CASE REPORT

The Successful Complete Remission Induction by Sorafenib Monotherapy in a FLT3-D835Y-Positive Patient with Refractory Acute Monocytic Leukemia

Yanhua Yue^{1,2} · Song Jin^{1,2} · Ting Xu^{1,2} · Jin Zhou^{1,2} · Liang Ma^{1,2} · Hongjie Shen^{1,2} · Depei Wu^{1,2} · Suning Chen^{1,2} · Miao Miao^{1,2}

Received: 31 March 2015 / Accepted: 18 August 2015 / Published online: 28 August 2015
© Indian Society of Haematology & Transfusion Medicine 2015

Abstract Sorafenib has been shown to be active in AML patients with FLT3-ITD. However, the effect of sorafenib in AML patients with FLT-TKD has never been well determined. Moreover, acquisition of secondary FLT3 TKD mutations, mainly at D835 (D835F/H/V/Y), are recognized as the major mechanisms of resistance of AML patients with FLT3-ITD to sorafenib. It has been reported that sorafenib induced death of cells that expressed the FLT3-ITD or FLT3-D835G but not cells that expressed the FLT3-D835Y point mutant or wild-type FLT3 in vitro. Here, we report the successful complete remission induction by sorafenib monotherapy in a FLT3-D835Y-positive patient with refractory AML-M5 followed by allogeneic stem cell transplantation.

Keywords Sorafenib · FLT3-D835Y mutation · Acute monocytic leukemia · Complete remission

Introduction

Activating mutations of the FMS-like tyrosine kinase-3 gene (FLT3) are one of the most frequent somatic alterations in acute myeloid leukemia (AML), occurring in approximately one-third of patients. FLT3 mutations consist of two major types: internal tandem duplication (ITD) mutations of the juxtamembrane region (head-to-tail duplication of 3–400 base pairs in exons 14 or 15) and point mutations involving the D835/I836 residues and others of the tyrosine kinase domain (TKD) [1, 2]. The FLT3-TKD mutations are reported to occur in approximately 7 % of patients, although they do not have a characteristic clinical signature [2, 3]. The FLT3-ITD mutations have been detected in about 23 % of patients with AML in several large studies and are associated with an increased risk of relapse and a shorter overall survival (OS) [4].

Sorafenib is a multi-targeted tyrosine kinase inhibitor (TKI), with activity against RAF kinases, KDR receptors, FLT3, PDGFR receptors, KIT, and RET kinase. [5] Sorafenib has been shown to be effective in FLT3-ITD mutated AML, alone or in addition to other cytotoxicity drugs. [6–9] Most AML patients with FLT3-ITD show an initial clinical response to sorafenib, followed by the development of resistance within a few months to a year of treatment. [10, 11] One of the most common mechanisms of resistance to FLT3 inhibitors is the acquisition of secondary FLT3-TKD mutations, especially amino acid exchanges at residue D835 (D835F/H/V/Y). [10, 11] Up to now, the effect of sorafenib in AML patients with FLT3-TKD has never been widely investigated. Here, we report the successful complete remission induction by sorafenib monotherapy in a FLT3-D835Y-positive patient with refractory AML prior to allogeneic stem cell transplantation (Fig. 1).

Yanhua Yue and Song Jin are contributed equally to this work.

✉ Miao Miao
mm85124@sina.com
Yanhua Yue
yyh19880922@163.com

¹ Jiangsu Institute of Hematology, Key Laboratory of Thrombosis and Hemostasis of Ministry of Health, the First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, Jiangsu province, People's Republic of China

² Collaborative Innovation Center of Hematology, Soochow University, Suzhou, People's Republic of China

Case Report

A 29-year-old male with a 2-week history of oral cavity ulcer and nasal bleeding was diagnosed as having acute myeloid leukemia (AML) on the basis of a marrow including 91.5 % blasts with morphologic features of AML-M5 on February 11th 2014. Examination of peripheral blood indicated a white blood cell count of $5.33 \times 10^9/L$, a platelet count of $30 \times 10^9/L$, and hemoglobin level of 69 g/L. Immunophenotyping showed moderate to strong expression of myeloid antigens (CD34, HLA-DR, CD33, and CD117) and negativity for lymphoid antigens. Cytogenetic study demonstrated an abnormal karyotype of 47, XY, +8 [10]. Several recurrent AML-related mutations of CEBPA, c-KIT, DNMT3A, FLT3-ITD, FLT3-TKD, and NPM1 were examined, but we only found FLT3-TKD (D835Y G > T) mutation in this patient. The patient firstly received standard induction chemotherapy of the IA regimen (idarubicin, 12 mg/m²/day, day 1–3; cytarabine, 100 mg/m²/day, day 1–7) on February 14th 2014. Subsequent BM aspiration revealed 69 % of blasts on February 21th 2014, indicating no response for this patient. Moreover, BM examination still remained 72 % of blast cells on March 7th 2014 after the second combination chemotherapy of AAG regimen (aclacinomycin, 10 mg/day, day 1–11; cytarabine, 20 mg/m²/day, day 1–12; G-CSF, 300 µg/day) on February 27th 2014, indicating refractory AML. From March 13th 2014, the patient received sorafenib orally as monotherapy at a dosage of 200 mg orally twice daily. However, he developed erythema spreading to whole body 12 days after starting sorafenib therapy. Erythema multiforme disappeared within 4 days after discontinuation of sorafenib and intravenous dexamethasone 5 mg/day. When sorafenib (200 mg/day) was rechallenged, erythema multiforme reappeared within 3 days and sorafenib was discontinued at once. On March 31th 2014, 18 days after sorafenib introduction, peripheral blood was normal and BM examination demonstrated normal richness, blast cells accounting for 2 % of the

nucleated BM cells, indicative of morphologic leukemia free state. FLT3-TKD (D835Y G > T) mutation was undetectable in BM mononuclear cells by Sanger sequencing. We evaluated the minimal residual diseases (MRD) level by multiparameter flow cytometry (MFC) and found absence of MRD in this patients. He received a matched related donor hematopoietic stem cell transplantation after a modified busulfan and cyclophosphamide conditioning regimen on April 30th 2014. He still remains in complete morphologic remission and undetectable MRD level by MFC, but with chronic GVHD, until the latest follow-up on June 25 2015.

Discussion

Sorafenib has been shown to be active in AML patients with FLT3-ITD. However, the effect of sorafenib in AML patients with FLT-TKD has never been well determined. Moreover, acquisition of secondary FLT3-TKD mutations, mainly at D835 (D835F/H/V/Y), are recognized as the major mechanisms of resistance of AML patients with FLT3-ITD to sorafenib. [10, 11] It has been reported that sorafenib induced death of cells that expressed the FLT3-ITD or FLT3-D835G but not cells that expressed the FLT3-D835Y point mutant or wild-type FLT3 in vitro. [12] However, we report here the successful complete remission induction by sorafenib monotherapy in a FLT3-D835Y-positive patient with refractory AML-M5 followed by allogeneic stem cell transplantation. Though duration of sorafenib was quite short, it is hard to achieve completion remission for him only with the late effect of previous combined chemotherapies. According to the NCCN guidelines 2014, he may have experienced induction failure. Therefore, sorafenib may have taken some work for the complete remission of the patient. Taken together, our data call for closer examination of effect of the sorafenib in AML patients with FLT3-TKD mutation within a wider scale.

Fig. 1 Identification of FLT3 D835Y mutation was carried out by bidirectional Sanger sequencing analysis

Acknowledgments This work was supported by grants from the Priority Academic Program Development of Jiangsu Higher Education Institutions, Jiangsu Provincial Special Program of Medical Science (BL2012005), and Jiangsu Province's Key Medical Center (ZX201102).

Compliance with Ethical Standards

Conflicts of interest The authors declare no conflict of interest.

References

1. Nakao M, Yokota S, Iwai T et al (1996) Internal tandem duplication of the *flt3* gene found in acute myeloid leukemia. *Leukemia* 10:1911–1918
2. Yamamoto Y, Kiyoi H, Nakano Y et al (2001) Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies. *Blood* 97:2434–2439
3. Abu-Duhier FM, Goodeve AC, Wilson GA, Care RS, Peake IR, Reilly JT (2001) Identification of novel FLT-3 Asp835 mutations in adult acute myeloid leukaemia. *Br J Haematol* 113(4):983–988
4. Levis M, Small D (2003) FLT3: ITD Does matter in leukemia. *Leukemia* 17:1738–1752
5. Wilhelm SM, Carter C et al (2004) BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. *Cancer Res* 64:7099–7109
6. Sammons SL, Pratz KW, Smith BD, Karp JE, Emadi A (2014) Sorafenib is tolerable and improves clinical outcomes in patients with FLT3-ITD acute myeloid leukemia prior to stem cell transplant and after relapse post-transplant. *Am J Hematol*. doi:10.1002/ajh.23782
7. Ravandi F, Arana Yi C, Cortes JE et al (2014) Final report of phase II study of sorafenib, cytarabine and idarubicin for initial therapy in younger patients with acute myeloid leukemia. *Leukemia* 28(7):1543–1545
8. Serve H, Krug U, Wagner R et al (2013) Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. *J Clin Oncol* 31(25):3110–3118
9. Ravandi F, Cortes JE, Jones D, Faderl S, Garcia-Manero G, Konopleva MY et al (2010) Phase I/II study of combination therapy with sorafenib, idarubicin, and cytarabine in younger patients with acute myeloid leukemia. *J Clin Oncol* 28:1856–1862
10. Man CH, Fung TK, Ho C, Han HH, Chow HC, Ma AC, Choi WW, Lok S, Cheung AM, Eaves C, Kwong YL, Leung AY (2012) Sorafenib treatment of FLT3-ITD(+) acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent nonresponsiveness associated with the emergence of a D835 mutation. *Blood* 119(22):5133–5143
11. Baker SD, Zimmerman EI, Wang YD, Orwick S, Zatechka DS, Buaboonnam J, Neale GA, Olsen SR, Enemark EJ, Shurtleff S, Rubnitz JE, Mullighan CG, Inaba H (2013) Emergence of polyclonal FLT3 tyrosine kinase domain mutations during sequential therapy with sorafenib and sunitinib in FLT3-ITD-positive acute myeloid leukemia. *Clin Cancer Res* 19(20):5758–5768
12. Zhang W et al (2008) Mutant FLT3: a direct target of sorafenib in acute myelogenous leukemia[J]. *J Natl Cancer Inst* 100(3):184–198