TREATMENT OUTCOMES IN UNFIT PATIENTS WITH NEWLY ACUTE MYELOID LEUKEMIA ACCORDING TO IDH1 MUTATIONAL STATUS: REAL WORLD EVIDENCE FROM THE PETHEMA EPIDEMIOLOGIC REGISTRY

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BACKGROUND

Current treatment of unfit acute myeloid leukemia (AML) patients includes hypomethylating agents (HMA) with or without venetoclax, low-dose cytarabine (LDAC), and supportive care only. Recently, the combination of azacytidine with ivosidenib, an IDH1 inhibitor, has showed a significant improvement in survival in unfit patients with IDH1 mutated (IDH1mut) AML compared to azacytidine plus placebo. Real world studies analyzing outcomes of IDH1mut AML patients are scarce.

This study aims to assess retrospectively the characteristics, therapeutic approaches, and outcomes of unfit patients with AML in an unselected population reported to the multicentric PETHEMA registry according to IDH mutational status. We present here a first interim analysis, as the study is aimed to enroll 3500 patients

METHODS

AML unfit patients reported to PETHEMA registry between January 2015 and June 2022 were included in the study, regardless of their therapeutic approach. IDH1 mutational status was analyzed with next generation sequencing (NGS) and polymerase chain reaction (PCR) technics performed in central labs from PETHEMA group, as well as locally as per standard practice. All clinical records were reviewed from diagnosis to death/last follow-up and data were analyzed with R statistical software.

RESULTS

From 9398 patients reported to the PETHEMA registry between 2015 and 2022, 4533 patients had information on IDH1 mutational status. Of them, 2096 patients were unfit for intensive chemotherapy, and therapeutic approach was available in 1255 patients who were evaluable for this interim report. Median age was 75 years, 716 (57%) were male, 312 (35%) had adverse cytogenetic-risk. Overall, 141 (11%) had IDH1mut [106 (12.4%) by NGS and 77 (9.9%) by PCR only] and 1114 (89%) had no IDH1 mutation (IDH1wt).

There were differences between IDH1mut vs IDH1wt cohorts regarding white blood cells (WBC) count (P=0.003), platelets count (P=0.002), bone marrow blasts percentage (P<0.001), MRC cytogenetic risk (P=0.02) and NPM1 mutational status (P<0.001). More detailed information is shown in Table 1.

Regarding treatments, 186 (15%) patients received only best supportive care (BSC), 293 (23%) were included in non-intensive clinical trials, 433 (34%) received HMAs, 281 (22%) LDAC schedules and 62 (5%) venetoclax plus HMA or LDAC (VEN).

Table 1. Demographic and baseline characteristics of the study population (IDH1mut vs IDH1wt).

Characteristic	Overall		IDH1 mutated		IDH1 wild type		*P value*
	Median (IQR)	n (%)	Median (IQR)	n (%)	Median (IQR)	n (%)	
Total		1255 (100)		141 (100)		1114 (100)	
Age, years	75 (71-80)	1255 (100)	75 (71-80)	141 (100)	75 (70-80)	1114 (100)	0.82*
<60		43 (3)		7 (5)		36 (3)	0.78
60-69		207 (16)		20 (14)		187 (17)	
70-79		688 (55)		78 (55)		610 (55)	
80-89		303 (24)		34 (24)		269 (24)	
≥90		14 (1)		2 (1)		12 (1)	
Gender		1255 (100)		141 (100)		1114 (100)	
Male		716 (57)		77 (55)		639 (57)	0.6
Female		539 (43)		64 (45)		475 (43)	
ECOG	1 (0-2)	1123 (100)	1 (0-2)	130 (100)	1 (0-2)	993 (100)	0.76*
0		305 (27)		38 (29)		267 (27)	0.63
1		476 (42)		54 (42)		422 (42)	
2		213 (19)		20 (15)		193 (19)	
3		95 (8)		12 (9)		83 (8)	
4		34 (3)		6 (5)		28 (3)	
Type of AML		1149 (100)		128 (100)		1021 (100)	
De novo		653 (57)		81 (63)		572 (56)	0.14
Secondary		496 (43)		47 (37)		449 (44)	
WBC, ×10⁹/l	6.9 (2.3-27.4)	1149 (100)	4.4 (1.8-17.4)	130 (100)	7.2 (2.3-29.2)	1019 (100)	0.003*
<5		501 (44)		70 (54)		431 (42)	0.02
5-10		150 (13)		14 (11)		136 (13)	
10-50		312 (27)		35 (27)		277 (27)	
≥ 50		186 (16)		11 (8)		175 (17)	
Hemoglobin, g/dl	9 (7.9-10.3)	1098 (100)	9.3 (8.1-10.5)	126 (100)	8.9 (7.9-10.2)	972 (100)	0.11*
Platelet count, ×10⁹/l	54 (27-98)	1086 (100)	72 (38-118)	125 (100)	52 (26-97)	961 (100)	0.002*
BM blasts, %	46 (28-72)	1026 (100)	57 (37.5-78)	119 (100)	44 (27-70)	907 (100)	<0.001*
Creatinine, mg/dl	1 (0.7-1.3)	1075 (100)	0.9 (0.7-1.1)	123 (100)	1 (0.8-1.3)	952 (100)	0.06*
Urea, mg/dl	43 (33-58)	885 (100)	41 (30-58)	96 (100)	43 (33-59)	789 (100)	0.26*
Uric acid, mg/dL	5.4 (3.9-7)	809 (100)	5.1 (3.9-6.6)	87 (100)	5.4 (3.9-7)	722 (100)	0.15*
Bilirubin, mg/dL	0.62 (0.45-0.92)	944 (100)	0.6 (0.4-0.91)	104 (100)	0.62 (0.46-0.92)	840 (100)	0.62*
Albumin, g/dl	3.7 (3.2-4.1)	950 (100)	3.6 (3.2-4)	114 (100)	3.7 (3.2-4.1)	836 (100)	0.46*
MRC Cytogenetic risk		893 (100)		96 (100)		797 (100)	
Favorable		24 (3)		1 (1)		23 (3)	0.02
Intermediate		557 (62)		72 (75)		485 (61)	
Adverse		312 (35)		23 (24)		289 (36)	
FLT3-ITD		977 (100)		117 (100)		860 (100)	
Positive		136 (4)		15 (13)		121 (14)	0.82
Negative		841 (86)		102 (87)		739 (86)	
NPM1		966 (100)		115 (100)		851 (100)	
Positive		193 (20)		38 (33)		155 (18)	<0.001
Negative		773 (80)		77 (67)		696 (82)	
Therapeutic approach		1255 (100)		141 (100)		1114 (100)	
HMA		433 (34)		53 (38)		380 (34)	0.89
VEN-based		62 (5)		8 (6)		54 (5)	
LDAC-based		281 (22)		31 (22)		250 (22)	
Clinical Trial		293 (23)		30 (21)		263 (24)	
Supportive care		186 (15)		19 (13)		167 (15)	

IQR: interquartile range; ECOG: Eastern Cooperative Oncology GroupWBC: White Blood Cells; BM: Bone Marrow; MRC: Medical Research Council; FLT3: FMS-like tyrosine kinase 3; IDH1: isocitrate dehydrogenase 1; ITD: internal tandem duplication; LDAC: low-dose cytarabine; NPM1: Nucleophosmin1; HMA: hypomethylating agents; VEN: venetoclax * P compare continuous variables.

From 818 patients with available response, 261 (32%) achieved complete remission (CR) or CR with incomplete recovery (CRi), 105 (13%) partial remission, 305 (37%) were resistant and 147 (18%) died before being assessed. No statistical differences were observed between IDH1mut and IDH1wt groups (P=0.18). Table 2 shows induction response according to IDH1 status.

Table 2. Induction response according to IDH1 mutational status.

Variable	Overall N (%)	IDH1 mutated N (%)	IDH1 wild type N (%)	*P*
All patients	818 (100)	95 (100)	723 (100)	
ORR (CR + CRi)	261 (32)	36 (38)	225 (31)	0.18
CR	231 (28)	31 (33)	200 (28)	
CRi	30 (4)	5 (5)	25 (3)	
PR	105 (13)	11 (12)	94 (13)	
Resistance	305 (37)	39 (41)	266 (37)	
Death	147 (18)	9 (9)	138 (19)	

CR: Complete Remission; CRi: CR with incomplete recovery; ORR: Overall response rate; PR: partial remission.

Median overall survival (OS) was 5.9 months (CI95, 5.3-6.7), with no differences in IDH1mut and IDH1wt cohorts [median 7.7 months (CI95, 5.9-11.2) vs 5.6 (CI95, 5-6.4)], with a 2y-OS of 15% (9.7-24.5) vs 15% (12.9-18.2), respectively (P=0.24) (Figure 1).

Median OS was 7.9 (CI95, 6.8-9.3) in patients receiving active treatment. Patients receiving VEN schedules had a median OS of 11.1 months (CI95, 9.4-14.1) vs 10.5 (CI95, 8.2-13.0) in patients included in clinical trials vs 8.3 (CI95, 6.7-10.0) in those receiving HMA vs 5.5 (CI95, 4.5-6.8) treated with LDAC-based schemes vs 0.4 (CI95, 0.3-0.7) in BSC patients (P<0.001). Figure 2 shows OS according to therapeutic approach in all patients.

Figure 1. OS in AML patients according to IDH1 mutational status (IDH1mut vs IDH1wt).

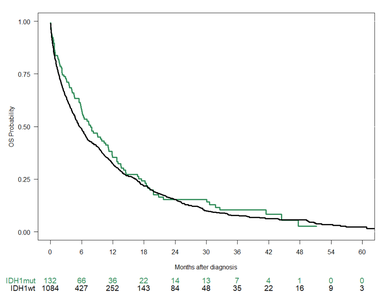
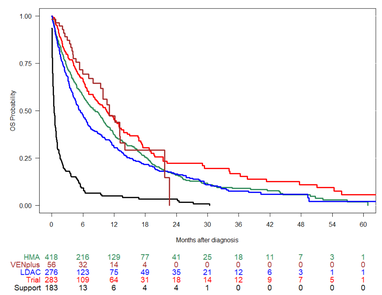


Figure 2. OS in AML patients according to therapeutic approach.



According to the therapeutic approach, IDH1mut patients included in clinical trials had a median OS of 16.8 (CI95, 6.0-NA) vs 10.6 months (CI95, 9.9-NA) in patients receiving VEN schedules vs 9.0 (CI95, 6.5-14.5) in those receiving HMA vs 7.0 (CI95, 5.5-12.7) with LDAC-based vs 0.6 (CI95, 0.2-3.7) in BSC patients (P<0.001).

CONCLUSIONS

We show a prevalence of 11% of IDH1 mutation among patients considered unfit to receive intensive chemotherapy. Although there were differences between IDH1mut and IDH1wt subgroups in some variables with demonstrated prognostic impact, no significant differences were observed in response to treatment or OS. This study was partially supported by Servier.

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