Abstract: P1319

Title: TREATMENT WITH MIDOSTAURIN AND OTHER FLT3 TARGETING INHIBITORS IS ASSOCIATED WITH AN INCREASED RISK OF CARDIOVASCULAR ADVERSE EVENTS IN PATIENTS WITH FLT3 MUTATED AML WHO UNDERWENT ALLOGENEIC HCT

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Background:

Cardiovascular complications are common among patients (pts) with acute myeloid leukemia (AML) after treatment with chemotherapy or targeted therapies. One of the most common side effects of FLT3 inhibitors (FLT3i) is prolongation of the QT interval. Other cardiac complications caused by these drugs have not been studied in detail in pts who underwent allogeneic hematopoietic cell transplantation (HCT) in a real-world setting, but have been identified as potential reasons for discontinuation of treatment.

Aims:

Aim of this retrospective study was to determine the frequency of and risk factors for cardiac adverse events (CAEs) in newly diagnosed AML pts receiving standard induction chemotherapy and subsequent allogeneic HCT with or without midostaurin (mido) and/or other FLT3i.

Methods:

Clinical data incl. preexisting cardiac comorbidities and CAEs (heart failure, arrhythmias and reduced left ventricular ejection fraction ≤50%) were collected from consecutive pts transplanted 2017-2021. Overall survival (OS) was calculated from diagnosis. Cumulative incidence (CI) of non-relapse mortality (NRM) was determined with relapse as competing risk and vice versa. Median follow-up of surviving pts was 1042 (97-2327) days. Pt. outcome was reported on day 1000 after HCT.

Results:

We included 132 AML pts, 90 pts (68.2%) with *FLT3* wildtype and 42 pts with mutated *FLT3*, i.e. *FLT3-ITD* (n=35, 26.5%), *FLT3-TKD* mutation (n=4, 3%) or both (n=3, 2.3%). Median age was 56 years (IQR 46, 65). Of the 42 pts with *FLT3* mutated AML, 34 pts (82%) received a FLT3i at some time during their treatment: 27 pts (79.4%) received mido, 24 pts (70.6%) another FLT3i (mainly sorafenib) and in 17 pts (50%) mido was followed by another FLT3i. 7 pts with mutated *FLT3* did not receive mido or another FLT3i mainly due to reimbursement issues. Pt characteristics of the "Mido/FLT3i" (n=34) and "no Mido/FLT3i" cohort (n=98) were well balanced, but a slightly higher percentage of pts in the "no Mido/FLT3i" group had preexisting cardiac comorbidities (18.4% vs. 11.8%), hypertension at baseline (30.6% vs. 23.5%) (p=ns) (Table 1). Overall, 39/132 pts (29.5%) developed a CAE after starting their antileukemic treatment: 19/98 pts (19.4%) in the "no Mido/FLT3i" group, and 20/34, (58.8%, $p<0.001$) in the "Mido/FLT3i" group. Most documented CAEs were grade 1-2 according to CTCAE. By univariate analysis, treatment with mido and/or FLT3i was associated with a significantly increased risk for CAEs (OR 5.94 [97.5% CI 2.58-14.16], $p<0.001$). Other known risk factors (i.e. age≥60 years, adverse or intermediate risk cytogenetics, obesity, preexisting cardiac comorbidity, female sex or cumulative daunorubicin equivalence dose) were not associated with a significantly higher number of CAEs. By multivariate analysis, only treatment with mido and/or FLT3i was confirmed as an independent risk factor for CAEs (OR 6.99 [97.5% CI 2.89-18.03], $p<0.001$). The CI of CAEs was significantly higher in the "Mido/FLT3i" group compared to the "no Mido/FLT3i" group (58% vs. 18%, p<0.001). However, cardiac toxicity did not translate into higher NR) in the "MidoFLT3i" group compared to the "no MidoFLT3i" group (6.5% vs. 11.1% p=0.5) or a difference in OS („MidoFLT3i" group: 78.8%, vs. „noMidoFLT3i" group: 70.6%; p=0.93).

Summary/Conclusion: We here identified mido and/or FLT3i treatment as an independent risk factor for CAEs in

pts undergoing HCT without higher NRM or impaired OS. The higher risk of rarely life-threatening CAE should not preclude administration of mido and/or FLT3i, even in pts with preexisting cardiac comorbidities, but close monitoring is warranted.

Table 1. Patient characteristics				
	Overall	**no Mido/FLT3i**	**Mido/FLT3i**	**p-value**
n	132	98	34	
Female, n(%)	50 (37.9)	32 (32.7)	18 (52.9)	0.058
Age, median [IQR]	56.00 [46.00, 65.00]	57.00 [46.50, 65.00]	52.50 [46.25, 63.00]	0.524
FLT3 mutation status, n (%)				<0.001
ITD	35 (26.5)	6 (6.1)	29 (85.3)	
TKD	4 (3.0)	1 (1.0)	3 (8.8)	
ITD + TKD	3 (2.3)	1 (1.0)	2 (5.9)	
WT	90 (68.2)	90 (91.8)	0 (0.0)	
VAF ratio, n (%)				0.804
high	20 (47.6)	3 (37.5)	17 (50.0)	
low	17 (40.5)	4 (50.0)	13 (38.2)	
NA	5 (11.9)	1 (12.5)	4 (11.8)	
NPM1 status, n (%)				<0.001
mut	36 (27.3)	16 (16.3)	20 (58.8)	
WT	93 (70.5)	79 (80.6)	14 (41.2)	
NA	3 (2.3)	3 (3.1)	0 (0.0)	
ELN classification, n(%)				0.109
favorable risk	26 (19.7)	16 (16.3)	10 (29.4)	
intermediate risk	67 (50.8)	49 (50.0)	18 (52.9)	
adverse risk	39 (29.5)	33 (33.7)	6 (17.6)	
Type of alloHSCT, n (%)				0.047
Haplo	54 (40.9)	42 (42.9)	12 (35.3)	
HLA-ident	76 (57.6)	56 (57.1)	20 (58.8)	
partially HLA-ident	2 (1.5)	0 (0.0)	2 (5.9)	
Induction cycles, n (%)				0.711
1	17 (12.9)	14 (14.3)	3 (8.8)	
2	108 (81.8)	79 (80.6)	29 (85.3)	
3	7 (5.3)	5 (5.1)	2 (5.9)	
Obese (BMI≥30), n (%)	18 (14.1)	12 (12.6)	6 (18.2)	0.617
Cardiac event, n (%)	39 (29.5)	19 (19.4)	20 (58.8)	<0.001
≥grade 3 cardiac event, n (%)	20 (15.2)	12 (12.2)	8 (23.5)	0.192
1st cardiac event pre alloHSCT, n (%)	15 (11.4)	7 (7.1)	8 (23.5)	0.023
Cardiac premorbidity, n (%)	22 (16.7)	18 (18.4)	4 (11.8)	0.533
Baseline hypertension, n (%)	38 (28.8)	30 (30.6)	8 (23.5)	0.571

alloHSCT, allogenous hematopoietic stem cell transplantation; BMI, body mass index; ELN, european leukemia network; FLT3i, FLT3 inhibitor; IQR, interquartile range; ITD, internal tandem duplication; mut, mutated; TKD, tyrosine kinase domain

Keywords: AML, Complications, flt3 inhibitor, Allogeneic hematopoietic stem cell transplant