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CASE REPORT

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Midostaurin added to standard therapy in *FLT3*-positive acute myeloid leukaemia treatment

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Abstract

Acute myeloid leukaemia (AML) is a complex disease with a dynamic course associated with a series of acquired and cumulative genetic changes. In recent years, significant advances have been made in the understanding of its pathogenesis. Moreover, diagnostic and therapeutic options have expanded. The current classifications consider cytogenetic and molecular disorders, including the presence of, among others, mutations within FMS-like tyrosine kinase 3 (FLT3) transmembrane tyrosine kinase, regulating the proliferation and differentiation of hematopoietic cells at an early development stage. FLT3 mutation is detected in approximately 30% of newly diagnosed AML cases and concerns mutations: internal tandem duplication (ITD) or tyrosine kinase domain (TKD) gene. The high ratio of FLT3-ITD mutation is associated with an unfavourable prognosis. It is recommended to includ patients in clinical trials due to insufficient standard therapy effects. The new AML treatment strategies include first- and second-generation tyrosine kinase inhibitors. Midostaurin, a non-specific kinase inhibitor, was approved in 2017 for treatment of patients with newly diagnosed FLT3-positive AML in combination with standard chemotherapy. The paper presents the experience of the Department of Haematology and Bone Marrow Transplantation in Poznan in the use of FLT3 tyrosine kinase inhibitors based on a case report of two patients with newly diagnosed AML.

Key words: acute myeloid leukaemia, mutation *FLT3*, tyrosine kinase inhibitors, midostaurin

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Introduction

Acute myeloid leukaemia (AML) is a complex, dynamic disease, characterized by multiple acquired somatic mutations, the coexistence of competing clones, and evolution over time. Genetic alterations include amplifications, deletions, gene rearrangements, and point mutations. Tremendous progress has been made recently in understanding disease pathogenesis, and diagnostic as well as therapeutic options. Both the current World Health Organization (WHO) 2016 classification and the European LeukaemiaNet (ELN) risk stratification takes into account cytogenetic and molecular abnormalities that affect therapeutic management [1, 2].

FMS-like tyrosine kinase (*FLT3*) is a transmembrane tyrosine kinase activated by binding the ligand to the receptor and expressed on hematopoietic and progenitor cells. It plays an important role in the early stages of myeloid and lymphoid lines development. The attaching extracellular ligand stimulates cell survival, proliferation and differentiation through *PI3K*-, *RAS*-, and *STAT5*--related signalling pathways. The *FLT3* mutation is detected in approximately 30% of newly diagnosed AML. Internal tandem duplication (ITD) mutation constitutes about 25% cases, resulting in the

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duplication of 3 to 100 amino acids attached to the cell membrane, and 7–10% of cases include point mutations of the tyrosine kinase domain (TKD) in codons D835 and I836 or deletion in the codon I836. The mutation causes ligand-independent kinase activation, resulting in the proliferation and survival of leukemic cells. For the *FLT3*-ITD gene, it is also important to calculate the wild-to--mutant *FLT3*-ITD allelic ratio (AR), as its prognostic significance has been proven in patients with AML. The presence of the *FLT3*-ITD mutation is associated with hyperleukocytosis at diagnosis, worse prognosis, higher relapse rate and shorter survival [3]. The results of treatment of AML *FLT3* with standard chemotherapy are suboptimal. The understanding of mutations in the genes encoding the *FLT3* tyrosine kinase led to the development of targeted inhibitors. The first generation includes tandutinib, sunitinib, lestaurtinib, sorafenib and midostaurin, and the second generation quizartinib, crenolanib and gilteritinib. These compounds differ in respect of the selectivity of *FLT3* kinase inhibition and toxicity profile. Midostaurin is a non-specific kinase inhibitor originally developed for the treatment of solid tumours. In the clinical trials using midostaurin as monotherapy in patients with refractory/relapsed AML (R/R AML), as in the case of other inhibitors, a weak anti-leukemic effect was found; however, relatively better tolerance was the advantage [4]. The breakthrough studies were RATIFY and AMLSG 16-10, which showed the effectiveness of midostaurin in combination with intensive chemotherapy in terms of overall survival (OS) [5, 6]. These studies became the basis for drug registration in 2017 in the treatment of newly diagnosed AML with the *FLT3* mutation and the development of currently applicable therapeutic recommendations [7, 8]. The presented publication presents the experience of the Department of Haematology and Bone Marrow Transplantation in Poznań in the use of FLT3 tyrosine kinase inhibitors, based on two case reports of patients with newly diagnosed AML.

Case reports

Case 1

A 36-year-old female patient was referred to the haematology department in July 2019 with suspected AML. In the medical history, the patient reported weakness and pharyngitis treated ineffectively with empiric antibiotic therapy. So far, she has not been chronically ill. Upon admission, the patient was in good general condition first garde of performance status according to Eastern Cooperative Oncology Group (ECOG) [1]. Laboratory tests confirmed hyperleukocytosis [white blood cells (WBC) 176.3 G/L], anaemia [haemoglobin (Hb) 4.4 mmol/L), thrombocytopenia [platelets (PLT) 95 G/L). In addition, biochemical tests showed increased activity of lactate dehydrogenase [(LDH) 1117 U/L), as well as C-reactive protein [(CRP) 113.7 mg/L] and D-dimers (27,171 ng/mL) levels. The cytology and flow cytometry (FCM) evaluation confirmed 95% infiltration by blast cells with leukaemia-associated immunophenotype (LAIP): CD13+, CD33+, CD117+, HLA DR(dim), CD38+, CD31+, CD11c+, CD64+, CD4+, CD123+, MPO(−). The cytogenetic test revealed a normal karyotype (46, XX), and the fluorescent *in situ* hybridization (FISH) method excluded the presence of *PML-RARA* and *CBFB-MYH11*-gene fusions. In molecular tests with the polymerase chain reaction (PCR) method, the presence of the *FLT3*-ITD (AR 0.66) and *NPM1* mutations were confirmed and *CEBPA*, *RUNX1-RUNX1T1*, and *BCR-ABL* mutations were excluded. Due to the hyperleukocytosis and leukemic cells phenotype (monoblastic), cerebrospinal fluid (CSF) analysis was also performed, showing involvement of the central nervous system (CNS) by AML cells with the baseline phenotype (12%). The diagnosis of AML with *NPM1* mutation according to WHO 2016 classification was established. The patient was classified as an intermediate-risk group according to ELN 2017 due to the presence of *FLT3*-ITD (high ratio) and *NPM1* mutations with normal karyotype. Abdominal screening ultrasound revealed hepatomegaly (16 cm), fluid in the pouch of Douglas (24 mm) and a trace fluid in both pleural cavities. The patient was qualified for intensive induction therapy according to DA-60 protocol (daunorubicin 60 mg/m^2 on days 1–3 and cytarabine 200 mg/ /m^2 on days 1–7 during a 24-hour infusion) along with intrathecal drugs administration (cytarabine, dexamethasone, methotrexate). Due to at this time of reimbursement for midostaurin in Poland, an application for the drug was submitted to a pharmaceutical company. According to complex administrative procedures, it was not possible to add midostaurin during the induction phase of chemotherapy. After induction treatment, a complete response (CR) was achieved with minimal residual disease (MRD) of 1.8%. In consolidation therapy, high doses of cytosine arabinoside [(HD--Ara-C) 3 g/m^2 on days 1, 3, 5) were used in combination with midostaurin at a dose of 50 mg every 12 hours, administered orally on days 8–21. The

triple-drug intrathecal treatment was continued until a negative CSF test using the FCM method. The patient was qualified for allogeneic hematopoietic stem cell transplantation (allo-SCT) and the donor selection procedure was started in accordance with the protocol of the transplant centre. The assessment after the first consolidation cycle showed a sustained CR with a current MRD of 1.4% in the FCM. Subsequently, the patient received a second cycle of HD-Ara-C along with midostaurin, after which a CR with a positive MRD of 0.15% was still observed. The evaluation before scheduled allo-SCT indicated early disease recurrence (79% of AML cells with *FLT3*-ITD mutation). Salvage chemotherapy was introduced according to the FLAG regimen (fludarabine, cytarabine, filgrastim), after which the disease was found to be resistant. The following salvage chemotherapy regimens were applied: HD-Ara--C, CLAG-Ida (cladribine, cytarabine, idarubicin, filgrastim), still with no remission. Emergency access to gilteritinib, a second-generation *FLT3* inhibitor, was obtained. In the evaluation, 20 days after drug initiation, complete remission with incomplete hematologic recovery (CRi) was found with 0.9% MRD. Due to the increased percentage of blasts in the following days, it was decided to perform the allo-SCT rescue procedure from a matched unrelated donor. Sequential conditioning with melphalan, treosulfan and fludarabine was used. The patient died due to multiple organ failure on day 23 after allo-SCT, before haematopoiesis reconstitution, in the course of septic shock.

Case 2

A 59-year-old male patient suffering from hypertension and hypercholesterolemia was admitted to the haematology clinic in March 2020 due to anaemia and thrombocytopenia, in good general condition (ECOG PS 1). Laboratory tests revealed leukopenia with neutropenia (WBC 3.8 G/L), anaemia (Hb 5.7 mmol/L) and a normal PLT count (161 G/L). Moreover, biochemical tests showed increased erythrocyte sedimentation rate ([ESR] 99 mm/h) as well as CRP (20 mg/L) and D-dimers (1532 ng/mL) level. Peripheral blood smears were dominated by blast cells (52%). The cytology and FCM evaluation confirmed marrow infiltration by leukemic cells (82% and 70%, respectively) with LAIP: CD13+, CD33+, CD117+, HLA DR+, CD38+, CD31+, CD36+, CD11c+, CD64+, CD18+, CD123+, CD15–, CD34–, MPO–, TdT–. The cytogenetic examination revealed a normal karyotype (46,XY), and the FISH method excluded the presence of *PML-RARA* and *CBFB-MYH11* gene fusions. In molecular tests using PCR, the presence of the *FLT3*-ITD mutation (AR 0.68) was confirmed and *FLT3*-TKD *D835*, *NPM1*, *CEBPA*, *RUNX1-RUNX1T1*, and *BCR-ABL* mutations were excluded. Moreover, in the study with the next-generation sequencing (NGS) method, the presence of the *RUNX1*, *TET2*, and *DNMT3A* mutations was demonstrated. Based on this, the diagnosis of AML with the *RUNX1* mutation was established (provisional entity according to WHO 2016 classification), morphologically without signs of maturation. The patient was classified as an unfavourable prognostic group according to ELN 2017. In the echocardiography performed before the treatment, asymmetric septal hypertrophy and left ventricular relaxation disorders with normal contractility were described. The patient was qualified for intensive induction treatment according to DA-90 protocol (daunorubicin 90 mg/m^2 on days 1–3 and cytarabine 100 mg/m^2 in 24-hour infusion on days 1–7). Due to at this time of reimbursement for midostaurin in Poland, an application for the drug was submitted to a pharmaceutical company. Due to complex administrative procedures, it was not possible to add midostaurin during the induction phase of chemotherapy. Early haematological evaluation on day 14 showed aplastic bone marrow with no increased blasts in FCM. During the neutropenia, fever was present which was resolved with empiric antibiotic therapy. The evaluation after induction treatment showed a CR with an MRD of 0.3%. Due to the high cytogenetic and molecular risk, the patient was qualified for allo-SCT and the procedure of selecting an unrelated donor was initiated under the protocol used in the transplant centre. The patient then received post-remission treatment: 2 cycles with HD-Ara-C at the dose of 2 g/m^2 on days 1, 3, and 5 in combination with midostaurin at a dose of 50 mg every 12 hours administered orally on days 8–21. In FMC evaluation after the second consolidation cycle, MRD was negative (0.004%), and there was no *FLT3*-ITD mutation in the PCR test. However, in the assessment immediately before the allo-SCT procedure, an increase in MRD of up to 0.7% was observed and a reappearance of the *FLT3*-ITD mutation. After conditioning according to the FluBu2 regimen (fludarabine, busulfan), a stem cell transplant from a matched unrelated donor was performed in September 2020. In the prevention of graft-versus-host disease (GvHD), anti-thymocyte globulin (ATG), cyclosporin and methotrexate were used. The post-regeneration evaluation showed

CR with MRD and the mixed donor chimerism of 93%. Immunosuppressive treatment was limited and active MRD monitoring was implemented. Symptoms of GvHD were not observed.

Discussion

The first evidence of an unfavourable prognosis associated with the *FLT3*-ITD mutation comes from retrospective studies that compared the presence of the mutation at diagnosis and in possible relapse. A significantly higher frequency of mutations present in resistant patients indicated the persistent subclone as the cause of relapse [9]. Three-quarters of patients with *FLT3*-ITD mutation at diagnosis also show its presence in the relapse, with an increasing AR ratio. In the case of the *FLT3*-ITD mutation, the relapse rate and shorter OS depend mainly on AR value. The prognosis is also influenced by the coexistence of other mutations, including *NPM1* mutation, found in approximately 30% of patients. Detection of *NPM1* mutation in the absence or with an *FLT3*-ITD mutation with a low AR (< 0.5) is associated with a favourable prognosis. The presence of *FLT3*--ITD mutation with a high AR (≥ 0.5) together with the *NPM1* mutation indicates an intermediate prognosis, while the wild-type of *NPM1* gene results in an unfavourable prognosis [1, 10]. The coexistence of other high-risk mutations (e.g. *TP53*, *KMT2A*) also significantly worsens the prognosis. The prognostic significance of the *TKD* mutation is less well documented.

According to the current standard, *FLT3* mutation status should be assessed in every AML patient within 48–72 hours [1]. Although routine testing for the presence of *FLT3* mutation has been recommended by ELN since 2010, the diagnostics methods differ significantly between centres [11]. The challenge for diagnosticians is the technique of determinations and the lack of appropriate standardization. So far, the use of AR determinations mainly in clinical trials, less frequently in daily clinical practice, may be a challenge both in the determination and interpretation of the obtained results concerning insufficiently validated reference values. It seems necessary to develop international testing standards [12]. The presence of *FLT3* mutation may evolve in the course of the disease, therefore it is suggested that genetic tests should be repeated at various stages of treatment, especially at the time of disease recurrence. To date, the exact value of the AR cut-off point, above which the unfavourable prognosis and the risk of relapse increase, is ambiguous. The value above which a shorter OS was observed significantly differs depending on the studies (AR 0.51 and 0.78) [13, 14]. In the case of low and intermediate AR values, the prognostic significance is unconfirmed [14]. Absent at diagnosis *FLT3* gene mutation may reveal itself in relapse and worsen the prognosis (this applies more often to *FLT3*-ITD than *FLT3*-TKD mutation, 8% vs. 2%, respectively). According to the currently applicable standards, *FLT3* mutation cannot be used for MRD monitoring due to the lack of sufficient standardization of determinations [1]. However, the analysis of *FLT3*-ITD mutation status monitoring with NGS in patients treated in AMLSG 16-10 study, presented at the 62nd American Society of Haematology (ASH) Annual Meeting, seems to be a promising diagnostic tool, although still unavailable in routine practice [15].

The treatment of newly diagnosed AML with the presence of *FLT3* mutation is one of the major challenges in the daily practice of haemato-oncologists. The results of treatment with the first FLT3 inhibitors in monotherapy were disappointing as their effects were limited to an only transient decrease in blasts percentage. The effects of combining with standard chemotherapy remain the subject of clinical trials. In the SORAML trial with the use of sorafenib in combination with standard chemotherapy in patients with the newly diagnosed disease, an extended event-free survival (EFS) was achieved, but without a significant effect on OS [16]. The combination of sunitinib with conventional chemotherapy during induction and consolidation allowed to obtain CR in 50% and 38% of patients with *FLT3*-ITD and *FLT3*-TKD mutations, respectively [17]. Only the introduction to the treatment of newly diagnosed AML patients midostaurin with standard chemotherapy (in the group of 360 patients up to 60 years of age), for the first time in many years resulted in a statistically significant EFS [median 8.2 vs. 3 months, hazard ratio (HR) 0.78; p = 0.002] and OS (median 74.7 vs. 25.6 months; HR 0.78; p = 0.009) prolongation as compared to chemotherapy alone. The 4-year survival ratio in the study groups was 51.4% to 44.3% in favour of the group receiving the study drug. The CR rate was higher in patients taking midostaurin, but without statistical significance. In a posthoc analysis of all reported CRs within 30 days of the end of the intervention, the ratio was 68% versus 59% (p = 0.04) [18]. Limited access to midostaurin in Poland, lack of reiumbursment at the time when our patients were treated, resulted in a delay in treatment initiation and insufficient

experience in haematology centres. This may translate into the effects of the treatment and the depth of the responses obtained. In both of the presented cases, midostaurin was administered in combination with high doses of cytarabine, as the drug was unavailable at the induction chemotherapy phase. However, despite this, the use of combination therapy allowed for remission (case 1) and negative MRD (case 2).

There is no single standard of care in the case of relapse and primary refractory disease, and the treatment of this group of patients remains a huge challenge. Recruitment to clinical trials should be a priority. The efficacy of midostaurin in the group of patients with R/R AML has not been confirmed [4]. The use of lestaurtinib in refractory patients did not show any improvement in response rates or increased OS [12]. In phase I clinical trial with R/R AML patients receiving sunitinib, only a short-term partial response was achieved [19]. In the QuANTUM-R study, the survival of patients in the quizartinib group was similar to that of patients receiving salvage chemotherapy, while the toxicity of the treatment turned out to be unacceptable [20]. The hopes were raised by the results of the ADMIRAL study, in which the use of gilteritinib compared to placebo resulted in OS extension (9.3 vs. 5.6 months, respectively) and a higher CR and CRi rate (35% vs. 15.3%, respectively) [21]. Also, the percentage of patients who qualified for allo-SCT was higher in the gilteritinib group. This study became the basis for the registration of gilteritinib monotherapy in 2019 in the treatment of R/R AML with *FLT3* mutation [21]. There is also evidence confirming the effectiveness of treatment with second-generation *FLT3* kinase inhibitors in patients previously treated with midostaurin or sorafenib [22]. The presented case of the first patient previously treated with midostaurin proves the validity of the use of gilteritinib in the treatment of chemoresistant AML *FLT3* recurrence. Unfortunately, gilteritinib is still unavailable for Polish patients due to the lack of reimbursement. Clinical trials with gilteritinib in induction, consolidation therapy and maintenance therapy after allo-SCT are ongoing.

The likelihood of regaining CR in R/R AML *FLT3*-ITD patients after conventional treatment is low and the responses are short-termed [23]. Therefore, it is crucial to qualify patients for allo-SCT as the only method that allows for a permanent prolongation of survival. However, relapse rates after allo-SCT remain high. Present MRD before the transplantation procedure is presented as one of the failure reasons. In light of new studies, it seems important to consider maintenance treatment after allo-SCT, and this decision should be made, for example, based on MRD status before allo-SCT. In the phase II RADIUS trial, the addition of maintenance midostaurin in patients after allo-SCT reduced the risk of relapse within 18 months of transplantation by 46%, but the safety of such treatment has not yet been confirmed [24]. On the other hand, in phase II and III study with sorafenib as maintenance therapy after allo-SCT, it was proved that the risk of relapse and death was reduced compared to the control group [25, 26]. Based on the above results, it seems justified to implement maintenance treatment with an *FLT3* kinase inhibitor in the second presented case to reduce recurrence risk. This therapy, however, is still not registered or reimbursed for this indication.

In conclusion, targeted therapy with midostaurin in combination with chemotherapy for AML with *FLT3* mutation has become the current standard of care, however, the incidence of disease relapses remains a serious problem. Therefore, it is necessary to conduct further studies on the use of tyrosine kinase inhibitors and combination therapy.

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