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Gilteritinib as treatment for extra-medullary relapse of FLT3-ITD acute myeloid leukemia FLT3-ITD, after allogeneic haematopoietic stem cell transplantation

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ABSTRACT

Case of a patient with acute myeloid leukemia (AML) positive for mutations in both genes NPM1 and FLT3-ITD who underwent two allogeneic haematopoietic stem cell transplants (HSCT); the second allograft one was followed by extramedullary relapse (granulocytic sarcoma of right breast), with blast cells positive for FLT3-ITD-mutation. Treatment with Gilteritinib, a second generation selective oral type I FLT3 inhibitor, was started after the second HSCT with complete regression of breast granulocytic sarcoma in absence of hematological and extra hematologic toxicity. We conclude that Gilteritinib can represent an effective therapy for extra hematologic relapse, with acceptable toxicity and outpatient management.

1. Introduction

About 30% of AML patients harbor mutation in the FLT3 gene, which is involved in the proliferation and normal differentiation of hematopoietic stem cells. More in detail, these mutations involve the iuxtamembrane region of the receptor (duplications in frame - ITD) or may be point mutations of the tyrosine kinase domain (TKD), with the effect of a receptor's constant activation in absence of ligand. Currently, new target therapies are available for these patients, such as the oral selective FLT3 inhibitor Gilteritinb, currently approved for the treatment of adults with relapsed/refractory FLT3 AML as well as Midostaurin for newly diagnosed patients in combination with chemotherapy [1]. Recurrence of AML can also occur at extramedullary level potentially involving different organs and most frequent localization is the skin, with cumulative incidence of 5–12% [1,2].

Currently, few cases [1,2,3] of extramedullary relapse of AML FLT3 treated with FLT3 inhibitors are reported, in particular after the first or second allogeneic HSCT [3,4,5]. We report here the case of a FLT3 AML patient with bone marrow and mammary extramedullary relapse, after 1st and 2nd allogeneic HSCT, respectively, and successfully treated with Gilteritenib in both cases.

2. Case presentation

In April 2019, a female patient, 35 years old, received diagnosis of NPM1 and FLT3-ITD positive AML, in absence of cytogenetic alterations. The patient presented with hyperleukocytosis, anemia, thrombocytopenia (blood count at diagnosis revealed WBC 175,94 × 10ˆ3/uL) and disseminated intravascular coagulation (DIC). The patient was classified as high-risk according to ELN criteria . In addition, bilateral hemovitreus and left retinal detachment were present with subsequent loss of bilateral vision. The first induction chemotherapy consisted of 3 + 7 schedule (cytarabine + daunorubicin) combined with midostaurin, according to current standard of care , with no hematological response. The subsequent salvage chemotherapy included IDA-FLA protocol (fludarabine 25 mg/mˆ2 d 1–2–3–4–5 – cytarabine 200 mg/mˆ2 d 1–2–3–4–5 - idarubicin 10 mg/mˆ2 d 1–3) with the achievement of morphological bone marrow complete remission (CR); minimal residual disease (MRD) evaluation by immunophenotype revealed 0.6% contamination in the bone marrow. In this phase, central nervous system involvement was excluded by cerobrospinsl fluid morphologic and immunophenoptypic examination. Consolidation therapy consisted of 1 cycle of FLA scheme (fludarabine 25 mg/mˆ2 d 1–2–3–4–5 and cytarabine 2.000 mg/mˆ2

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Table 1
MRD and Chimeric Status after 1st allogeneic HSCT.

Timing after 1st HSCT (days)	% donor chimerism	NPM1 copies
+30	98.53	1.10
+60	98.14	491
+90	22.36	3191
+120	45.05	0
+150	70.7	229
+180	62.8	267

Table 2
MRD and Chimeric Status after 2nd allogeneic HSCT.

Timing after 2nd HSCT (days)	% donor chimerism	NPM1 copies
+30	99.64	NA
+60	99.85	0.003
+90	99.93	0.003
+120	99.95	0.023
+150	99.76	0
+180	99.80	0
+200	99.94	0.003
+230	99.99	0.025
+260	99.98	0.033
+300	99.95	NA
+360	99.96	NA
+400	99.93	NA
+460	99.96	0.001
+500	99.57	0.001
+560	99.67	0
+600	99.70	0
+660	99.80	0
+700	99.80	0

NA: not available.

d 1–2–3–4–5).

Familiar HLA compatibility test revealed the presence of an identical HLA sister, who resulted eligible only for bone marrow harvest, due to the lack of suitable venous accesses for peripheral blood stem cells collection. In August 2019, the patient performed HLA identical allogeneic HSCT from her sister using bone marrow as stem cell source. Conditioning regimen and graft versus host disease (GVHD) prophylaxis consisted of myeloablative combination of thiotepa, busulfan and fludarabine (TBF - MAC) and cyclosporine + methotrexate short course, respectively. Engraftment was achieved on day + 15 and + 20 for ANC and PLTS, respectively [5]. No early severe complications occurred and quantitative chimerism, evaluated through the QPCR method (indelqRT-PCR) showed full donor status on day +30 and +60. The monitoring of MRD was carried out with the evaluation of the mutational status of the NPM1 gene in peripheral and marrow blood [4,6].

On day + 90 after the 1st allogeneic HSCT procedure, the peripheral blood count showed leucopenia, anemia and thrombocytopenia whereas the bone marrow aspiration showed a morphological relapse with a loss of donor chimerism (quantitative donor chimerism = 23%). Moreover, the bone marrow morphologic and immunopenotypic analysis IP documented 84% of blast cells with the same markers' expression as at diagnosis (CD34+/-,CD117+,CD33+,CD13+/-,CD7+,CD45+/-) and 3191 copies of NPM1. Subsequently, the patient started oral Gilteritinib at dose of 120 mg/day, as compassionate use, with reduction of bone marrow blast cells from 84% to 10% .

Gilteritinib was well tolerated for 1 month until the occurrence of klebsiella pneumonia associated with prolonged neutropenia and a persisting bone marrow blasts percentage of 10%. For this reason, the FLT3 inhibitor was withdrawn and a life-saving 2nd allogeneic HSCT was planned from the same sibling. Donor's ineligibility to PBSC collection was confirmed so the transplant procedure was performed using bone marrow stem cells. A single dose of Melphalan at 140 mg/mˆ2 was used as conditioning regimen while no immunosuppression prophylaxis for GVHD was administered because of the high risk of relapse of the

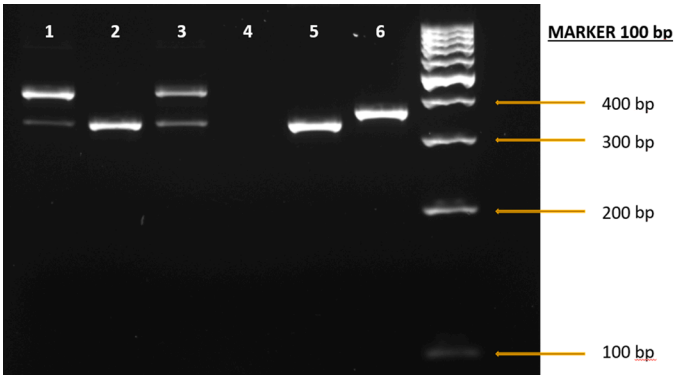


Fig. 1. Breast presence of FLT3 ITD was documented by PCR and agarose gel electrophoresis (Kit LeukoStrat FLT3 Mutation Assay- Gel detection, Invivoscribe).

underlying hematological disease. The main complications after the 2nd allogeneic HSCT were represented by acute and chronic GVHD [6,7].

Chimerism status and MRD evaluation after the 1st and the 2nd allogeneic HSCT are reported in table 1 and 2, respectively.

On day + 40 after the second allogeneic procedure, acute cutaneous grade III GVHD, involving 90% of the body surface, occurred and high dose of 6-Metilprednisone (2 mg/kg) was promptly started. Due to the progression of skin aGVHD into bullous erythroderma and appearance of grade I liver GVHD, a second line therapy with infliximab at 10 mg/kg was started in association with ancillary cutaneous treatment based on heterologous platelet gel local application [7,8]. Given the gradual resolution of the skin and liver GVHD after 2 courses of Infliximab, slow steroid tapering was performed [6,7].

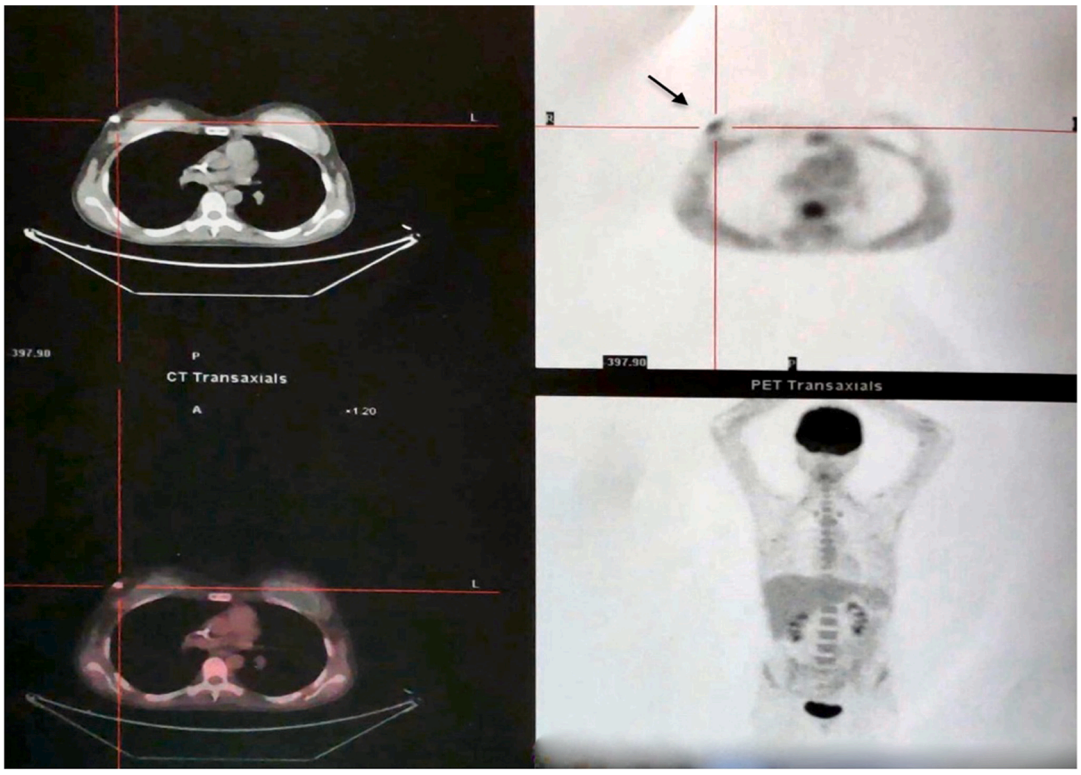
On day + 90 after the 2nd allogeneic HSCT, bone marrow aspiration showed morphological CR, full donor chimerism (99.93%) and NPM1 of 0.003 copies with a reduction of six logarithms compared to the pre-transplant check (corresponding at day +90 after 1st allogeneic HSCT procedure).

After a few months, the patient developed severe chronic GVHD, involving skin and lung, that was treated with steroid and FAM protocol (montelukast, azithromycin, and fluticasone) achieving partial cutaneous response and a significant FEV1 recovery. On day+ 120 after the 2nd allogeneic SCT, the follow up confirmed morphological CR and full donor chimerism at bone marrow aspiration associated with NPM1 of 0.023 copies. However, clinical occurrence of three right breast lesions was highlighted by ultrasound. PET /TC (positron emission tomography) with a SUV uptake of 6.8,7.8 and 2.6, respectively. Stereotaxic biopsy of the 3 mammalian nodules was performed. The histological assay confirmed the suspected relapse of AML CD34+ / CD68+ / Ckit +/ LCA+ / CD33+ and focally CD34+ cells occasionally positivity for myeloperoxidase and negativity for pancytokeratin. Breast presence of FLT3 ITD was also documented by PCR and agarose gel electrophoresis (Kit LeukoStrat FLT3 Mutation Assay- Gel detection, Invivoscribe) as shown in Fig.1.

The patient was ineligible for breast surgery and radiotherapy due to chronic cutaneous GVHD with scleroderma. Given the molecular FLT3 positivity of breast lesions and ineligibility to further salvage chemotherapy, therapy with Gilteritinib was started at a dosage of 120 mg/day; dose reduction was performed because of concurrent cutaneous cGVHD.

On day + 400 after the 2nd allogeneic HSCT, while on treatment Gilteritinib, QTc lengthening was documented with subsequent withdrawn of the FLT3 inhibitor. The target therapy was restored at a reduced dose of 80 mg/day after 7 days of stop following electrocardiographic normalization. After 3 months of Gilteritinib, bone marrow aspiration confirmed morphological CR, full donor chimerism (99.96%), in absence of NPM1positivity. Reduction of breast nodules was

a



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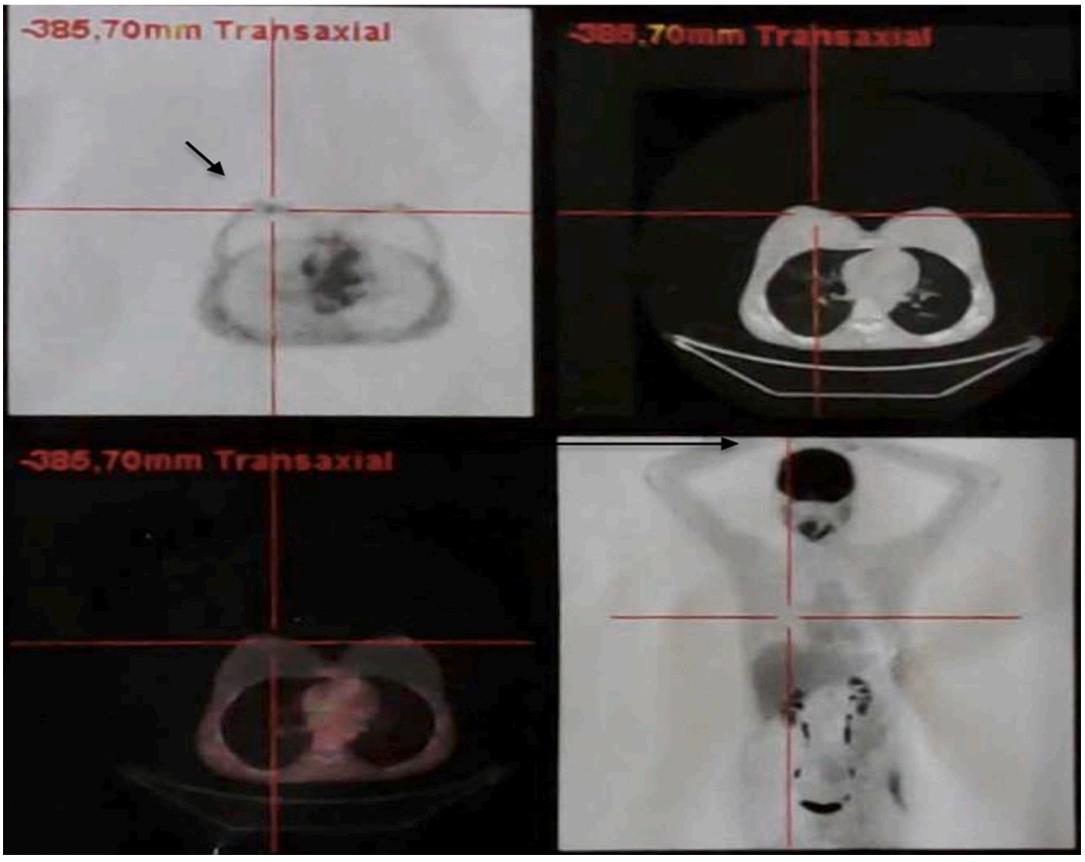

Fig. 2A. PT TC before treatment with Gilteritinib. B: PT TC after treatment with Gilteritinib.

documented by breast ultrasound and PET-CT [2,3].

Currently, almost 2 years after the 2nd allogeneic HSCT, the patient is alive in hematological and extramedullary CR with cutaneous GVHD responding to photo-apheresis and is still being treated with a FLT3 inhibitor at a dosage of 80 mg/ day, as maintenance therapy. Fig. 2A and 2B respectively show the PT-TC breast images before and after Gilteritinib treatment.

3. Discussion

The second generation FLT3 inhibitors, such as Gilteritinib, have the advantage of being selective for FLT3 and therefore of acting in specific manner on cells expressing the mutation of this gene. The selectivity of these agents results in limited treatment-related adverse effects, increasing overall survival in patients with relapsed/refractory AML FLT3 in comparison to conventional chemotherapy. [3,4,5]. However, their use after allogeneic HSCT is still matter of debate. Recently, a randomized clinical trial (EURADRACT 2010–018,539–16) assessed the efficacy of maintenance therapy with Sorafenib in the setting of FLT3+AML who underwent allogeneic HSCT. This clinical trial showed a significant benefit in terms of overall survival and relapse free survival in the study arm versus the control group who received placebo [10,11]. Moreover, data about the use of TKI for extramedullary relapse of FLT3 AML after allogeneic HSCT are still very scarce [1,2,5].

In this context, we reported the case of a young patient affected by AML NPM1 and FLT3-ITD who underwent two allogeneic HSCT and who was treated with Gilteritinib for the 1st hematological and the second extramedullary relapse after the first and the second allogeneic procedure, respectively. In this single experience, treatment with Gilteritinib can be defined as manageable and safe with a low cardiac toxicity occurrence, although it was administered during GVHD. Worthy of note, the 2nd allogeneic HSCT was performed without immunosuppression in order to enhance the graft versus leukemia effect of the transplant procedure and this choice determined the onset of grade IV aGVHD followed by extensive cGVHD [5,9,10]. However, although a full donor chimerism and the persistent hematological CR after the second allograft, the occurrence of leukemic breast localization confirmed the possibility of blast cells escapement as mechanism of action for AML relapse, also in presence of aGVHD, underlying the potential dissociation between graft versus leukemia and host effect. In conclusion, this case report points out 4 main effects of Gilteritinib: 1) the potential utility of FLT3 inhibitors in patients who relapse after allogeneic transplant, 2) the efficacy on the extra-hematological relapse 3) the safe administration during GVHD 4) the persistent efficacy of the same FLT3 inhibitor in two different episodes of AML relapse after allogenic HSCT [9,10]. Further cases will be needed to establish the long-term efficacy of Gilteritinib in the treatment of extramedullary relapses after allogeneic HSCT and its possible impact on GVHD.

Declaration of Competing Interest

Authors have no relevant financial conflict of interest to declare.

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