Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Report

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

López-Pereira P[1], Figuera A[1], Sola E[1], Cornago J[1], Alegre A[1], Aguado Bueno B[1]*

Hematology Department, Hospital Universitario La Princesa, Madrid, Spain

***Corresponding author:** Beatriz Aguado, Hematology Department, Hospital Universitario La Princesa, Madrid, Spain

Received: December 06, 2019; **Accepted:** January 24, 2020; **Published:** January 31, 2020

Abstract

We present a case of Acute Myeloid Leukemia (AML) with FLT3-ITD mutation, relapsing as extramedullary cardiac disease after allogeneic hematopoietic stem cell transplantation. This 50-year-old woman with FLT3-mutated AML, was treated with standard chemotherapy followed by allotransplant. Despite presenting chronic graft versus host disease, she experienced one first medullary relapse treated with chemotherapy and DLI, and a second extramedullary relapse treated with chemo and radiotherapy. As third relapse, she developed cardiac extramedullary sarcoma, without marrow involvement, and because of comorbidities she was treated with sorafenib monotherapy, reaching rapid and complete sustained response.

This case demonstrate a long-term control of refractory AML disease with Sorafenib as salvage therapy in a heavily pretreated allotransplant receptor.

Keywords: Acute myeloid leukemia; FLT-3-ITD; Extramedullary relapse; Transplantation; Sorafenib

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

Citation: López-Pereira P, Figuera A, Sola E, Cornago J, Alegre A, Aguado Bueno B. Long Term Sorafenib Response for Extramedullary FLT3+AML Relapse after Allogeneic Stem Cell Transplantation. Ann Hematol Oncol. 2020; 7(1): 1281.

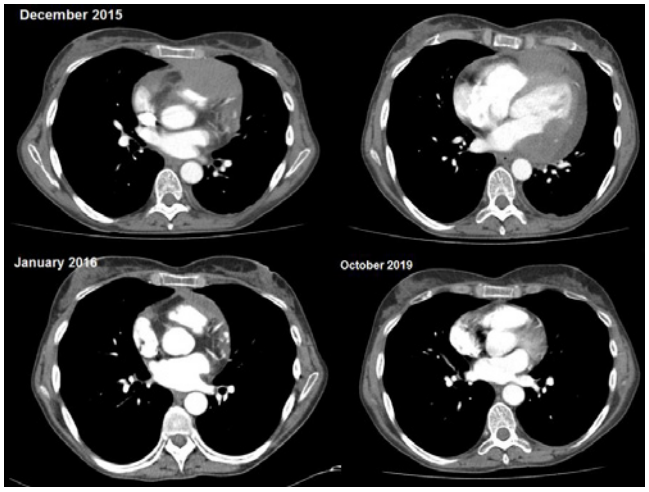

Figure 1: Sorafenib was started (in December 2015) at dose of 400 mgr/12 h. After first month of treatment, pericardial lesions decreased from 5 to 1.7 cm in diameter. Subsequent CT scans showed progressive decrease of lesions until resolution in July 2016. In last CTs pericardial thickening is almost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

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 hypometilating 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

1. Yoshihara S, Ando T, Ogawa H. Extramedullary Relapse of Acute Myeloid Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation: An Easily Overlooked but Significant Pattern of Relapse. Biology of Blood and Marrow Transplantation. 2012; 18: 1800–1807.
2. Ossenkoppele GJ, Janssen JJ, Van de Loosdrecht AA. Risk factors for relapse after allogeneic transplantation in acute myeloid leukemia. Haematologica. 2015; 101: 20–25.
3. Short NJ, Kantarjian H, Ravandi F, Daver N. Emerging treatment paradigms with FLT3 inhibitors in acute myeloid leukemia. Therapeutic Advances in Hematology. 2019.
4. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2016; 129: 424–447.
5. Antar A, Otrock ZK, El-Cheikh J, Kharfan-Dabaja MA, Battipaglia G, Mahfouz R, et al. Inhibition of FLT3 in AML: a focus on sorafenib. Bone Marrow Transplantation. 2016; 52: 344–351.
6. Solh M, DeFor E, Weisdorf DJ, Kaufman DS. Extramedullary Relapse of Acute Myelogenous Leukemia after Allogeneic Hematopoietic Stem Cell Transplantation: Better Prognosis Than Systemic Relapse. Biology of Blood and Marrow Transplantation. 2012; 18: 106–112.
7. Shem-Tov N, Saraceni F, Danylesko I, Shouval R, Yerushalmi R, Nagler A, et al. Isolated Extramedullary Relapse of Acute Leukemia after Allogeneic Stem Cell Transplantation: Different Kinetics and Better Prognosis than Systemic Relapse. Biology of Blood and Marrow Transplantation. 2017; 23: 1087–1094.
8. Kara IO, Sahin B, Paydas S, Kara B. Granulocytic sarcoma of the heart: Extramedullary relapse of acute myeloblastic leukemia after allogeneic stem cell transplantation successfully treated by chemotherapy alone. Leukemia & Lymphoma. 2005; 46: 1081–1084.
9. Waselewski A, Joiner M, Miller SR. Acute myeloid leukaemia relapse presenting as cardiac myeloid sarcoma. BMJ Case Report. 2018.
10. Yang WC. Complete response of myeloid sarcoma with cardiac involvement to radiotherapy. Journal of Thoracic Disease. 2016; 8: 1323-1328.
11. Evers D, Bär BMAM, Gotthardt M, van der Velden WJFM. Activity of decitabine in pericardial myeloid sarcoma. International Journal of Hematology. 2018; 108: 121–122.
12. Safaian NN, Czibere A, Bruns I., Fenk R, Reinecke P, Dienst A, et al. Sorafenib (Nexavar®) induces molecular remission and regression of extramedullary disease in a patient with FLT3-ITD+ acute myeloid leukemia. Leukemia Research. 2009; 33: 348–350.
13. Xuan L, Wang Y, Chen J, Jiang E, Gao L, Wu B, et al. Sorafenib therapy is associated with improved outcomes for FLT3-ITD AML relapsing after allo-HSCT. Biology of Blood and Marrow Transplantation. 2019.
14. Metzelder SK, Schroeder T, Lübbert M, Ditschkowski M, Götze K, Scholl S, et al. Long-term survival of sorafenib-treated FLT3-ITD–positive acute myeloid leukemia patients relapsing after allogeneic stem cell transplantation. European Journal of Cancer. 2017; 86: 233–239.
15. Rautenberg C, Nachtkamp K, Dienst A, Schmidt PV, Heyn C, Kondakci M, et al. Sorafenib and azacitidine as salvage therapy for relapse of FLT3-ITD mutated AML after allo-SCT. European Journal of Hematology. 2017; 98: 348–354.
16. De Freitas T, Marktel S, Piemontese S, Carrabba MG, Tresoldi C, Messina C, et al. High rate of hematological responses to sorafenib in FLT3-ITD acute myeloid leukemia relapsed after allogeneic hematopoietic stem cell transplantation. European Journal of Hematology. 2015; 96: 629–636.
17. Bewersdorf JP, Stahl M, Zeidan AM. Are we witnessing the start of a therapeutic revolution in acute myeloid leukemia? Leukemia & Lymphoma. 2019; 1–16.
18. Battipaglia G, Ruggeri A, Massoud R, El Cheikh J, Jestin M, Antar A, et al. Efficacy and feasibility of sorafenib as a maintenance agent after allogeneic hematopoietic stem cell transplantation for Fms-like tyrosine kinase 3-mutated acute myeloid leukemia. Cancer. 2017; 123: 2867–2874.
19. Brunner AM, Li S, Fathi AT, Wadleigh M, Ho VT, Collier K, et al. Hematopoietic

cell transplantation with and without sorafenib maintenance for patients withFLT3-ITD acute myeloid leukemia in first complete remission. British Journal of Hematology. 2016; 175: 496–504.

20. Schiller GJ, Tuttle P, Desai P. Allogeneic Hematopoietic Stem Cell Transplantation in FLT3 -ITD–Positive Acute Myelogenous Leukemia: The Role for FLT3 Tyrosine Kinase Inhibitors Post-Transplantation. Biology of Blood and Marrow Transplantation. 2016; 22: 982–990.