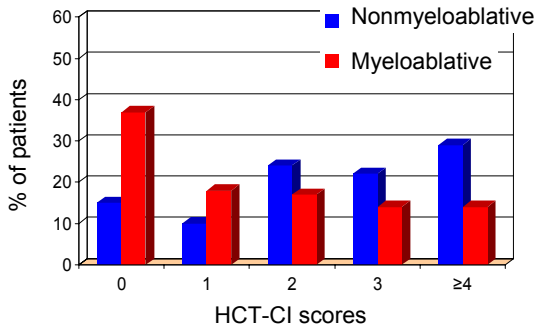
- Predict HCT outcomes
- Determine how patients tolerate different conditioning regimens

Correlation with Conditioning Intensity

Patients diagnosed with MDS or AML

Sorror ML et al, ASH 2005

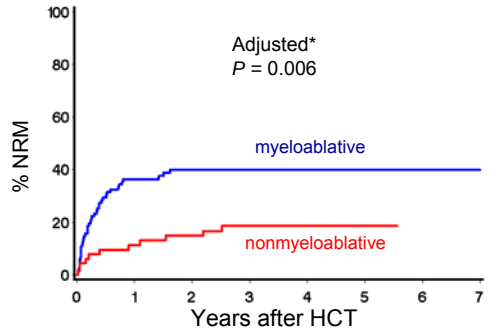
HCT-CI scores



Multivariate analysis
Risk factors for NRM

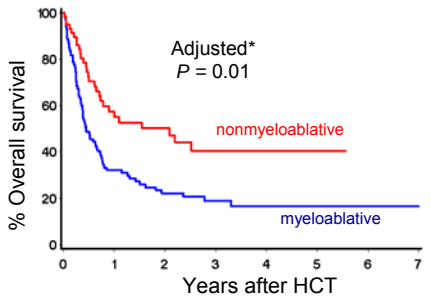
Risk factors	HR	*P*
HCT-CI scores of ≥2	3.32	<0.0001
High-risk disease	2.00	0.002
Unrelated donor	1.80	0.005
Recipient age ≥50 years	1.82	0.01
Marrow	1.75	0.01
myeloablative conditioning	1.92	0.03
Recipient CMV positive	1.59	0.03

Patients with high-risk MDS/AML and HCT-CI scores of ≥2



*Adjusted for age, diagnosis, stem cell source, donor type, prior HCT, and CMV serostatus

Patients with high-risk MDS/AML and HCT-CI scores of ≥2



*Adjusted for age, diagnosis, stem cell source, donor type, prior HCT, and CMV serostatus

Summary

- Patients with high-risk MDS or AML and HCT-CI scores of ≥2 receiving nonablative conditioning:
  - Less NRM
  - Survival benefit
- More data are needed for patients with:
  - Low-risk MDS or AML
  - Low HCT-CI scores
- HCT-CI should be considered among other risk factors:
  - Prospective trials
  - Patient counseling

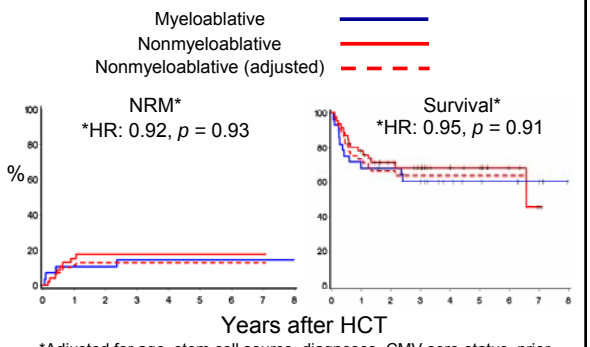
Correlation with Conditioning Intensity

Lymphoid malignancies

Sorror ML et al, ASH 2006

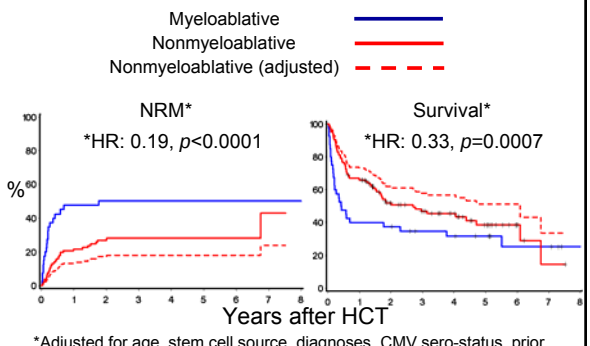
Characteristics	Nonablative (n=152)	Ablative (n=68)
Median age, years	52	40
Median (range) # of prior regimens	3 (0 - 10)	2 (0 - 8)
Diagnoses	%	%
NHL	53	79
CLL	27	15
HD	20	6
URD	45	34
G-PBMC	99	69
Prior HCT	45	10
Refractory/untreated relapse	53/13	48/3

HCT-CI score 0: Adjusted outcomes



*Adjusted for age, stem cell source, diagnoses, CMV sero-status, prior regimens, donor type, and disease chemo-sensitivity

HCT-CI score ≥1: Adjusted outcomes



*Adjusted for age, stem cell source, diagnoses, CMV sero-status, prior regimens, donor type, and disease chemo-sensitivity

Summary and future directions

Lymphoid malignancies

- Patients with no comorbidities: At 3-years
  - NRM of 15%-18% regardless of conditioning
- Patients with comorbidities receiving nonablative compared to ablative conditioning:
  - Less NRM
  - Better survival
- Prospective randomized studies for patients:
  - NO comorbidities
  - Age ≤60 years

Comparing patients at different institutions

MD Anderson Cancer Center

Patients with AML in 1st complete remission

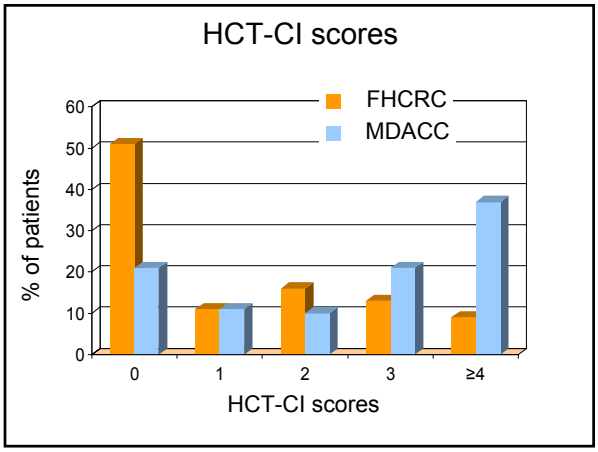
Sorror ML et al, Tandem BMT 2006

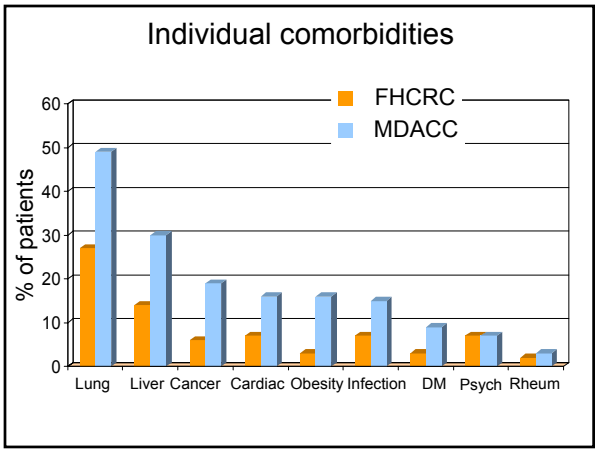
AML in first complete remission

Characteristics		FHCRC (n=177)	MDACC (n=67)
Age, median (range) years		41 (19 – 75)	39 (19 – 67)
Interval from Dx to HCT, months		4.8	5.1
Donors	Matched related	68%	78%
	Mismatched related	4%	7%
	Unrelated	28%	15%
G-PBMC		35%	42%

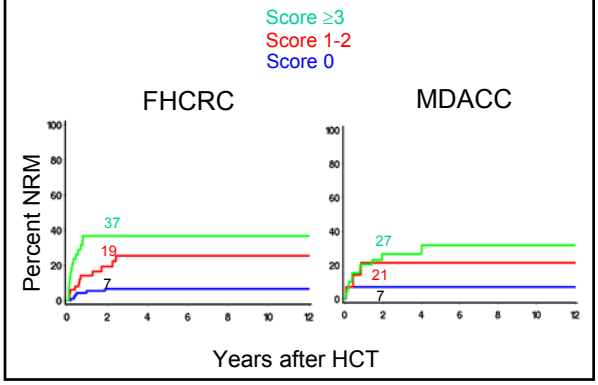
Conditioning regimens		FHCRC (n=177), %	MDACC (n=67), %
Myeloablative	TBI-based	45	43
	Non TBI-based	44	24
Reduced intensity*		2	22
Nonablative§		10	10

*Includes fludarabine/alkylating agent-based regimens
§Includes 2 Gy TBI-based regimen or fludarabine/Ara-C/idarubucin

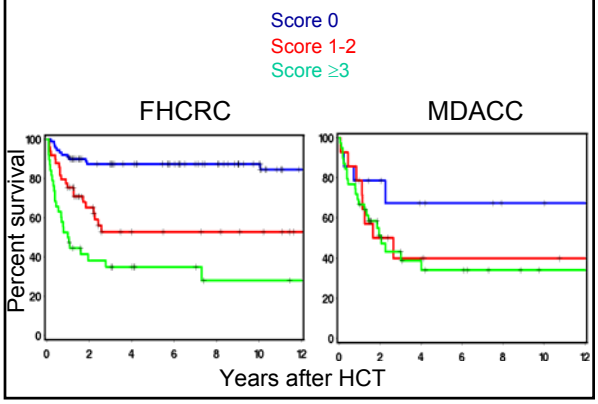




2-year NRM stratified by HCT-CI scores



2-year survival stratified by HCT-CI scores



High Early Mortality

Palliative Care Discussion Programs

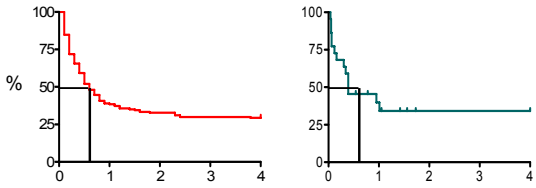
	Group 1	Group 2
Conditioning	Myeloablative	Nonmyeloablative
Relapse-risk	High*	High*
HCT-CI scores	≥3	≥6

*All except AML in 1st CR, CML in 1st chronic phase, MDS-RA or RARS

Patients with High-risk for relapse

Myeloablative
HCT-CI scores ≥3

Nonmyeloablative
HCT-CI scores ≥6



Years after HCT

- Correlation with causes of death

HCT-CI and acute GVHD

Sorror ML et al, Tandem BMT 2006

Patients

- Hematological malignancies
- 1993-2002
- myeloablative conditioning
- CSP/MTX GVHD prophylaxis

Characteristics		Related (n=709)	Unrelated (n=249)
Median age, years		42	38
Disease-risk	Low	54%	58%
Stem cell source	Marrow	67%	77%
HCT-CI scores	≥1	53%	56%
Conditioning	BU/CY	66%	17%
	CY/TBI	34%	83%

Factors analyzed

- Recipient age
- Donor age
- Recipient/donor sex
- Type of donor
- TBI versus no TBI
- Dose of TBI
- HCT-CI
- Disease risk
- Year of HCT
- Marrow vs. G-PBMC
- Full vs. reduced dose:
  - CSP
  - MTX

Multivariate analysis
Risk factors for grades II-IV acute GVHD

Risk factors		HR	*P*
HCT-CI scores	≥5	1.63	0.008
TBI	Yes	1.71	<0.0001
CSP dose reduction	< 80%	1.95	0.05
Recipient age	>20	1.42	0.001
Donor	Unrelated	1.85	< 0.0001

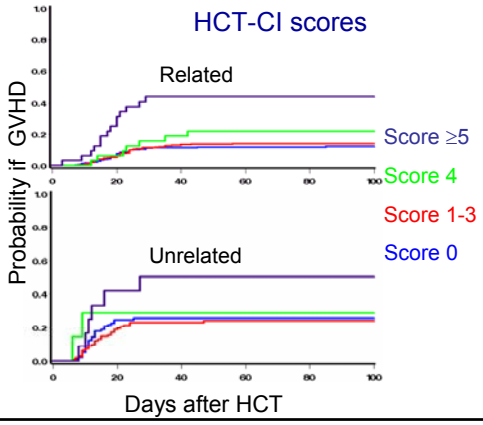
Multivariate analysis
Risk factors for grades III-IV acute GVHD

Risk factors		HR	*P*
HCT-CI scores	≥5	3.05	< 0.0001
Disease-risk	High	1.55	0.008
CSP dose reduction	< 80%	1.95	0.008
MTX dose reduction	< 80%	1.96	0.02
Donor	Unrelated	2.60	< .0001

Correlation between age, comorbidity and CSP dose reduction

	Recipient age		*P*
	< 20 years	≥ 20 years	
HCT-CI scores of 0	68%	46%	0.0002
CSP dose reduction	34%	73%	<0.0001

Grades III-IV acute GVHD HCT-CI scores



Summary

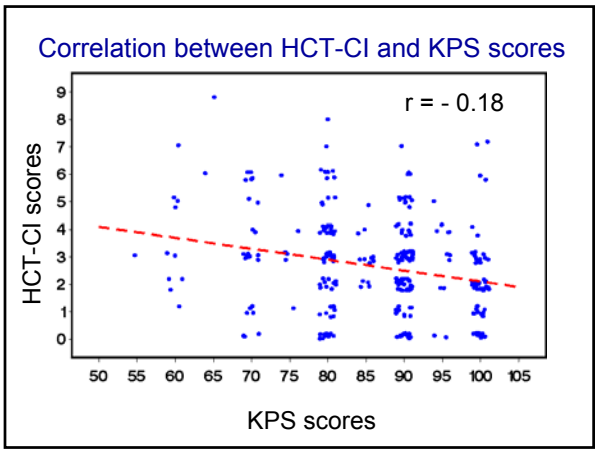
- The age related reductions of CSP dosing were likely due to increasing comorbidities with increasing age.
- Patients with high comorbidity scores or advanced disease should be stratified in future clinical trials for GVHD prophylaxis.

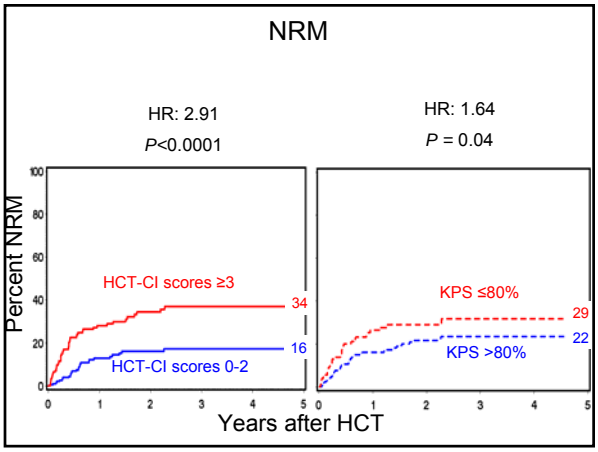
- Interaction with other pretransplant risk factors

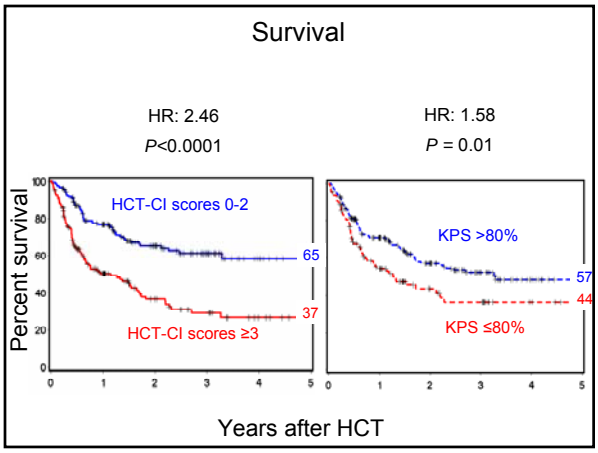
HCT-CI and Performance Status

Nonmyeloablative Conditioning

Sorror ML et al, ASH 2006


Correlation between HCT-CI and KPS scores
r = - 0.18
HCT-CI scores
KPS scores

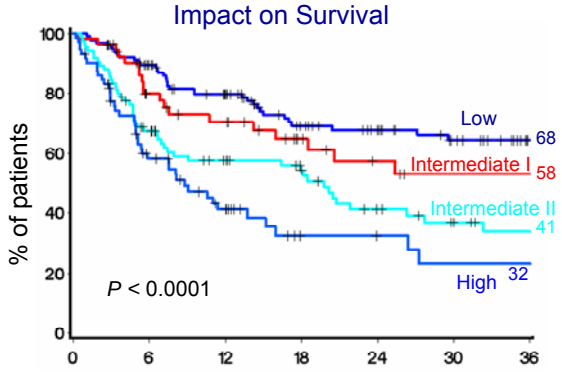

NRM
HR: 2.91
P<0.0001
HR: 1.64
P = 0.04
Percent NRM
HCT-CI scores ≥3
34
16
HCT-CI scores 0-2
KPS ≤80%
29
22
KPS >80%
Years after HCT


Survival
HR: 2.46
P<0.0001
HR: 1.58
P = 0.01
Percent survival
HCT-CI scores 0-2
65
37
HCT-CI scores ≥3
KPS >80%
57
44
KPS ≤80%
Years after HCT

Consolidated HCT-CI and KPS

Risk Groups		Definitions		Patients (n=341)
		HCT-CI	KPS	%
Low		0-2	>80%	38
Intermediate	I	0-2	≤80%	16
	II	≥3	>80%	25
High		≥3	≤80%	21

Consolidated HCT-CI and KPS Impact on Survival



Conclusion: HCT-CI

- One measure for different comorbidities
- Higher performance
- Stratify patients
  - Nonmyeloablative versus myeloablative
- Prognostic
- Compare trial results at different institutions
- Impact on GVHD prophylaxis regimens
- Consolidated with Performance Status

Future Aims

- Multi-institutional validation
- Inter-rater reliability
- Interaction with aging
- Post-HCT toxicities and quality of life
- Causes of death
- Simplifying assessment
  - Different methods
  - Education program