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Acute Leukemias

DISCONTINUATION OF VENETOCLAX-BASED THERAPIES IN MOLECULARLY SELECTED PATIENTS WITH ACUTE MYELOID LEUKEMIA IN COMPLETE REMISSION

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Introduction: Venetoclax (VEN) in combination with hypomethylating agents (HMAs) has been established as the standard of care for older or unfit patients (pts) with newly diagnosed acute myeloid leukemia (AML). This regimen is also increasingly used in the relapsed/refractory (R/R) setting. In the VIALE-A study, treatment was given until progression. However, the optimal duration of therapy in pts achieving a complete response remains undefined, and treatment discontinuation in such cases is an emerging area of interest in clinical practice. Recent retrospective studies have begun to explore the outcomes of VEN discontinuation in pts in sustained remission, suggesting that treatment-free remission (TFR) may be feasible in selected cases (*Chua et al Blood Adv. 2022; Garciaz et al Am J Hematol. 2024*). Furthermore, specific molecular profiles predictive of response to VEN-based regimens are increasingly recognized and may help identify pts eligible for safe treatment discontinuation, paving the way for more personalized, time-limited treatment strategies.

Methods: We report a retrospective analysis of 10 consecutive AML pts treated with VEN + HMAs at the AOU Careggi Centre of Florence. All pts achieved MRD^{neg} CR and subsequently discontinued VEN-based therapy due to toxicity, comorbidities or pts preference.

Results: Nine patients received VEN in combination with azacitidine, one with decitabine. Median age was 78.5 years (range 56-85 years). Nine pts received VEN based treatment as frontline therapy, 1 pt was treated in the R/R setting. Treatment discontinuation occurred for treatment-related toxicity despite dose reductions (20%), comorbidities requiring treatment (30%) and pts preference (50%). The median number of cycles prior to discontinuation was 21.5 (range 2-29). ELN 2024 risk stratification of pts was favorable (80%), intermediate (10%) or not available (10%). Molecular profiling showed *NPM1* mutations in 3 pts and *IDH1/2* mutations in 6 pts; mutations involving signaling pathways—*FLT3*-ITD and *NRAS*, which are generally associated with poorer outcomes with VEN-based therapy—were detected in only 1 pts. Notably, they occurred in a pt who also carried *NPM1* and *IDH1/2* mutations. Eight pts (80%) maintained MRD^{neg} CR following treatment discontinuation over a median follow-up period of 19.5 months. Two pts (20%) experienced MRD relapse, assessed by molecular (n=1) or flow cytometry(n=1) techniques; one harbored inv(16) and one had MDS-related mutations, without *NPM1* or *IDH1/2*. Both resumed VEN-based treatment and achieved a second MRD^{neg} CR. The median duration of TFR was not reached. All pts are alive at the time of this analysis, except one who died due to a concomitant neoplasm while still in CR.

Conclusions: Our single-center experience on a series of AML pts having discontinued VEN-based therapy for several reasons allows some consideration in this setting. Although the number of relapses observed was limited, all relapsing pts achieved a second CR following the reintroduction of VEN. This small case series suggests that treatment discontinuation followed by close MRD monitoring allows for timely reintroduction of therapy in case of relapse. Prospective studies are warranted to define molecular and clinical criteria for guiding safe discontinuation.

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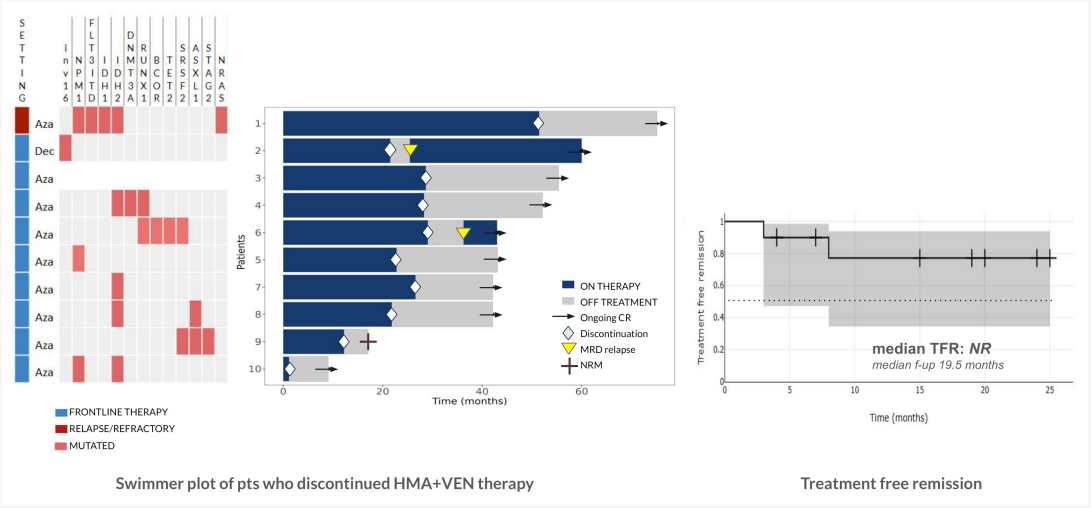

Swimmer plot of pts who discontinued HMA+VEN therapy

Treatment free remission