Does conditioning intensity matter? the NO position



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No conflict of interest to declare

What can we expect from a modern transplant platform (conditioning regimen + GVHD prophylaxis?)

- Engraftment (do we always need myeloablation?)
- Low extrahematological toxicity
- High anti-leukemia efficacy to let time for GVL effect to take over
- Low rates of aGVHD, no grade 3-4 aGVHD
- No or mild cGVHD

The conditioning intensity axiom:

- Reduced intensity has the rationale of reduced non-relapse mortality (NRM)
- Increased intensity results in reduced relapse (REL)
- NRM and REL are inversely proportional
- Survival depends on the sum of the competing factors NRM + REL

The survival equation:

OS = 1 – (NRM + REL)

NRM * REL = \mathbf{k}

The dilemma of dose intensity – a paradigmatic example



Let's solve the equation:

TBI 15.75 GyTBI 12 GyOS = 1 - (NRM + REL)OS = 1 - (NRM + REL)= 1 - (0.4 + 0.1)= 1 - (0.1 + 0.4)= 1 - 0.5= 0.5

Different intensity: similar survival

The evolving concept of transplant elegibility

Relative Proportion of Allogeneic HCTs for Malignant Diseases* in the US by Recipient Age



Comorbidity Score in Allogeneic HCTs in the US by HCT CI Group, Adults



Higher flexibility in transpant elegibility

Older/unfit patients: intensity = toxicity

We are forced to de-escalate intensity in this population

What do we need intensity for?

- 1. To engraft stem cells: no need for high intensity in AML
- 2. To eradicate residual disease: does intensity really matters?

Let's get rid of dose intensity!

Let's prove the axiom wrong - we need randomized studies

Let's get rid of dose intensity – 1

GITMO phase III, randomized trial. Pivotal study Bu-Cy vs Bu-FLU (2 vs 1 alkylator) AML 40-65y, HLA matched related or UD (>=9/10)



Primary endpoint: 1 year NRM: met NRM: 19% (BuCy) vs 10% (BuFlu) Organ failure: 7% (BuCy) vs less than 1% (BuFlu) No difference in survival

Reduced NRM, however REL not increased

Rambaldi, Lancet Oncol 2015

Let's get rid of dose intensity - 2

RICMAC EBMT trial, Phase III, randomized RIC vs MAC (Bu2-Flu vs Bu-Cy) MDS + secondary AML HLA matched related or UD (>=9/10)



RIC: trend for better OS compared to MAC (in MDS)

Yes, we can! The axiom was wrong: Reduced NRM does not necessary lead to increased REL

De-escalating dose intensity for all patients? RIC for everybody!

US-CTN 0901 study, Phase III randomized trial, MAC vs RIC 271 patients with AML or MDS Age 18-65, HCT-CI max 4 MAC: Bu/Cy or Cy/TBI; RIC: Bu2/Flu or Flu/Mel



Increased relapse in AML (not in MDS): 48% (RIC) vs 14% (MAC) Increased LFS MAC vs RIC

De-escalating dose intensity for all patients? NO, we can't



MAC vs RIC: improved survival (AML only)

Was the axiom right, after all?

Don't even think about RIC in young, fit AML patients!

Scott, Transplantation and cellular therapy 2021

Randomized, phase III Trial (MC-FludT.14/L Trial), Bu-Flu vs Treo-Flu

18–70 years, AML CR or MDS

HLA-matched related or UD (>=9/10)

Key inclusion criteria: considered inelegible for Myeloablative regimen based on:

- Age >= 50y

And/or HCT-CI >2

Treo 10 g/m2 (3 days) vs Bu 3,2 mg/kg (2 days)

+ Fludarabine 30 mg/m2 (5 days)



NRM gap widens beyond 6 months

Primary endpoint: met. Improved EFS

Beelen, Lancet Hematol 2020

Can we improve over conventional RIC regimens? Treosulfan



Improved OS

	Busulfan group		Treosulfan group				HR	HR (95% CI)	р
	n/N	24 month event-free survival	n/N	24 month event-free survival	n e				
All									
Crude*	100/240	50.4%	68/220	64.0%				0.70 (0.51-0.95)	0.021
Adjusted								0.65 (0.47-0.90)	0.010
Donor type									
MUD	74/181	50.6%	46/168	66.8%				0.61 (0.42-0.90)	0.012
MRD	26/59	49.6%	22/52	55.4%				0.78 (0.40-1.53)	0.47
Risk group									
RGI	36/121	61.9%	19/99	77.9%			<u>l</u>	0.74 (0.41–1.32)	0.30
RGII	64/119	38.8%	49/121	51.7%				0.61 (0.41-0.90)	0.013
Disease									
AML	53/138	55.2%	48/155	63.9%			+ !	0.69 (0.44–1.07)	0.69
MDS	47/102	44·1%	20/65	64.5%			+	0.59 (0.32–1.09)	0.59
Age group (y	ears)								
<50	5/11	46.8%	5/15	58.7%	◀───			0-31 (0-04–2-25)	0.25
≥50	95/229	50.7%	63/205	64.3%				0.65 (0.47-0.91)	0.013
HCT-CI score									
≤2	36/100	56.4%	20/89	74.3%	_			0.51 (0.25-1.01)	0.053
>2	64/140	46.2%	48/131	57.1%			+	0.84 (0.55-1.27)	0.40
				0-1	1 Favours	0.5	1 1.3 Favours	5 10 busulfan	

After all, is conditioning intensity the right focus?

Conditioning intensity is the result of the combination of:

- 1. The inherent pharmacodynamic properties of the single conditioning agents
- 2. The resultant toxicity to that given patient

(patient-related variables as, Age/comorbidities/dynamic fitness previous chemotherapy, alkylator dosing in obese pts, drug-drug interactions etc.)

+ GVHD prophylaxis should be taken into account (ptCY vs ATG/MTX/CSA vs T-cell depleted HSCT)

The ptCY case:

i.e. Myeloablative TBI-based conditioning + ptCY Double alkylator conditioning + ptCY

High toxicity is expected

Treosulfan as an alternative to double alkylator in ptCY haplo for AML



d) OS

	2-years OS
Treo	76%
TBF	73%
Р	0.53

	2y	NRM	RI	2y	LFS	OS
RIC	Treo	13%	20%	Treo	67%	77%
subgroup	TBF	24%	13%	TBF	64%	68%
		P=0.2	P=0.7		P=0.6	P=0.3

Saraceni, submitted

Don't forget we are in 2023, we have MRD! The FIGARO trial

1:1 Randomisation Stratified by the following: Phase III, randomized trial Underlying disease (AML s MDS) Disease status at transplant (CR1 or CR2 vs primary refractory disease) 244 AML or MDS patients Age (>60 vs <60) Donor type (sibling vs unrelated) Not eligible to MAC **Control arm** RIC vs intensified sequential conditioning **Experimental arm** Fludarabine/Busulphan/Alemtuzumab (FBA) Flamsa-Bu Fludarabine/Melphalan/Alemtuzumab (FMA) MRD prospectively evaluated by MFC Day 0 PBSCT 2 year follow-up for survival Control 100% Control 100% Control FLAMSA-BU FLAMSA-BU FLAMSA-BU Patients 122 122 HR (85% CI): 1.048 (0.8 to 1.38) P = .8 75% 75% Events 40 38 2-Year CIR (95% CI) 30% (22 to 38) 27% (19 to 35) CIR SO 50% 50% FLAMSA-BU HR (95% CI) = 0.94 (0.60 to 1.46) P = .81Contro Patients 122 122 25% 25% Events 57 56 2-Year OS (85% Cl) 59% (52 to 65) 61% (54 to 67) 0% 0% 8 12 14 16 18 20 22 24 26 28 30 32 34 36 0 2 10 8 12 14 16 18 20 22 24 26 28 30 32 34 36 0 2 6 10 Time From Random Assignment (months) Time From Random Assignment (months)

Intensified regimen did not improve outcome Relapse rate 25-30% as expected, different from US-CTN 0901 trial

FIGARO UK trial - MRD

Detrimental effect of pre-transplant MRD (0,2% cutoff) on cumulative incidence of relapse



No benefit of regimen intensification in positive MRD RIC MRDpos: relapse 40% (2y), survival 50% (2y)

RIC - HSCT is not futile in an elderly/unfit patient with positive MRD

Seattle – MAC vs NMA/RIC, MRD pre/post HSCT

810 AML CR1 or CR2; MAC vs non-MAC (RIC/NMA) MRD by flow pre/post HSCT (peritransplant MRD)



MAC

NMA/RIC

Look at the green curve: RIC better than MAC in MRDpos (?) RIC in MRDpos: 3y OS about 50%

Paras, blood 2022

Conclusion

- Crude conditioning intensity is not the best focus
- To design a patient-oriented HSCT platform (not just conditioning) is probably a better target (Donor choice, GVHD prophylaxis, AML therapy before HSCT, post-HSCT interventions significantly interact with conditioning intensity for NRM)
- To transplant an high risk >65y AML patient remains a main challenge
- Reduced intensity regimens represent a valid choice in patients not eligible for MAC
- RIC regimen can deliver good long term outcome even in high risk pts (i.e. MRDpos)
- Let's base our practice on good quality evidence, we have (few) data from randomized trials

Strike firmly but gently, transplant is not all about conditioning!



