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ORAL ABSTRACTS

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Preferential Efficacy of Remission Maintenance with HDC/IL-2 in Age Groups of Patients with Chemoresponsive or Normal Karyotype AML

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Background Relapse in complete remission (CR) remains a leading cause of morbidity and mortality in acute myeloid leukemia (AML). Previous phase 3 trial data show that combinatorial immunotherapy with histamine dihydrochloride and low-dose interleukin-2 (HDC/IL-2) reduces relapse incidence in the post-consolidation phase, in particular among younger adult AML patients (<60 years old) in CR1 (Brune *et al.*, *Blood* 108:88). Recent post-hoc analyses identified subgroups of responding patients including (1) those achieving CR1 after the first induction course of chemotherapy (referred to as chemoresponsive AML) and (2) those carrying leukemic cells of normal karyotype (NK-AML), *i.e.* devoid of structural or numerical chromosomal aberrations. Here we report analyses of treatment efficacy in a phase 3 trial within age groups of patients with chemoresponsive AML or NK-AML.
Methods Three hundred and twenty AML patients (18-84 years old, median 57) who were ineligible for allogeneic stem cell transplantation were randomly assigned to receive HDC/IL-2 or no treatment (control) for remission maintenance in a phase 3 trial. Patients were recruited in Europe, Israel, Oceania, and USA. Treatment was initiated in CR after the completion of consolidation chemotherapy and comprised 10 consecutive 3-week cycles of HDC/IL-2 for 18 months (mo) with 3- or 6-week rest periods. In each cycle, patients received HDC at 0.5 mg and human recombinant low-dose IL-2 (aldesleukin; 16,400 IU/kg) s.c. twice daily (n=160) or no treatment (control; n=160). After 18 months of treatment, all patients were monitored for >18 additional mo (median follow-up 48 mo).
Results Among study subjects in CR1 203/261 (78%) of evaluable patients attained CR after the first induction cycle (chemoresponsive AML) and 128/220 (58%) had NK-AML. Within both subgroups, analysis of efficacy by age at diagnosis implied preferred benefit of HDC/IL-2 vs. control in patients 40-59 years old (Figure 1) with independent efficacy in patients 40-49 and 50-59 years old (Table 1). The treatment arm was not significantly superior over the control arm for LFS or OS in the youngest patients (18-39 years old) or in patients >60 years old (P>0.2, logrank test, for all comparisons (LFS and OS)) within subgroups of chemosensitive AML or NK-AML.
Conclusions We speculate that the observed benefit of HDC/IL-2 in patients responding swiftly to initial chemotherapy may be explained by more efficient immune-mediated elimination of leukemic cells at a lower burden of leukemia. The preferential efficacy of HDC/IL-2 in NK-AML points towards efficacy in subgroups of leukemic mutations that are less common in the youngest group of patients. The reason for the lack of significant efficacy in patients >60 years old, despite achievement of CR1 after the initial chemotherapy and despite having NK-AML, remains unknown but may be explained by fading anti-leukemic immunity in old patients. Overall, these findings may be considered for the selection of patients suitable for immunotherapy with HDC/IL-2 in an emerging landscape of strategies for relapse prevention in AML.

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Figure 1: Efficacy of HDC/IL-2 for remission maintenance in AML.
Results show post-hoc analyses for patients achieving CR1 after the first course of induction chemotherapy (chemoresponsive AML) and patients with AML of normal karyotype (NK-AML) from a randomized phase 3 trial (Brune et al., Blood 108:88). P-values (two-sided) were derived from log-rank tests. LFS: leukemia-free survival.

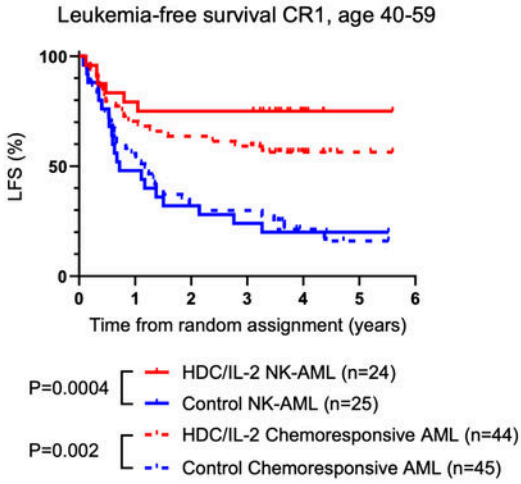

Table 1

		Chemoresponsive					NK-AML				
		n	HR	95% CI[a]	Log-rank, p	36mo survival rate, %[b]	n	HR	95% CI[a]	Log-rank, p	36mo survival rate, %[b]
LFS[d]	**All patients[c]**		0.65	0.46-0.92	0.01			0.58	0.37-0.91	0.02	
	Control	99				29.8	67				27.7
	HDC/IL-2	104				45.1	61				50.0
	18-59[c]		0.48	0.30-0.76	0.001			0.40	0.20-0.79	0.006	
	Control	64				32.0	37				31.3
	HDC/IL-2	66				55.9	35				65.6
	40-49		0.23	0.07-0.72	0.006			0.08	0.01-0.62	0.002	
	Control	16				15.6	11				9.1
	HDC/IL-2	12				66.7	8				87.5
	50-59		0.53	0.27-1.02	0.05			0.33	0.11-0.97	0.03	
	Control	27				37.0	14				35.7
	HDC/IL-2	32				56.3	16				68.8
OS[d]	**All patients[c]**		0.71	0.48-1.05	0.09			0.66	0.39-1.13	0.13	
	Control	99				49.7	67				52.6
	HDC/IL-2	104				59.3	61				63.0
	18-59[c]		0.53	0.31-0.92	0.02			0.43	0.18-1.01	0.04	
	Control	64				54.2	37				58.7
	HDC/IL-2	66				70.4	35				76.5
	40-49		0.02	0.001-4.51	0.005			0.02	0.001-52.55	0.05	
	Control	16				49.2	11				60.6
	HDC/IL-2	12				100	8				100
	50-59		0.67	0.33-1.37	0.26			0.33	0.11-1.00	0.04	
	Control	27				51.9	14				42.9
	HDC/IL-2	32				61.4	16				68.8

[a] Confidence intervals for the hazard ratios
[b] Kaplan-Meier estimates at 36 months from random assignment in each treatment arm
[c] Data for all patients and patients 18-59 years old are adapted from Nilsson, MS *et al.*, *Br J Haematol*. 2020 188(4):e49-e53 and Nilsson, MS *et al.*, *Hum Vaccin Immunother.* 2020;16:109-111 and shown for reference
[d] LFS: leukemia-free survival, defined as time from random assignment to relapse or death whichever comes first; OS: overall survival from random assignment

Figure 1

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