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Managing post-transplant relapse in FLT3-mutated AML with gilteritinib

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INTRODUCTION

Acute myeloid leukemia (AML) represents 80% of acute leukemias in the adult population. The mutation of the fms-like tyrosine kinase 3 (FLT3) receptor gene occurs in c.30% of patients with newly diagnosed AML, with FLT3-ITD mutation (ITD, internal tandem duplication) accounting for 25% of those cases [1]. C.50% of AML patients relapse and 10–40% are refractory to initial first-line treatment [2]. Currently, gilteritinib is the only FLT3 inhibitor for relapsed/refractory AML registered in Europe. It has been shown to increase the rate of achieving a complete response and prolong overall survival compared to salvage chemotherapy [3]. This clinical vignette highlights challenges in the treatment of FLT3 AML patients.

CASE REPORT

A 63-year-old male was referred to the hematology outpatient clinic due to leukocytosis, anemia, and thrombocytopenia in routine laboratory tests. Based on a bone marrow examination, a diagnosis of acute myeloid leukemia with maturation features, with blast cells accounting for 48%, was made in November 2021. In cytogenetic-molecular analyses, FLT3-ITD mutation was confirmed with the exclusion of other recurrent aberrancies, and the karyotype was assessed as that of a normal male (46; XY). The patient was burdened with chronic internal conditions such as type 2 diabetes, hypertension, and chronic obstructive pulmonary disease. He required antibiotic administration because of diffuse erythematous skin changes and middle ear inflammation with accompanying discharge.

The patient was qualified as an unfit patient (ECOG 3, HCT-CI 4) and started treatment with a non-intensive AZA--VEN (azacitidine, venetoclax) regimen. During the first cycle, he required hospitalization. After the first cycle was complete, he achieved partial remission (PR) and his general condition improved. Therefore, the therapy was continued in one--day-hospitalization settings. He achieved complete remission (CR) after the second course of AZA-VEN, and this was maintained until the sixth course when AML relapse was confirmed. Despite losing remission during AZA-VEN treatment, that regimen facilitated improvement in his general condition (ECOG 1, HCT-CI 3). Gilteritinib was already a registered molecule but, at that time, was not covered by the reimbursement program in Poland. However, at that time there was an opportunity to enrol the patient in the clinical trial of the Polish Adult Leukemia Group PALG AML-1/2018 for refractory and relapsed AML [4].

He started treatment with CPX-351 (a liposomal form of daunorubicin and cytarabine) with the addition of cladribine. After the induction cycle, the patient achieved CR with a positive measurable residual disease maintained after two consolidation courses. In January 2022, 10/10 human leukocyte antigen (HLA) matched unrelated hematopoietic cell transplantation with FluBu2 (fludarabine, busulfan) reduced-intensity conditioning was implemented. ABO blood group incompatibility with a graft donor was noted. The post-transplant assessment observed CR MRD positive (0.39%) with complete donor chimerism. Over the next control visits, immunosuppression was reduced gradually, achieving MRD of 0.12% six months post-transplantation. Clinically, the patient did

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not present any GvHD (graft-versus-host disease) symptoms, but was transfusion-dependent for red blood cell concentrate, probably due to blood group incompatibility. Seven months after the procedure, a second relapse was diagnosed. Molecular analysis confirmed FLT3-ITD mutation with chimerism decreased to 84%. The patient started treatment with gilteritinib, and exhibited good tolerance. Hemoglobin concentration gradually increased, and the patient achieved transfusion independence. After four weeks of treatment, bone marrow flow cytometry showed 7% of blast cells (PR). The dosage of gilteritinib was increased to 200 mg together with the implementation of donor lymphocyte infusions (DLI). The patient maintained good treatment tolerance and independence from transfusions. Among the adverse effects, the patient showed only an increase in alanine transaminase and aspartate transaminase levels, classified as grade 1 according to CTCAE (Common Terminology Criteria for Adverse Events). He did not present any symptoms of GvHD, and his quality of life significantly improved, allowing him to stay at home and visit the hospital only for check-ups. During treatment, the patient received amoxicillin, acyclovir, and sulfamethoxazole with trimethoprim, as the post-transplant prophylaxis. After three cycles of gilteritinib and one DLI (dosage 1 × 10^6/kg $CD3^+$ cells), he achieved hematological CR with positive MRD, reducing blast cells to 4.5%. Following six cycles and three DLI (dosages 5 × 10^6/kg $CD3^+$ cells), CR with a positive MRD of 1.8% was confirmed. A second transplant is not indicated due to the patient's overall clinical status and existing comorbidities.

SUMMARY

The presented patient was treated with various molecules such as azacitidine, venetoclax, cytarabine and anthracylines with distinct mechanisms of action. The data concerning the efficacy of CPX-351 in FLT3 AML patients is encouraging, although it is still based on small patient groups [5]. Multiple clinical trials are in progress featuring the addition of FLT3 inhibitors to CPX-351 [6]. Treatment with gilteritinib, due to the possible delayed response, should be continued for up to six months. In cases of a lack of response, it is recommended to administer it until the patient derives clinical benefit such as transfusion independence (one third of patients in the ADMIRAL trial), or until unacceptable toxicity occurs [3]. Gilteritinib represents a significant component in numerous clinical trials and future treatment regimens [7].

Ethics statement

The authors declare that the research presented in this manuscript has complied with ethical guidelines outlined by the relevant institutional and international standards. Consent from a bioethical committee was not required. The patient has given informed consent for the publication.

Author contributions

Zuzanna Rzetelska: Data collection and analysis, manuscript preparation, final approval of the version to be published.

Andrzej Szczepaniak: Data collection and analysis, manuscript preparation, final approval of the version to be published.

Lidia Gil: Critical review for important intellectual content, final approval of the version to be published.

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Conflict of interest

The authors declare no conflict of interest.

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