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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Chronic Myelomonocytic Leukemia (CMML) with AML Typical Mutations (*NPM1, FLT3* or *CEBPA*) Identify a High-Risk CMML Group Independent of Molecular-Cpss

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CMML is rarely associated with AML typical mutations such as *NPM1, FLT3, CEBPA* and *IDH*1/2 (mutAML-CMML). It is unknown what its clinical meaning is and if its presence should change our management into an AML-type treatment. The aim was to describe the characteristics, prognosis and treatment of mutAML-CMML patients.
We studied 83 CMML patients of Hospital Clinic diagnosed between 1998-2022, with Next Generation Sequencing (NGS). We included 53 patients with mutAML-CMML from other institutions.
We identified 31 patients with mutated *IDH2* (all c.419G>A p.(Arg140Gln)), 13 with *IDH1*, 14 with *NPM1,7* with *CEBPA* (4 bZIP) and 11 with *FLT3* (3 *FLT3*-ITD and 7 *FLT3*-TKD: 6 TKD1 and 2 TKD2 variants, all different from p.(Asp835Tyr) except one).

Patient characteristics and outcome of the group with mut *IDH*1/2 was not significantly different from wt *IDH*.
Those patients with mut *NPM1, FLT3* and/or *CEBPA*presented adverse characteristics and worse prognosis. Therefore, we grouped the patients with these mutations into a category named mutCFN (n=26) (Table 1). The mutCFN incidence in our series was 9%.
The mutCFN patients (n=26) vs wtCFN (n=96) were younger (63 vs 71 years, p=0.004), had more leucocytes (16 vs 7.7x10 ^{9}/L, p=0.015), monocytes (2.9 vs 1.7x10 ^{9}/L, p=0.006), anemia (9.1 vs 11.2 g/L, p<0.001) and bone marrow blasts (11.5 vs 4%, p<0.001). They belonged more frequently to myeloproliferative variant (57.7 vs 30.2%, p=0.012), CMML-2 (69.2 vs 14.7%, p<0.001), high risk CPSS and CPSS-Mol (72 vs 31%, p<0.001; 88.2 vs 44.9%, p=0.001). They showed more transfusion dependence (69.2 vs 22.9%, p<0.001). Co-mutational representation is shown in Figure 1. mutCFN patients have a different co-mutational pattern from wtCFN with more frequently mutated *DNMT3A* (42.9 vs 6.3%, p<0.001), *SF3B1* (15.8 vs 2.3%, p=0.04), *WT1* (10 vs 0%, p=0.03), and less *TET2* (24 vs 58.3%, p=0.003) .
mutCFN patients received treatment more frequently than wtCFN (84.6 vs 36.5%, p<0.001) and earlier (0.97 vs 4.6 months, p=0.005). They were more frequently treated with chemotherapy (53.8 vs 7.3%, p<0.001) and alloSCT (61.5 vs 11.5%, p<0.001).
The median follow-up was 9.3 years (95% CI, 8-11). The 2-year cumulative incidence of AML (CIR-AML) transformation was higher in mutCFN patients (44% vs 13%, p<0.001) and overall survival (OS) was shorter (25 vs 38 months, p=0.057). Besides, when those who received and alloSCT were censored at time of alloSCT, mutCFN showed an inferior survival (9.6 vs 35.7 months, p<0.01). Multivariate analysis confirmed mutCFN as an adverse prognostic factor independent of age and CPSS-Mol (HR 2.42, IC 95% 1.23-4.76, p=0.011). Because CFN mutation showed independent prognostic value not captured by CPSS-Mol, we added to CPSS-Mol 1 point if patient had mutCFN. We derived a modified CPSS-Mol-CFN score and identified five groups with different median OS of 85 (95% CI, 54-117) vs 74 (95% CI, 53-94) vs 40 (95% CI, 17-63) vs 22 (95% CI, 11-33) vs 15 (95% CI, 5-25) months, p<0.001with a better predictive capacity than CPSS-Mol (C-index 0.66 vs 0.64).
Nowadays, there is no consensus between the two recent 2022 ICC and WHO classifications, but the identification of *NPM1* or *CEBPA* mutations in cases of CMML could define AML. We analysed the group of patients who harboured bZIP- *CEBPA* or *NPM1* mutations ("mutCN") (n=17) and we found that these patients retained its chemosensitivity (90%CR) and those treated with chemotherapy had better OS (27 vs 9 months, p<0.001).
10 mutCFN patients received alloSCT with a median OS post-alloSCT of 21 months (95% CI, 16-26) and a 2year-CIR-AML of 37.5% (95% CI, 15-61). 5 patients received targeted therapy for a post-transplant relapse: 3 received sorafenib after a molecular relapse with prolonged responses and 2 received an *IDH* inhibitor, one of them persisting with a complete response after 4 years.
We analyzed 5 paired samples (diagnostic CMML-AML transformation). All of the AML related mutations were retained at AML transformation and emerged new mutations in genes of signaling (*FLT3, NRAS*), transcription (*RUNX1, CEBPA*) and splicing (*STAG2*) pathways.
Independently of CPSS-Mol, mutCFN CMML patients have a different profile, closer to AML and with worse prognosis. They could benefit from more aggressive AML-treatment based on chemotherapy and alloSCT when possible. Interestingly, some patients may benefit from approved targeted therapy for AML
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Figure 1. Co-occurrence or exclusivity of genes at diagnosis of the whole cohort. *p<0.05. The interaction of those genes repeatedly found commutated in the same patient is presented in purple. The interaction of those genes observed to be mutually exclusive and those not frequently altered in the same patient is represented in orange.

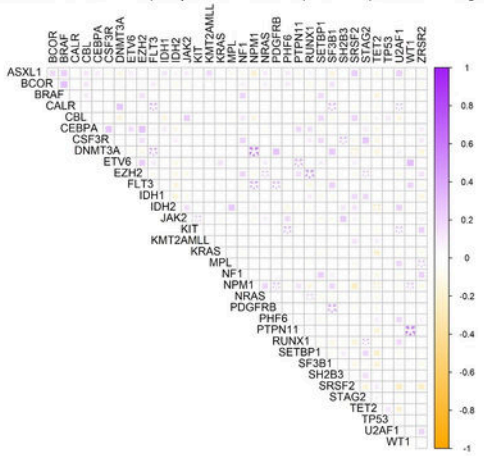

Table 1. Clinical characteristics of patients at diagnosis with mutations in CEBPA, FLT3, NPM1.

Characteristics at diagnostic	mut*CEBPA* (n=7)	wt*CEBPA* (n=107)	p	mut*FLT3* (n=11)	wt*FLT3* (n=122)	p	mut*NPM1* (n=14)	wt*NPM1* (n=117)	p	mut*CFN* (n=26)	wt*CFN* (n=96)	p
Age, years median (range)	64 (50-76)	71 (28-95)	NS	58 (42-75)	71 (28-95)	0.005	63 (47-86)	71 (28-95)	0.06	63 (42-86)	71 (28-95)	0.004
Sex (men/women) n (%)	7/0 (100/0)	80/27 (74.8/25.2)	NS	8/3 (72.7/27.3)	92/30 (75.4/24.6)	NS	11/3 (78.6/21.4)	88/29 (75.2/24.8)	NS	21/5 (80.8/19.2)	73/23 (76/24)	NS
Leucocytes, x10^9/L median (range)	8.9 (3.6-77.7)	8.3 (2.4-93.7)	NS	17.3 (2.7-55.8)	7.7 (2.4-93.7)	0.02	17.3 (4.4-30.6)	7.6 (2.4-93.7)	0.004	16 (2.7-77.7)	7.7 (2.4-93.7)	0.015
Neutrophils, median (range)	2.6 (0.4-41)	4 (0.4-40.3)	NS	6.5 (0.5-20)	3.4 (0.4-41)	NS	5.1 (0.7-20)	3.5 (0.4-41)	NS	5 (0.4-41)	3.5 (0.4-40.3)	NS
Monocytes, median (range)	1.4 (1.1-29)	1.8 (0.5-33.7)	NS	3.1 (1.5-24)	1.6 (0.5-34)	0.01	5 (1.5-12.2)	1.6 (0.5-33.7)	0.002	2.9 (1.1-29)	1.7 (0.5-33.7)	0.006
% Monocytes, median (range)	22.5 (15-36.1)	21.5 (10-62.4)	NS	25.3 (10-42)	21.9 (10-62.4)	NS	28 (10-62.4)	21.1 (10-60.9)	NS	28 (10-62.4)	19.1 (10-60)	NS
PLT, x109/L median (range)	107.5 (39-207)	111.5 (6-982)	NS	70 (6-223)	127 (7-982)	0.02	86 (13-263)	125 (6-982)	NS	92 (6-263)	115 (7-982)	0.07
Hb, g/L median (range)	10.6 (6.4-13.3)	10.9 (4.9-16.3)	NS	8.6 (4.9-16.3)	11.1 (6.4-16.1)	0.04	8.1 (4.9-11)	11.3 (6.4-16.3)	<0.001	9.1 (4.9-16.3)	11.2 (6.5-15.9)	<0.001
Blasts MO, % median (range)	12 (6-19)	4 (0-19)	0.002	15 (2-19)	4 (0-19)	<0.001	13.5 (0-19)	4 (0-19)	0.007	11.5 (0-19)	4 (0-18)	<0.001
Cytogenetic alterations n (%)	2 (28.6)	20 (20.6)	NS	2 (18.2)	22 (19.6)	NS	1 (7.7)	22 (20.4)	NS	4 (16)	19 (21.8)	NS
Cytogenetic risk, n (%) Low Intermediate High	5 (83.3) 1 (16.7) 0	79 (81.4) 8 (8.3) 10 (10.3)	NS	9 (81.8) 2 (18.2) 0	92 (82.9) 7 (6.3) 12 (10.8)	NS	12 (92.3) 1 (7.7) 0	88 (82.2) 8 (7.5) 11 (10.3)	NS	21 (87.5) 3 (12.5) 0	70 (80.5) 6 (6.9) 11 (12.6)	NS
Therapy related, n (%)	0	4 (3.9)	NS	0	5 (4.4)	NS	0	5 (4.6)	NS	0	4 (4.4)	NS
FAB, n (%) myelodysplastic myeloproliferative	4 (57.1) 3 (42.9)	71 (66.4) 36 (33.6)	NS	4 (36.4) 7 (63.6)	84 (68.9) 38 (31.1)	0.044	4 (28.6) 10 (71.4)	82 (70.1) 35 (29.9)	0.005	11 (42.3) 15 (57.7)	67 (69.8) 29 (30.2)	0.012
ICC/OMS 2022 n (%) CMML -1 CMML -2	1 (14.3) 6 (85.7)	82 (77.4) 24 (22.6)	0.001	3 (27.3) 8 (72.7)	93 (76.9) 28 (23.1)	0.001	4 (28.6) 10 (71.4)	90 (77.6) 26 (22.4)	<0.001	8 (30.8) 18 (69.2)	81 (85.3) 14 (14.7)	<0.001
CPSS n (%) Low Intermediate-1 Intermediate-2 High	1 (14.3) 1 (14.3) 4 (57.1) 1 (14.3)	33 (34) 30 (30.9) 28 (28.9) 6 (6.2)	NS	0 3 (27.3) 7 (63.6) 1 (9.1)	42 (37.5) 33 (29.5) 29 (25.9) 8 (7.1)	0.028	1 (7.7) 1 (7.7) 11 (84.6) 0	41 (38) 34 (31.5) 25 (23.1) 8 (7.4)	<0.001	2 (8) 5 (20) 16 (64) 2 (8)	33 (37.9) 27 (31) 21 (24.2) 6 (6.9)	0.001
Dichotomic CPSS n (%) Low + intermediate-1 Intermediate-2 + high	2 (28.6) 5 (71.4)	63 (64.9) 34 (35.1)	0.1	3 (27.3) 8 (72.7)	75 (67) 37 (33)	0.02	2 (15.4) 11 (84.6)	75 (69.4) 33 (30.6)	<0.001	7 (28) 18 (72)	60 (69) 27 (31)	<0.001
CPSS-Mol n (%) Low Intermediate-1 Intermediate-2 High	0 1 (16.7) 1 (16.7) 4 (66.6)	20 (23) 24 (27.6) 26 (29.9) 17 (19.5)	0.06	0 0 6 (85.7) 1 (14.3)	23 (23) 28 (28) 26 (26) 23 (23)	0.009	0 1 (12.5) 7 (87.5) 0	23 (23.5) 27 (27.6) 25 (25.4) 23 (23.5)	0.003	0 2 (11.8) 10 (58.8) 5 (29.4)	20 (25.6) 23 (29.5) 17 (21.8) 18 (23.1)	0.005
Dichotomic CPSS-Mol n (%) Low + intermediate-1 Intermediate-2 + high	1 (16.7) 5 (83.3)	44 (50.6) 43 (49.4)	NS	0 7 (100)	51 (51) 49 (49)	0.013	1 (12.5) 7 (87.5)	50 (51) 48 (49)	0.06	2 (11.8) 15 (88.2)	43 (55.1) 35 (44.9)	0.001
Transfusion dependence n (%)	3 (42.9)	30 (28)	NS	10 (90.9)	31 (25.8)	<0.001	11 (78.6)	28 (24.3)	<0.001	18 (69.2)	22 (22.9)	<0.001
Patients who received modifying treatment n (%)	6 (85.7)	45 (42.1)	0.04	9 (81.8)	50 (41)	0.01	12 (85.7)	44 (37.6)	<0.001	22 (84.6)	35 (36.5)	<0.001
Patients treated with HMA	5 (71.4)	36 (33.6)	0.096	6 (54.5)	41 (33.6)	NS	6 (42.9)	38 (32.5)	NS	15 (57.7)	30 (31.3)	0.02
Patients treated with chemotherapy	4 (57.1)	14 (13.1)	0.01	6 (54.5)	15 (12.3)	0.002	9 (64.3)	11 (9.4)	<0.001	14 (53.8)	7 (7.3)	<0.001
HMA response n (%) Complete response Marrow response Partial remission Clinical Benefit No response	3 (60) 0 1 (20) 0 1 (20)	10 (30.3) 1 (3) 3 (9.1) 3 (9.1) 16 (48.5)	NS	0 0 0 1 (25) 3 (75)	13 (38.2) 1 (2.9) 4 (11.8) 2 (5.9) 14 (41.2)	NS	2 (40) 0 0 0 3 (60)	11 (33.3) 1 (3) 4 (12.1) 3 (9.2) 14 (42.4)	NS	5 (41.7) 0 1 (8.3) 1 (8.3) 5 (41.7)	8 (30.8) 1 (3.8) 3 (11.5) 2 (7.7) 12 (46.2)	NS
Chemotherapy response n (%) Complete response Partial response No response	3 (75) 0 1 (25)	9 (64.3) 1 (7.1) 4 (28.6)	NS	5 (83.3) 0 1 (16.7)	9 (64.3) 1 (7.1) 4 (28.6)	NS	8 (88.9) 1 (11.1) 0	6 (54.5) 0 5 (45.5)	0.046	11 (78.6) 1 (7.1) 2 (14.3)	3 (50) 0 3 (50)	NS
Time to treatment, median (range)	1.3 (0.3-4.3)	3 (0.07-111.7)	NS	0.9 (0.3-41.3)	4 (0.07-111.7)	NS	0.9 (0.07-6.3)	3 (0.1-111.7)	0.045	0.97 (0.07-41.3)	4.6 (0.1-111.7)	0.005
Allogeneic transplant n (%)	5 (71.4)	18 (16.8)	0.004	8 (72.7)	20 (16.4)	<0.001	8 (57.1)	18 (15.4)	0.001	16 (61.5)	11 (11.5)	<0.001
Overall survival median (95% CI)*	10 (3.6-16.4)	31 (19.5-42.6)	0.002	7.6 (5.1-10.1)	34.4 (22.5-46.3)	<0.001	9.1 (7.9-10.3)	35.8 (22.5-49)	<0.001	9.6 (6.5-12.7)	35.8 (21-51)	<0.001
Overall survival median (95% CI)	22.2 (3.2-41)	36.6 (16.2-57)	0.048	28.5 (27-29.9)	38.2 (19.6-56.8)	NS	25.1 (4.8-45.5)	38.2 (18.8-57.6)	NS	25.1 (16.3-34)	38.2 (19-57.3)	0.057
Cumulative incidence of transformation to AML at 2 years % (95% CI)	28.6 (2.5-65.4)	17.7 (11-25.8)	0.5	40 (10.8-68.5)	16.5 (10.3-23.8)	0.04	50 (20.9-73.5)	14.7 (8.8-22)	<0.001	44 (24-63)	13 (7-21)	<0.001

*Patients who received an alloSCT were censored at the time of alloSCT.

Figure 1

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