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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

What Is the Optimal Treatment Modality in Molecularly Defined Secondary AML? a Multicenter Cohort Study

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Introduction

Secondary ontogeny acute myeloid leukemia (AML), defined by the presence of mutations in ASXL1, BCOR, EZH2, SF2B1, SRSF2, STAG2, U2AF1 or ZRSR2 was recently integrated into both the ICC and WHO diagnostic criteria, as well as into the ELN 2022 risk classification as adverse risk. However, it is unknown whether cytarabine + anthracycline (7+3), liposomal cytarabine and daunorubicin (CPX-351) or hypomethylating agent + venetoclax (HMA+VEN) is the optimal frontline treatment for these patients (pts). We performed the largest multicenter retrospective cohort study to date, dedicated to pts with molecular-defined secondary ontogeny AML, comparing treatment modalities and assessing the impact of clinical and molecular characteristics on response and survival.

Methods

We included pts with newly diagnosed (ND) AML who were treated at 4 large academical centers with 7+3, CPX-351 or HMA+VEN. Secondary ontogeny was defined as absence of *TP53* mutation and presence of at least one of the aforementioned mutations. Composite complete response (cCR) was defined as complete response (CR) + CR with incomplete count recovery (CRi). Logistic regression was fitted to evaluate odds ratio (OR) for cCR. Overall survival (OS) was compared between groups by log-rank test. COX regression for OS were fitted to evaluate effect of secondary/co-mutations within each treatment group, as well as the effect of treatment and allogeneic stem cell transplantation (SCT) as a time-varying covariate. *Results*

Out of 1132 ND AML pts in the entire cohort, 401 (35%) were molecularly defined as secondary ontogeny and included in the final analysis. Initial treatment was 7+3 in 173 (43%), HMA+VEN in 162 (40%) and CPX-351 in 66 pts (17%). Pts in the HMA+VEN group were older (median age 74 years[yrs]; CPX351 66 yrs; 7+3 63 yrs, p < 0.001), while pts in the CPX351 group were more likely to have prior myeloid neoplasm (n=52 [79%]; HMA+VEN n=72 [44%]; 7+3 n=48 [28%], p < 0.001) and prior HMA exposure (n=27 [41%]; HMA+VEN n=23 [14%]; 7+3 n=28 [16%], p < 0.001).

The cCR rates were 56% (97/173), 56% (90/162) and 44% (29/66) in 7+3, HMA+VEN and CPX-351, respectively (p=0.21). In the 7+3 group, the presence of *RUNX1* co-mutation was associated with lower cCR rate (OR 0.8, 95% confidence interval [CI]

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0.7-0.95, p=0.01), while *PTPN11* was associated with higher cCR rate (OR 1.4, 95% CI 1.1-1.8, p=0.011). In the HMA+VEN group, monosomal karyotype (OR 0.7, 95% CI 0.5-0.9, p=0.002), *NRAS* co-mutation (OR 0.6, 95% CI 0.5-0.8, p<.001) and *SF3B1* mutation (OR 0.76, 95% CI 0.6-0.9, p=0.008) were associated with lower cCR rate and *FLT3-TKD* with higher cCR rate (OR 1.5, 95% CI 1.1-2.1, p=0.01). In the CPX-351 group, *NRAS* co-mutation was associated with lower cCR rate (OR 0.65, 95% CI 0.5-0.9, p=0.005).

As most younger pts (aged \leq 60 yrs, n=85) were treated with 7+3 (n=64) or CPX-351 (n=13) and almost exclusively older pts (age >75, n=78) were treated with HMA+VEN (n=74), we performed age-group based analyses. In pts aged > 60 yrs (n=318), the median OS (mOS) was comparable between groups (7+3: 16 months [mo], 95% CI 13-27; HMA+VEN 15 mo, 95% CI 13-19; CPX-351 11 mo, 95% CI 9-28 p=0.57). Similar results were seen in pts 60-75 yrs (n=238): 7+3 mOS 16 mo, 95% CI 13-27; HMA+VEN mOS 16 mo, 95% CI 13-26; CPX-351 mOS 10 mo, 95% CI 8-28, p=0.74.

The effect of secondary/co-mutations on survival differ between groups: For 7+3 splicing mutations were associated with worse OS, whereas *IDH1/2* were associated with improved OS (**Figure**). Conversely, in HMA+VEN and CPX351 groups *K/NRAS* co-mutations were associated with worse survival. *NPM1* co-mutation did not affect survival in any treatment group. In multivariable analysis, age, prior myeloid disease, *K/NRAS* co-mutations and monosomal karyotype were associated with worse OS (**Table**). Conversely, *BCOR* mutation, *IDH1/2* co-mutation and SCT were associated with improved OS. Treatment with HMA+VEN or CPX351 were not statistically different *vs* 7+3, although there was a trend for better OS with HMA+VEN *vs* 7+3 (HR 0.68, 95% CI 0.44-1.03, p=0.069).

Conclusion

In pts with ND secondary ontogeny AML the OS with HMA+VEN was at least comparable to 7+3 or CPX351 when adjusted for multiple covariates. The effect of co-mutations on response and OS differed between treatment modalities and may aid in optimal treatment selection in this population. Prospective trials should evaluate the potential superiority of HMA+VEN and effect of co-mutations in secondary ontogeny AML.

Disclosures Shallis: Rigel: Consultancy; Gilead Sciences: Consultancy; Servier: Consultancy; Curio Science: Consultancy; Bristol Myers Squibb: Consultancy. Zeidan: Astellas: Consultancy, Honoraria; Janssen: Consultancy, Honoraria; Tyme: Consultancy, Honoraria; Gilead: Consultancy, Honoraria; Foran: Consultancy, Research Funding; Chiesi: Consultancy, Honoraria; Astex: Research Funding; Ionis: Consultancy, Honoraria; Notable: Consultancy, Honoraria; Lox Oncology: Consultancy, Honoraria; Syndax: Consultancy, Honoraria; Pfizer: Consultancy, Honoraria; Celgene/BMS: Consultancy, Honoraria; Takeda: Consultancy, Honoraria; Amgen: Consultancy, Honoraria; Schrödinger: Consultancy, Honoraria; Mendus: Consultancy, Honoraria; Syros: Consultancy, Honoraria; Otsuka: Consultancy, Honoraria; Servier: Consultancy, Honoraria; Genentech: Consultancy, Honoraria; Novartis: Consultancy, Honoraria; BevondSpring: Consultancy, Honoraria; Geron: Consultancy, Honoraria; Daiichi Sankyo: Consultancy, Honoraria; Agios: Consultancy, Honoraria; Regeneron: Consultancy, Honoraria; Taiho: Consultancy, Honoraria; Orum: Consultancy, Honoraria; BioCryst: Consultancy, Honoraria; Seattle Genetics: Consultancy, Honoraria; Jazz: Consultancy, Honoraria; Boehringer-Ingelheim: Consultancy, Honoraria; ALX Oncology: Consultancy, Honoraria; Zentalis: Consultancy, Honoraria; Incyte: Consultancy, Honoraria; Shattuck Labs: Research Funding; Kura: Consultancy, Honoraria; Abb-Vie: Consultancy, Honoraria; Epizyme: Consultancy, Honoraria. Goldberg: Abbvie: Consultancy, Research Funding; Astellas Pharma: Consultancy; Daiichi Sankyo: Consultancy, Research Funding; DAVA Oncology: Honoraria; AROG: Research Funding; Pfizer: Research Funding; Prelude: Research Funding; Celularity: Research Funding; Aptose: Research Funding; Aprea: Research Funding; Genentech: Consultancy; Trillium: Research Funding; ADC Therapeutics: Research Funding. Stein: Agios: Consultancy; Jazz: Consultancy; Menarini: Consultancy; Genentech: Consultancy; Astellas: Consultancy; Genesis: Consultancy; Syros: Consultancy; Calithera: Consultancy; Daiichi: Consultancy; Aptose: Consultancy; Ono Pharma: Consultancy; Servier: Consultancy; Abbvie: Consultancy; Janssen: Consultancy; PinotBio: Consultancy; Novartis: Consultancy; Eisai: Research Funding; Bristol Myers Squib: Consultancy, Research Funding; Neoleukin: Consultancy; Foghorn: Consultancy; Gilead: Consultancy; CTI Biopharma: Consultancy; Syndax: Consultancy; OnCusp: Consultancy; Blueprint: Consultancy. Marcucci: Ostentus Therapeutics: Current equity holder in private company, Research Funding. Chen: Abbvie Pharmaceuticals: Research Funding; Rigel Pharmaceuticals: Consultancy, Honoraria. Lindsley: Bluebird bio: Consultancy, Membership on an entity's Board of Directors or advisory committees; Qiagen: Consultancy; Sarepta Therapuetics: Consultancy; Verve Therapuetics: Consultancy; Jazz Pharmaceuticals: Consultancy; Vertex Pharmaceuticals: Consultancy; Takeda Pharmaceuticals: Consultancy. Stein: Amgen: Speakers Bureau. DeAngelo: Takeda: Honoraria; Incyte: Honoraria; Jazz: Honoraria; Kite: Honoraria; GlycoMimetics: Research Funding; Blueprint: Honoraria; Amgen: Honoraria; Pfizer: Honoraria; Gilead: Honoraria; Servier: Honoraria; Novartis: Honoraria; Autolus: Honoraria; Novartis: Research Funding; Blueprint: Research Funding; AbbVie: Research Funding. Neuberg: Madrigal Pharmaceuticals: Current equity holder in private company. Stone: Cellularity: Consultancy; BerGenBio: Consultancy; AvenCell: Consultancy; Amgen: Consultancy; Rigel: Consultancy; Takeda: Other: DSMB; CTI Biopharma: Consultancy; Aptevo: Other: DSMB; Lava Therapeutics: Consultancy; Ligand Pharma: Consultancy; Jazz: Consultancy; Hermavant: Consultancy; GSK: Consultancy; Epizyme: Other: DSMB; Syntrix: Other: DSMB; Kura One: Consultancy; Abbvie: Consultancy. Stahl: Rigel: Membership on an entity's Board of Directors or advisory committees; Boston Consulting: Consultancy; Novartis: Membership on an entity's Board of Directors or advisory committees, Other: GME activity; Dedham group: Consultancy; Curis Oncology: Other: GME activity; Sierra Oncology: Membership on an entity's Board of Directors or advisory committees; Clinical care options: Other: GME activity; GSK: Membership on an entity's Board of Directors or advisory committees; Haymarket Media: Other: GME activity ; Kymera: Membership on an entity's Board of Directors or advisory committees.

Co	variate	Univariable analysis (HR, CI 95%)	p-value	Multivariable analysis (HR, Cl 95%)	p-value
Ag	e	1.03 (1.01, 1.04)	< 0.001	1.04 (1.02, 1.06)	<0.001
Sex (male vs. female)		1.04 (0.79, 1.38)	0.77		
Prior myeloid disease		1.78 (1.37, 2.32)	< 0.001	1.90 (1.38, 2.62)	<0.001
Prior HMA exposure		1.42 (1.04, 1.92)	0.025		
Kar	ryotype				
•	normal	0.77 (0.58, 1.02)	0.064		
20	Monosomal	1.97 (1.34, 2.89)	< 0.001	1.86 (1.24, 2.79)	0.003
	Complex	1.62 (1.11, 2.36)	0.013		
Mo	olecular				
-	SRSF2	0.82 (0.61, 1.11)	0.20		
-	SF3B1	1.50 (1.09, 2.07)	0.013		
•	U2AF1	1.23 (0.87, 1.75)	0.25		
-	ZRSR2	0.44 (0.11, 1.79)	0.25		
•	ASXL1	1.14 (0.87, 1.48)	0.34		
-	BCOR	0.61 (0.41, 0.90)	0.012	0.60 (0.40, 0.92)	0.018
	EZH2	1.53 (1.00, 2.33)	0.050	1.54 (0.97, 2.43)	0.065
	STAG2	1.03 (0.71, 1.50)	0.88	Wr - 13	
150	FLT3-ITD	1.11 (0.72, 1.71)	0.63		
-	NPM1	1.05 (0.68, 1.63)	0.81		
-	IDH (1/2)	0.59 (0.42, 0.83)	0.002	0.67 (0.46, 0.97)	0.035
	NRAS/KRAS	1.63 (1.21, 2.20)	0.001	1.81 (1.29, 2.54)	<0.001
Tre	atment				
(vs	. 7+3 as baseline)				
-	HMA+Ven	1.53 (1.14, 2.05)	0.004	0.68 (0.44, 1.03)	0.069
	CPX351	1.48 (1.02, 2.15)	0.041	0.85 (0.54, 1.34)	0.48
All	oSCT as time- rying covariate	0.37 (0.27, 0.51)	<0.001	0.37 (0.25, 0.54)	<0.001

	Sec. mutations (HR, 95% CI)	Co-mutations (HR, 95% Cl)			
	Splicing vs. non-splicing	IDH (IDH1/2)	RAS (NRAS/KRAS)	NPM1	
7+3	1.64 (1.02-2.64)	0.48 (0.29-0.81)	1.4 (0.88-2.21)	0.85 (0.41-1.77)	
	p=0.042	p=0.006	p=0.18	p=0.67	
HMA+Ven	0.69 (0.44-1.07)	0.9 (0.54-1.49)	2.3 (1.35-3.93)	1.21 (0.67-2.18)	
	p=0.094	p=0.67	p=0.002	p=0.53	
CPX351	1.07 (0.57-2.01)	0.49 (0.18-1.39)	2.12 (1.12-4.00)	1.52 (0.36-6.33)	
	p=0.84	p=0.18	p=0.021	p=0.57	

Table. COX regression univariable and multivariable analysis for OS. All variables with p<.1 in the univariate model and pre-defined variables of treatment and alloSCT as time varying covariate were included in the multivariable model. In **bold**: covariates with a p<.05 in the multivariable model. HR – hazard ratio; HMA – hypomethylating agents; Ven – venetoclax; AlloSCT – allogeneic stem cell transplantation. Figure. Effect of secondary mutations type and co-mutations on overall survival within each treatment group. Presented with Hazard ratio (HR), 95% confidence interval (CI) and p values. Secondary splicing mutations: SRSF2, SF3B1, U2AF1, ZRSR2; secondary non-splicing mutations: ASXL1, BCOR, STAG2, EZH2.

Figure 1

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