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Case Report

A new FLT3 inhibitor with two cases: the gilteritinib experience

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Abstract: Introduction: In acute myeloid leukemia (AML), a heterogeneous group of leukemias, there are various factors to determine prognosis. Among these prognostic factors, cytogenetic results are increasing in importance day by day. FLT3 mutations are among the most common molecular abnormalities in AML, patients with recurrent or refractory (R/R) AML with this mutation have a low response rate to salvage therapy. Gilteritinib has activity against FLT3, ALK and AXL. This article shall present two cases, for which Gilteritinib was used, a new FLT3 inhibitor, and the results of the treatment. Case 1: A 52-year-old female patient presented to the emergency clinic with weakness and fever. In initial biochemical analysis, leukocyte was 104000/mm^3. Peripheral smear contained diffuse myeloid blastoid cells, peripheral blood flow cytometry also supported the AML M0-1 phenotype. The bone marrow biopsy aspiration performed on the 14th day of induction "3+7" treatment, contained diffuse blastic infiltrate and supported refractory disease. In addition to the FLAG-IDA salvage regimen, 120 mg/day Gilteritinib was also started. Bone marrow aspiration performed on the 28th day of salvage therapy was compatible with remission. Case 2: 53 years old male patient with also no comorbidity other than known hypertension. In the initial biochemical analysis of the patient, leukocyte was 156000/mm^3, platelet 58000/mm^3 and hemoglobin 7.6 g/dl. Peripheral blood flow cytometry supported the AML M5 phenotype, whose peripheral smear showed diffuse monoblastoid cells. On the 14th day of the patient's 3+7 induction treatment, the control bone marrow aspiration showed diffuse blast infiltration and was considered refractory, FLAG-IDA salvage therapy with again 120 mg/day Gilteritinib per oral were started. On the 28th day, control bone marrow aspiration was evaluated as remission. Discussion and conclusion: Unlike other FLT 3 inhibitors, Gilteritinib has been shown to be a highly effective agent in R/R AML with FLT3 mutations. Being the first data to be reported from Turkey, we think it would be quite guiding the titular.

Keywords: Acute myeloid leukemia, refractory, FLT3, gilteritinib, prognosis

Introduction

In acute myeloid leukemia (AML), a heterogeneous group of leukemias, there are various factors to determine prognosis. Among these prognostic factors, cytogenetic results are increasing in importance day by day. The cytogenetic poor prognosis criteria can be summarized as t(6; 9) (p23; q34.1) DEK protooncogene-Nucleoporin 214 Fusion gene (DEK-NUP214), t(v; 11q23.3) Lysine Spesific Methyltransferase 2A Fusion gene (KMT2A), inv (3) (q21.3q26.2), t(3; 3) (q21.3; q26.2); GATA Binding Protein 2 (GATA2), Myelodysplasia Syndrome-Associated Protein 1 (MECOM)-5 or del (5q); -7; 17/abn (17p) complex karyotype and monosomal karyotype Nucleophosmin-1 (NPM), FMS Like Tyrosine Kinase 3-Internal Tandem Duplication (FLT3-ITD) and FMS Like Tyrosine Kinase 3 TKD Tyrosine Kinase Domain (FLT3-TKD) [1].

FLT3 mutations are among the most common molecular abnormalities in AML, patients with recurrent or refractory (R/R) AML with this mutation have a low response rate to salvage therapy. FLT3 mutation leads to FLT3 overactivation and consequently growth signal transmission [2, 3]. Receptor tyrosine kinase (RTK) FLT3 is a member of the "split kinase" type 3 family, and share the same homology with platelet driven growth factor (PDGFR), KIT and

the colony stimulating factor-1 (CSF-1) receptor. Therefore, FLT3 inhibitors often inhibit one or more of these other family members [4].

After evaluation of different FLT3 tyrosine kinase inhibitors (TKIs), important findings of antileukemic activity were obtained. Although midostaurin, lestaurtinib and sunitinib demonstrate their effective clinical activity, they show also an important toxicity profile. First generation agents do not inhibit specific FLT3 due to their multi-kinase inhibition. In addition, it is seen that the anti-leukemic effects usually last for a few weeks due to the rapid and deep reduction, and elimination of circulating blasts. It is not preferred to be used as a single agent [5].

Quizartinib (formerly AC220) is the first agent developed as a potent selective FLT3 inhibitor. Its effect is limited to FLT3, KIT, CSF-1, PDGFR and rearranged during transfection (RET) kinase receptors with high selectivity. Plasma inhibitory activity (PIA) assay, an ex vivo pharmacodynamics test that estimates the potential for FLT3 inhibition in vivo testing shows that it is more potent than previous FLT 3 inhibitors. Unlike prior FLT3 inhibitors, responses to quizartinib in patients with R/R FLT3-ITD AML paired near-universal clearance of peripheral blasts with frequent reduction, if not complete elimination, of marrow blasts. Blast clearance is different from conventional cytotoxic therapy; peripheral blast clearance develops within a few days, while bone marrow blast clearance requires 4 weeks [5, 6].

Gilteritinib is a pyrazine carboxamide derivative. It has activity against FLT3, ALK and AXL. AXL is a receptor tyrosine kinase of the Tyro3-Axl-Mer family and exerts various hematopoethical effects in multiple tissues. Besides targeting ITD and TKD mutations, it also inhibits c-kit mutation at a low rate [7-9]. AXL activation contributes to chemoresistance in AML and specifically contributes to FLT3 activation and response or resistance to FLT3 inhibition. It has a synergistic effect with cytarabine and anthracyclines as an agent approved for monotherapy in R/R AML with FLT3 mutation. Conventional chemotherapy, targeted agents, allogeneic transplantation and immunotherapy increase the possibility of cure.

Gilteritinib treatment provided longer survival and higher remission rates in patients with FLT3 mutations compared with salvage therapy. This article shall present two cases, for which Gilteritinib was used, a new FLT3 inhibitor, and the results of the treatment.

Case presentation

Case 1: A 52-year-old female patient without comorbidity presented to the emergency clinic with weakness and fever. In hemogram and biochemical analysis, leukocyte was 104000/mm^3. Peripheral smear contained diffuse myeloid blastoid cells, peripheral blood flow cytometry also supported the AML M0-1 phenotype. The bone marrow biopsy aspiration performed on the 14th day of induction "3+7" (idarubicin 45 mg/m^2, three days; cytosine arabinoside 100 mg/m^2, seven days) treatment, contained diffuse blastic infiltrate and supported refractory disease. In addition to the FLAG-IDA (The combination of fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor) salvage regimen, 120 mg/day Gilteritinib was also started. Bone marrow aspiration performed on the 28th day of salvage therapy was compatible with remission. It also demonstrated with flow cytometry and pathology (2% blast) (**Figure 1**). Last follow up after 3 months of gilteritinib: Leukocyte 6400/mm^3, hemoglobin: 12.5 gr/dl, platelet: 145000/mm^3 with a peripheral smear and peripheral blood flow cytometry containing no blast cells.

Case 2: 53 years old male patient with also no comorbidity other than known hypertension. In the hemogram and biochemical analysis of the patient who applied to the emergency department with fever, leukocyte was 156000/mm^3, platelet 58000/mm^3, hemoglobin 7.6 g/dl, creatinine 1.4 mg/dl and LDH was 860 IU/L. Peripheral blood flow cytometry supported the AML M5 phenotype, whose peripheral smear showed diffuse monoblastoid cells. On the 14th day of the patient's 3+7 induction treatment, the control bone marrow aspiration showed diffuse blast infiltration and was considered refractory, FLAG-IDA salvage therapy with again 120 mg/day Gilteritinib per oral were started. On the 28th day, control bone marrow aspiration was evaluated as remission with biopsy and flow cytometry (3% blast) (**Figure 2**). Last follow

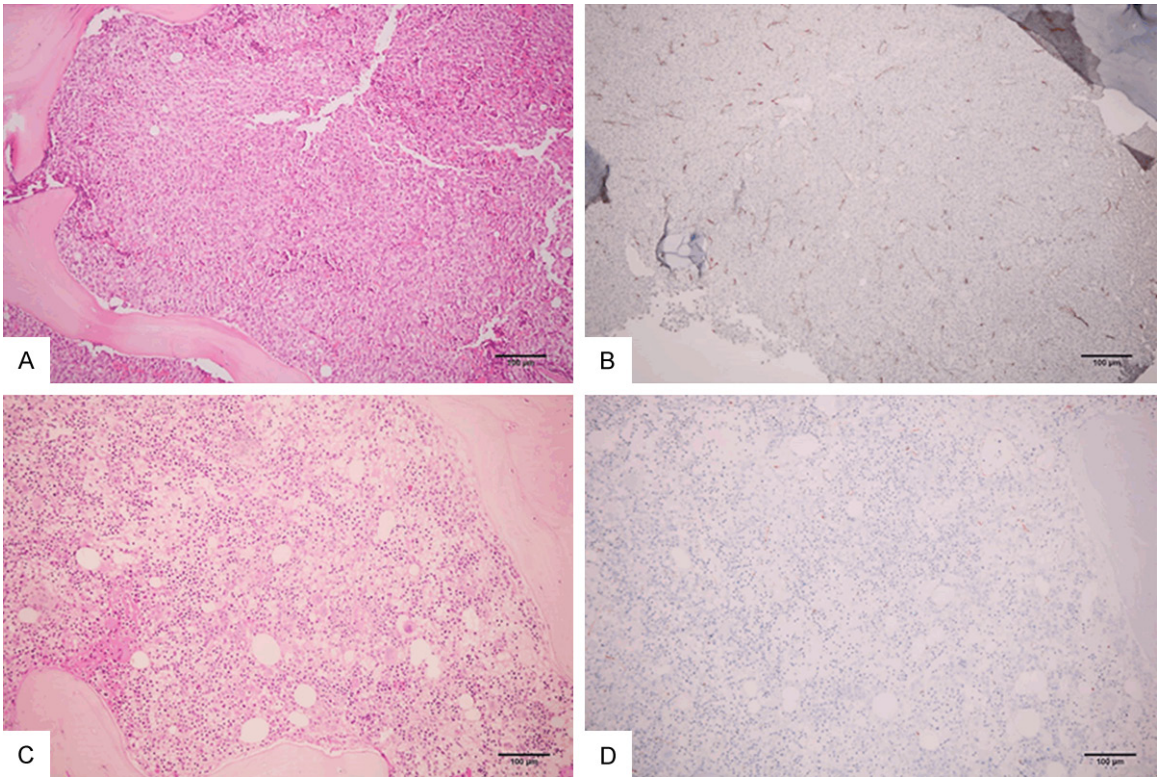

Figure 1. Case 1-Bone Marrow Biopsy Sections: (A) 14th Day of Induction Chemotylin & Eosin Staining, (B) 14th Day of Induction Chemoherapy-Hematoxtherapy-CD-34 Antibody Staining, (C) Salvage Therapy-Gilteritinib 28th Day-Hematoxylin & Eosin Staining, (D) Salvage Therapy-Gilteritinib Day 28-CD-34 Antibody Staining **Figure 1**.

up after 3 months of gilteritinib: Leukocyte 4900/mm^3, hemoglobin: 13.6 gr/dl, platelet: 219000/mm^3 with a peripheral smear and peripheral blood flow cytometry containing no blast cells.

Discussion

We see that different FLT 3 inhibitors are used in the treatment of AML. Midostaurin emerges as the first member of this group [9]. Likewise, lestaurtinib is preferred with combination chemotherapies. Both drugs have been found effective in combination regimens, their efficacy in monotherapy has not been demonstrated. Quizartinib and sorafenib are used as other FLT 3 inhibitors. Quizartinib has a myelosuppressive effect as it also plays a role in the inhibition of other tyrosine kinases such as c-kit. Although its effectiveness as a single agent has been proven, it has been shown that its effect lasts for a very short time due to TKD mutations that develop during treatment. It should be noted that a similar problem is also valid for sorafenib [10-12].

FLT mutation resistance severely limits the use of target drugs. Gilteritinib has a very important place because it targets the TKD mutation that plays a serious role in drug resistance. Gilteritinib also inhibits the tyrosine kinase AXL, which is involved in the FLT3 inhibitor, and weakly inhibits c-kit. Contrary to other FLT 3 inhibitors, salvage appears to be a highly effective agent that has been found superior to monotherapy compared to chemotherapy [13-15].

The combination with gilteritinib, which we preferred as a FLT-3 inhibitor in our own cases, did not show any serious side effects; besides, a very effective response was obtained. Thus, it was aimed to overcome important resistance mechanisms and obtain tumor apoptosis. Various mechanisms of resistance to FLT3 inhibitors have been described, including upregulation of compensatory signaling pathways and mutations within the TKD of FLT3 [16]. Although FLT3 TKD mutations have been identified in newly diagnosed cases of AML, they are known to be one of the primary mecha-

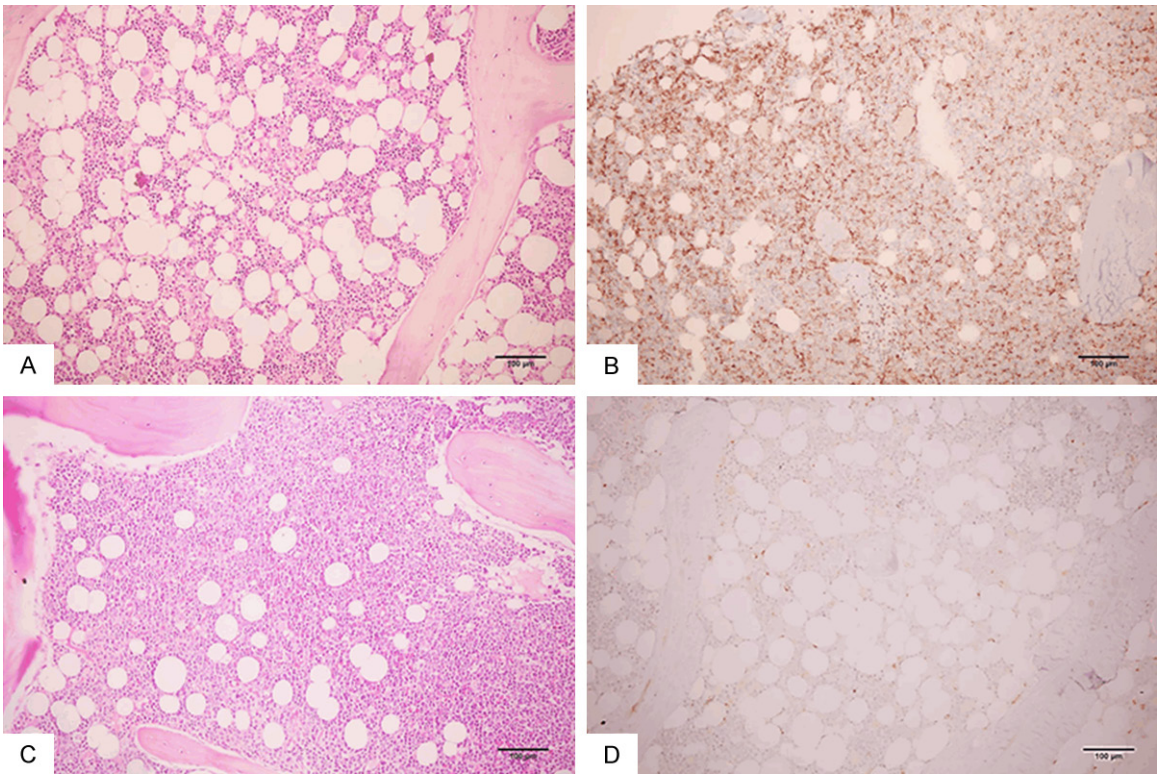

Figure 2. Case 2-Bone Marrow Biopsy Sections: (A) 14th Day of Induction Chemotherapy-Hematoxylin & Eosin Staining, (B) 14th Day of Induction Chemotherapy-CD-34 Antibody Staining, (C) Salvage Therapy-Gilteritinib 28th Day-Hematoxylin & Eosin Staining, (D) Salvage Therapy-Gilteritinib Day 28-CD-34 Antibody Staining.

nisms of acquired resistance to FLT3 inhibitor therapy. The two primary mutation sites following FLT3 inhibitor therapy have been shown to reduce the binding and inhibiting potential of many FLT3 inhibitors. These mutations include residues in the activation loop (eg. aspartate 835, D835) or the gatekeeper residue (phenylalanine 691, F691). Activation cycle mutations were identified after exposure to quizartinib and sorafenib, whereas F691L mutations were found in patients following gilteritinib treatment [17]. Mutations involving D835 are the most common genetic mechanism of relapse and resistance in FLT3-mutant AML following treatment with TKIs. Several studies have shown that type II inhibitors such as quizartinib lose potency in D835-mutant FLT3 AML [17-22]. Cellular analysis demonstrated strong inhibitor effects of gilteritinib on FLT3 mutations (particularly FLT3-ITD and FLT3-D835Y point mutations) [17]. Both FLT3-ITD and FLT3-TKD mutations induce FLT3 kinase activity by promoting proliferation and survival of leukemic cells. The inhibitory effects of gilteritinib may thus reduce leukemic burden in patients with AML. As a type I inhibitor, gilteritinib is largely unaffected by activation loop mutations (eg. FLT3-D835) [22]. Gilteritinib also induces apoptosis in tumor cells expressing FLT3-ITD mutations [17].

A summary of case reports from recent literature that may be seen similar is shown in **Table 1**. Unlike the case reports in the literature, we preferred FLAG-IDA as a salvage regimen in our cases. This choice of treatment may have prevented gilteritinib related differentiation syndrome, which was often mentioned in case reports. The majority of patients in the literature were R/R AML cases as in our report. While no significant toxicity was observed in both of our cases, we see that hepatotoxicity stands out in the literature data. Especially, the interaction between molecular target agents and azole antifungals constitutes an important discussion topic. We used posaconazole prophylaxis in our cases and did not encounter any toxicity.

In our cases, gilteritinib was given in combination with the rescue regimen, and the most common side effect, myelosuppression, was

Table 1. Summary of similar case reports from recent literature data

	Patient, age, gender, ND/RR	Leukemia subtype	Starting dose of Gilteritinib (/day)	Combination of any chemotherapy	Adverse effect(s)	Status achieved by Gilteritinib
Wilson et al., 2020 [23]	29, male, ND	AML	Unknown	100 mg/m^2/day cytarabine, 3 days	None	CR
Ando et al., 2020 [24]	18, female, RR	AML-M4	120 mg	2. BMT	Grade 3 hepatotoxicity due to possible interaction with fluconazole	CR
Tollkuchi et al., 2020 [25]	68, female, RR	AML-M4	120 mg	None	Fatigue, muscle weakness	Unknown
Kida et al., 2020 [26]	56, male, RR	AML-M4	120 mg	100 mg/m^2/day etoposide, 5 days; prednisolone 0.5 mg/kg for cGVHD; 90 mg/m^2 ranimustine, 1 day	None	CR
Kamitani et al., 2020 [27]	38, male, RR	AML	120 mg	None	Grade 3 hepatotoxicity	SD
DiNardo et al., 2020 [28]	36, male, RR	AML	120 mg	None	Grade 2 hepatotoxicity	CR
Yun et al., 2019 [29]	63, female, RR	AML-M5b	120 mg	None	None	CR
Kondo et al., 2021 [30]	81, male, RR	AML	120 mg	Low dose cytarabine, mitoxantrone	Gastrointestinal bleeding, differentiation syndrome	SD

**Table 1 contains similar case reports from the literature. Preferred combination regimens, gilteritinib doses, adverse effects, and treatment response could be seen. ND: Newly diagnosed, RR: Relapsed/refractory, AML: Acute myeloid leukemia, CR: Complete remission, SD: Stable disease, BMT: Bone marrow transplantation.

not observed at a significant level. In addition, we did not observe QT prolongation or hepatotoxicity, which are defined as important side effects, in both patients. The magnesium and potassium levels of the patients were checked for this condition before starting the drug, and replacement was performed at regular intervals to keep them within normal limits. It was thought that there was significant erythroid hyperplasia in the bone marrow on the 28th day in case 2 and this situation developed secondary to the drug. Other important side effects, such as posterior reversible encephalopathy or pancreatitis were also not observed.

As a result, unlike other FLT 3 inhibitors, Gilteritinib has been shown to be a highly effective agent in R/R AML with FLT3 mutations. Being the first data to be reported from Turkey, we think it would be quite guiding the titular.

Acknowledgements

We respectfully remember all the colleagues we lost in the COVID-19 fight. Patients gave informed consent before the beginning of the study. The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations. Ethics committee approval was obtained (Approval number-date: 30.4.2021/2813).

An informed consent was obtained as written forms from all of our patients to publish.

Disclosure of conflict of interest

None.

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