Case Report

Acute Myeloid Leukemia with Platelet-Derived Growth Factor Receptor β (PDGFRβ) Rearrangement Successfully Treated with Intensive Chemotherapy in Combination Withimatinib- A Case Report

Ewelina Witkowska¹,², Katarzyna Jerzmanowska¹,², Ewa Wawrzniak¹,², Marta Robak², Agnieszka Wierzbowska¹,², Agnieszka Pluta¹,²*

¹Department of Haematology, Medical University of Lodz, Lodz, Poland
²Department of Haematology, Copernicus Provincial Multidisciplinary Oncology and Traumatology Centre, Lodz, Poland

*Corresponding Author: Agnieszka Pluta, Assistant Professor, Department of Haematology Medical University of Lodz, Copernicus Provincial Multidisciplinary Oncology and Traumatology Centre, ul. Ciolkowskiego 2, 93-510 Lodz, Poland, Tel: 48426895191

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Abstract

Acute myeloid leukemia (AML) is a heterogeneous clonal stem cell malignancy. Several subgroups of AML have been identified based on multiple genomic and proteomic aberrations; these demonstrate different clinical features, response to treatment and prognosis. Rearrangements in the platelet-derived growth factor receptor β (PDGFRβ) gene result in greater constitutive enzymatic activity (tyrosine kinase) and deregulation of haematopoiesis, similarly to BCR-ABL1 in chronic myeloidleukemia (CML). PDGFRβ
gene rearrangements are infrequent entities, which are mostly diagnosed in patients presenting with atypical CML, chronic myelomonocytic leukemia (CMML), myelodysplastic/myeloproliferative disorders (MDS/MPN) or juvenile myelomonocytic leukemia (JMML). PDGFRβ-positive AML is extremely rare, accounting for well below 1% of all cases.

In this article, we present the case of a 31-year-old woman with AML and abnormal karyotype with PDGFRβ rearrangement, who was treated with intensive chemotherapy combined with low-dose imatinib. Complete remission (CR) was achieved and imatinib was used as maintenance treatment. The patient remains in CR with disease-free survival (DFS) of 41 months.

**Keywords:** Acute myeloid leukemia; PDGFRβ; Imatinib

1. **Introduction**

Acute myeloid leukemia (AML) is a malignant haematological disease characterized by an abnormal proliferation of myeloid progenitor cells that interferes with normal haematopoiesis [1]. The disease accounts for approximately 80% of adult acute leukemias and approximately 15% of childhood leukemias [1-3], with four new cases per 100000 people per year [1-3]. AML may affect people at any age, but most patients are over 65 at the time of diagnosis [4]. Acute myeloid leukemias are classified according to the presence of cytogenetic abnormalities and the corresponding fusion genes. The presence of such cytogenetic and molecular aberrations is of diagnostic importance, acts as an independent prognostic factor, and hence influences the choice of treatment [5]. The platelet-derived growth factor receptor (PDGFR) consists of two subunits, α and β, and acts as a protooncogene; it belongs to the receptor tyrosine kinase (RTK) family, together with various other transmembrane receptors including KIT receptor, colony stimulating factor 1 receptor (CSF1R) and Fms-like tyrosine kinase 3 receptor (FLT3) [6-8]. The platelet-derived growth factor ligands (PDGF-L): A, B, C, D and their receptors play a key role in proliferation, differentiation, growth and development of the cell, as well as in regulating the cell microenvironment [9, 10]. The activation of PDGFR results in inciting pathways that promote cell survival, such as mitogen-activated protein kinase (MAPK) or signal transducer and activator of transcription (STAT) [11]. Their abnormal expression plays an important role in many diseases, including cancer [10]; a high rate of PDGFR defects (more than 10%) have been reported in melanoma (~10–30%), lung (~10–20%), glioblastoma (~15–20%), bladder (15–20%), prostate (~20%), colorectal (~10–15%), and ovarian (~10–20%) cancers [11]. However, breast, liver and renal cancer as well as acute myeloid leukaemia and myeloproliferative disorders, are characterized by consistently lower incidences (<10%) [11, 12]. PDGFR gene rearrangements account for well below 1% of all cases of AML [12]. PDGFR mutations, including PDGFRα and PDGFRβ, are most often encountered in chronic myeloproliferative neoplasm (MPN) [12]: the incidence of PDGFRβ rearrangement cases in MPN is 1.8% [13].

2. **Case Report**

In June 2017, a 31-year-old woman was admitted to the Department of Hematology, Medical University of Lodz, for a diagnosis of hyperleukocytosis. The patient had
previously been hospitalized for eight days in the Department of Infectious Diseases with a suspicion of mononucleosis due to fever, enlarged submandibular lymph nodes, massive sores on the tonsils and hepatomegaly. She complained of recurrent pharyngitis, four times in the previous six months, with no response to the administered treatment: cefuroxime and glucocorticosteroids. Finally, mononucleosis was excluded. AML was suspected, and the patient was admitted to the Hematology department. Upon admission, peripheral blood morphology revealed mild anaemia (haemoglobin of 10.8 g/dl, mean corpuscular volume (MCV) 91.7 fL), hyperleukocytosis (white blood cells 131.87 G/L), thrombocytopenia (platelets 134 G/L). A peripheral blood smear showed 50% blasts, 7% promyelocytes, 2% segmented neutrophils, 30% monocytes, 10% lymphocytes and 1% eosinophils. Notably, no eosinophilia or basophilia was observed (Figure 1a).

Bone marrow aspirate revealed 69% of myeloblasts (Figure 1b) without dysplastic features. Immunophenotypic analysis with eight-colour flow cytometry confirmed the myeloid origin of the blasts, with an expression of CD13 (32.4%), CD14 (15.7%), CD33 (96.8%), CD117 (14.7%), CD15 (88%), CD38 (87.4%), HLA-DR (82.2%), CD45 (99.3%). Laboratory studies showed normal kidney function (creatinine 0.66 mg/dl; urea 28.7 mg/dl; uric acid 4.8 mg/dl; potassium 3.3 mmol/l; sodium 140 mmol/l), no signs of enzymatic liver damage (total bilirubin 0.2 g/dl; direct bilirubin 0.1 mg/dl; ALT 47 U/l; AST 31 U/l; GGTP 45 U/l), increased lactate dehydrogenase activity (LDH 543 U/l), hyperferritinemia (463.4 ng/ml), normal CRP values (2.50 mg/l). The following infections were excluded: hepatitis B virus (anti-HBs negative), hepatitis C virus (anti-HCV negative), human immunodeficiency virus (anti-HIV negative), Epstein-Barr Virus (anti-EBV IgM negative, anti-EBV IgG positive) and cytomegalovirus (anti-CMV IgM negative, anti-CMV IgG positive). Cytogenetic analysis of bone marrow cells performed at diagnosis revealed abnormal karyotype: 46, XX, t(2;5) (q32-33;q32) [11]/46, XX[3] with PDGFRβ (5q32-33.1) rearrangement confirmed by fluorescent in situ hybridization (FISH). Break Apart Probe (MetaSystems) was performed and showed PDGFRβ gen rearrangement in 90% of interphase nuclei and 8/10 metaphases. Additionally, painting probes for chromosome 2 and 5 were used to confirm balanced translocation t (2;5) (Figure 2).

The following diagnosis was thus established: de novo AML, NOS (not otherwise specified), 46, XX, t(2;5) (q32-33;q32) [11]/46, XX[3].ish(2;5) (5`PDGFRB+;3`PDGFRB+) [8/10].nucish (PDGFRBx2) (3`PDGFRBsep5`PDGFRBx1) [90/100], FLT3-ITD (negative), BCR-ABL1 (negative), WT1 (positive), MLL-PTD (negative), RUNX1-RUNXI (negative), CBFB-MYH11 (negative), intermediate cytogenetic and molecular risk according to European LeukemiaNet classification (ELN 2017). The patient met the criteria for intensive chemotherapy and was offered standard induction treatment according to Polish Adult Leukemia Group (PALG) recommendations. A DAC (daunorubicin: 60 mg/m², iv, days 1-3; cytarabine: 200 mg/m², iv, days 1-7; cladribine: 5 mg/m², iv, days 1-5) induction cycle was commenced [14, 15].

Before starting chemotherapy, the patient was diagnosed with superficial vein thrombosis in the left calf, which was treated with low molecular weight heparin. Doppler ultrasound showed complete regression of thrombotic changes in four weeks.
The post-treatment aplasia period lasted 18 days and was complicated by fever up to 39°C with clinical and radiological features of bilateral pneumonia. Moreover, bacteraemia of methicillin-resistant *Staphylococcus haemolyticus* was diagnosed. Broad-spectrum and targeted antibiotic therapy (glycopeptides, carbapenems) was applied, resulting in improved general condition and pneumonia regression. During the period of aplasia, G-CSF (granulocyte colony-stimulating factor) was not administrated. Throughout hospitalization, the patient required a transfusion of six units of red blood cells and 20 units of platelets. Due to the *PDGFRβ* rearrangement, 100mg imatinib was administered once a day from the thirtieth day of the induction cycle. The hospitalization time was 35 days. Complete remission (CR) was achieved within 43 days. Between July and December 2017, the patient received three intensive consolidation courses (first course of cytarabine in a dose 2000 mg/m² every 12 hours, iv, days 1-3; mitoxantrone: 10 mg/m², iv, days 3-5, second and third cytarabine: 2000 mg/m² every 12 hours, iv, days 1-3-5).

During each consolidation, imatinib was discontinued during the period of bone marrow aplasia for approximately 14 days. The patient was not qualified for allogeneic stem cell transplantation (allo-HCT) due to the lack of a sibling donor. The patient is in follow up in CR. Karyotype by conventional cytogenetics and *PDGFRβ* by FISH remain normal after 44 months from diagnosis. Molecular minimal residual disease, *PDGFRβ* is also negative. The imatinib treatment (100 mg daily) is ongoing. Overall survival is 44 months, and disease-free survival is 42 months.

![Figure 1: Peripheral blood, magnification 31.5x (Panel A) and bone marrow smear, magnification 31.5x (Panel B).](image-url)
3. Discussion

This report examined a case of t(2;5) (q32-33;q33) translocation resulting in a rearrangement of the PDGFRβ gene (5q32-33.1) in an AML patient. This kind of gene abnormality is extremely rare in patients diagnosed with AML [16]. Only a few cases of this AML subtype have been recorded to date. The fourth edition of the WHO classification, published 2008, introduced a new class of hematopoietic diseases: myeloid and lymphoid neoplasms with eosinophilia and abnormalities in PDGFRα, PDGFRβ, and FGFR1 genes [17]. This list was supplemented with the PMCL-JAK2 aberration in 2016 [18]. The myeloid neoplasms characterised by PDGFRβ rearrangement have wider phenotypic and genotypic diversity than the neoplasms associated with PDGFRα rearrangement. For example, phenotypic changes have been observed in chronic eosinophilic leukemia, chronic myelomonocytic leukemia (usually with eosinophilia), atypical chronic myeloid leukemia (usually with eosinophilia), primary myelofibrosis, juvenile myelomonocytic leukemia with eosinophilia, AML (without eosinophilia), and chronic basophilic leukemia [19]. It has been reported that patients with PDGFRβ rearrangements, including those with AML, respond well to tyrosine kinase inhibitors such as imatinib [16]. Previous studies indicate that low-dose imatinib (100 mg/day) might have the same efficacy as higher dose imatinib (400 mg/day) in treating myeloid neoplasms with PDGFRβ abnormalities, such as atypical chronic myeloid leukemia [20].

The present study reports the case of a 31-year-old woman who was diagnosed with AML 46, XX, t(2;5) (q32-33;q32) with PDGFRβ rearrangement, stratified to the intermediate cytogenetic and molecular risk group according to European LeukemiaNet 2017 [21, 22]. The patient did not have an
Michel et al. present a case of a 53-year-old woman with a diagnosis of an AML and NPM1 with PDGFRβ mutations. The patient initially received induction chemotherapy and one cycle of consolidation, followed by allo-SCT on account of persistence of NPM1-positive measurable residual disease (MRD). The patient relapsed three months later; at that point, PDGFRβ rearrangements were given as the reason for recurrence. As she demonstrated no response to intensive reinduction chemotherapy, 400 mg/day imatinib was administered. After achieving a fast hematologic response, a second allo-HCT was performed, and the dosage of imatinib was decreased to 100 mg/day, three times a week. The imatinib maintenance was stopped after 10 months when patient achieved NPM1-negative molecular remission. This led to a molecular relapse in less than a year and a half. Treatment with imatinib was restarted and again, molecular remission was achieved. This example confirms the efficacy of TKI treatment in AML with PDGFRβ rearrangement [24]. Arefi et al. [13] examined the incidence of myeloproliferative neoplasms (MPN) with PDGFRβ rearrangements and the frequency of responses to imatinib therapy. The findings indicate the effectiveness of imatinib treatment in patients with PDGFRβ mutations. Hence, this kind of rearrangement leads to the production of constitutive enzymatic activity (tyrosine kinase activity) and deregulation of haematopoiesis [13]. The published data generally recommends the use TKI-based treatment in all patients with PDGFRβ rearrangements.

Chan et al. studied 26 cases of patients with MPN and PDGFRβ rearrangements who received therapy with imatinib. Three patients started the imatinib treatment with a dose of 100 mg/day, and all achieved hematologic response in four months. This article suggests that patients with this kind of mutation may be more sensitive to imatinib than those who are CML-BCR-ABL1 positive: four patients who began therapy with a dosage lower than 400 mg demonstrated rapid and durable complete cytogenetic response or molecular remission, and none of the seven patients whose imatinib doses were reduced experienced disease progression. Importantly, the reported durability of responses to tyrosine kinase inhibitors indicates that allo-HCT does not appear necessary in cases of chronic MPN with detected PDGFRβ mutation. Unfortunately, this report
does not indicate whether deliberate withdrawal of imatinib may be safe, as only three patients stopped treatment [16]. Other tyrosine kinase inhibitors targeting this genetic abnormality, such as dasatinib, pomatinib, sorafenib, quizartinib, suinotinib or sorafenib could also be active in the treatment of AML with PDGFRβ rearrangement [25].

However, none has been introduced into clinical practice. Based on these previous studies, we decided to use a combination of conventional chemotherapy with TKI. Due to the unfavourable experiences with alloHSCT in literature, and the lack of a matched, sibling donor in our patient, we shifted our decision to maintenance treatment. Fortunately, the treatment strategy appeared to be the right: the patient remains in molecular and cytogenetic CR, with a DFS almost 3.5 years. AlloHSCT could be saved for any potential relapse, if it occurs. However, it remains an open question whether we may interrupt the imatinib course: the patient is in a permanent relationship, and would like to have children.

References


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