Long Term Sorafenib Response for Extramedullary FLT3+AML Relapse after Allogeneic Stem Cell Transplantation

López-Pereira P, Figuera A, Sola E, Cornago J, Alegre A, Aguado Bueno B.*
Hematology Department, Hospital Universitario La Princesa, Madrid, Spain
*Corresponding author: Beatriz Aguado, Hematology Department, Hospital Universitario La Princesa, Madrid, Spain
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Introduction

Acute Myeloid Leukemia (AML) relapse after allogeneic Hematopoietic Stem Cell (HSCT) Transplantation has a dismal prognosis. Extramedullary relapse has been considered as a rare event, although it could be misdiagnosed [1].

Internal Tandem Duplications (ITDs) of the FMS-Like Tyrosine Kinase 3 gene (FLT-3) occur in approximately 20%-30% of newly diagnosed patients, mostly cases with normal karyotype, and confers a worse prognosis when treated with chemotherapy alone [2,3]. However, recently this receptor is being used as a target expanding the therapeutic scenario [3,4].

Treatment with FLT3 tyrosine kinase inhibitors is changing the standard of care for FLT-3 mutated AML [3]. Sorafenib, a multikinase inhibitor, have been used in monotherapy or combined with chemotherapy, either in induction and relapsed AML [5].

Case Report

A 50 year-old woman was diagnosed with AML secondary to Myelodysplastic Syndrome (MDS) with NPM1 mutation and internal tandem duplications of the FLT3 gene (FLT3-ITD) in October 2013. After achieving Complete Remission (CR) with conventional chemotherapy (idarubicine+cytarabine), she received a myeloablative allogeneic HSCT from a HLA sibling donor in February 2014 (conditioning regimen BuCy).

Four months later, AML relapsed only at medullary level (FLT3 ratio: 0.67%), treated with chemotherapy (IDICE) and Donor Lymphocytes Infusions (DLI). She achieved 2nd CR and developed limited chronic Graft- Versus-Host Disease (cGVHD).

Nine months later (April 2015), she suffered the first extramedullary relapse, with breast and skin involvement, with full donor chimerism. Disappearance of the lesions at all levels was achieved with chemo (cytarabine) and radiotherapy.

In December 2015, she referred atypical precordial pain irradiated to the back, without symptoms or echocardiographic signs of cardiac failure. A cardiac MRI and chest CT scan was performed finding moderate pericardial effusion and several masses in the pericardial sac, up to 5 cm in diameter. BM remained in CR with full donor chimerism.

Pericardial fluid showed massive infiltration by myeloid blasts with phenotype CD34+, CD117+, CD33+, CD16-, CD11b weak, CD14-, HLA-DR heterogeneous with FLT3 positive cells (ratio: 0.7%).

She was not considered candidate for further systemic chemotherapy nor radiotherapy, so treatment with FLT3 inhibitor (Sorafenib) was started.

Sorafenib was started (in December 2015) at dose of 400 mgr/12 h. After first month of treatment, pericardial lesions decreased from 5 to 1.7 cm in diameter. Subsequent CT scans showed progressive decrease of lesions until resolution in July 2016. In last CTs pericardial thickening is almost non-existent, without new lesions (see figure) (Figure 1).

In June 2016, the dose of Sorafenib was reduced to 200 mg/12 h because of GI toxicity, without any impact on efficacy.

Since June 2017, Sorafenib dose was again tapered to 200 mg/day, due to mild skin and GI toxicity. After almost 4 years of treatment, she maintains CR at medullary and extramedulary levels, with no
evidence of a disease that had escaped the mechanisms of action of chemo, HSCT and DLI.

Discussion

There is no standard therapeutic regimen for relapsed AML. In spite of improvement of survival with allotransplant, patients with AML with FLT3-ITD are still associated with a higher risk of relapse after transplantation [13]. The prognosis of patients who relapse after allogeneic HCT is particularly poor [4]. Multiple factors can influence relapse after allogeneic stem cell transplantation, and the therapeutic approach must be individualized [2].

Some authors have reported a better survival outcome in patients with extramedullary relapse after transplantation [6,7].

Cardiac myeloid sarcoma is a rare entity. Only several cases have been reported, with different treatment strategies applied, including chemotherapy, radiotherapy, DLI, surgery and hypomethylating agents with variable outcomes [8-12].

In 2009, Safaian NN et al, reported the first extramedullary AML FLT3-ITD relapse treated with Sorafenib [12]. More recently some reports have demonstrated the sustained efficacy of sorafenib treatment for AML with FLT3-ITD relapsing post-transplant [13-15].

In our patient, treatment with Sorafenib has provided long-term control of this refractory extramedullary disease, even at adjusted doses. Novel targeted therapies could be a low toxicity therapeutic option for AML relapse in allotransplant receptors heavily pretreated, even in patients with comorbidities derived from previous GVHD, as represents our case. Further studies are needed to confirm the efficacy of FLT3 inhibitors in the control of relapses after allo-HSCT, extramedullary disease and its potential role as maintenance agent [17-20].

References
