



To rechallenge or not to rechallenge, that is the question? An unsuccessful attempt of hypomethylating agent plus venetoclax in an elderly FLT3-positive relapsed acute myeloid leukemia patient after a yearlong period of remission

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Dear Editor,

Acute myeloid leukemia is the most common sub-type of acute leukemia in adulthood [1]. It has a detrimental prognosis with conventional combination chemotherapy, mainly with anthracyclines and cytarabine. Allogeneic stem cell transplantation has significantly prolonged the overall survival in a particular “eligible” patient population, but as AML is a disorder of the elderly, not all patients are able to proceed with allogeneic stem cell transplantation [1–3].

Recent advances made it possible to obtain prolonged deep responses even in elderly and/or unfit patients. One of those advances is to combine venetoclax (Ven) with a hypomethylating agent (HMA) or subcutaneous cytarabine [4]. With this kind of lower intensity therapy, more than 80% of newly diagnosed AML patients were able to achieve a remission [5, 6]. There is still paucity in the data regarding the optimal schedule of Ven and optimal dose and schedule of hypomethylating agents and even the optimal duration of the therapy. This kind of lower intensity combination of Ven and HMAs or sc. cytosine arabinoside (ARA-C) is continued until disease progression or unmanageable side effects. Another open question is the efficacy of re-challenge with this combination after a certain period of time of drug interruption.

There are reports indicating successful restoration of a morphological bone marrow remission after re-challenge, but those cases are anecdotal. In this case report, we wanted to share an Fms-tyrosine kinase-internal tandem duplication (FLT3-ITD)-positive AML case of ours who responded well to HMA plus Ven but eventually relapsed after a short while of drug interruption due to a COVID-19 infection and failed to respond a re-challenge with HMA plus Ven.

A 75-year-old male presented with shortness of breath and palpitations. He was febrile with a body temperature of 38.4 °C. His complete blood count revealed a leukocytosis with a white blood cell (WBC) count of 216,000/μL; he also suffered from an accompanying anemia (Hb: 9.8 g/dL) and thrombocytopenia (76,000/μL). He was diagnosed with an uncontrolled type 2 diabetes for at least 10 years and was on oral antidiabetics. Physical examination revealed crackles all over the lungs and a painful diabetic ulcer just at the perimalleolar region of the left foot. His peripheral smear showed the abundance of immature myeloid cells, and the bone marrow biopsy and flow cytometry ascertained acute myeloid leukemia. He rapidly put on to a short course of hydroxyurea 4 g/day and switched to intravenous azacitidine (AZA) 75 mg/m² and Ven 100 (day1), 200 (day2), and 400 mg po thereafter. The next generation sequencing (NGS) panel of bone marrow aspiration documented the presence of FLT3-ITD mutation (Variant allele frequency (VAF): 47%), NPM1 mutation (VAF: 39%), TET2 mutation (47%), and DNMT3A mutation (VAF: 43%). He was complicated with a bacterial pneumonia during the first course of therapy which was successfully treated with broad-spectrum antibiotics. He received micafungin as a fungal prophylaxis in order not to diminish the efficacious dose of Ven.

He rapidly achieved a CR on day 21 of AZA + Ven. The NGS panel indicated a decline in all four clonal

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abnormalities. He also underwent a bone marrow sampling after the 4th course of AZA + Ven to ascertain a minimal residual disease (MRD) negative response, and all the four clonal abnormalities were found to be completely immeasurable (Fig. 1).

He continued to receive AZA + Ven with a Ven schedule of every 14 days of 28-day cycles. He never re-hospitalized after being discharged at the 24th day of the first cycle. He was doing perfectly well until the 11th cycle of AZA + Ven which was disturbed with a COVID-19 infection. He was off therapy for a month because of a severe COVID-19 infection which required a hospitalization and administration of favipiravir. As soon as he fully recovered from COVID-19 infection as he remained leukopenic, a bone marrow sampling repeated and revealed a relapsed disorder with a blast count of 85%. NGS panel showed re-occurrence of four ancestral clonal abnormalities (FLT3-ITD, NPM1, TET2, DNMTA3) with accompanying TP53, WT, CALR, and a novel TET2 mutation. As the patient was suffering from an ongoing bacterial pneumonia, a re-challenge was planned with switching AZA with decitabine (DEC) and combining with Ven 400 mg/day. He unfortunately did not respond to the DEC + Ven combination with persistent clonal architecture at the 21st day and rapidly lost to a septicemia complicated with a thrombotic microangiopathy.

Although rechallenge in the treatment of AML is an important topic of discussion, the literature data is limited.

In addition, data on the role of low-intensity treatments on MRD and the effect of MRD negativity especially in this patient group are controversial. Our patient has important results in this respect.

In a study from 2020, Othman et al. retrospectively examined HMA + Ven rechallenge cases [7]. The median latency period of discontinuation of treatment was 224 days (range: 73–407), the number of patients with response was 5 (33%), and the number of patients with CR was reported as 3. Two out of the 5 responders achieved MRD-negativity. One patient underwent the 2nd allogeneic stem cell transplantation. Rechallenge could be seen as an advantage, especially for patients who are not suitable for clinical trials. We could not obtain a response to HMA rechallenge in our patient with MRD negativity.

Data on MRD follow-up in AML cases receiving lower-intensity therapy are also limited. Pratz et al. [8] examined the role of MRD in patients receiving AZA + Ven in their study. An MRD result of $<10^{-3}$ was achieved by 67 of 164 (41%), and 97 of 164 (59%) had $\text{MRD} \geq 10^{-3}$. In this study, patients who achieved CRc (CRc: complete remission + complete remission with incomplete hematologic recovery) and $\text{MRD} < 10^{-3}$ with AZA + Ven had longer duration of remission, event-free survival, and overall survival, than responding patients with $\text{MRD} \geq 10^{-3}$. In another study, Maiti et al. [9] examined the role of MRD negativity in older or unfit patients who received DEC + Ven.

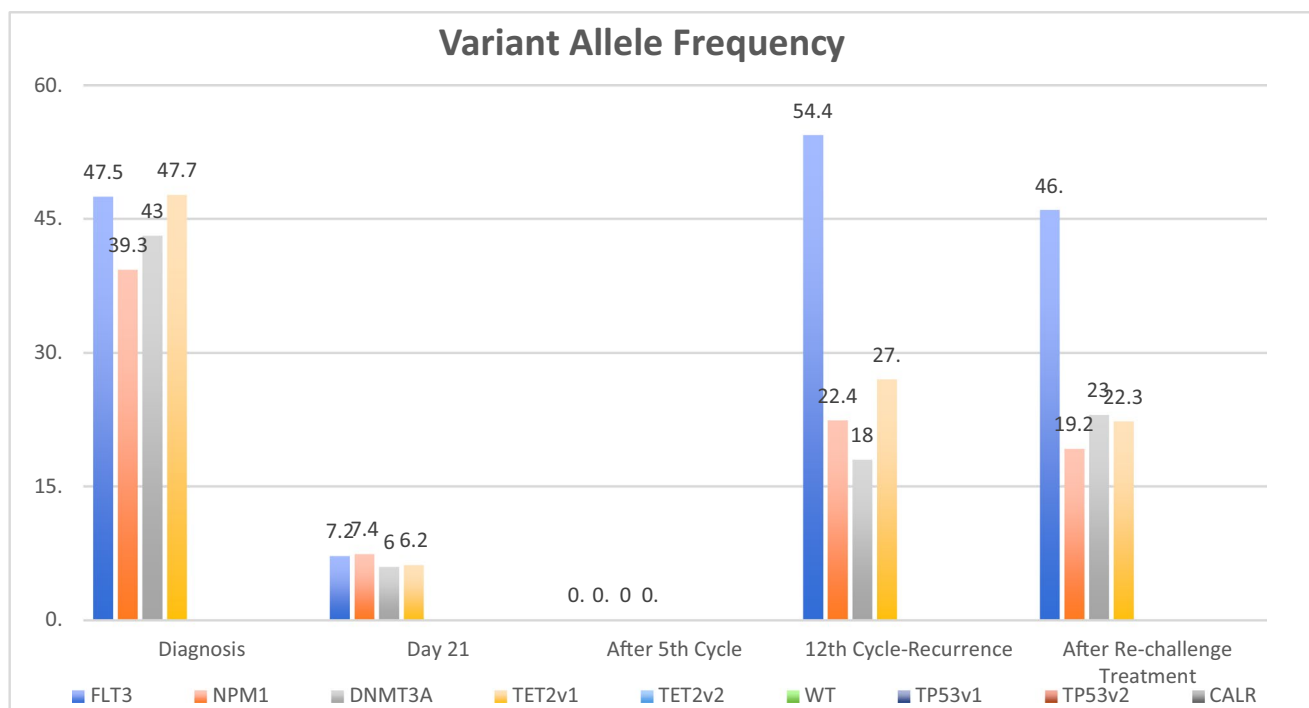


Fig. 1 The next generation sequencing (NGS) follow-up of the patient: from diagnosis to the rechallenge

In this study, MRD-negativity at 1, 2, and 4 months after starting therapy has been shown to be a sign for significantly better survival in older/unfit patients with AML receiving first-line therapy with DEC + Ven. In our own case, we were able to achieve MRD-negativity with AZA + Ven, but could not achieve a response with HMA rechallenge.

In conclusion, although MRD negativity was obtained with AZA + Ven in an unfit AML case, the patient's failure to respond to HMA rechallenge contributes to an important discussion point. HMA rechallenge is a topic that needs more data, especially in cases of unfit and old AML.

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Author contribution All the authors contributed to the editing of the manuscript. MM and SM prepared the accompanying figure.

Data availability Data are included in this published article and its additional file.

Declarations

Ethics approval and consent to participate Informed consent was obtained from our patient to publish the presentation.

Consent for publication Written informed consent was obtained from the patient for publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests The authors declare no competing interests.

References

1. Newell LF, Cook RJ (2021) Advances in acute myeloid leukemia. *BMJ* 375:2026
2. Eisfeld AK, Kohlschmidt J, Mrózek K et al (2018) Mutation patterns identify adult patients with de novo acute myeloid leukemia aged 60 years or older who respond favorably to standard chemotherapy: an analysis of alliance studies. *Leukemia* 32:1338–1348
3. Ostronoff F, Othus M, Lazenby M et al (2015) Prognostic significance of NPM1 mutations in the absence of FLT3-internal tandem duplication in older patients with acute myeloid leukemia: a SWOG and UK National Cancer Research Institute/Medical Research Council report. *J Clin Oncol* 33:1157–1164
4. Stomper J, Rotondo JC, Greve G, Lübbert M (2021) Hypomethylating agents (HMA) for the treatment of acute myeloid leukemia and myelodysplastic syndromes: mechanisms of resistance and novel HMA-based therapies. *Leukemia* 35:1873–1889
5. Othman TA, Azenkot T, Moskoff BN, Tenold ME, Jonas BA (2021) Venetoclax-based combinations for the treatment of newly diagnosed acute myeloid leukemia. *Future Oncol* 17:2989–3005
6. Santini V (2019) How I treat MDS after hypomethylating agent failure. *Blood* 133:521–529
7. Othman TA, Zhang J, Mei M et al (2020) Retreatment with venetoclax and hypomethylating agents among AML patients who have relapsed after initial response and subsequent interruption of therapy. *Leuk Lymphoma* 61:3532–3533
8. Pratz KW, Jonas BA, Pullarkat V et al (2022) Measurable residual disease response and prognosis in treatment-naïve acute myeloid leukemia with venetoclax and azacitidine. *J Clin Oncol* 40:855–865
9. Maiti A, DiNardo CD, Wang SA et al (2021) Prognostic value of measurable residual disease after venetoclax and decitabine in acute myeloid leukemia. *Blood Adv* 5:1876–1883

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