Annals of Clinical Case Reports

Case Report
Published: 15 Oct, 2021

Poor Prognosis of Acute Myeloid Leukemia with *FIP1L1-PDGFRA* Fusion Gene in 27-Year-Old Male Treated with Tyrosine Kinase Inhibitors and Allo-HSCT

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Abstract

Acute Myeloid Leukemia (AML) with *FIP1L1-PDGFRA* fusion gene is a group of uncommon myeloid neoplasms. *FIP1L1-PDGFRA* positive AML is considered to have a good prognosis when using tyrosine kinase inhibitors in the course of treatment.

Hereby we report a case of a 27-year-old male with *FIP1L1-PDGFRA* positive eosinophilia-associated AML, resistant to imatinib, dasatinib as well as intensive chemotherapy followed by allogeneic hematopoietic stem cell transplantation. The course of our patient's treatment is not consistent with the reports of most authors.

Case Presentation

A 27-year-old male was diagnosed in December 2013 as Acute Myeloid Leukemia (AML) FAB M4. In Peripheral Blood (PB) leukocytes is was 113 G/l with 58% of myeloid blasts infiltration, anemia and thrombocytopenia. He did not have peripheral lymphadenopathy or organomegaly. Cytogenetics showed normal male karyotype with no chromosomal aberrations in FISH. *CBFB-MYH11*, *BCR-ABL1*, *FLT3-ITD*, *NPM1* and c-kit were excluded in RT-PCR. The diagnosis was preceded by mild megaloblastic anemia. As induction chemotherapy the patient received DAC regimen (daunorubicin, cytarabine, cladribine) and he achieved hematological Complete Remission (CR), however, with eosinophilia observed both in BM and PB smears. Eosinophilia as a reaction has been ruled out. Identification of *FIP1L1-PDGFRA* by RT-PCR was performed using material from the diagnosis (PB) and the time of remission assessment (BM). Both specimens were positive. Then the patient received HAM (high dose cytarabine/mitoxantrone) chemotherapy. One month later the patient experienced progressive leukocytosis with eosinophilia. Immunophenotype of BM showed 63% myeloid blasts infiltration, and then imatinib 400 mg daily was administered. After one month, the patient achieved hematological CR and the treatment continued with imatinib 200 mg daily. After four months, the patient reported general symptoms. His leukocytosis reached 27 G/L with eosinophilia. BM was infiltrated in 94% by myeloid blasts with positive *FIP1L1-PDGFRA*, and then dasatinib 100 mg daily was started. The therapy was complicated by severe pneumonia, oral candidiasis, *Clostridium difficile* infection and enteropathy. The patient achieved hematological CR and then the search for a donor for allogeneic Hematopoietic Stem Cells Transplantation (allo-HSCT) began. After three months, another relapse was noted with leukocytosis 70 G/L and BM infiltration by 24% of blasts with no eosinophilia. CLAG-M (cladribine, cytarabine, filgrastim, mitoxantrone) reinduction chemotherapy was administered. The patient achieved hematologic CR and received allo-HSCT from an unrelated donor. A reactivation of CMV infection was a problem after the transplantation. After four months, a relapse was documented with 30% of BM infiltration. At this time, BM cytogenetics showed complex karyotype including del (17p) and RT-PCR revealed the presence of the *FIP1L1- PDGFRA* fusion. The patient received DAC reinduction chemotherapy. The second rescue, haploidentical stem cell transplant from the patient's brother as a donor was carried out. Despite intensive supportive care the patient died due to pulmonary infection in +13 day after procedure.

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Received Date: *10 Sep 2021*
Accepted Date: *30 Sep 2021*
Published Date: *15 Oct 2021*

Citation:
Spyra-Górny Z, Barchnicka A, Bodzenta E, Jaźwiec B, Grosicki S. Poor Prognosis of Acute Myeloid Leukemia with FIP1L1-PDGFRA Fusion Gene in 27-Year-Old Male Treated with Tyrosine Kinase Inhibitors and Allo-HSCT. Ann Clin Case Rep. 2021; 6: 2031.

ISSN: 2474-1655

Discussion

FIP1L1-PDGRA mutation is extremely rarely detected in AML [1-4]. This fusion gene generates protein complex, which acts like tyrosine kinase and causes constant proliferation of eosinophils from progenitor cells despite lack of ligand. The mechanism is analogous to *BCR-ABL1* mutation in Chronic Myeloid Leukemia (CML). Furthermore, *FIP1L1-PDGFRA* fusion gene is proved to be about 100-fold more sensitive to inhibitors of tyrosine kinase enzymes than *BCR-ABL1*. That is why it is possible to treat patients with *FIP1L1-PDGFRA* positive AML-Eo with lower doses of imatinib with success [1,2,5]. Nevertheless, a resistance to imatinib might occur related to the acquisition of the T674I mutation in most cases, which is analogous to *BCR-ABL1 T315I* mutation in CML or because of D842V mutation [1-5].

We know that several descriptions of the course of treatment of patients with *FIP1L1-PDGFRA* positive AML, whose treatment with TKIs was successful. Barraco et al. described 41-year-old patient with *FIP1L1-PDGFRA* positive *AML-Eo*, *BCR-ABL1*, *CBFB-MYH11*, *RUNX1-RUNX1T1*, *KIT D816V* negative who was treated using imatinib 100 mg to 200 mg daily. The patient achieved hematologic, cytogenetic and molecular response without side effects [1]. Metzgerold et al. presented in their paper seven patients with eosinophilia and *FIP1L1-PDGFRA* fusion gene. Five of them were diagnosed as AML and two others as lymphoblastic T-cell non-Hodgkin lymphoma. All patients were treated using imatinib 100 mg to 400 mg daily and all of them achieved hematologic and molecular CR [3].

In this case we observed resistance to imatinib, dasatinib, intensive chemotherapy and allo-HSCT with fatal outcome in our patient. Undoubtedly, the course of the disease of our patient is different compared to most previous reports. Sorour et al. had similar observation in the case of a 25-year-old male with *FIP1L1-PDGFRA* positive AML-Eo and myelodysplasia resistant to imatinib. In the beginning the patient received FLAG-Ida induction, and reached CR. Subsequently, imatinib 400 mg daily was given, and patient underwent allo-HSCT. Six months after transplantation BM was positive for *FIP1L1-PDGFRA* and imatinib 400 mg to 600 mg was ordered. After 12 months AML relapsed with the presence of *D842* mutation, which is known to be resistant to imatinib, so sensitive to dasatinib and he was started with dasatinib treatment, which was not tolerated and the patient died. Authors suggested that the outcome of this kind of AML is not as good as previously thought [4]. Our patient's case was probably preceded by myelodysplasia and the course of treatment proved to be relapsed and ultimately refractory. Other authors described a case report of a patient *FIP1L1-PDGFRA* positive with AML-Eo, treated with imatinib 100 mg daily. After five months of therapy the relapse and *T674I* mutation were revealed. A patient received sorafenib 400 mg daily and underwent allo-HSCT with hematologic and cytogenetic remission. Unfortunately, the patient died because of respiratory failure five months after the transplantation [5].

In conclusion, we suggest performing the identification of *FIP1L1-PDGFRA* fusion gene in all patients with diagnosis of AML and eosinophilia. Mutational studies of *FIP1L1-PDGFRA* should be also completed to choose the most effective TKI. Unfortunately, at the time we treated the described patient mutational studies were not available in our department (Figure 1).

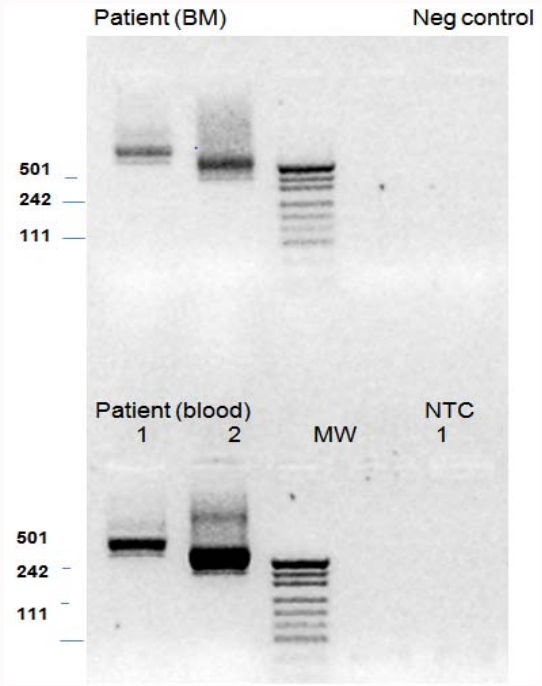

Figure 1: Illustration of agarose gel electrophoresis of *FIP1L1-PDGFRA* fusion transcript detection by two step amplification of cDNA from peripheral blood and Bone Marrow (BM) of analyzed patient. Nested PCR amplification of was performed using primers published by Vandenberghe P et al., Leukemia (2004) 18, 734-742. Amplification product was easily detectable already after single round of amplification, both in BM and peripheral blood. *Nega/ve control*-cDNA from *FIP1L1-PDGFRA* negative HL60 cell line, *NTC*-non template control - water instead of cDNA, *MW*-pUC/Msp I DNA size marker.

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