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Review Article

Sorafenib in combination with low-dose-homoharringtonine as a salvage therapy in primary refractory FLT3-ITD-positive AML: a case report and review of literature

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Abstract: The presence of internal tandem duplications (ITD) in the Fms-related tyrosine kinase 3 receptor (FLT3) has been associated with a poor prognosis in acute myeloid leukemia (AML). Over the past decade, FLT3 is a promising target in FLT3-ITD-positive AML. Sorafenib which is one of the commonly focused FLT3 inhibitors may improve outcome, but only few patients display long-term responses in previously reported cases, prompting the search for underlying resistance mechanisms and therapeutic strategies to overcome them. To the best of our knowledge, this is the first case report about sorafenib in combination with low-dose-homoharringtonine as a salvage therapy successfully administrated and got complete remission (CR) in primary refractory FLT3-ITD-positive AML. Our result demonstrates the combination of this two drugs may be a good choice for the primary refractory FLT3-ITD-positive AML patient, although cooperative studies of large numbers of these patients are needed to evaluate and optimize this combination.

Keywords: ITD, FLT3, AML, sorafenib, refractory

Case report

A 61-year-old man presented to our emergency department with worsening fatigue and toothache for ten days on 2 Jun, 2014. A blood count showed WBC 113.7×10^9/L with 93% blasts, haemoglobin, 91 g/dl and platelets, 51×10^9/L. So he was admitted to hematology department immediately. Bone morrow aspiration revealed: Primitive myeloid cell abnormalities increased and occupied 79% of nucleated cells, AML1-ETO-negative, FLT3-ITD positive. Immunophenotyping showed: Myeloblasts accounted for 73.76% of non-erythroid. Most blasts appeared agranular, however, rare cytoplasmic granules and Auer rods were seen. The blasts expressed MPO, CD13, CD33, CD45, partial CD38, partial CD71, partial CD117, negative for CD34, HLA-DR. A cytogenetic analysis of the leukemic cells showed normal male chromosomes, 46, XY. A diagnosis of AML (subtype: M2 plus with FLT-ITD positive) was made. And the evaluation of prognosis was divided to high-risk group [1]. His past medical history was significant for aortic dissection for four-years without surgery, diabetes mellitus and hypertension. Family history was nothing. The patient denied smoking or drinking alcohol. Whenever the relative examination was done, the patient received induction chemotherapy with 7-day infusion cytarabine (100 mg/m^2/d) and 3-day idarubicin (12 mg/m^2/d). A repeat bone marrow aspiration after one cycle demonstrated residual disease with 55.56% blasts. After a lengthy discussion regarding different chemotherapy options, the patient chose to be treated with standard HAA chemotherapy (homoharringtonine 2 mg/m^2 per day on days 1-7, cytarabine 100 mg/m^2 per day on days 1-7, and aclarubicin 20 mg/day on days 1-7) [2]. However, WBC was out of control even after the standard HAA chemotherapy and the bone marrow at the 7 days demonstrated the residual leukemia with 45.13% blasts, the standard GHA regimen (G-CSF 100 μg/m^2 per

day on days 0-14, homoharringtonine 1.0 mg/m^2 per day on days 1-14, Ara-C 10 mg/m^2 q12h on days 1-14) was given following the HAA on day 8 and was stopped on day 12 due to severe infection on the left leg and the chemotherapy program was discontinued until 8 Dec, 2014 because of the life-threatening infection on the left leg [3]. From 2 Jun, 2014 to 2 Dec, 2014, several reviewed bone marrow showed the AML at a state of stable disease (SD). And the bone marrow showed the blast cells was up to 93% in 2 Dec, 2014. At this point, WBC was up to 89×10^9/L and the platelet was fluctuated between 10-20×10^9/L. So we selected sorafenib (400 mg b.i.d. ×21 days in a 28-day cycle) in combination with low-dose-homoharringtonine (2 mg per day on days 1-14) [4]. To our great relief, the repeated bone marrow examination showed the disease was at a state of CR and the blast cell was reduced to 4% on day 14 at the first cycle of sorafenib in combination with low-dose-homoharringtonine chemotherapy. So the regimen was continued and repeated on the patient. The CR was last for 6 months and the patient was relapsed on 14 June, 2015.

Discussion

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults, with an estimated incidence of 3 cases per 100,000 people. Factors associated with poor prognosis include advanced age, unfavorable cytogenetics, molecular markers (such as FMS-like receptor tyrosine kinase-3 [FLT3], internal tandem duplication [ITD] mutation, or absence of nucleophosmin [NPM1] mutation), poor performance status, multiple comorbidities, inability to tolerate chemotherapy, and multidrug resistance [5-8]. The management of patients with relapsed/refractory AML remains a huge clinical challenge with few therapeutic options available, particularly for older patients. There are no currently acceptable conventional treatments for high-risk AML. Large, well-designed clinical trials of novel agents are the only way to make progress in this lethal disease, since traditional cytotoxic agents are inadequate.

The FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) gene is one of the most frequently observed genetic alterations in AML, with an incidence of about 20% to 30% [9, 10]. The presence of an FLT3-ITD mutation in AML has been associated with higher rates of relapse and shorter disease-free and overall survivals. Increasing recognition of the *FLT3*-ITD mutation as an adverse prognostic factor in patients with AML has led to the development of potent tyrosine kinase inhibitors targeting this mutation. Limited phase I/II studies on the different FLT3 inhibitors have suggested a potential benefit of these agents, however, benefits had a short duration in most of these studies. The long-term utility of these agents has been hampered by the development of drug resistance. Sorafenib, as one of the most focused FLT3 inhibitors, has demonstrated efficacy in inhibiting the activities of FLT3 in the previously reported cases [5, 11, 12]. Sorafenib has been tested in patients with AML both as a mono-therapy and in combination with other chemotherapies, most reported together with cytarabine, daunorubicin and azacytidine.

To our best knowledge, this is the first successful case report of sorafenib in combination with low-dose-homoharringtonine as a salvage therapy in primary refractory FLT3-ITD-positive AML. In our case, we combined sorafenib with low-dose-homoharringtonine, which leaded the patient to CR for 6 months. After the administration of the combination of these two drugs, the patient did not observe significant adverse reactions. As far as we know, this is the first case report of this combination which benefit the FLT3-ITD-positive AML patient for more than 6 months.

Of course, sorafenib also has its side effects, which most commonly reported interstitial pneumonia. Most patients can tolerate the side effects of sorafenib. However, there are the reports to be very serious, even to be fatal. Clinicians in the clinical application process should pay sufficient attention and timely take measures [13-17].

In summary, our case report and the existing literature indicate that sorafenib appears to provide a useful option for treatment of relapsed/refractory FLT3-ITD-positive AML patients. However, the optimal role of sorafenib in patients with AML remains unanswered. Despite promising results of sorafenib in the existed clinical trials, the development of resistance during the course of therapy is a major clinical challenge. Thus, given their short-term efficacy and relatively few adverse effects, a large prospective study is needed to confirm the results.

The authors believe that the field of research for FLT3 inhibitors remains promising and the combination of sorafenib with homoharringtonine maybe a good choice for these patients, although further prospective studies are necessary to validate and optimize the efficacy of this combination treatment.

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Disclosure of conflict of interest

None.

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