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Allogeneic Hematopoietic Cell Transplantation (HCT) in the Eighth Decade of Life: How Much Does Age Matter?

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Median ages of patients (pts) with most blood cancers range from 65-75 years of age. The use of nonmyeloablative conditioning regimens allows offering potentially curative allogeneic HCT to older pts. Yet, pts ≥70 years old are still rarely referred for allogeneic HCT. Here, we asked whether or not the reluctance to refer older pts for transplant is justified. In

Table 2
Adjusted rates of outcomes at 2 years by age group.

Age - Years	Adjusted[1]			
	OS	PFS	Relapse	NRM
20-39	66	46	34	18
40-49	62	52	28	20
50-59	53	42	35	23
60-69	56	45	32	22
70-79	55	46	35	19

[1] adjusted for all factors in Table 1.

1637 consecutive pts who were received nonmyeloablative allogeneic HCT between December 1997 and 2015, we compared outcomes among those of ≥70 years old (n = 101) to those among younger age groups, 20-39 (n = 143), 40-49 (n = 230), 50-59 (n = 580), and 60-69 (n = 583) years old, respectively. Pts aged ≥70 years were more frequently referred in recent years to transplants, had more frequently diagnoses of myeloid malignancies, received more frequently total body irradiation (TBI) doses ranging from 3-4.5 Gy, but had similar comorbidity burden and disease risks compared to younger pts (Table 1). After HCT, 2-year rates of non-relapse mortality, relapse, overall and progression free survivals for pts aged ≥70 years were 19%, 35%, 52%, and 46%, respectively which, when adjusted for risk factors were similar to those observed among younger age groups (Table 2). Between days -10 before and +120 after transplant, 58%, 49%, 61%, 77%, and 78% of pts were hospitalized, respectively; and among them, the median days of hospitalizations were 13, 11, 13, 12, and 8, respectively. All age groups had a median of a single hospital admission.

In multivariate analyses of risk factors, pts aged 20-39 years experienced less NRM and overall mortality, while those risks were similar among the remaining four age groups. Less comorbidities, 2 Gy conditioning alone, HLA-matched grafts, and more recent years of transplants predicted lessened NRM and overall mortality; while favorable disease risks and chronic

Table 1
Patient characteristics

	Age groups, years					
	20-39 (n = 143)	40-49 (n = 230)	50-59 (n = 580)	60-69 (n = 583)	≥70 (n = 101)	P
	%					
Donor type						
HLA-Matched related	50	62	50	38	35	
HLA-Matched URD	36	29	39	50	51	
HLA-Mismatched URD	14	9	11	13	14	<0.0001
HCT-CI scores						
0	20	22	19	20	16	
1-2	28	39	30	28	29	
≥3	52	39	51	52	55	0.12
Disease risk						
Low	21	30	27	21	7	
Standard	22	50	55	53	68	
High	57	20	18	26	25	<0.0001
Diagnosis						
Acute leukemia	15	10	24	36	57	
Chronic leukemia	5	15	20	16	7	
Lymphoma/myeloma	76	69	45	24	8	
Myelodysplastic syndromes	4	6	11	24	28	<0.0001
Conditioning regimens						
2 Gy TBI + Flu or Clo*	75	66	74	75	60	
2 Gy TBI	21	30	19	7	6	
3-4.5 Gy TBI	4	3	7	18	34	<0.0001
CMV serostatus						
Negative	53	46	38	38	36	
Positive	47	54	62	62	64	0.003
Gender match						
Other	83	74	72	74	75	
Female to male	17	26	28	26	25	0.12
Race						
Caucasian	90	92	94	97	94	
Other	10	8	6	3	6	0.006
Year of transplant						
1997 – 2003	41	49	40	23	19	
2004 – 2009	38	29	37	41	20	
2010 - 2015	20	22	23	36	61	<0.0001

Flu indicates fludarabine and Clo indicates clofarabine

Table 3
Multivariate analysis of outcomes

	Overall survival		Relapse/progression		Non-relapse mortality	
	HR	P	HR	P	HR	P
Age at HCT						
20-39	0.63	0.0008	0.84	-	0.65	0.05
40-49	0.86	-	0.84	-	0.85	-
50-59	1.0		1.0		1.0	
60-69	1.00	-	0.87	-	1.05	-
70-79	1.08	-	0.95	-	1.10	-
Donor type						
Matched related	1.0		1.0		1.0	
Matched URD	1.04	-	0.82	0.05	1.17	-
Mismatched URD	1.29	0.02	0.85	-	1.65	0.001
HCT-CI						
0	1.0		1.0		1.0	
1,2	1.34	0.004	1.09	-	1.76	0.0004
3+	1.55	<0.0001	1.13	-	1.97	<0.0001
Disease risk (Kahl)						
Low	0.78	0.01	0.51	<0.0001	1.02	-
Standard	1.0		1.0		1.0	
High	1.32	0.004	1.41	0.003	1.03	-
Diagnosis						
Acute leukemia	1.0		1.0		1.0	
Chronic leukemia	0.78	0.02	0.67	0.006	1.11	-
Lymphoma/MM	0.89	-	1.08	-	1.16	-
MDS	1.02	-	0.82	-	1.40	-
Conditioning						
2Gy TBI + Flu/Clo	1.0		1.0		1.0	
2 Gy TBI	0.80	0.03	1.11	-	0.44	<0.0001
3-4.5 Gy TBI	0.92	-	0.79	-	1.03	-
CMV serostatus						
Negative	1.0		1.0		1.0	
Positive	1.10	-	0.90	-	1.31	0.007
Gender match						
Other	1.0		1.0		1.0	
Female to male	1.13	-	0.96	-	1.25	0.04
Race						
Caucasian	1.0		1.0		1.0	
Other	0.69	0.02	0.69	-	0.73	-
Year of transplant						
1997 – 2003	1.0		1.0		1.0	
2004 – 2009	0.86	0.05	0.97	-	0.79	0.05
2010 - 2015	0.67	0.0002	0.72	0.01	0.59	0.0007

Only p-values of 0.05 or less are listed in this table.

leukemias predicted lessened risks of relapse and overall mortality.

Pts 70 years or older had comparable comorbidity burden and disease risk before and similar outcomes after transplant than pts as young as 40-49 years. Outcomes have continued improving in recent years. Yet, the group of pts aged ≥70 years who were given transplants represents only a very small fraction of those diagnosed annually with blood cancers. This could in part be due to reluctance of physicians to refer patients for transplant and partly because they lack objective criteria when evaluating pts. Current results suggest that comorbidities and disease risks should be used when assessing pts in their 8th or even 9th decades of age for transplant eligibility.

In order to facilitate such evaluations and encourage community oncologists to refer pts aged ≥70 for transplant consults, we are investigating the role of geriatric assessments in further improving outcome prediction. These include domains of physical, emotional, functional, cognitive, social, and psychiatric health of older individuals. (Table 3)

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Functional Genetic Variants on 14Q32 Associate with Death Due to Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS) Within One Year after HLA-Matched Unrelated Donor Blood and Marrow Transplantation (DISCOVeRY-BMT Study)

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The most frequent cause of death after BMT is disease. To assess the contribution of genetics to survival outcomes we measured the association of variants typed on the Illumina HumanOmniExpress-24 Chip and 1-year survival in 3,532 AML, ALL or MDS patients reported to CIBMTR from 2000-2011 and their 8/8 HLA-matched URDs (DISCOVeRY-BMT cohorts). After quality control and imputation, almost 9 million typed and imputed SNPs were available on donor-recipient pairs in cohorts 1 (N = 2,111) and 2 (N = 779). Cox proportional hazard models adjusted for age, disease status, and graft source were used to estimate variant effect on survival. Meta P-values and hazard ratios were estimated using METAL software (P_{meta}) and fixed effects models in R (HR_{meta}), respectively. We report genome-wide significant AML and MDS SNP associations with disease death (DD).

The donor genome has three significant DD associated regions, 5p15, 9p21 and 14q32 (Figure 1, inner circle & Table 1); no significant hits are seen in recipients (Figure 1, middle circle)
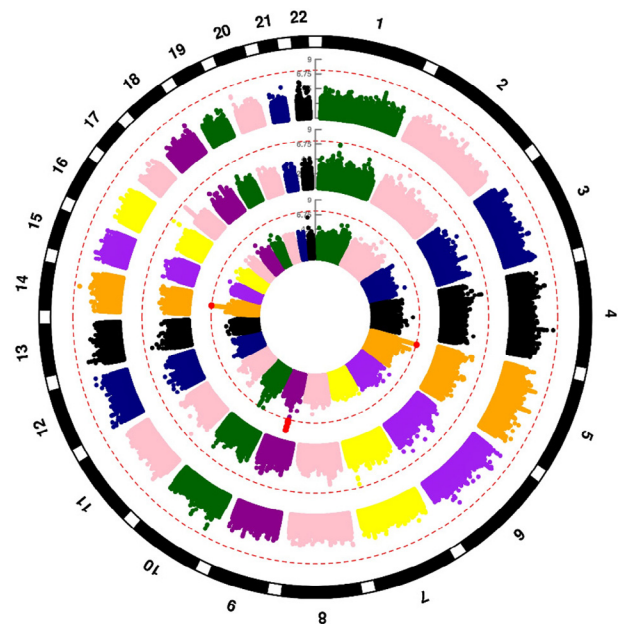

Figure 1. Genome wide association with disease death inner to outermost circular Manhattan plots are donor SMP p-values, recipient SNP p-values and p-values from testing donor-recipient allele mismatch at each SNP with disease death, respectively. Red dashed line show significance at $p < 5 \times 10^{-08}$ and red filled circles indicate genome-wide significant SNP p-values. Chromosome numbers are designated on the outer edge.

or when comparing allele matching at each SNP in the recipient and donor (Figure 1, outer circle). The most significant SNP on chromosome 5, rs32250, is in linkage disequilibrium (LD, $r^2 > .8$) with rs2215201, which likely affects binding of several nuclear receptor superfamily transcription factors. On chromosome 9 the donor contribution to risk of DD is genome-wide significant in both AML and MDS and AML only; variants near this region reside in a nuclear receptor superfamily motif (NR3C1) in multiple cell lines. The chromosome 14 region (60262026-60597197 bp) contained several donor variants at $P_{meta} < 5 \times 10^{-8}$ that increased risk of DD in patients with AML and MDS and near genome-wide significance ($P_{meta} < 5 \times 10^{-7}$) in patients with AML only. Many of these significant linked SNPs have biochemical function: a typed missense variant in *PCNX4*, rs150687 (60581935 bp), associated with DD at near genome-wide significance, was determined to be deleterious and possibly damaging in its impact on human health by software used to assess clinical variant significance and this variant has been identified in cancer tissue in the upper aerodigestive tract; in monocytes, rs8011499, rs160235, rs160236 and rs160240 ($r^2 > .8$ with rs150687) are *cis* expression quantitative trait loci of *DHRS7*, a steroid and retinoid metabolizer gene, and are predicted likely to affect

Table 1

Most significant donor genome* association with disease death in AML and MDS patients by region.

SNP	Chromosome: Base pair position	Effect Allele / Effect Allele Frequency	HR (95% CI), P-value	HR_{meta} (95% CI) P_{meta}	Gene
rs32250	5:12465740	T:45%	1.46 [1.26, 1.70] ,7.7 x 10⁻⁰⁷ 1.36 [1.07, 1.72] , .013	1.43 [1.26, 1.62] 3.8 x 10⁻⁰⁸	*RP11-308B16.2*
rs72720973	9:33048584	T:12%	1.51 [1.24, 1.84] ,3.4 x 10⁻⁰⁵ 1.90 [1.39, 2.61] ,6.4 x 10⁻⁰⁵	1.61 [1.36, 1.90] 1.8 x 10⁻⁰⁸	*SMU1*
rs117104143⁺	14:6041296	C:7%	1.57 [1.24, 1.83] ,4.9 x 10⁻⁰⁵ 1.89 [1.36, 2.62] ,1.5 x 10⁻⁰⁴	1.61 [1.36, 1.90] 4.6 x 10⁻⁰⁸	*LRRC9*

*donors and recipients taken from the Determining the Influence of Susceptibility COnveying Variants Related to one-Year mortality after BMT (DISCOVeRY-BMT) cohorts
⁺rs79076914 (60559239 bp) is also associated at genome-wide significance level and is in LD (r^2=1) with this variant