REAL WORLD USE OF AZACITIDINE AND VENETOCLAX IN ACUTE MYELOID LEUKEMIA IN FRONTLINE AND RELAPSE/REFRACTORY SETTINGS : A MULTICENTRIC STUDY FROM FRENCH AURAML GROUP

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INTRODUCTION

Azacytidine and venetoclax combination regimen (AZA/VEN) is now the standard of care in acute myeloid leukemia (AML) settings for unfit to intensive chemotherapy patients [1]. However, AZA/VEN is also associated with an increased hematological toxicity compared to azacytidine alone. In this context, alternative AZA/VEN regimens emerged progressively based on each physician experience and local procedures. Moreover, AZA/VEN is now recognized as a valuable therapeutic option in relapse/refractory settings, even if no prospective trials addressed this question.

AIM

In this multicentric study, we aimed to evaluate the efficacy and safety of various AZA/VEN regimen in frontline AML patients in real life setting.

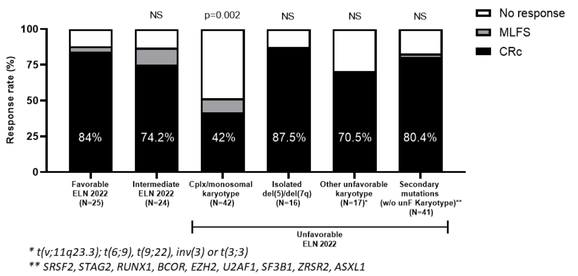
METHOD

- We retrospectively analyzed 331 patients from 11 different French centers (Saint-Etienne, Clermont-Ferrand, Lyon (Hopital Lyon Sud, Centre Léon Bérard), Vichy, Annecy, Chambery, Valence, Bourgoin-Jallieu, Grenoble, Roanne) in Auvergne Rhône Alpes (AURA) region, between January 2019 and February 2023.
- Overall, the entire cohort was composed of 186 patients in frontline settings
- Composite complete remission was defined as in VIALE-A trial [1].
- Measurable residual disease (MRD) negativity was defined as ≤ 10-3 by flow cytometry (on bone marrow) and/or ≤ 10-4 for NPM1 by RT-qPCR.

RESULTS

- Median age was 74.5 (19.1-86.1) and ELN 2022 risk groups were favorable, intermediate and unfavorable in 14.5, 16.7 and 68.8% respectively.
- *De novo* AML, MRC-AML, post-MPN/MDS AML and t-AML were 32.4%, 29.7%, 23.2% and 14.5% respectively. Median CRc rates are reported in **figure 1**. Venetoclax dosage (400mg vs 100mg/d) and duration per cycle (28 days vs 21 days vs others) did not influence significantly CRc rate probability and OS.
- With a median follow-up of 7.3 months, median overall survival (OS) was 12.4 months (IC95%: 3.4-18.5). ELN 2022 risk group classification did not influence OS (**figure 2**).
- In responding patients (CRc/MLFS), 22/122 withdrew VEN while continuing AZA, mainly due to excessive hematological toxicity. Relapse free survival was similar between patients who stopped compared to those who continued up to progression (**Figure 3**)
- Variables influencing OS in multivariate analysis are summarized in **figure 4**.

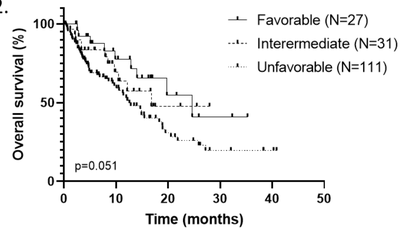
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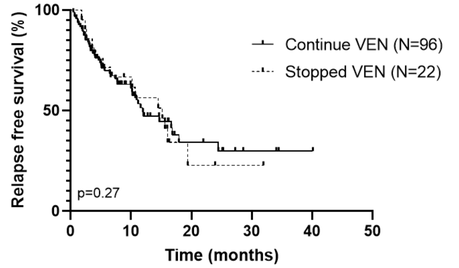
* t(v;11q23.3); t(6;9), t(9;22), inv(3) or t(3;3)

** SRSF2, STAG2, RUNX1, BCOR, EZH2, U2AF1, SF3B1, ZRSR2, ASXL1

2.



3.



4.

Variables	Comparison	HR	CI95_low	CI95_high	Adj_P.Value
ECOG	Continuous	1.6	1.13	2.28	0.048
Leucocytes	Continuous	1.01	1	1.02	0.206
Platelets	Continuous	1	1	1	0.870
LDH	Continuous	1	1	1	0.870
Normal karyotype	Yes_vs_No	0.29	0.1	0.79	0.048
Unfavorable karyotype	Yes_vs_No	2.19	0.94	5.09	0.152
IDH1/2 mutation	WT_vs_MUT	3.1	1.25	7.67	0.048
ELN_2022	FAV_vs_DEF	1.46	0.45	4.77	0.686
	INT_vs_DEF	2.56	0.84	7.86	0.180

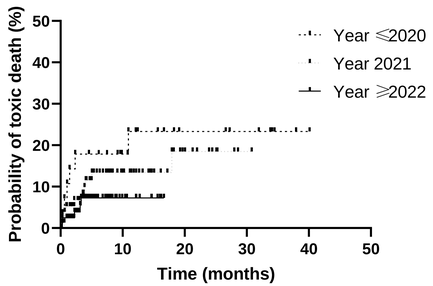


Figure 5 : cumulative incidence of toxic death (toxic death rate (TDR). Patients are censored at the time of last follow-up if they are alive or in case of non-toxic related death.

CONCLUSIONS

- In this real life settings study, our results suggest that outcome in frontline AZA/VEN treated patients is mainly driven by unfavorable cytogenetics.
- Alternative AZA/VEN regimens were not associated with lower response rate and overall survival, while reducing venetoclax exposure during cycle 1 may reduce FN incidence without significant consequences on CR rate.
- TDR reduction through time suggest a learning curve and might be related to physician's skills improvement regarding AZA/VEN dosage schedules and supportive care management. .

REFERENCES

1. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Eng J Med 2020; 383(7):617-629.

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