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ORAL ABSTRACTS

732.ALLOGENEIC TRANSPLANTATION: DISEASE RESPONSE AND COMPARATIVE TREATMENT STUDIES

Outcome of Children with B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL) with Hypodiploidy or BCR-ABL1 Fusion Given Allogeneic Hematopoietic Stem Cell Transplantation (HSCT): Results from the Prospective Forum Study

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Introduction:
Hypodiploid karyotype (HYPO) and bcr-abl1 fusion (BCRABL) define high-risk BCP-ALL subtypes, with historically worse outcomes. Many front-line treatment protocols recommend allogeneic HSCT for these patients (pts), either in first complete remission (CR1) irrespective of response (adolescents/young adults with HYPO), if minimal residual disease (MRD) signals persist at specific time points (younger pts with HYPO and all pts with BCRABL), or following leukemic relapse.
We have assessed the outcomes of BCP-ALL pts aged 4 to 18 years (y) with either HYPO or BCRABL who participated in the phase III ALL SCT PED FORUM study (EudraCT: 2012-003032-22) and underwent HSCT from either a matched sibling (MSD) or matched unrelated donor (MUD).
Patients and Methods:
Between 2014 and January 2023, 741 evaluable BCP-ALL pts were enrolled in FORUM (Table 1). HYPO was present in 61 pts, BCRABL in 82 pts, and neither lesion in 598 pts (NEITHER). 43/61 (70%), 40/82 (49%) and 215/598 (36%) pts with HYPO, BCRABL and NEITHER were in CR1, respectively (p= n.s.). Prior to HSCT, 82 of 101 HYPO/BCRABL pts with available MRD data were MRD negative by PCR and/or flowcytometry (<10-4). Total body irradiation (TBI) + VP16 was administered to 42 and 50 pts in the HYPO and BCRABL groups, respectively, while 18 HYPO and 30 BCRABL pts received non-TBI conditioning (busulfan or treosulfan + fludarabine and thiotepa, as per study protocol). Randomization determined allocation to TBI/non-TBI treatment arms until randomization closure in 03/2019, while treatment in some pts was dictated by lack of access to TBI, or contraindication to TBI in individual pts. An MSD was available in 14 (23%) and 24 (29%) HYPO and BCRABL pts, respectively. Notably, 24 out of 143 pts (17%) with HYPO/BCRABL received immunotherapy before HSCT (blinatumomab, inotuzumab ozogamicin, and/or CAR-T cells). Post-HSCT, 14 out of 82 BCRABL pts (17%) received a tyrosine kinase inhibitor (TKI), either prophylactically or pre-emptively.
Results:
With a median follow-up of three years post-HSCT, the 5-y probabilities of overall survival (OS) for pts with HYPO, BCRABL and NEITHER were 0.79±0.06, 0.83±0.05, and 0.74±0.02 (p=n.s.), while those of event-free survival (EFS) were 0.73±0.06, 0.65±0.07, and 0.61±0.02, respectively (p=n.s.). The 5-y cumulative incidence of relapse (CIR) for HYPO/BCRABL and NEITHER pts was 0.21±0.04 and 0.29±0.02 (p=0.036), and 5-y non-relapse mortality (NRM) was nearly identical for these groups (0.07±0.2 and 0.08±0.1).
Among pts who received TBI, 5-y OS and EFS for HYPO, BCRABL, and NEITHER groups were 0.76±0.08 and 0.70±0.08, 0.89±0.05 and 0.70±0.10, and 0.80±0.03 and 0.71±0.03, respectively (p=n.s., Figure 1), while 5-y CIR and NRM post TBI were 0.15±0.06 and 0.11±0.05, 0.15±0.06 and 0.11±0.05, and 0.20±0.02 and 0.07±0.02, for the three groups, respectively (p=n.s.). The 3-y GvHD-free/relapse-free survival (GRFS) was similar between HYPO/BCRABL and NEITHER (0.60±0.06 and 0.58±0.03, respectively) and reached a plateau at 5-years (0.60±0.06 and 0.57±0.03, respectively). In subgroup analyses of pts in CR1 and >CR1, comparable outcomes were observed for HYPO, BCRABL, and NEITHER, hence results were not affected by the remission status.
BCRABL and NEITHER pts receiving non-TBI conditioning had inferior outcomes (5-y EFS of 0.56±0.10 and 0.47±0.04, respectively) with a high 5-y CIR (0.36±0.09 and 0.43±0.04, respectively) as compared to those who received TBI. Similar 5-y OS and EFS were seen in HYPO pts whether receiving TBI (0.76±0.8 and 0.70±0.08) or chemo conditioning (83±0.09 and 83±0.09). Rates of NRM and acute/chronic graft-versus-host disease were similar in pts receiving TBI/ non-TBI conditioning and in BCRABL/HYPO vs. NEITHER pts.
In multivariate analysis adjusted for CR status, conditioning and MRD, EFS did not differ between HYPO/BCRABL and NEITHER pts.
Conclusions:
Children receiving HSCT for treatment of BCP-ALL with either hypodiploidy or bcr-abl1 fusion showed outcomes comparable to BCP-ALL pts without these genetic lesions. CIR and EFS reached plateaus beyond 3 y post-HSCT, indicating that approximately two-thirds of these pts can be cured by HSCT with low rates of treatment-related mortality. Pts with BCRABL achieved favorable outcomes without the need for long-term or lifelong TKI therapy.

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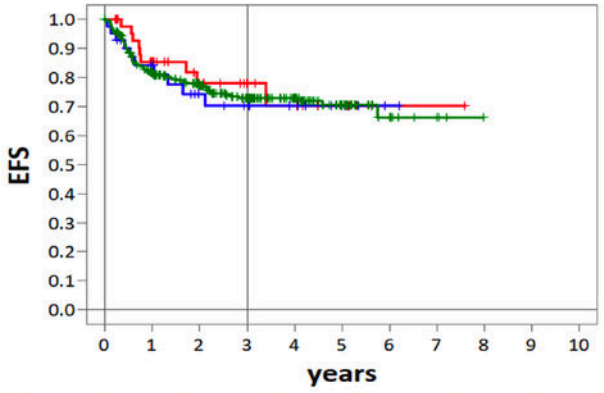
Table 1: Patient characteristics

	Total		hypo		BCR-ABL		neither		p-value
	n	%	n	%	n	%	n	%	
Total	741	100%	61	100%	82	100%	598	100%	
Sex									
Male	457	62%	36	59%	49	60%	372	62%	0.826
Female	284	38%	25	41%	33	40%	226	38%	
Age at SCT									
median	10		11		10		10		
(min-max)	(4-21)		(4-18)		(4-19)		(4-21)		0.922
4-6	123	17%	17	28%	8	10%	98	16%	0.009
6-10	237	32%	12	20%	29	35%	196	33%	
10-14	204	28%	11	18%	28	34%	165	28%	
>14	177	24%	21	34%	17	21%	139	23%	
Remission status									
CR1	298	40%	43	70%	40	49%	215	36%	0.967*
CR2	382	52%	16	26%	39	48%	327	55%	
CR3	57	8%	2	3%	3	4%	52	9%	
>CR3	4	1%	0		0		4	1%	
Source									
BM	517	70%	43	70%	59	72%	415	69%	0.151
pB	197	27%	15	25%	20	24%	162	27%	
CB	25	3%	3	5%	3	4%	19	3%	
BM+pB	2	0%	0		0		2	0%	
Conditioning									
TBI/VP16	496	67%	42	69%	50	61%	404	68%	0.313
FLU/THIO/BU	144	19%	12	20%	20	24%	112	19%	
FLU/THIO/TREO	85	11%	6	10%	10	12%	69	12%	
Other cond.	16	2%	1	2%	2	2%	13	2%	
Arm									
TBI/VP16	143	19%	17	28%	10	12%	116	19%	-
CHC	124	17%	10	16%	14	17%	100	17%	
not randomized	474	64%	34	56%	58	71%	382	64%	
Donor									
MSD	209	28%	14	23%	24	29%	171	29%	0.631
MD	532	72%	47	77%	58	71%	427	71%	
MRD pre SCT									
<10-4	453	61%	39	64%	43	52%	371	62%	0.692
> 10-4	110	15%	7	11%	12	15%	91	15%	
not available	178	24%	15	25%	27	33%	136	23%	

Figure 1: EFS, evaluable patients who received TBI



group	Patients	eval patients	Events	3-yrs EFS	5-yrs. EFS	p-value
BCR-ABL	50	50	9	0.78±0.07	0.70±0.10	0.837
hypo	42	42	10	0.70±0.08	0.70±0.08	.
neither	404	404	92	0.73±0.03	0.71±0.03	.

Figure 1

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