Outcomes of relapsed or refractory acute myeloid leukemia after front-line hypomethylating agent and venetoclax regimens

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. Outcomes of intensive chemotherapy (IC) in older patients with AML continue to be suboptimal due to comorbidities, frailty, complex biology and resistance to chemotherapy.[1-3] Front-line venetoclax (VEN) with hypomethylating agents (HMA) (VEN+HMA) have shown good tolerability with potentially better outcomes compared to HMA alone.[4-6] Consequently, VEN+HMA regimens have emerged as a reasonable new standard of care for older patients.[7] However, little is known about outcomes of patients after failure of front-line venetoclax-based regimens. We found that patients failing front-line VEN+HMA have high-risk biology, dismal overall survival (OS) despite salvage therapy, and new putative mechanisms of resistance. This knowledge may help guide physicians' expectations, inform discussion with patients, and design clinical trials in patients after venetoclax failure.

This was a retrospective study to determine the outcomes of patients after failure of front-line VEN+HMA therapy. Patients with newly diagnosed (ND) AML enrolled on two clinical trials of VEN and HMA at our institute, either with primary refractory disease or relapse (R/R) after initial response were included (*Online Supplementary Figure S1*). In one trial, patients with ND AML aged 65 years or older received venetoclax 400-1,200 mg daily with decitabine 20 mg/m^2 for 5 days or azacitidine 75 mg/m^2 for 7 days every 4 weeks (*clinicaltrials.gov identifier: NCT02203773*).[4] The other trial enrolled patients with ND AML aged 60 years or older, and patients received venetoclax 400 mg daily or equivalent with decitabine 20 mg/m^2 for 10 days every 4 weeks until response, followed by 5-day decitabine with venetoclax cycles (*clinicaltrials.gov identifier: NCT03404193*).[5] None of the patients included in these analyses received any third agents such as targeted therapies. Responses included complete remission (CR), CR with incomplete hematologic recovery (CRi), or morphologic leukemia-free state (MLFS) according to the European LeukemiaNet 2017 criteria.[8] Primary refractory disease was defined as lack of reduction of bone marrow (BM) blasts to 5% or less by up to cycle 4 of VEN+HMA, as originally defined in these two protocols designed in 2014 and 2017. Relapse was defined as clinically significant progressive disease with increase in BM blasts to more than 5% after achievement of CR/CRi/MLFS. OS was measured from the date of establishment of primary refractory disease or relapse after VEN+HMA therapy, until death or censored at last follow-up. The data cut-off date for this report was July 8th, 2019.

To provide context for this analysis, we compared outcomes, both from initial therapy, and from time of R/R disease, with front-line IC using a historical cohort. We found 278 patients treated with IC who matched for both age and European LeukemiaNet (ELN) 2017 cytogenetic risk status with 88 out of 95 patients treated with VEN+HMA. There were no patients in our historical IC cohort who matched for both age and cytogenetic risk status of seven patients who received VEN+HMA, and hence the comparison was limited to those 88 patients. Two out of those seven unmatched patients had R/R disease after VEN+HMA. The patients in the IC cohort were diagnosed between 2000 and 2018, and received treatment with IC containing at least 1 g/m^2/day of cytarabine (*Online Supplementary Table S1*). For comparison of OS with front-line VEN+HMA *versus* IC, OS was measured from start of therapy until death, or censored at last follow-up. χ^2 test was used to compare proportions between groups and Kaplan-Meier method with log-rank test was used to compare OS.

Table 1. Baseline characteristics of patients with relapsed or refractory acute myeloid leukemia (AML) after front-line venetoclax and hypomethylating agent-based regimens, n=41.

Characteristics	N (%), median [range]
Age	74 [62-85]
ECOG PS ≥2	23 (56)
Peripheral blood blasts, %	2 [0-44]
Bone marrow blasts, %	15 [1-95]
Diagnosis	
de novo AML	22 (54)
Secondary AML	12 (29)
Therapy-related AML	7 (17)
ELN 2017 risk group at diagnosis	
Intermediate	8 (19)
Adverse	33 (81)
Venetoclax and hypomethylating agent regimen	
DEC10-VEN	19 (46)
DEC5-VEN	18 (44)
AZA-VEN	4 (10)
Response to VEN+HMA	
CR	19 (46)
CRi	11 (27)
MLFS	3 (7)
Primary refractory	8 (20)
Duration of response, months	5.3 [0.9-34.1]
No. of VEN+HMA cycles received	4 [1-29]
Allo-SCT in CR1	4 (10)

ECOG PS: Eastern Co-operative Oncology Group Performance Status; ELN: European LeukemiaNet; DEC10: decitabine for 10 days; DEC5: decitabine for 5 days; AZA: azacitidine; VEN: venetoclax; HMA: hypomethylating agents; CR: complete remission; Cri: CR with incomplete hematologic recovery; CR1: first CR; MLFS: morphologic leukemia-free state; allo-SCT: allogeneic stem cell transplantation.

Between November 2014 and February 2019, we treated 95 patients with ND AML on two front-line VEN+HMA trials, and we identified 41 patients (43%) with R/R disease after front-line VEN+HMA. Eight patients (20%) had primary refractory disease while 33 patients (80%) had relapse after initial response. The median age was 74 years (range 62-85), 12 patients (29%) had secondary AML (sAML), 33 patients (81%) had ELN adverse risk AML, 16 patients (39%) had *TP53*^{mut}, 11 patients (27%) had *N/KRAS*^{mut}, and five patients (12%) had *FLT3-ITD*^{mut} at screening. Patients had received a median of four cycles of therapy (range 1-29) (Table 1). The median follow-up duration for all patients was 21 months.

The median OS after VEN+HMA failure for all 41 patients was 2.4 months (range 0.1-21.2) (Figure 1A). Patients who received salvage therapy (n=24) had longer OS compared to patients who could not or did not receive salvage therapy (n=17, 2.9 *vs.* 1.3 months, hazard ratio [HR]=0.41, 95% confidence interval [CI]: 0.19-0.88; *P*=0.003) (Figure 1B). When compared to an age- and cytogenetic risk-matched cohort of 278 patients receiving

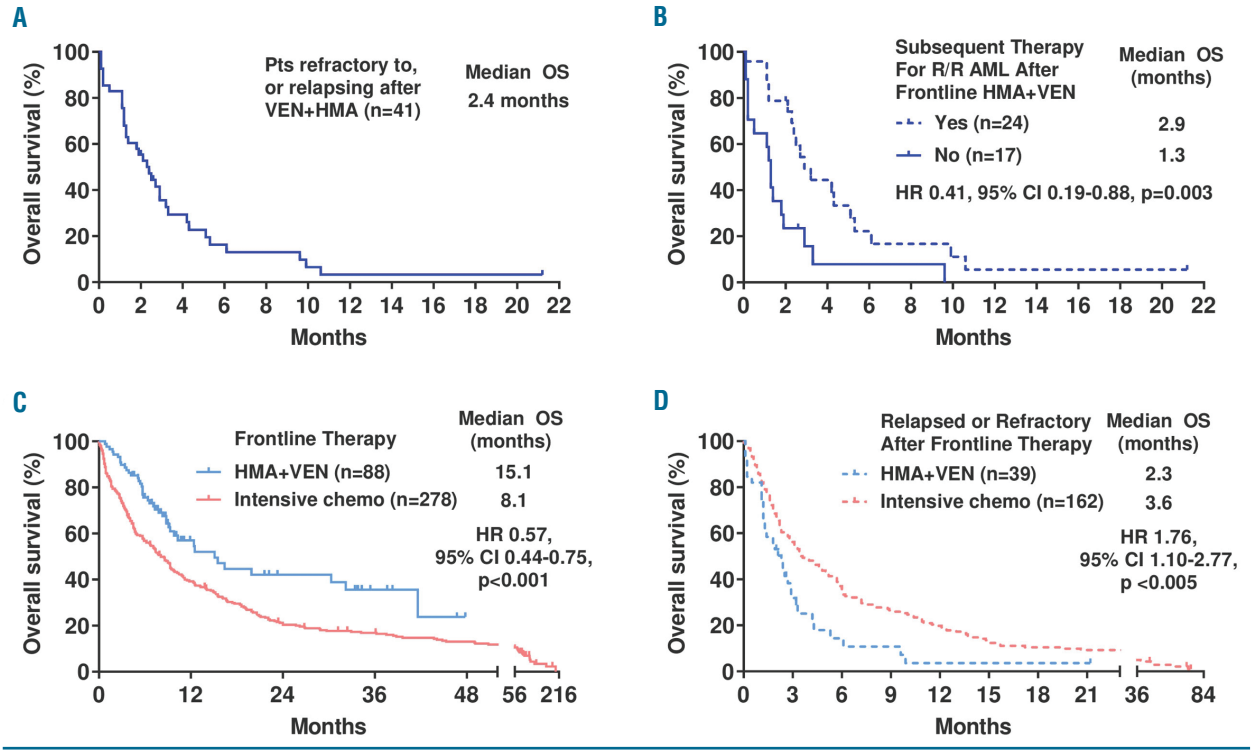

Figure 1. Overall survival (OS). (A) Patients (pts) with relapsed or refractory (R/R) acute myeloid leukemia (AML) following front-line venetoclax (VEN) and hypomethylating agent (HMA) regimens, (B) according to receipt of salvage therapy; (C) patients receiving front-line HMA and VEN compared to front-line intensive chemotherapy in a population matched for age and European LeukemiaNet 2017 cytogenetic risk status; (D) patients with R/R disease after front-line HMA and VEN *versus* intensive chemotherapy. n: number; HR: hazard ratio; CI: confidence interval.

front-line IC, VEN+HMA showed a significantly better CR/CRi rate of 87% compared to 59% with IC (odds ratio [OR] 3.29, 95%CI: 1.79-6.01; *P*=0.0001), lower rate of primary refractory disease of 8% *versus* 24% with IC (OR 0.32, 95%CI: 0.14-0.74; *P*<0.01), and a lower rate of relapse of 42% *versus* 58% with IC (OR 0.52, 95%CI: 0.30-0.90; *P*=0.02). Additionally, VEN+HMA conferred superior OS of 15.1 months compared to 8.1 months with IC (HR 0.57, 95%CI: 0.44-0.75; *P*<0.001) (Figure 1C). However, and of interest, patients who failed front-line VEN+HMA had shorter survival of 2.3 months compared to 3.6 months in patients failing front-line IC (HR 1.76, 95%CI: 1.10-2.77; *P*<0.005) (Figure 1D).

Median OS after relapse were comparable for patients who achieved CR *versus* those who achieved CRi with VEN+HMA (*Online Supplementary Figure S2*). Patients with primary refractory disease *versus* relapse had comparable OS of 1.7 *versus* 2.3 months, respectively (*Online Supplementary Figure S3*). Median OS for *de novo* AML at relapse/failure was 2.5 months, for sAML was 2.8 months, and for therapy-related (t-AML) was 1.1 months (*Online Supplementary Figure S4*). Out of the 24 patients who received salvage therapy (see *Online Supplementary Table S2* for regimens), five patients (21%) responded with CR (n=1), CRi (n=2), and MLFS (n=2). One patient underwent allogeneic stem-cell transplantation in second complete remission (CR2). Eight patients received IC, and 2 of 8 patients achieved CR and CRi with CLIA and CLIA with gemtuzumab ozogamicin, respectively. Both patients harbored *NRAS* mutations. Nine patients received non-intensive chemotherapy-based regimens, and 3 of 9 patients responded, including two patients with *FLT3*^{mut}, with CRi in one patient with azacitidine and quizartinib, and MLFS in two patients with azacitidine, nivolumab, ipilimumab, and low-dose cytarabine with quizartinib, respectively. These five responding patients (Figure 2 and *Online Supplementary Table S2*) continue in remission with median DOR not reached (NR) (range 0.7-20.1) and OS NR (range, 2-21.2).

The most frequently occurring mutations in this R/R population, at initial diagnosis, included *TP53, DNMT3A, N/KRAS, TET2*, and *ASXL1* (Figure 2). Twenty patients had 81-gene next-generation sequencing (NGS) panel results at diagnosis and at the time of R/R disease. The most frequent mutations gained at the time of R/R disease were mutations in signaling pathways (30%, *NF1, FLT3-ITD, NRAS, JAK1*), RNA splicing (30%, *U2AF1, U2AF2, SRSF2, ZRSR2*), transcription factors (30%, *IKZF1, SETBP1, RUNX1, STAT5A*), tumor suppressors (15% *TP53, WT1*), and epigenetic modifiers (10%, *BCOR, CREBBP*).

Among five patients with *FLT3*-ITD, two patients responded to salvage regimens containing a FLT3 inhibitor (Figure 2 and *Online Supplementary Table S3*). Out of ten patients with *K/NRAS* mutations receiving salvage therapy, three patients (30%) responded to IC (n=2) and HMA-based regimens (n=1). Of the five patients with *TP53*^{mut} receiving salvage therapy, one patient achieved MLFS with azacitidine, nivolumab and ipilimumab. This patient was also the only one among seven patients with complex karyotype who responded to salvage therapy.

These findings summarize the characteristics and poor outcomes of patients who develop R/R disease after front-line VEN+HMA therapy. These patients presented with high-risk biology including t-AML, sAML, complex karyotype, *FLT3-ITD*^{mut}, *TP53*^{mut}, and *N/KRAS*^{mut} at diagnosis and also evolved with treatment. Patients who

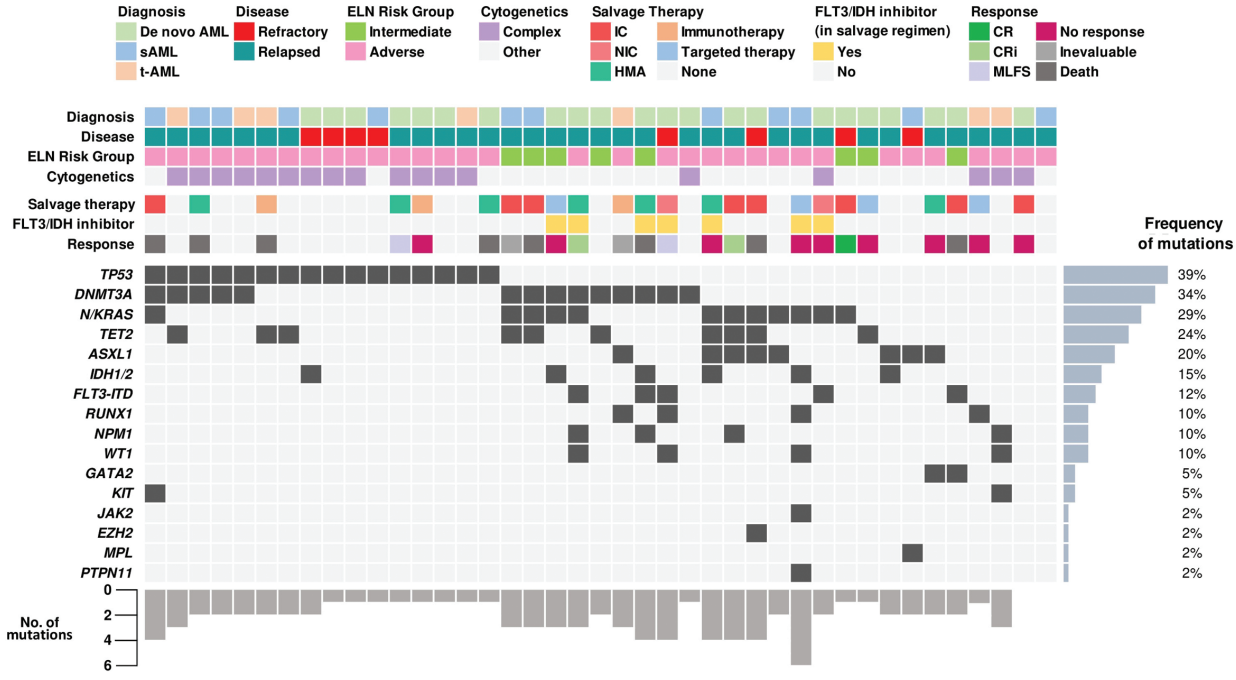

Figure 2. Landscape of mutations, salvage therapies, and responses in 41 patients with refractory disease or relapse after front-line venetoclax and hypomethylating agent (HMA). AML: acute myeloid leukemia; sAML: secondary AML; tAML: treatment-related AML; ELN: European LeukemiaNet; IC: intensive chemotherapy; NIC: non-intensive chemotherapy; CR: complete remission; CRi: incomplete hematologic recovery; MLFS: morphologica leukemia-free state.

were expected to have durable outcomes but relapsed, e.g., *NPM1*^{mut} and *IDH1/2*^{mut} patients, had adverse-risk cytogenetics or co-occurring mutations in *TP53, N/KRAS, FLT3*, and/or *KIT*. The particularly high incidence of aggressive biology in these R/R patients was the likely driving factor behind the poor outcomes seen after VEN+HMA failure. Patients with AML after failure of front-line HMA and no salvage therapy have a median OS of 2 months which was comparable to our report of 1.3 months.[9] However, for patients who receive salvage therapy, front-line VEN+HMA failure appears to confer a worse prognosis with median OS of 2.9 months compared to 9.5 months for patients after failure of front-line HMA.[9] We believe that incorporating FLT3 inhibitors in the front-line setting as triplets with VEN+HMA may further improve outcomes in older *FLT3*-mutant patients.[10,11] However, a sequential approach may be worth investigation in patients who achieve excellent response to induction therapy and are closely monitored by molecular methods.

Genomic analysis demonstrated a heterogeneous group of underlying genetic mechanisms of resistance to VEN+HMA. These findings add to the accumulating knowledge of venetoclax-resistance mechanisms including *N/KRAS*^{mut}, *PTPN11*^{mut}, dependence on other anti-apoptotic proteins, e.g., BCL-X_L, MCL1; *TP53*^{mut} and alterations in mitochondrial homeostasis.[12-15] These insights may provide new directions for biological understanding and drug development in populations that fail venetoclax and provide a rationale to test novel therapeutics such as spliceosome inhibitors, MCL1, MDM2, BET inhibitors, PRIMA1 analogs, and others in VEN-resistant models as potential ways to prevent or abrogate such resistance.[16-18]

This was a retrospective study with all the inherent limitations of such a design. Forty-two percent of patients could not or did not receive salvage therapy. The patients who were treated received a heterogeneous group of regimens. Based on the limited number of patients who received salvage therapy, it was unclear if any specific regimen was superior after front-line VEN+HMA failure, and hence these patients should ideally be treated on clinical trials. Patients progressing after IC may have had better functional status compared to patients progressing after VEN+HMA, and this could have contributed to the difference in OS after progression. However, age is one important determinant of 'fitness' and we matched all patients for age to minimize this imbalance in functional status due to age alone. Notably, some patients with *FLT3*-ITD responded well to salvage regimens with second-generation FLT3 inhibitors and *N/KRAS*^{mut} patients appeared to respond to IC. Additional work on dissecting the underlying biology in pre-clinical models and testing novel combinations in this setting is ongoing.[19]

In summary, VEN+HMA offers superior responses and survival in older patients with ND AML; however, patients who have R/R disease after front-line VEN+HMA display high-risk disease biology and particularly poor survival. In this era of venetoclax-based regimens increasingly being utilized as front-line AML therapy, this knowledge of outcomes after failure of VEN+HMA provides useful information to discuss with patients and highlights the urgent need for novel therapies to abrogate venetoclax resistance.

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