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CASE REPORT

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Treatment of a patient with acute myeloid leukaemia with *FLT3*-ITD mutation

Katarzyna Jerzmanowska, Agnieszka Pluta

Department of Haematology, Medical University of Lodz, Łódź, Poland

Abstract

Acute myeloid leukaemia (AML) is an aggressive myeloid malignancy characterized by ineffective haematopoiesis. A hallmark of AML is unusual cytogenetic and molecular diversity, which determines treatment and has a major impact on patient response to treatment and survival. The mutations most detected in AML are those in the FMS-like tyrosine kinase 3 gene (FLT3). A case report is presented of a patient with AML with FLT3-ITD mutation who was treated with standard induction and consolidation chemotherapy in combination with midostaurin.

Key words: AML, *FLT3*, midostaurin

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Introduction

Acute myeloid leukaemia (AML) is an aggressive malignancy of bone marrow characterized by abnormal proliferation of leukemic progenitor cells leading to the displacement of normal haematopoiesis. This is a heterogeneous disease from a clinical, morphological and genetic standpoint [1, 2]. The incidence of AML is 4 cases per 100,000 population per year, increasing with age, and with a median age at diagnosis about 67 years [3]. The diagnosis of AML is based on peripheral blood and marrow cytology along with immunophenotypic and genetic testing. For more than three decades, karyotype along with tumour burden has been one of the most important prognostic factors. Over the past twelve years, a better understanding of AML biology has contributed to the establishment of new genetic factors affecting the prognosis of AML patients [4]. This led to the development of modified prognostic scales based on the analysis of cytogenetic and molecular abnormalities [5]. Within the European LeukemiaNet (ELN), cytogenetic and molecular prognostic groups of AML patients were established in 2010 and updated in 2017 [6]. Patients are classified into three prognostic groups: favourable, intermediate, and unfavourable, which translates into response rate to induction therapy and survival (Table 1) [6]. One of the eligibility criteria for the appropriate prognostic group is the FMS-like tyrosine kinase 3 (*FLT3*) gene abnormality [6].

FLT3 belongs to the family of class III receptor tyrosine kinases (RTKs) along with KIT, FMS and PDGFR [7–9]. These receptors exhibit tyrosine kinase activity, and their activation is crucial during the early stages of haematopoiesis [7–9]. In normal hematopoietic cells, activation of this receptor initiates the transduction of intracellular signals that regulate cell proliferation and differentiation. In neoplastic cells, the mutated *FLT3* gene leads to constant activation of tyrosine kinase, which promotes uncontrolled cell proliferation [7–9]. Patients with AML usually present two types of mutations in the gene encoding the FLT3 receptor: an internal tandem duplication (ITD) occurring in gene fragment encoding the perimembranous domain of the receptor, and point mutations, deletions and insertions in codon D835 of the kinase domain (TKD, tyrosine kinase domain). *FLT3*-ITD and *FLT3*-TKD mutations are found in approximately

Address for correspondence: Agnieszka Pluta, Klinika Hematologii, Uniwersytet Medyczny Łodzi, ul. Ciołkowskiego 2, 93–510 Łódź, Poland, phone +48 42 689 51 94, e-mail: agnieszka.pluta@op.pl

Table 1. The stratification of the relapse risk by genetic abnormalities (acc. to European LeukemiaNet 2017 [6])

Prognostic group	Cytogenetic and molecular abnormalities
Favourable	t(8; 21)(q22; q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* *NPM1* mutation without *FLT3*-ITD or *FLT3*-ITD^{low} Biallelic mutation *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high} Normal *NPM1* and no *FLT3*-ITD or *FLT3*-ITD^{low} (without change of unfavourable genetic risk) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic alterations not captured by favourable or unfavourable prognosis group
Unfavourable	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); KMT2A rearrangements t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3; q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM (EVI1)* –5 or del(5q); –7; –17/abn (17p) Complex or monosomal karyotype Normal *NPM*1 and *FLT3*-ITD^{high} *RUNX1* mutation *ASXL1* mutation *TP53* mutation

FLT3-ITD^{high} and *FLT3*-ITD^{low} — *FLT3*-ITD/*FLT3* normal allelic ratio ≥ 0.5 is defined as "high", <0.5 as "low"

20% and 10% of AML patients with a normal karyotype, respectively [10–12]. In the clinical manifestation, *FLT3*-ITD gene abnormalities have a detrimental effect on prognosis, as they are associated with a high tumour burden at onset, more frequent relapses, shorter survival, and a more aggressive course, especially in young AML patients [13–15]. *FLT3*-TKD mutations are completely different and probably not associated with such an unfavourable prognosis as *FLT3*-ITD [16, 17].

The following report presents the case of a young woman with AML with normal karyotype and internal tandem duplication in the *FLT3* gene and *NPM1* mutation.

Case report

In February 2020, a 42-year-old female patient was admitted to the Department of Haematology, Medical University Lodz for further diagnostics of pancytopenia. She had not previously been treated for chronic disease. Medical history revealed upper respiratory tract infection about 3 weeks before admission, not improving after oral antibiotic treatment. On admission, the patient was in moderately severe, stable general condition. She reported difficulty swallowing. Physical examination revealed enlargement of the left palatine tonsil. ENT examination found an inflammatory infiltration, probably of infectious aetiology. Complete blood count (CBC) indicated severe macrocytic normochromic anaemia [haemoglobin 7.9 g/dL, mean corpuscular volume (MCV) 105 fL, mean corpuscular hemoglobin concentration (MCHC) 34.3 g/dL], mild leukopenia (white blood cells 3.12 G/L), severe thrombocytopenia (platelets 36 G/L). The peripheral blood smear showed 34% myeloblasts, 2% promyelocytes, 1% rod neutrophils, 18% partitioned neutrophils, 1% eosinophils, 41% lymphocytes, and 3% monocytes. Cytomorphologic marrow examination revealed 58% myeloblasts and no evidence of dysplasia (Figure 1A, B). Flow cytometry immunophenotyping showed the expression of following antigens: CD13 (83.6%), CD31 (99.2%), CD33 (92%), CD117 (81.3%), CD38 (98.9%), HLA-DR (57.1%).

Laboratory tests showed normal renal function (creatinine 0.64 mg/dL, urea 24.5 mg/dL, uric acid 2.9 mg/dL, potassium 3.7 mmol/L, sodium 138 mmol/L), mild liver dysfunction [total bilirubin 0.34 mg/dL, alanine aminotransferase (ALT) 59 U/L, aspartate aminotransferase AST 49 U/L), increased lactate dehydrogenase (LDH) activity (681 U/L), hyperferritinemia (2,315 ng/mL) and increased C-reactive protein (CRP) level (286.7 mg/L). Infections with hepatitis B virus (nonreactive HBs antigen), hepatitis C virus (nonreactive anti-HCV antibodies), human immunodeficiency virus (nonreactive HIV antigen/antibodies) and Epstein-Bárr virus (nonreactive anti-EBV IgM antibodies, reactive anti-EBV IgG antibodies) and cytomegalovirus (nonreactive anti-CMV IgM antibodies, reactive anti-CMV IgG antibodies) were excluded.

Cytogenetic and molecular studies of bone marrow indicated a normal female karyotype (46, XX) with the coexistence of *FLT3*-ITD as well as *NPM1* and *WT1* mutations. *FLT3*-mutation/wild-type allelic ratio (AR) was 0.15; however, neither

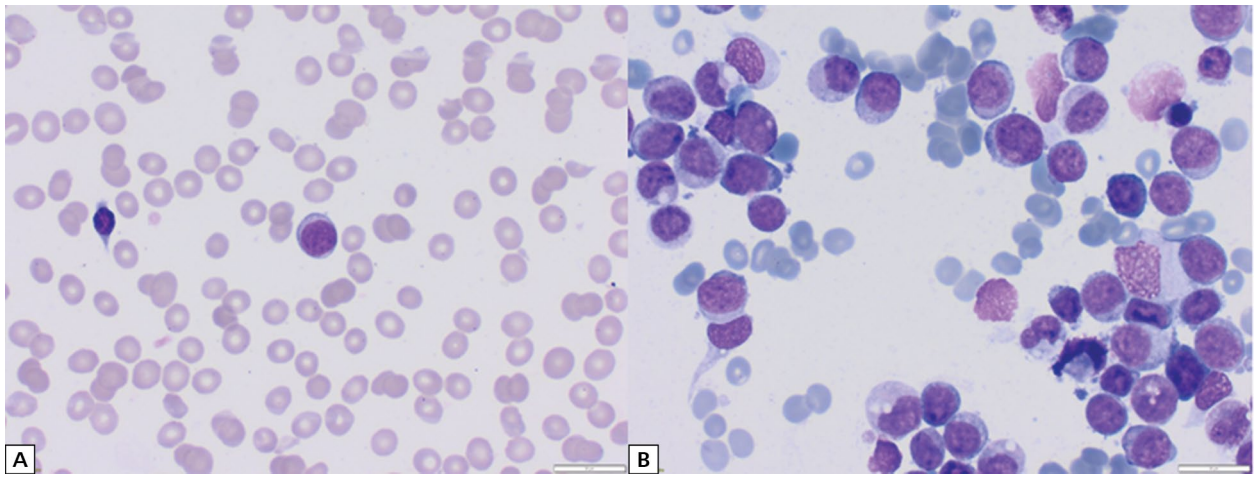

Figure 1. A peripheral blood smear (**A**) and a bone marrow smear (**B**) of the patient at the time of diagnosis; haematoxylin and eosin stain, 31.5× magnification

BCR-ABL1 nor *AML1-ETO*, *CBFbeta-MYH11*, *MLL-PTD* were not detected. According to the 2017 ELN classification, the patient was allocated to the cytogenetic/molecular low-risk group.

Before deciding on intensive chemotherapy, broad-spectrum antibiotic therapy with ceftazidime, vancomycin, and metronidazole was initiated, leading to an improved patient's general condition.

The patient was qualified for intensive chemotherapy within the Polish Adult Leukemia Group (PALG) AML1/2016 study and received induction treatment according to the DAC regimen [daunorubicin: 60 mg/m^2, intravenous (i.v.), days 1–3; cytarabine: 200 mg/m^2, i.v., days 1–7; cladribine: 5 mg/m^2, i.v., days 1–5). The duration of chemotherapy-induced aplasia with an absolute neutrophil count (ANC) of less than 500 g/L was 14 days. The aplasia was complicated by fever with *Enterobacter cloacae* ESBL (+) bloodstream infection (EcBSI) treated with meropenem. In addition, during the chemotherapy-induced aplasia, abdominal pain and severe diarrhoea have occurred. The results of stool culture, as well as *Clostridioides difficile* toxin A/toxin B test and fungal culture were negative. Based on the clinical manifestation and computed tomography (CT) of the abdominal cavity, neutropenic enterocolitis was diagnosed. Broad-spectrum antibiotic therapy, granulocyte colony-stimulating factor (G-CSF), as well as analgesic and spasmolytic agents were introduced, resulting in the gradual improvement of the patient's general condition. During hospitalization, the patient required a transfusion of 12 packed red blood cells (PRBCs) units and 8 platelet concentrate units. The total hospital stays during induction treatment lasted 33 days. Follow-up bone marrow examination after completion of induction treatment showed complete remission with a negative result of immunophenotyping residual disease analysis.

During the next hospitalization, the first cycle of consolidation therapy was administered according to the high-dose cytosine arabinoside (HD-Ara-C) + midostaurin regimen (cytarabine: 2,000 mg/m^2, i.v., days 1, 3, 5; midostaurin: 2 × 50 mg every 12 hours, days 8–21). Chemotherapy-induced aplasia duration with ANC below 500 g/L was 16 days and was complicated by fever up to 40°C with EcBSI. After antibiotic treatment with meropenem, inflammatory markers and the patient's general condition improved. In addition, headaches have occurred during taking midostaurin. Blood pressure monitoring showed normal values throughout the treatment period. Symptoms resolved after cessation of therapy. During hospitalization, the patient required a transfusion of 3 PRBCs units and 4 platelet concentrate units.

During the second consolidation chemotherapy cycle according to the HD-Ara-C + midostaurin regimen, no infectious complications were observed. Chemotherapy-induced aplasia duration with ANC below 500 g/L was 20 days. After midostaurin administration, persistent headache again reappeared, improving after administration of paracetamol. During hospitalization, the patient required a transfusion of 2 PRBCs units and 3 platelet concentrate units.

The third consolidation chemotherapy cycle according to the HD-Ara-C + midostaurin

regimen was administered without any deviation. Chemotherapy-induced aplasia duration with ANC below 500 g/L was 20 days. At this time, fever up to 40°C and severe sore throat were observed, with CRP level-up to 324 mg/L. The throat swab culture detected carbapenem-resistant, carbapenemase-producing [metallo-β-lactamases (MBL) positive] *Pseudomonas aeruginosa* strain. Broad-spectrum antibiotic treatment with colistin and linezolid led to temperature normalization, sore throat improvement, and a decrease in inflammatory markers. Midostaurin administration was additionally complicated by headaches. During hospitalization, the patient required a transfusion of 2 PRBCs units and 5 platelet concentrate units.

The patient is being monitored in the Department of Haematology in Lodz. She has been qualified for unrelated donor allogeneic hematopoietic stem cell transplantation and currently is on the waiting list. As a bridge to transplantation, she received maintenance therapy with midostaurin at a dose of 50 mg twice daily in 28-day cycles. During this treatment, the patient also reported headaches, which resolved after the administration of acetaminophen. Initially, this symptom was accompanied by a slight increase in blood pressure, which resolved spontaneously after the first few days of midostaurin treatment.

At her last visit to the haematology clinic in December 2020, she was in complete remission and has continued maintenance therapy.

Discussion

This case report describes the treatment of the patient with AML from the cytogenetic-molecular low-risk group according to ELN 2017. The patient received intensive chemotherapy in combination with a tyrosine kinase inhibitor — midostaurin.

FLT3 mutations belong to the most common genetic abnormalities identified in AML, occurring in 20–30% of patients with newly diagnosed malignancy [15,18]. The prognosis depends on the mutated/wild-type transcripts ratio (AR) [19]. However, regardless of the AR value, any patient with the *FLT3*-ITD or *FLT3*-TKD mutation is eligible for and benefits from treatment with a tyrosine kinase inhibitor [20].

The diagnosis of AML with normal karyotype, *FLT3* mutation and AR less than 0.5 and concomitant *NPM1* gene mutation qualifies patients for the cytogenetic-molecular low-risk group according to ELN 2017 and the National Comprehensive Cancer Network (NCCN) [6, 21].

According to ELN or NCCN guidelines, in this clinical situation standard treatment with daunorubicin and cytosine arabinoside in combination with tyrosine kinase inhibitor midostaurin should be administered, and after achieving disease remission, consolidation treatment with high-dose cytosine arabinoside should also be used in combination with midostaurin [6]. After achieving remission, the patient should be eligible for allogeneic hematopoietic stem cell transplantation [6, 20]. While waiting for this procedure, maintenance treatment with midostaurin should be considered as a bridge therapy to keep the patient in the best response until transplantation [6, 21].

Currently, there is no standard treatment for AML patients with FLT3 kinase inhibitors available in Poland. According to the procedures that must be undertaken to have access to that agent by a given patient, this is only possible starting from consolidation treatment. Due to the presence of mentioned mutation, induction therapy with daunorubicin and cytosine arabinoside in combination with cladribine (DAC) was used, resulting in complete remission. In the PALG study [14, 22] evaluating the efficacy of DA versus DAC versus DAF (DA + fludarabine), it was shown that the combination of cladribine with the standard induction treatment with DA resulted in a comparable response rate in the group of patients with and without *FLT3*-ITD mutation [2, 14, 22]. Similarly, Pluta et al. showed no negative impact of *FLT3*--ITD mutation on response rate and overall survival in a study evaluating intensification of induction therapy with DAC based on early assessment of blasts percentage in bone marrow [2]. On the other hand, Boissel et al. [23] found that the adverse effect of *FLT3*-ITD expression can be overcome with high doses of cytarabine arabinoside during induction therapy. Treatment with a tyrosine kinase inhibitor appears to be the best option for patients with *FLT3* gene abnormalities; however, if the drug is not available, an add-on treatment that overcomes the adverse effect of *FLT3* mutation can be used. In the pivotal study, Stone et al. demonstrated that midostaurin was well tolerated and that the side effects reported during therapy were typical and consistent with those observed during AML intensive chemotherapy [20, 24]. Participants were randomly assigned in a 1:1 ratio to the group receiving standard induction-consolidation therapy in combination with midostaurin (n = 360) or to the group receiving placebo (n = 357) [20]. Serious adverse event rates were similar in both cohorts [20]. Reported complications were divided into

hematologic and nonhematologic toxicities. In the midostaurin group, the most reported hematologic adverse events were thrombocytopenia (97%), neutropenia (95%), anaemia (93%), leukopenia (26%), and lymphopenia (19%). The duration of red cell aplasia was significantly longer in the midostaurin treated group ($p = 0.03$), whilst other hematopoietic disorders were comparable in both groups [20].

Among the nonhematologic complications in the midostaurin-treated group, the most common were febrile neutropenia (82%), infections (52%), diarrhoea (16%), hypokalaemia (14%), rash or exfoliative dermatitis (14%), pain (13%), transient hepatic toxicity (13%), asthenia (9%), nausea (6%), hyponatremia (9%), hyperbilirubinemia (7%), gastrointestinal mucositis (6%), hypophosphatemia (5%), and hypocalcaemia (7%) [20]. Nonhematologic toxicities did not differ significantly between the groups.

In the presented case a lingering headache was observed, strongly associated with each administration of midostaurin, and responding to treatment with acetaminophen. In the pivotal study, headaches occurred in 11.5% of patients receiving midostaurin and in the same percentage in the placebo group [25]. Based on the literature data, they are not a common complication [20, 25]. Considering the benefits associated with midostaurin, treatment was continued both in the authors' centre and in patients treated in the RATIFY study [20].

Summary

The use of midostaurin in AML patients in induction and consolidation therapy contributes to the optimization of hematologic response. The goal of continued use of midostaurin in maintenance therapy is to maintain an optimal response until hematopoietic stem cell transplantation.

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