Ten-day Decitabine with Venetoclax vs. Intensive Chemotherapy in Relapsed or Refractory Acute Myeloid Leukemia: A Propensity Score Matched Analysis

Abhishek Maiti, MBBS[1], **Courtney D. DiNardo, MD, MSCE**[1], **Wei Qiao, PhD**[2], **Tapan M. Kadia, MD**[1], **Elias J. Jabbour, MD**[1], **Caitlin R. Rausch, PharmD**[3], **Naval G. Daver, MD**[1], **Nicholas J. Short, MD**[1], **Gautam Borthakur, MD**[1], **Naveen Pemmaraju, MD**[1], **Musa Yilmaz, MD**[1], **Yesid Alvarado, MD**[1], **Kathryn S. Montalbano, RN**[1], **Allison Wade, RN**[1], **Rita E. Maduike, RN**[1], **Julio A. Guerrero, RN**[1], **Kenneth Vaughan, RN**[1], **Carol A. Bivins, RN**[1], **Sherry Pierce, RN**[1], **Jing Ning, PhD**[2], **Farhad Ravandi, MD**[1], **Hagop M. Kantarjian, MD**[1], **Marina Y. Konopleva, MD, PhD.**[1]

[1.]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX;

[2.]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX.

[3.]Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX.

Abstract

Background: Relapsed/refractory (R/R) acute myeloid leukemia (AML) has poor outcomes. While lower-intensity venetoclax-containing regimens are standard for older/unfit patients with newly diagnosed AML, it is unknown how such regimens compare to intensive chemotherapy (IC) for R/R AML.

Methods: We compared outcomes of R/R AML treated with 10-day decitabine and venetoclax (DEC10-VEN) vs. IC-based regimens including idarubicin with cytarabine (IA), with or without cladribine (CLIA), clofarabine (CIA), or fludarabine (FIA or FLAG-IDA), with or without additional agents. Propensity scores derived from baseline characteristics of were used to match DEC10-VEN and IC patients to minimize bias.

Results: Sixty-five patients in DEC10-VEN cohort were matched to 130 IC recipients. The median age for DEC10-VEN and IC groups were 64 and 58 years, respectively, and baseline characteristics were balanced between the two cohorts. DEC10-VEN conferred significantly higher responses compared to IC including higher overall response rate (60% vs 36%, odds ratio [OR]= 3.28, p<.001), CRi (19% vs 6%, OR 3.56, p=.012), MRD-negative by flow cytometry (28% vs 13%, OR 2.48, p=.017) and lower rates of refractory disease. DEC10-VEN led to

Data sharing: Please contact the corresponding author with request for original patient level data.

significantly longer median event-free survival (EFS) compared to IC (5.7 vs 1.5 months, hazard ratio [HR]=0.46, 95%CI 0.30–0.70, p<.001) as well as median overall survival (OS, 6.8 vs 4.7 months, HR=0.56, 95%CI 0.37–0.86, p=.008). DEC10-VEN was independently associated with improved OS compared to IC in multivariate analysis. Exploratory analysis for OS in 27 subgroups showed that DEC10-VEN was comparable to IC as salvage therapy for R/R AML.

Conclusion: DEC10-VEN represents an appropriate salvage therapy and may offer better responses and survival compared to IC in adults with R/R AML.

Precis for use in Table of Contents

Ten-day decitabine with venetoclax (DEC10-VEN) offers potentially better outcomes compared to intensive chemotherapy for patients with relapsed or refractory acute myeloid leukemia. DEC10-VEN was associated with higher response rates, MRD-negativity and longer overall and event-free survival compared to intensive chemotherapy in R/R AML.

Keywords

venetoclax; decitabine; intensive chemotherapy; AML; relapsed; refractory

INTRODUCTION

Acute myeloid leukemia (AML) with intermediate or adverse risk features have poor outcomes and more than 30–60% patients experience either refractory disease or relapse.[1] Apart from AML with actionable mutations (e.g. *FLT3*, *IDH1/2*), there are no standard treatments for relapsed or refractory (R/R) AML and outcomes are poor with long-term survival of only 10–20%.[2,3] With disease progression or each subsequent therapy, including stem-cell transplantation (SCT), it often becomes challenging to continue intensive chemotherapy (IC) in such patients. Consequently, R/R AML remains to be a therapeutic challenge with urgent need for novel lower-intensity therapies.

In newly diagnosed patients, venetoclax-containing lower intensity regimens are the current standard of care for older or unfit patients with AML.[4,5] Venetoclax with hypomethylating agents (HMA) is potentially better than IC as frontline therapy for older patients including those who are eligible for IC.[6] Such venetoclax-based lower intensity regimens are potentially efficacious in younger patients as well and prospective trials in this population are currently ongoing. We reported the results of the first prospective trial of venetoclax with decitabine in patients with R/R AML who are older than 18 years.[7] However, it is unknown how such venetoclax and HMA regimens compare to IC for R/R AML.

Herein, we compared the outcomes of adult patients with R/R AML treated with 10-day decitabine and venetoclax (DEC10-VEN) on a phase 2 trial (NCT03404193) with outcomes of patients treated with IC.

METHODOLOGY

Patients and Treatment

The R/R cohort in the prospective phase 2 trial of DEC10-VEN enrolled adults older than 18 years with ECOG performance status (PS) of 3 or lower. Patients with ELN favorable risk cytogenetics or prior exposure to venetoclax were excluded. Patients received decitabine 20 mg/m^2 daily for 10 days every 4–6 weeks with venetoclax 400 mg daily or equivalent (with concomitant azole antifungals) for induction. Subsequently after achievement of a response, patients received decitabine for 5 days with daily venetoclax for consolidation. Patients received cytoreduction to WBC <10×10^9/L prior to starting. All patients received monitoring and prophylaxis for tumor lysis syndrome (TLS), and antimicrobial prophylaxis during neutropenia.[8]

Patients in the comparator IC cohort were older than 18 years with ECOG performance status of 3 or lower. Patients received salvage therapy with either IA, CLIA, CIA, FIA or FLAG-Ida-based regimens without venetoclax on prospective phase 1b/2 clinical trials or as standard of care (Table S1A). The IA-based regimen comprised of idarubicin 10–12 mg/m^2 IV on days 1–3 and cytarabine 1–2 g/m^2 IV on days 1–4. CLIA-based regimens comprised of cladribine 5 mg/m^2 IV on days 1–5, cytarabine 1–2 g/m^2 IV on days 1–5 and idarubicin 10 mg/m^2 IV on days 1–3. CIA-based regimens included clofarabine 15 mg/m^2 IV daily on days 1–5, idarubicin 10 mg/m^2 IV daily on days 1–3, and cytarabine 1 g/m^2 IV daily on days 1–5. FLAG-Ida or FIA-based regimens included fludarabine 30 mg/m^2 IV on D1–5, idarubicin 10 mg/m2 IV daily on days 1–3, and cytarabine 1–2 g/m^2 IV daily on days 1–5, with or without filgrastim 5 mcg/kg SC on days 1–7. Details of additional agents in overall population and matched population are mentioned in Table S1B and S1C.

Response Assessment and Outcomes

Responses were graded per the European LeukemiaNet 2017 guidelines.[9] Overall response rate (ORR) include complete remission (CR), CR with incomplete hematologic recovery (CRi) and morphologic leukemia-free state (MLFS). Response was established by the time of completion of up to two cycle of IC and up to four cycles of DEC10-VEN. Minimal residual disease was assessed in bone marrow specimens using multiparametric flow cytometry validated to a sensitivity level of 0.01–0.1%.[10] Adverse events were determined per the NCI Common Terminology Criteria for Adverse Events v4.0. Event-free survival (EFS) was defined for all patients and was measured from start of therapy to the date of primary refractory disease, or relapse from CR/CRi, or death from any cause; patients not known to have either of these events were censored at last follow-up. Overall survival (OS) was measured from start of therapy until death or censored at last follow-up. Relapse-free survival was measured from date of achievement of CR/CRi, until relapse, death or censored at last follow-up.

Statistical Analysis

Propensity score methods in retrospective studies attempt to approximate populations in randomized controlled trials. This is achieved by selecting for comparable patient characteristics by balancing specified co-variates between comparator groups using

propensity scores to reduce the potential for confounding or bias in estimating treatment effect in observational studies.[11] A propensity score is the probability that a given patient would receive a given treatment based on their clinical scenario, treating clinician, and care setting.[12] Propensity scores were calculated by logistic regression using baseline characteristics well recognized to be prognostic in the salvage setting including age, ECOG performance status, number of prior lines of therapies, primary refractory vs relapsed disease, CR1 duration, prior allogeneic stem-cell transplantation, ELN cytogenetic risk, *FLT3* and *TP53* mutation status.[13,14] Propensity score matching (PSM) with the nearest neighbor method was used to select the IC comparison group using a 1:2 matching with a caliper control of 0.3.[15,16]

Pairwise comparison of patient characteristics and outcomes were performed using the t-test or the Wilcoxon signed-rank test for continuous variables, and the McNemar's test for categorical variables or the Fischer's exact test for unpaired comparisons. The Kaplan-Meier method with stratified log-rank test were used to compare time-to-event variables. The Cox proportional-hazards model with stratification to account for matched pairs was used to estimate the hazard ratio between comparator groups. Univariate and multivariable Cox models were used in the unmatched population to evaluate the associations between patient characteristics and OS. Factors significant in the univariate models at significance level 0.1 were included in the multivariate model. Backward model selection was used to remove variables from the model until all remaining variables were statistically significant with p<0.05 while treatment effect variable was forced in the final multivariable model. SPSS 24 (IBM Corp., Armonk, NY), R Essentials for SPSS version 24, PSMATCHING3.03 package, and R version 3.2 (R Foundation, Vienna, Austria) were used for analysis.

RESULTS

Patients

Sixty-five out of 65 patients treated with DEC10-VEN were best matched to 130 out of 291 patients treated with IC (Fig. S1). The standardized mean differences of variables selected for PSM before and after matching was low (range, −0.04 to 0.23) suggesting significant reduction of bias between the two intervention groups (Table S2). Patients in DEC10-VEN cohort were treated between January 2018 and September 2020 while patients in IC cohort received treatment between June 2005 and July 2019. The median age of the DEC10-VEN cohort was 64 years (range 18–85) and for the IC cohort was 58 years (range 19–80) and baseline characteristics were well balanced between the two groups (Table 1). The median number of prior lines of therapy was similar in DEC10-VEN and IC cohorts at 2 (range 1–8) vs. 2 (range 1–10), respectively (p=.721). Details of regimens administered in the IC cohort are shown in Table S1C. In DEC10-VEN cohort, patients received a median of 2 cycles of therapy (range 1–16) and in IC cohort patients had received a median of 1 cycle of therapy (range 1–5). FLT3 inhibitors were used in 16 out of 16 patients treated with DEC10-VEN compared to 25 out of 34 patients treated with IC (p=.043). No patients in either group received IDH1/2 inhibitors.

Efficacy: Response Rates

Rates of overall response (ORR), CRi, MLFS and negative MRD by flow cytometry were significantly higher with DEC10-VEN compared to IC. ORR was achieved in 60% patients with DEC10-VEN vs 36% patients treated with IC, odds ratio [OR], 3.28, 95% confidence interval [CI] 1.73, 6.23, stratified test p<.001, (Table 2). CRi rates were 19% vs 6%, respectively, OR 3.56, 95% CI 1.32, 9.61, stratified test p=.012, rates of MLFS were 15% vs. 5%, respectively, OR 3.33, 95% CI 1.21, 9.17, stratified test p=.020, and MRD-negative rate was 28% vs 13%, respectively, OR 2.48, 95% CI 1.17, 5.24, stratified test p=.017. The rate of refractory disease was significantly lower with DEC10-VEN (35% vs 55%, OR 0.46, 95% CI 0.25, 0.84, stratified test p=.011). The median no. of cycles to best response in DEC10-VEN cohort was 1 (range 1–4) and in IC cohort was 1 (range 1–3).

Efficacy: Survival Outcomes

The median follow-up for the DEC10-VEN cohort was 17.5 months and for IC cohort was 49.3 months. The median EFS with DEC10-VEN was 5.7 months versus 1.5 months with IC (hazard ratio [HR] 0.46, 95% CI 0.30, 0.70, stratified test p<.001, Fig. 1a). The median OS with DEC10-VEN was 6.8 months compared to 4.7 months with IC (HR 0.56, 95% CI 0.37, 0.86, stratified test p=.008, Fig. 1b). Relapse-free survival was similar with DEC10-VEN and IC (8.4 vs 8.4 months, HR 1.103, 95% CI 0.59, 2.07, p=.743, Fig. S2). Fifteen patients (23%) in the DEC10-VEN cohort and 21 patients (16%) in the matched IC cohort received SCT after achievement of a response (p=.247). The median OS after SCT was numerically higher in DEC10-VEN vs IC cohorts (18.7 vs 12.9 months, HR 1.11, 95% CI 0.44, 2.84, p=.813, Fig. S3).

Exploratory subgroup analyses for OS in unmatched cohorts showed that DEC10-VEN was comparable to IC across most subgroups of age, diagnosis, cytogenetic risk, line of salvage therapy, type of previous therapy, and major mutational subgroups (Fig. 1c). Although 95% CI were wide, the HRs marginally favored DEC10-VEN in most subgroups and the benefit was significant in patients with CR1 duration of more than 6 months and patients with antecedent hematological disorder. In patients with CR1 duration more than 6 months, the median OS with DEC10-VEN was 21.8 months (n=13) compared to 6.5 months with IC (n=76, HR 0.52, 95% CI 0.28, 0.96, p=.023). In patients with antecedent hematological disorder, the median OS with DEC10-VEN was 6.7 months (n=11) compared to 3.5 months with IC (n=56, HR 0.42, 95% CI 0.23, 0.76, p=.017). Patients with $FLT3^{mut}$ AML treated with DEC10-VEN and FLT3 inhibitor (n=16) versus IC with FLT3 inhibitor (n=48) had comparable OS (6.4 months vs 7.0 months, HR 0.83, 95% CI 0.44, 1.58, p=0.587).

Multivariate analysis for OS in unmatched population showed that DEC10-VEN was independently associated with significant improvement in OS (HR 0.66, 95% CI 0.48, 0.92, p=.012; Table S3) and *IDH1/2* mutation was associated with a lower risk of death (HR 0.70, 95% CI, 0.51, 0.97, p=.029). There was higher risk of death in patients with an antecedent hematological disorder (HR 1.84, 95% CI 1.35, 2.51, p<.001), ELN adverse risk cytogenetics (HR 1.57 95% CI 1.21, 2.03, p<.001), *TP53* mutation (HR 1.71, 95% CI 1.25, 2.34, p<.001), and failure two or more lines of therapy. Overall survival was comparable among patients who achieved CR or CR/CRi with DEC10-VEN or IC (Fig. S4, S5)

Safety

The 60-day mortality was 12% (n=8) with DEC10-VEN compared to 27% (n=35) with IC (OR 0.40, 95% CI 0.18, 0.91, stratified test p=.029). Prospectively collected adverse event data was available for all patients in DEC10-VEN cohort compared to 28 patients (22%) in IC cohort. Non-hematologic grade 3/4 treatment-emergent adverse events (TEAE), at least possible related to study regimen, occurred in 21 (75%) of 28 patients receiving IC and 45 (69%) of 65 patients receiving DEC10-VEN (p=.628, Table 3). Grade 3/4 infectious AEs occurred in 25 out of 65 (38%) patients in DEC10-VEN cohort compared to 5 out of 28 (18%) patients in IC (p=.057). Febrile neutropenia was noted in 20 patients (30%) in DEC10-VEN cohort compared to 14 patients (50%) in IC cohort (p=.101).

DISCUSSION

Heterogeneous biology in R/R AML without actionable mutations make it a challenging disease for drug development and only modest progress has been made in the last several decades. While IC has been the mainstay so far, declining functional status in R/R AML and treatment-related toxicities are considerable barriers to treatment and limit the testing of novel agents due to risk of additive toxicity. Venetoclax-based lower intensity regimens have been a paradigm shifting development in the field owing to modest end-organ toxicity apart from myelosuppression and resultant infections. This has enabled treatment delivery in frail patients who otherwise would not have tolerated intensive therapies and have accelerated the development of rational combination therapies in AML.

Our retrospective comparison shows that DEC10-VEN is an appropriate option for venetoclax-naïve patients with R/R AML. In a population with a median of 2 prior lines of therapy and majority with adverse risk AML, DEC10-VEN showed significantly higher ORR, rate of CRi, MRD-negativity, lower rates of 60-day mortality, refractory disease and significantly longer EFS and OS. The OS benefit noted was further confirmed on multivariate analysis. While OS was only modestly improved compared to IC, it was encouraging to note that the despite potential confounders, the HRs across most subgroups favored DEC10-VEN over IC. In particular, the trend noted in patients with antecedent hematological disorder, CR1 duration longer than 6 months and *RUNX1* mutations was encouraging. It is possible that the improvement in OS may have been due to patients surviving with MLFS. Although significantly more patients achieved MLFS compared to IC, it did not translate into significantly higher number of patients transitioning to SCT in the DEC10-VEN cohort. However, attaining MLFS does provide the opportunity to take such patients to transplant as suboptimal responders can still experience OS benefit with SCT even in the absence of full count recovery.[17] While our safety analysis focused on non-hematologic toxicity, some CRi and MLFS responses noted with DEC10-VEN can be potentially related to venetoclax-induced myelosuppression.

Based on these results we have initiated two phase II trials of oral regimens of 10-day and 5-day decitabine/cedazuridine (ASTX727) with venetoclax for R/R AML (NCT04746235), however, prospective randomized studies are needed to confirm these findings. Ongoing evaluation of venetoclax with FLAG-IDA (NCT03214562), CPX-351 (NCT03629171), and CLIA (NCT02115295) have shown promising early results and will help determine the

optimal backbone for venetoclax in R/R AML.[18,19] However, for patients with multiply R/R AML with poor PS who are venetoclax-naïve and ineligible for intensive therapy, DEC10-VEN maybe a potential salvage option.

This was a retrospective study with all inherent limitations. However, propensity score matching for important effect modifiers and treatment in prospective clinical trials helped to minimize such bias, as noted from the low standardized mean differences after matching and similar baseline characteristics in the cohorts. Although propensity score matching can balance important effect modifiers, there could have still been other factors which influenced the differences observed. While many other baseline characteristics and comorbidities could have influenced findings in our multivariable analysis, retrospective nature of this study and some missing data precluded inclusion of those factors. We had limited patients in the DEC10-VEN cohort for exploratory subgroup analysis which resulted in large confidence intervals decreasing the precision of our findings. All these trials were single-center studies and outcomes maybe have been different in other institutions or the community, particularly with other common regimens like MEC, CLAG, etc. Provision of two more cycles of treatment for responses assessment with DEC10-VEN compared to IC introduced the potential for immortal time bias in our analysis. However, retrospective results of venetoclax with HMA in R/R AML have shown identical to better outcomes supporting reproducibility of our findings.[20] Overall, these results raise new questions and warrant validation in larger studies.

In conclusion, this retrospective analysis suggests that DEC10-VEN may be considered as a potential salvage option offering outcomes comparable to non-venetoclax based IC in patients with R/R AML who have not received venetoclax before. The high ORR, rates of CRi, MLFS, MRD-negativity, better OS, EFS, and low-intensity nature makes this regimen a potential option as a bridge to SCT, and as a reasonable choice for a low-intensity backbone for adding novel therapies in the salvage setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

Financial disclosures:

References

1. Herold T, Rothenberg-Thurley M, Grunwald VV, et al. Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia 2020;1–12.

2. Roboz GJ, Rosenblat T, Arellano M, et al. International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. J Clin Oncol 2014;32(18).

3. Bose P, Vachhani P, Cortes JE. Treatment of Relapsed/Refractory Acute Myeloid Leukemia. Curr Treat Options Oncol 2017;18(3):17. [PubMed: 28286924]

4. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 2020;383(7):617–29. [PubMed: 32786187]

5. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood 2020;135(24):2137–45. [PubMed: 32219442]

6. Maiti A, Qiao W, Sasaki K, et al. Venetoclax with decitabine vs intensive chemotherapy in acute myeloid leukemia: A propensity score matched analysis stratified by risk of treatment-related mortality. Am J Hematol 2021;96(3):282–91. [PubMed: 33264443]

7. DiNardo CD, Maiti A, Rausch CR, et al. 10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial. Lancet Haematol 2020;7:e724–36. [PubMed: 32896301]

8. DiNardo CD, Maiti A, Rausch CR, et al. 10-day Decitabine with Venetoclax in Acute Myeloid Leukemia: A Single-center Phase 2 Trial. Lancet Haematol 2020;In press.

9. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424–47. [PubMed: 27895058]

10. Short NJ, Ravandi F. How close are we to incorporating measurable residual disease into clinical practice for acute myeloid leukemia? Haematologica 2019;104(8):1532–41. [PubMed: 31273094]

11. Haukoos JS, Lewis RJ. The Propensity Score. JAMA 2015;314(15):1637–8. [PubMed: 26501539]

12. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70(1):41–55.

13. Breems DA, Van Putten WLJ, Huijgens PC, et al. Prognostic Index for Adult Patients With Acute Myeloid Leukemia in First Relapse. J Clin Oncol 2005;23(9):1969–78. [PubMed: 15632409]

14. Schlenk RF, Müller-Tidow C, Benner A, Kieser M. Relapsed/refractory acute myeloid leukemia: any progress? Curr Opin Oncol 2017;29(6):467–73. [PubMed: 28857842]

15. Thomas L, Li F, Pencina M. Using Propensity Score Methods to Create Target Populations in Observational Clinical Research. JAMA 2020;323(5):466–7. [PubMed: 31922529]

16. Rubin DB. Using Propensity Scores to Help Design Observational Studies: Application to the Tobacco Litigation. Health Serv Outcomes Res Methodol 2001;2(3):169–88.

17. Short NJ, Rafei H, Daver N, et al. Prognostic impact of complete remission with MRD negativity in patients with relapsed or refractory AML. Blood Adv 2020;4(24):6117–26. [PubMed: 33351107]

18. Aboudalle I, Konopleva MY, Kadia TM, et al. A Phase Ib/II Study of the BCL-2 Inhibitor Venetoclax in Combination with Standard Intensive AML Induction/Consolidation Therapy with FLAG-IDA in Patients with Newly Diagnosed or Relapsed/Refractory AML. Blood 2019;134(Supplement_1):176–176.

19. Kadia TM, Garcia-Manero G, Yilmaz M, et al. Venetoclax (Ven) added to intensive chemo with cladribine, idarubicin, and AraC (CLIA) achieves high rates of durable complete remission with low rates of measurable residual disease (MRD) in pts with newly diagnosed acute myeloid leukemia (AML). J Clin Oncol 2020;38(15_suppl):7539–7539.

20. Bewersdorf JP, Giri S, Wang R, et al. Venetoclax as monotherapy and in combination with hypomethylating agents or low dose cytarabine in relapsed and treatment refractory acute myeloid leukemia: a systematic review and meta-analysis. Haem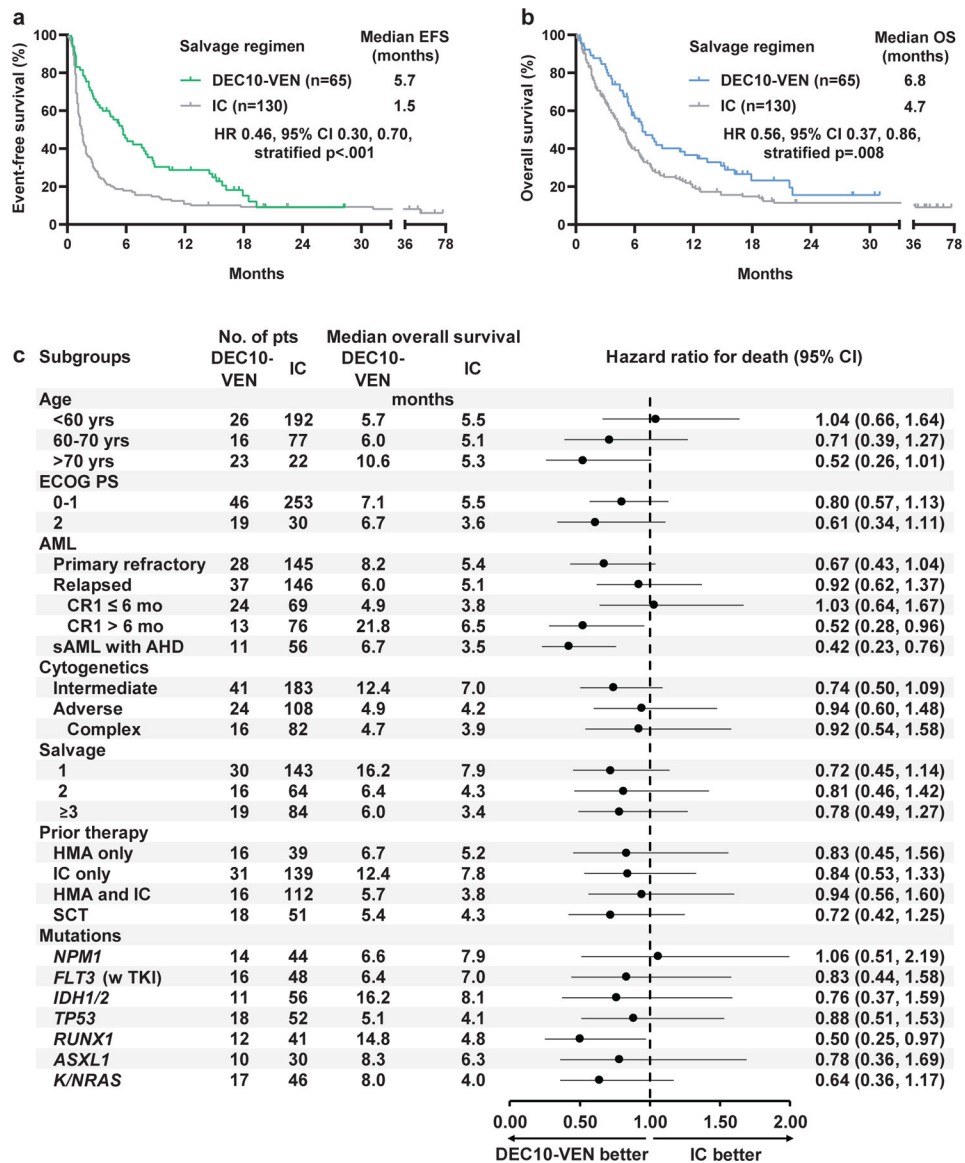atologica [Internet] 2020 [cited 2020 Jul 8];Available from: http://www.haematologica.org/content/early/2020/01/21/haematol.2019.242826

a. Event-free survival (%) vs Months. Salvage regimen — DEC10-VEN (n=65), IC (n=130). Median EFS (months): DEC10-VEN 5.7, IC 1.5. HR 0.46, 95% CI 0.30, 0.70, stratified p<.001

b. Overall survival (%) vs Months. Salvage regimen — DEC10-VEN (n=65), IC (n=130). Median OS (months): DEC10-VEN 6.8, IC 4.7. HR 0.56, 95% CI 0.37, 0.86, stratified p=.008

c.

Subgroups	No. of pts DEC10-VEN	IC	Median overall survival DEC10-VEN	IC	Hazard ratio for death (95% CI)
			months		
Age					
<60 yrs	26	192	5.7	5.5	1.04 (0.66, 1.64)
60-70 yrs	16	77	6.0	5.1	0.71 (0.39, 1.27)
>70 yrs	23	22	10.6	5.3	0.52 (0.26, 1.01)
ECOG PS					
0-1	46	253	7.1	5.5	0.80 (0.57, 1.13)
2	19	30	6.7	3.6	0.61 (0.34, 1.11)
AML					
Primary refractory	28	145	8.2	5.4	0.67 (0.43, 1.04)
Relapsed	37	146	6.0	5.1	0.92 (0.62, 1.37)
CR1 ≤ 6 mo	24	69	4.9	3.8	1.03 (0.64, 1.67)
CR1 > 6 mo	13	76	21.8	6.5	0.52 (0.28, 0.96)
sAML with AHD	11	56	6.7	3.5	0.42 (0.23, 0.76)
Cytogenetics					
Intermediate	41	183	12.4	7.0	0.74 (0.50, 1.09)
Adverse	24	108	4.9	4.2	0.94 (0.60, 1.48)
Complex	16	82	4.7	3.9	0.92 (0.54, 1.58)
Salvage					
1	30	143	16.2	7.9	0.72 (0.45, 1.14)
2	16	64	6.4	4.3	0.81 (0.46, 1.42)
≥3	19	84	6.0	3.4	0.78 (0.49, 1.27)
Prior therapy					
HMA only	16	39	6.7	5.2	0.83 (0.45, 1.56)
IC only	31	139	12.4	7.8	0.84 (0.53, 1.33)
HMA and IC	16	112	5.7	3.8	0.94 (0.56, 1.60)
SCT	18	51	5.4	4.3	0.72 (0.42, 1.25)
Mutations					
NPM1	14	44	6.6	7.9	1.06 (0.51, 2.19)
FLT3 (w TKI)	16	48	6.4	7.0	0.83 (0.44, 1.58)
IDH1/2	11	56	16.2	8.1	0.76 (0.37, 1.59)
TP53	18	52	5.1	4.1	0.88 (0.51, 1.53)
RUNX1	12	41	14.8	4.8	0.50 (0.25, 0.97)
ASXL1	10	30	8.3	6.3	0.78 (0.36, 1.69)
K/NRAS	17	46	8.0	4.0	0.64 (0.36, 1.17)

0.00   0.50   1.00   1.50   2.00
DEC10-VEN better   IC better

Fig. 1.

a. Event-free survival (EFS), and **b.** Overall survival (OS) in patients with relapsed or refractory acute myeloid leukemia who received salvage therapy with 10-day decitabine with venetoclax (DEC10-VEN) versus intensive chemotherapy (IC); **c.** exploratory subgroup analysis for OS in unmatched populations.

The dotted line represents hazard ratio of 1.00. Only patients receiving FLT3 inhibitors were chosen for the subgroup analysis comparing outcomes in *FLT3*[mut] AML. All 16 patients treated with DEC10-VEN received FLT3 inhibitor including gilteritinib (n=7), sorafenib (n=6), midostaurin (n=3); and all 48 selected patients treated with intensive chemotherapy received FLT3 inhibitor including sorafenib (n=33), crenolanib (n=10), gilteritinib (n=2), midostaurin (n=2), and ponatinib (n=1). ECOG PS = Eastern Co-operative Oncology Group

performance status, sAML = secondary AML, AHD = antecedent hematological disorder, HMA = hypomethylating agent, SCT = allogeneic stem-cell transplantation.

Table 1.

Baseline characteristics of matched patients with relapsed or refractory acute myeloid leukemia who received 10-day decitabine with venetoclax (DEC10-VEN), and intensive chemotherapy (IC)

Patient characteristics	DEC10-VEN (N=65)	IC (N=130)	p
Age, years	64 [18–85]	58 [19–80]	.113
<60 years	26 (40)	74 (57)	.038
Male sex	39 (60)	72 (55)	.539
AML type			
Primary refractory AML	28 (43)	54 (42)	.837
Relapsed AML	37 (57)	76 (58)	.891
Secondary AML from AHD	11 (17)	21 (16)	
ECOG performance status			
0–1	46 (71)	95 (73)	.734
2	19 (29)	35 (27)	
Bone marrow blasts, %	34 [1–96]	35 [0–98]	.536
ELN 2017 cytogenetic group			
Favorable	0 (0)	0 (0)	.958
Intermediate	41 (63)	80 (62)	
Adverse	24 (37)	50 (38)	
Mutations			
NPM1	14 (22)	15 (12)	.605
FLT3-ITD/TKD	16 (25)	34 (26)	
IDH1/2	11 (17)	28 (22)	
TP53	18 (28)	32 (25)	
RUNX1	12 (18)	22 (17)[1]	
ASXL1	10 (15)	14 (11)[1]	
ELN 2017 risk group			
Favorable	10 (15)	11 (8)	.302
Intermediate	12 (18)	30 (23)	
Adverse	43 (66)	89 (68)	
No. of prior therapies	2 [1–8]	2 [1–10]	.721
Prior therapies			
HMA only	16 (25)	24 (18)	.214
IC only	31 (48)	53 (41)	
IC and HMA	16 (25)	53 (41)	
SCT	18 (28)	36 (28)	

Results reported as n (%), or median [range]. AHD = antecedent hematological disorder, ELN = European LeukemiaNet. IC = intensive chemotherapy, HMA = hypomethylating agent, SCT = allogeneic stem cell transplantation.

[1] RUNX1 and ASXL1 status was unknown for 9 patients.

Table 2.

Outcomes of propensity of matched patients with relapsed or refractory acute myeloid leukemia who received 10-day decitabine with venetoclax (DEC10-VEN), and intensive chemotherapy (IC)

Outcomes	DEC10-VEN (N=65)	IC (N=130)	OR / HR (95% CI)	Stratified p
Overall response rate (ORR)	37 (60)	36 (28)	3.28 (1.73, 6.23)	**<.001**
CR/CRi	27 (42)	30 (23)	2.52 (1.26, 5.03)	**.009**
CR	15 (23)	22 (17)	1.44 (0.70, 2.94)	.320
CRi	12 (19)	8 (6)	3.56 (1.32, 9.61)	**.012**
MLFS	10 (15)	6 (5)	3.33 (1.21, 9.17)	**.020**
MRD negativity	18 (28)	17 (13)	2.48 (1.17, 5.24)	**.017**
Refractory	22 (35)	71 (55)	0.46 (0.25, 0.84)	**.011**
Inevaluable [1]	1 (2)	1 (1)	2.00 (0.13, 31.98)	.624
Relapse	19 (51)	17 (47)	0.75 (0.24, 2.38)	.630
30-day mortality	5 (8)	16 (12)	0.58 (0.2, 1.70)	.322
60-day mortality	8 (12)	35 (27)	0.40 (0.18, 0.91)	**.029**

Results reported as n (%), n/N (%). ORR = CR+CRi+MLFS, CR = complete remission; CRi = CR with incomplete hematologic recovery, MLFS = morphologic leukemia-free state. MRD = minimal residual disease evaluated using multiparametric flow cytometry validated to a sensitivity level of 0.1–0.01%; OR = odds ratio; HR = hazard ratio, NA= not applicable,

[1]. One patient was taken off DEC10-VEN after receiving only 2 days of therapy and another patient was taken off IC after 1 day off therapy due to adverse event

Table 3.

Adverse events in propensity score matched patients with relapsed or refractory acute myeloid leukemia who received 10-day decitabine with venetoclax (DEC10-VEN) versus intensive chemotherapy (IC).

Event	DEC10-VEN (n=65)		IC (n=28)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Infection with ANC $<1.0 \times 10^9$/L	25 (38)	25 (38)	6 (21)	5 (17)
Febrile neutropenia	20 (30)	20 (30)	14 (50)	14 (50)
Infection with ANC $>1.0 \times 10^9$/L	14 (21)	11 (16)	3 (10)	3 (10)
Mucositis	4 (6)	..	4 (14)	1 (3)
Hyperbilirubinemia	3 (4)	3 (4)	8 (28)	2 (7)
Nausea	3 (4)	..	1 (3)	.
Tumor lysis syndrome	3 (4)	1 (1)	1 (3)	1 (3)
Constipation	2 (3)	..	..	.
Renal Failure	2 (3)	2 (3)	..	.
Pain	1 (1)	1 (1)	4 (14)	2 (7)
Hypokalemia	1 (1)	..	..	.
Vomiting	1 (1)	..	..	.
ALT/AST elevation	..	..	10 (35)	1 (3)
Hemorrhage	..	..	4 (14)	3 (10)
Rash	..	..	4 (14)	..
Creatinine elevation	..	..	3 (10)	..
Altered mental status	..	..	1 (3)	1 (3)
Cardiac arrhythmia	..	..	1 (3)	..
Cholecystitis	..	..	1 (3)	1 (3)
Dyspnea	..	..	1 (3)	1 (3)
Hypoxia	..	..	1 (3)	1 (3)
Pruritus	..	..	1 (3)	..

ANC = absolute neutrophil count, ALT = alanine aminotransferase, AST = aspartate aminotransferase CNS = central nervous system.