Real-life outcome after failure to venetoclax and hypomethylating-based therapy for acute myeloid leukemia

Venetoclax and azacitidine became the gold standard front-line treatment for patients diagnosed with acute myeloid leukemia (AML) ineligible for intensive chemotherapy (unfit) since the publication of the phase III Viale-A trial in 2020[1] with a better composite response rate and an increased median overall survival (OS) compared to azacitidine.

Though the treatment changed the paradigm in unfit AML patients, the results of the long-term follow-up of the Viale-A[2] and the real-life series[3] have shown that eventually most patients will relapse. Outcome after failure has not been broadly studied. Only selected patients, especially those with actionable targets (e.g., *NPM1, IDH1/2 or FLT3* mutation, or *KMT2A* rearrangement) may benefit from salvage treatment if available at this moment in disease course, including clinical trial enrollment.

Here, we analyze the outcomes of AML patients after failure to venetoclax in combination with hypomethylating agents (VenHMA), with an emphasis on salvage feasibility after relapse.

We performed a retrospective study with patients treated with VenHMA at three academic centers in the metropolitan area of Barcelona (Hospital Clínic de Barcelona, Hospital de la Santa Creu i Sant Pau, and Hospital Duran i Reynals) between September 2019 and December 2023. All patients received VenHMA as front-line therapy, with an initial dose of venetoclax 400mg daily during 21 or 28 days and hypomethylating agents at standard dose in 4-week cycles. Patients who subsequently underwent allogeneic hematopoietic cell transplantation were excluded from the study. Dose decrease was decided based on myelotoxicity during treatment at the discretion of the physicians. The study was approved by the Ethics Committee of the Hospital Clínic de Barcelona and conducted following standards set out in the Declaration of Helsinki. Our primary endpoint was to analyze OS after treatment failure to VenHMA, defined as treatment inefficacy to obtain any morphological response according to the European LeukemiaNet (ELN 2022) response criteria. Secondary objectives included studying salvage treatments offered in patients who relapsed, including their overall response rate (ORR) and the palliative care policy applied.

Acute myeloid leukemia was classified according to the International Consensus Classification of myeloid neoplasms 2022 (ICC 2022) and World Health Organization (WHO) 5th classification of myeloid neoplasms.[4,5] AML disease risk stratification and response criteria during treatment were assessed locally at each center, in all cases according to the 2022 European LeukemiaNet risk criteria[6] (ELN 2022). Cytogenetics were assessed on G-banded metaphase cells and next-generation sequencing (NGS) at diagnosis was performed with the Ion AmpliSeq™ AML Research Panel, Oncomine™ Myeloid Research Assay, and the Healthincode Haematology OncoKitDx™. Performance status (PS) was assessed according to the Eastern Cooperative Oncology Group (ECOG) score.[7]

Median and range were used for continuous variables and frequency, and percentage for categorical variables. OS was defined as survival from confirmed morphological relapse or treatment refractoriness onwards, and was estimated using the Kaplan-Meier method. Univariate analyses for survival were performed using the log-rank test. Time-dependent variates for survival were analyzed using the Mantel-Byar method. All *P* values were two-sided with statistical significance evaluated at the 0.05 alpha level. All statistical analyses were performed with R statistics version 4.0.3 (R core Team, R Foundation for Statistical Computing, Vienna, Austria).

Sixty-seven patients were included, 42 of them relapsing after an initial response (62.7%) and 25 after treatment refractoriness (27.3%). Baseline characteristics are shown in Table 1. Median age was 75 years (range 33-91) in both subgroups, with males making up 61.6% of the participants. Acute myeloid leukemia with myelodysplasia-related (MR) gene mutations was the most frequent diagnosis (29/67 of all patients, 38.2%). According to the ELN 2022 risk classification, 4 patients had a favorable (6%), 16 (23.9%) an intermediate, and 47 an adverse (70.1%) risk. Most frequent mutations were observed in *TET2* (29.8%), *ASXL1* (26.3%), and *RUNX1* (24.6%) (*Online Supplementary Figure S1*). Seventeen patients (33%) harbored an actionable mutation, including *FLT3* (N=7), *IDH1/2* (N=15) and/or *NPM1/KMT2Ar* (N=10). Eight of these patients (10.5%) had previously received azacytidine during the myelodysplastic syndrome (MDS) phase.

Characteristics of response to VenHMA can be seen in *Online Supplementary Table S1*. Out of the 67 patients, 25 (37%) were initially refractory while 42 (63%) relapsed. Complete response (CR) with incomplete hematologic recovery (Cri) (66.6%, 28/42) was the most frequent response; CR + CRi rate was 92.3% (median cycles to response=1 [range 1-3]; median cycles received=6 [range 2-16]).

Overall survival was 2.3 months (95% CI: 1.8-4.6) (*Online Supplementary Figure S2*) with no difference between patients who achieved any response and refractory patients

(4 *vs*. 1.2 months, *P*=0.2) (Figure 1A). There were no differences in OS according to patient mutational profile (2.5 *vs*. 1 month, *P*=0.27). After relapse, a molecular reassessment was performed in 18 patients, with emergent mutations in 11 of them (61.1%). Emergent mutations in *FLT3-TKD, NRAS, TP53* (N=2 each) and *KRAS* and *FLT3-ITD* (N=1 each) were the most relevant mutations.

Only 13 patients (30.9%) were able to undergo salvage treatment, including 6 patients enrolled in different clinical trials. Three patients underwent standard chemotherapy after VenHMA with no response to treatment. Five patients were treated with targeted therapies: 2 with *FLT3* inhibitor gilteritinib, 2 enrolled in clinical trials with *IDH1/2* inhibitors, and one in a clinical trial with a menin inhibitor. Salvage ORR rate was 3/13 patients (23.3%): one CR and one CRi with IDH1/2 inhibitors within clinical trials, and one CR to gilteritinib.

Reasons to rule out salvage treatment included lack of suitable treatment according to physician's choice in 20 patients (54.9%), comorbidities (13.7%), lack of available clinical trial (CT) or targeted therapy in 2 patients, and CT screening failure in one patient. We observed no differences in OS on receiving a salvage treatment (2.2 *vs*. 4 months, *P*=0.22) (Figure 1B and *Online Supplementary Table S2*). OS on achieving a CR after salvage was 11.6 months *versus* 2.53 in refractory patients (*P*=0.17) (Figure 1C)

Finally, a hospice care team was set up for 19 patients after relapse (45.2%), while the rest of the patients did not have access to any special care system at home that could enhance comfort and quality of life during their last days of life. Within these palliative measures, 9 of these patients died at home (21.4%) while the rest of the patients required a final admission and died in hospital.

This study highlights the poor outcome of unfit patients diagnosed with AML after front-line therapy failure with VenHMA. The low percentage of patients that are able to undergo salvage treatment in our setting (30%) and its lack of efficacy would explain the dismal survival after VenHMA discontinuation (2.3 months). To our knowledge, this study represents the first investigation into survival after progressive disease to VenHMA in AML in a European real-world data cohort.

In this context, one of the main challenges in offering ad-

Table 1. Baseline characteristics of all patients.

Characteristics	All patients N=67	Response N=42	Initial refractoriness N=25
Age in years, median (range)	75 (33-86)	75 (33-86)	75 (52-85)
Sex, N (%)			
Male	41 (61.2)	23 (54.8)	18 (72)
Female	26 (38.8)	19 (45.2)	7 (28)
ICC 2022 AML diagnosis, N (%)			
Myelodysplasia-related gene mutations	28 (41.8)	17 (40.5)	11 (44)
Mutated *TP53*	10 (14.9)	6 (14.3)	4 (16)
Myelodysplasia-related cytogenetical abnormalities	9 (13.4)	7 (16.7)	2 (8)
Mutated *NPM1*	8 (11.9)	6 (14.3)	2 (8)
NOS	7 (10.4)	5 (11.9)	2 (8)
t(9;11), *KMT2A* rearrangement	2 (3)	0 (0)	2 (8)
MECOM(EVI1) rearrangements	2 (3)	0 (0)	2 (8)
t(8;21), *RUNX1::RUNX1T1*	1 (1.)	1 (2)	0 (0)
ELN 2022 risk genetic scale, N (%)			
Favorable	4 (6)	4 (16.7)	0 (0)
Intermediate	16 (23.9)	9 (21.4)	7 (28)
Adverse	47 (70.1)	29 (69)	18 (72)
Treatment prior to VenHMA, N (%)			
Hypomethylating agent-based regimens	8 (11.9)	4 (9.5)	4 (12)
Hypomethylating agent, N (%)			
Azacitidine	59 (88.1)	36 (85.7)	23 (92)
Decitabine	8 (11.9)	6 (14.3)	2 (8)
Blood values at PD, median (range)			
WBC, $x10^9$/L	2.8 (0.6-56.3)	2.43 (0.6-41.9)	5.27 (0.7-56.3)
Hemoglobin, g/dL	8.6 (6.7-12.5)	8.7 (6.7-12.5)	8.4 (7-10.7)
Platelets, $x10^9$/L	58 (3-537)	58 (3-442)	47 (9-537)

AML: acute myeloid leukemia; ELN 2022: European LeukemiaNet 2022 risk stratification; ICC 2022: International Consensus Classification of myeloid neoplasms 2022; MDS: myelodysplastic syndrome; N: number; NOS: not otherwise specified; PD: progressive disease; VenHMA: venetoclax in combination with hypomethylating agents; WBC: white blood cell.

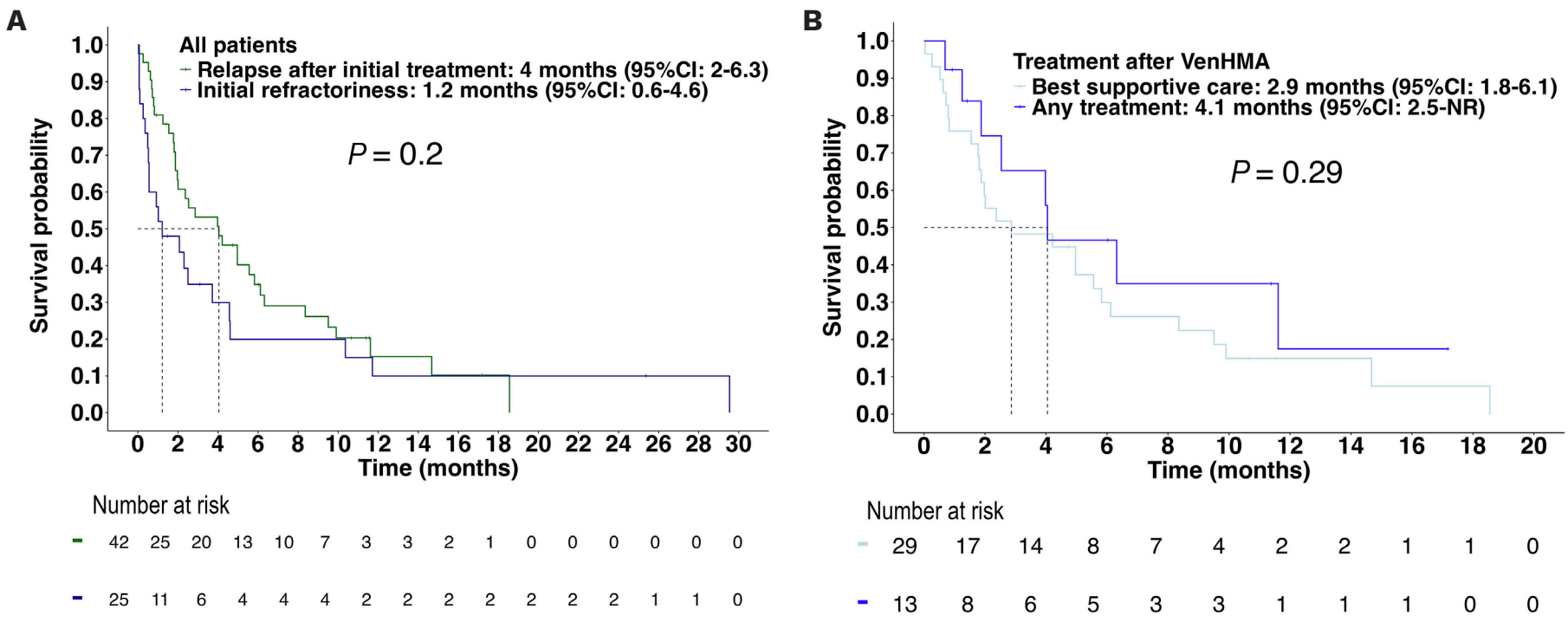

Figure 1. Overall survival in patients after treatment failure with venetoclax and hypomethylating agents. (A) Patient subgroups by previous response to treatment. (B) Patients who obtained a response to venetoclax and hypomethylating agents (VenHMA) by ulterior treatment. (C) Patients with a previous response to venetoclax and hypomethylating agents by response to salvage treatment. NR: not reached.

equate salvage treatments relies on accessibility. Previous to this report, the only series of patients to have been published concerned those treated mostly within the United States of America and, in 2 cases, patients who had been enrolled in the Viale A study.[2,8,9] Interestingly, the percentage of patients that underwent salvage treatment (24/41 [58.5%],[2] 11/71 [15%][8] and 59/171 [34.5%][9]) and ORR differ a lot between the studies, remarking also the variability of therapeutical options between centers in this context and the feasibility to receive therapy after failure. The recent long-term follow-up of the Viale A shows longer survival after treatment failure (6 months), probably based on a relatively high percentage of patients treated afterwards and the CT selection bias.[2]

Some targeted therapies have shown promising activity in this setting of patients refractory/relapsed (r/r) to VenHMA, such as revumenib[10] in *KMT2A* rearranged and *NPM1* AML, or, more recently, myeloid kinase inhibitor tuspetinib.[11] However, only gilteritinib[12] in monotherapy for r/r AML with *FLT3* mutation is approved in Europe, while enasidenib[13] and ivosidenib[14] have been approved for such patients by the US Food and Drug Administration.

Treatment after VenHMA failure is a current unmet need in unfit AML patients, and this is clearly observed in our series. The salvage treatment rate was only 25%, although 33% of the patients presented an actionable target, and all responses after VenHMA were achieved using therapies against these actionable targets. Therefore, in this setting, where the main objective is to offer salvage treatment to all eligible patients, targeted therapies have now become essential. There are, though, important differences in drug access between the European and American settings that hinder prescription and this should be made clear in the standard treatment guidelines.

If there are no available options, patients should be enrolled on a clinical trial in order to add new options to the thera-

peutical arsenal, since this is likely to be the best option in all patients without any actionable targets after VenHMA. Finally, we would like to underline the importance of palliative care in this setting, the rates of which have not yet been published. Although activation of hospice care has improved over the years, in our study, less than 50% of the patients were able to benefit. We consider these figures to be extremely low, although they are similar to those shown in other studies related to the disease.[15] Since survival is still short after failure, the speed at which palliative care is set up needs to improve so more patients can benefit from hospice care in the future.

Limitations of this study include its retrospective nature, the limited size of the cohort and the small number of the patients receiving salvage treatments, which underpowers the likely differences observed. Further studies including more patients are needed.

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Contributions

CJV and MDB designed the study, performed the statistical analysis, and wrote the manuscript. JE and MDB supervised the study. HP, IA, GR, SCD, AIPV, ASL, MLG, AMR, IZ, FG, ACB, BM, AT, IM, GO and AG collected data. All authors contributed valuable revisions and approved the final version of the manuscript.

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Data-sharing statement

Due to privacy and ethical considerations, the data underlying the findings of this study can be obtained by contacting the corresponding author.

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