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Midostaurin in the treatment of a patient with acute myeloid leukaemia with *FLT3*-TKD mutation and *NPM1* mutation

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Abstract

Acute myeloid leukaemia (AML) is aggressive cancer with a diverse clinical course which mainly results from the heterogeneous and complex molecular landscape of the disease. For some genetic alterations, in particular mutations in the FMS-like tyrosine kinase 3 (FLT3) gene, the progno-sis of patients with newly diagnosed AML depends on the coexistence of other genetic disorders. A thorough understanding of the interactions between mutations is key to improving risk strati-fication in newly diagnosed AML and personalizing therapy. The addition of midostaurin, an FLT3 tyrosine kinase inhibitor, to standard chemotherapy improved outcomes in the unfavourable prognostic group of AML patients. This research describes a therapeutic strategy in a patient with newly diagnosed AML with FLT3-tyrosine kinase domain (TKD) mutation and wild-type NPM1 who has received a standard remission induction and consolidation chemotherapy in combination with midostaurin, followed by maintenance therapy with an FLT3 inhibitor and haploidentical allogeneic hematopoietic stem cell transplantation.

Key words: acute myeloid leukaemia, *FLT3*-TKD mutation, midostaurin, haploidentical hematopoietic stem cell transplantation

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Introduction

Acute myeloid leukaemia (AML) is a dynamic malignant neoplasm characterized by the uncontrolled proliferation of blasts derived from a precursor myeloid cell undergoing neoplastic transformation. Bone marrow infiltration by blast cells leads to haematopoiesis failure, manifested by anaemia, neutropenia and thrombocytopenia. Due to the invasive potential of leukaemia cells in the course of the disease, tissues and internal organs may also be affected, in particular the central nervous system (CNS).

The results of standard intensive AML treatment in the group of younger patients remain unsatisfactory, with a 5-year relapse-free survival (RFS) and 5-year overall survival (OS) rates of 53.4% and 54%, 25.8% and 30.6%, and 11.9% and 12.2% of patients, respectively, in the favourable, intermediate and unfavourable prognosis group, defined based on cytogenetic and molecular revised 2017 European LeukemiaNet (ELN) criteria [1, 2]. Due to the genetic heterogeneity of AML, the possibility of improving outcomes is seen in personalized therapy, consisting in supplementing standard intensive chemotherapy with new drugs targeting molecular disorders present in an individual patient with newly diagnosed AML. *FLT3* (fsm-like tyrosine kinase 3) gene mutations occurring in the

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form of internal tandem duplication (ITD) or point mutations in the tyrosine kinase domain (TKD), resulting in increased activity of FLT3 kinase are found in 25% and 7–10% of cases, respectively, which makes them the most common single genetic alteration in patients with newly diagnosed AML [3, 4]. The introduction of midostaurin, a non-selective tyrosine kinase inhibitor that inhibits, in particular, the activity of FLT3 kinase, significantly changed the current management of patients with newly diagnosed AML with *FLT3*-ITD or TKD mutations and constituted a milestone in the process of personalizing AML treatment.

This paper describes the management strategy of the patient with newly diagnosed *FLT3*-TKD/ /*NPM1*^{wt} AML, initially treated at the Department of Haematology, Institute of Haematology and Transfusion Medicine in Warsaw.

Case report

A 63-year-old female patient was transferred in June 2019 to the Department of Haematology of the Institute of Haematology and Transfusion Medicine in Warsaw from the Hospital Emergency Department, where she was admitted because of fainting without losing consciousness in the course of fever above 40°C. On admission, the patient's general status was average, with an Eastern Cooperative Oncology Group (ECOG) performance level of 2. On physical examination, evidence of generalized mucocutaneous haemorrhagic diathesis, inflammatory infiltration in the right groin area, and pneumonia symptoms were discovered. Agranulocytosis (neutrophils 0.04 G/L), significant thrombocytopenia (platelets 37 G/L), and anaemia (haemoglobin 6.0 g/dL) were discovered in the peripheral blood counts. In the manual peripheral blood smear, 89 per cent of blasts were identified. High levels of C-reactive protein (CRP) (250 mg/L), increased activity of lactate dehydrogenase (1360 IU/L), and slight coagulogram deviations [time prothrombin time (PT) 18 s; activated partial thromboplastin time (APTT) 42 s; international normalized ratio (INR) 1.7] were among the significant biochemical deviations. The myelogram can describe 87 per cent of blasts. According to the FAB (French–American–British) classification, the immunophenotype of the blasts analysed revealed AML M1/M2. In cytogenetic analysis, a normal female karyotype was identified. The *FLT3*-TKD mutation (D835/I836) was discovered in molecular assays. The nucleophosmin gene (*NPM1*^{mut}), *FLT3*-ITD mutation, and *CBF* (core-binding factor) gene rearrangement, i.e. t(8;21)(q22;q22.1) or inv(16)(p13;1q22) or t(16;16)(p13.1;q22) were all negative.

Intensive supportive care was introduced, leading to significant improvement in the general condition. The patient was qualified for the intensive treatment indicated for patients over 60 years of age according to the DA60 protocol (daunorubicin 60 mg/m^2 on days 1–3, cytarabine 100 mg/ /m^2 on days 1–7) in combination with midostaurin. The course of remission-inducing treatment was complicated by bacteraemia of *Pseudomonas aeruginosa* and *Enterococcus faecium* aetiology, and by fainting without loss of consciousness. Diagnostics were extended to include a head computed tomography (CT) scan, which revealed a hyperdense band located at the base of the right frontal lobe. A diagnostic lumbar puncture was performed. The general examination of the cerebrospinal fluid (CSF) revealed normal cytosis and elevated protein levels. The result of cytological examination: 66% lymphocytes, 30% monocytes, and 2% atypical cells. Flow cytometry test detected 30% of AML cells. Primary CNS leukemic involvement was diagnosed. Intrathecal chemotherapy (cytarabine, methotrexate and dexamethasone) was administered, resulting in the eradication of AML cells from CSF.

The haematological evaluation was performed after complete CBC regeneration revealing complete remission (CR). The patient then received 4 consolidation cycles with high dose cytarabine in combination with midostaurin. At the same time, intrathecal treatment was continued. No significant treatment complications were observed. Since November 2019, midostaurin has been used as monotherapy as part of the maintenance treatment until allogeneic hematopoietic stem cell transplantation (allo-HSCT). Despite having human leukocyte antigens (HLA) fully matched unrelated donor, the patient chose the allo-HSCT option from a haploidentical donor and underwent this procedure outside the Institute of Haematology and Transfusion Medicine in Warsaw. Hematopoietic stem cell transplantation after fludarabine-busulfan conditioning was performed in August 2020. No significant complications were observed in the early post-transplant period. The haematological evaluation performed on +28 post-transplant days revealed measurable residual disease (MRD) with donor chimerism of more than 95%. The patient was qualified for further follow-up at the transplant outpatient clinic.

Discussion

According to genomic data, the prognostic value of *FLT3*-TKD mutation in patients with newly diagnosed AML should be considered in the context of coexistence of other genetic disorders, including *NPM1*^{mut}, and *CBF* gene rearrangement or *CEBPA* gene biallelic mutation, which define subgroups with favourable prognosis [5–7]. The results of a recently published study with a total of 1,282 cases of AML, including 21 (8%) patients with the *FLT3*-TKD mutation coexisting with *NPM1*^{mut} and 18 (7%) patients with the *FLT3*-TKD mutation without the *NPM1* mutation (*NPM1*^{wt}, wild-type), showed that patients with *FLT3*-TKD mutation coexisting with *NPM1*^{mut} (*FLT3*-TKD/ /*NPM1*^{mut}) achieve significantly longer median OS compared to patients with *FLT3*-TKD mutation alone (*FLT3*-TKD/*NPM1*^{wt}) (median OS not reached vs. 13.8 months) [5]. Importantly for the interpretation of these results, the *FLT3*-TKD/ /*NPM1*^{mut} and *FLT3*-TKD/*NPM1*^{wt} groups, although relatively few, were well balanced in terms of cytogenetics according to ELN risk stratification criteria [2], as well as in terms of remission induction treatment applied and post-remission therapy [5]. The constellation of *FLT3*-TKD/*NPM1*^{mut} mutations defined the group with the best prognosis and significantly longer RFS (median not reached vs. 18.3 months) and a trend towards longer OS compared to the group with isolated *NPM1*^{mut}. This group did not benefit from allo-HSCT as part of post-remission consolidation [5].

The positive and negative prognostic value of the constellation of *FLT3*-TKD/*NPM1*^{mut} and *FLT3*-TKD/*NPM1*^{wt} mutations, respectively, is confirmed by the preliminary results of genomic analysis in over 7,000 AML patients, conducted as part of the Harmony Alliance public-private partnership, presented at 2020 European Society of Haematology (EHA) Annual Congress, but so far unpublished [8]. Taken together, these data indicate that the favourable prognostic value of *NPM1*^{mut} is, paradoxically, significantly enhanced by the coexistent *FLT3*-TKD mutation, in contrast to the *FLT3*-ITD mutation, which antagonizes this effect [4].

The combination of intensive chemotherapy with midostaurin is currently the treatment of choice in patients with newly diagnosed AML and *FLT3*-TKD or *FLT3*-ITD mutations eligible for intensive therapy [9, 10]. The phase III RATIFY trial, which was the basis for establishing the new standard of care, assumed the combination of classic induction (DA60) and post-remission consolidation (4 cycles of high-dose cytarabine) chemotherapy with midostaurin or placebo, followed by 12-month maintenance treatment with midostaurin or placebo as monotherapy [11]. Allo-HSCT was acceptable in the first CR (CR1) or later during the treatment. Treatment with midostaurin was associated with a 22% reduction in the risk of death compared with placebo [hazard ratio (HR); 0.78; p = 0.009]. During the median follow-up period of 59 months, the median OS in the group treated with classic chemotherapy combined with midostaurin was 74.7 months and was significantly longer than in the group treated with classic chemotherapy plus placebo (median OS was 25.6 months). The clinical benefits of adding midostaurin to chemotherapy were observed both in the group of patients with the *FLT3*-ITD mutation (regardless of the level of mutant allele burden) and in the group of patients with the *FLT3*-TKD mutation [11].

The results of a recently published post hoc analysis of the phase III RATIFY study, including only AML patients with the *FLT3*-TKD mutation (n = 163), showed that the addition of midostaurin to intensive chemotherapy is associated with a significant improvement in event-free survival (EFS) with a 5-year EFS rate of 45.2% compared to 30.1% in the group treated with intensive chemotherapy for combination with placebo [6]. However, better EFS in the group of patients treated with midostaurin did not translate into a significant OS improvement [6]. This can be explained by the possibilities of effective salvage therapy for recurrent AML with the *FLT3*-TKD mutation. It is worth noting, however, that the RATIFY study was not statistically powered to perform a subgroup analysis, and therefore the presented data should be interpreted with caution. As in previous studies, the coexistence of *FLT3*-TKD and *NPM1*^{mut} mutations or *CBF* gene rearrangement defined the groups with the best prognosis [6]. The 5-year OS and EFS rates in patients with the *FLT3*-TKD/ *NPM1*^{wt} mutations were 45.7% and 24.6%, respectively, and were significantly lower compared to the *FLT3*-TKD/*NPM1*^{mut} group (69.8% and 48.4%, respectively) [6].

According to the results of the presented studies, therapeutic decisions, particularly qualification for allo-HSCT in CR1, should consider the constellation of genetic alterations, and not the presence of individual mutations. In the case of the coexistence of the *FLT3*-TKD mutation with *NPM1*^{mut} or one of the *CBF* gene rearrangements, it seems acceptable to withdraw from allo-HSCT,

unless there are independent indications, including the presence of MRD. In the discussed case, the patient was qualified for allo-HSCT due to both the presence of isolated *FLT3*-TKD mutation (*FLT3*--TKD/*NPM1*^{wt}) and CNS leukemic involvement. Primary CNS involvement, found in 0.6–5% of newly diagnosed AML cases, is a poor prognosis factor [12]. According to the results of the recently published retrospective analysis, the 5-year overall survival rate in the group of patients with primary CNS involvement is 11%, compared to 30% in the group of patients without CNS involvement at the time of AML diagnosis [13].

The role of maintenance therapy with FLT3 inhibitors after allo-HSCT in AML patients with the *FLT3*-TKD mutation is unclear. Contrary to patients with AML and the *FLT3*-ITD mutation [14], there are currently no data that would justify the use of maintenance therapy with FLT3 inhibitor in AML patients with the *FLT3*-TKD mutation [14].

Summary

Midostaurin in combination with classical chemotherapy is currently the treatment of choice in patients with newly diagnosed AML with the *FLT3*-TKD mutation. Qualification for allo-HSCT in CR1 should be based on the coexistence of other genetic alterations (such as *NPM1*^{mut}, *CBF* gene rearrangement, or *CEBPA* biallelic mutation) as well as MRD status. The role of maintenance treatment after allo-HSCT in the group of AML patients with the *FLT3*-TKD mutation remains undefined.

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