Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Sustained Remission in an Elderly Patient with Acute Myeloid Leukemia Following Gilteritinib Treatment as Third-Line Salvage Therapy

Keywords: Elderly patient; Acute myeloid leukemia; Gilteritinib; Third-line salvage therapy.

Published: November 01, 2024 **Received: September 26, 2024** **Accepted: October 10, 2024**

Citation: Molica M., De Fazio L., Rossi M. Sustained remission in an elderly patient with acute myeloid leukemia following gilteritinib treatment as third-line salvage therapy. Mediterr J Hematol Infect Dis 2024, 16(1): e2024079, DOI: http://dx.doi.org/10.4084/MJHID.2024.079

To the editor.

Historically, patients with acute myeloid leukemia (AML) harboring FMS-like tyrosine kinase 3 (FLT3) mutations have had a poor prognosis. However, the advent of tyrosine kinase inhibitors (TKIs), such as midostaurin, quizartinib, and gilteritinib, has significantly improved patient outcomes. Gilteritinib, a second-generation TKI, has shown superior efficacy compared to first-generation TKIs by effectively targeting both FLT3-internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations.[1]

In the Phase I/II Chrysalis trial, gilteritinib demonstrated a favorable safety profile with manageable adverse effects and achieved an overall response rate (ORR) of 49% among 191 patients with relapsed/refractory (R/R) FLT3-mutated AML.[2] The subsequent ADMIRAL trial in 2019 further validated gilteritinib efficacy, showing a significant improvement in median overall survival (9.3 months vs. 5.6 months) and a higher ORR (67.6% vs. 25.8%) compared to chemotherapy alone in first-line R/R AML.[3] These findings led to gilteritinib approval by the U.S. Food and Drug Administration (FDA). Subsequent real-world studies[4-7] have reinforced its role as an effective first-line salvage therapy in R/R AML.

Despite these advances, data on gilteritinib effectiveness as a third-line salvage therapy remain limited. We present a case of an elderly AML patient who achieved sustained remission with gilteritinib monotherapy following failure of intensive chemotherapy combined with a first-generation FLT3 inhibitor and hypomethylating agents in combination with venetoclax.

Case Report. In March 2023, a 70-year-old woman presented with several weeks of persistent fatigue and shortness of breath. Laboratory results revealed anemia (Hb 8.8 g/dL), thrombocytopenia (platelet count 23,000/mm³), and leukocytosis (white blood cell count 32,000/mm³). Peripheral blood smear analysis indicated 70% of blasts, suggestive of myeloid lineage. A subsequent bone marrow aspirate confirmed the diagnosis of AML (80% blasts, positive for CD45, CD13, CD33, CD34, CD36, CD117, HLADR, and MPOdim). The cytogenetic analysis identified translocations involving chromosomes 6 and 9, while molecular testing confirmed the presence of an FLT3-ITD mutation.

The patient developed dyspnea and fever shortly after admission. A chest C.T. scan revealed diffuse interstitial pneumonia, necessitating ventilatory support, and broad-spectrum antimicrobial therapy. Given her critical condition, bronchoalveolar lavage was not performed, and antibiotics and antifungals were continued empirically. After three weeks, the patient's condition improved, allowing for ventilatory support to be withdrawn, and follow-up imaging showed the resolution of the pneumonia.

Due to her recent infection and clinical frailty, she was deemed unfit for intensive chemotherapy and started on first-line therapy with decitabine and venetoclax (100 mg daily), alongside antifungal prophylaxis with posaconazole. The regimen was well tolerated, and after one cycle, the patient achieved normalized blood counts, with a bone marrow aspirate showing 2% myeloblasts, consistent with complete remission. Unfortunately, following the third cycle, she experienced leukocytosis (WBC 45,000/mm³), and repeat bone marrow analysis confirmed AML relapse, with 35% myeloid blasts and persistence of the FLT3-ITD mutation.

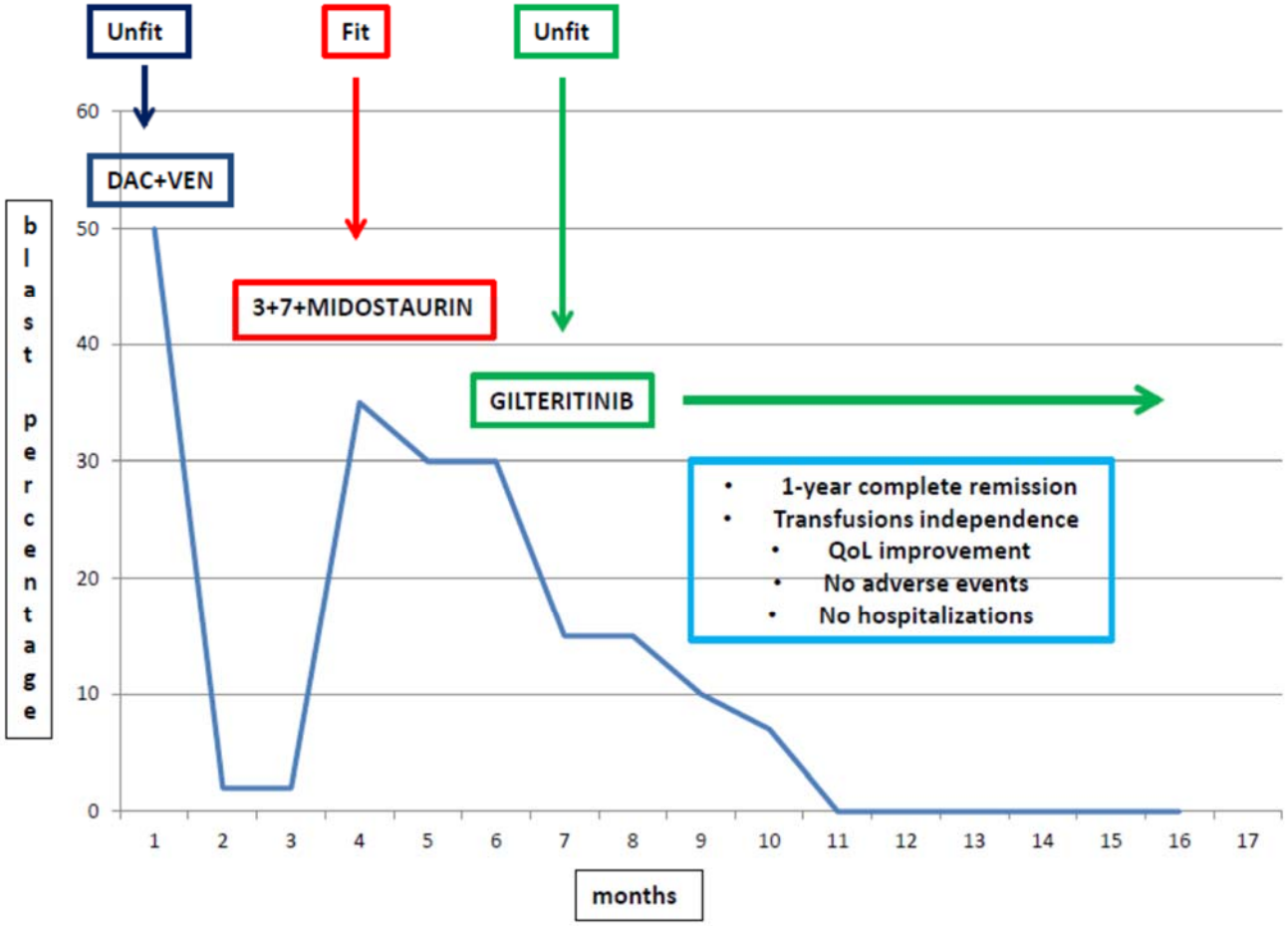
Despite the relapse, the patient's clinical condition remained stable. With the resolution of her pulmonary infection, she was considered eligible for intensive chemotherapy. She underwent the 3+7 (cytarabine and daunorubicin) regimen combined with midostaurin, but it was poorly tolerated. The patient developed sepsis caused by *Staphylococcus aureus* and fungal pneumonia and remained pancytopenic post-treatment. A bone marrow aspirate performed on day 37 showed persistent

disease, with 30% blasts, classifying her as resistant to chemotherapy.

In August 2023, the patient commenced third-line therapy with gilteritinib (120 mg daily). At initiation, she was neutropenic and required frequent transfusions (approximately twice per week), reporting significant fatigue. Two months after starting gilteritinib, bone marrow evaluation revealed a reduction in blasts to 15%, and her clinical condition had markedly improved. She achieved granulocyte recovery and reduced transfusion needs (to once every 15 days) with no reported drug-related toxicities or hospitalizations.

After six cycles of gilteritinib, bone marrow evaluation revealed 0.78% myeloblasts, indicating complete remission. The patient became transfusion-independent and reported significant improvements in her quality of life. After one year of drug administration, she remains in complete remission, free from treatment-related adverse events, and has resumed her normal daily activities (**Figure 1**).

Figure 1. Successful disease response and clinical improvement in an elderly FLT3-positive patient treated with gilteritinib as third-line salvage therapy.



Discussion. This case report presents the first documented instance of an elderly patient with FLT3-positive acute myeloid leukemia (AML) achieving sustained remission with gilteritinib as a third-line salvage therapy. This achievement followed unsuccessful treatments with hypomethylating agents plus target therapy (decitabine and venetoclax) and intensive chemotherapy combined with midostaurin. Despite the patient's advanced age and prior infectious complications, including sepsis and pneumonia, she experienced prolonged remission, transfusion independence, and significant improvements in quality of life without notable adverse effects.

The outcome underscores gilteritinib potential as a viable third-line treatment for elderly patients who have exhausted other options. This is particularly significant because third-line therapies for AML typically have limited efficacy and high toxicity. The durable response and overall clinical improvement in this patient suggest that gilteritinib could be a valuable option for those otherwise deemed unsuitable for aggressive treatments. As more real-world data emerge, gilteritinib role in the AML treatment landscape is expected to become clearer, potentially offering new therapeutic opportunities for this challenging patient group.

Matteo Molica[1], Laura De Fazio[1] and Marco Rossi[1].

[1] Department of Hematology-Oncology, Azienda Universitaria Ospedaliera Renato Dulbecco, Catanzaro, Italy.

Competing interests: The authors declare no conflict of Interest.

Correspondence to: Matteo Molica, MD, PhD. E-mail address: molica@bce.uniroma1.it

References:

1. Molica M, Perrone S and Rossi M. Gilteritinib: The Story of a Proceeding Success into Hard-to-Treat FLT3-Mutated AML Patients, J Clin Med. 2023 Jun; 12(11): 3647. https://doi.org/10.3390/jcm12113647
2. Perl A.E., Altman J.K., Cortes J., Smith C., Litzow M., Baer M.R., Claxton D., Erba H.P., Gill S., Goldberg S., et al. Selective Inhibition of FLT3 by Gilteritinib in Relapsed or Refractory Acute Myeloid Leukaemia: A Multicentre, First-in-Human, Open-Label, Phase 1-2 Study. Lancet Oncol. 2017;18:1061-1075. https://doi.org/10.1016/S1470-2045(17)30416-3
3. Perl A.E., Martinelli G., Cortes J.E., Neubauer A., Berman E., Paolini S., Montesinos P., Baer M.R., Larson R.A., Ustun C., et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. N. Engl. J. Med. 2019;381:1728-1740. https://doi.org/10.1056/NEJMoa1902688
4. Dumas P.-Y., Raffoux E., Bérard E., Bertoli S., Hospital M.-A., Heiblig M., Desbrosses Y., Bonmati C., Pautas C., Lambert J., et al. Gilteritinib Activity in Refractory or Relapsed FLT3-Mutated Acute Myeloid Leukemia Patients Previously Treated by Intensive Chemotherapy and Midostaurin: A Study from the French AML Intergroup ALFA/FILO. Leukemia. 2023;37:91-101. https://doi.org/10.1038/s41375-022-01742-7
5. Othman J., Afzal U., Amofa R., Austin M.J., Bashford A., Belsham E., Byrne J., Coats T., Dang R., Dennis M., et al. Gilteritinib for Relapsed Acute Myeloid Leukaemia with FLT3 Mutation during the COVID-19 Pandemic: Real World Experience from the U.K. National Health Service. Blood. 2021;138:1254. https://doi.org/10.1182/blood-2021-150169
6. Numan Y., Abdel Rahman Z., Grenet J., Boisclair S., Bewersdorf J.P., Collins C., Barth D., Fraga M., Bixby D.L., Zeidan A.M., et al. Gilteritinib Clinical Activity in Relapsed/Refractory FLT3 Mutated Acute Myeloid Leukemia Previously Treated with FLT3 Inhibitors. Am. J. Hematol. 2022;97:322-328. https://doi.org/10.1002/ajh.26447
7. Shimony S., Canaani J., Kugler E., Nachmias B., Ram R., Henig I., Frisch A., Ganzel C., Vainstein V., Moshe Y., et al. Gilteritinib Monotherapy for Relapsed/Refractory FLT3 Mutated Acute Myeloid Leukemia: A Real-World, Multi-Center, Matched Analysis. Ann. Hematol. 2022;101:2001-2010. https://doi.org/10.1007/s00277-022-04895-8