Case Report

Sorafenib As Monotherapy or in Association With Cytarabine and Clofarabine for the Treatment of Relapsed/Refractory FLT3 ITD-Positive Advanced Acute Myeloid Leukemia

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Clinical Practice Points

- Acute myeloid leukemia (AML) associated with fms-related tyrosine kinase 3 (FLT3) internal tandem duplication mutation has an increased relapse rate and a reduced overall survival.
- Here we report 3 cases of advanced refractory AML treated using sorafenib alone or in association with chemotherapy, at a standard dose of 400 mg twice daily. All the patients had been previously treated with several chemotherapy lines and their status was complicated by severe infectious disease.
- After sorafenib treatment, clinical complete remission but not molecular remission was achieved in all cases. Median duration of the response of these patients was relatively short (40 days), but in 1 patient it was possible to continue the therapy at the reduced dose of 600 mg daily as a bridge to allogeneic stem cell transplantation.
- We confirm that sorafenib is active in FLT3 mutated AML and we suggest that this drug could be used in more precocious stages of this disease to achieve a deeper hematological response as a bridge to bone marrow transplant.

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Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, often with unfavorable prognosis. Causes of therapeutic failure in AML treatment include different patient clinical characteristics, disease biology, and intensity of treatment.[1] The therapeutic options for relapsed or refractory AML are limited, particularly in cases of poor performance status.[2] In one-third of cases, mutations in the fms-related tyrosine kinase 3 (FLT3) receptor are reported. These have been suggested to be associated with an increased relapse rate and reduced overall survival.[2,3] The most frequent of the FLT3 mutations is the internal tandem duplication (ITD), reported in approximately 25% adult AML patients and in approximately 3% to 5% of newly diagnosed myelodysplastic syndromes (MDS). FLT3 is also overexpressed in B-precursor cell acute lymphoblastic leukemia (ALL), a fraction of T-cell ALL, and chronic myelogenous leukemia in blast crisis.[4] In FLT3-negative MDS patients, the mutations sometimes appear during progression to AML.[2,5] In addition to FLT3/ITD, a number of mutations might occur in the second kinase domain of FLT3, with the point mutation in position 835, accounting for 5% to 10% of adult AML. Dual ITD/tyrosine kinase domain (TKD) mutations in AML are rarely reported (1%-3%).[4,6,7] FLT3 ITD is associated with high white blood cell count, elevated lactate dehydrogenase level, high blood and bone marrow blast percentages, and poor clinical outcome, but it seems to have no effect on the ability of adult patients to achieve complete remission.[8-10]

Although FLT3/ITDs are associated with a worse prognosis, some authors reported different risk score according to size of FLT3 ITD. In fact, the sizes of FLT3 ITDs are variable and increasing

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ITD size was associated with decreasing overall survival (OS) in relation to a major loss of autoinhibitory function of FLT3.[11,12]

Furthermore, FLT3 TKD mutations have a variable prognostic effect depending on possible associated mutations of genes such as *NPM1* (nucleophosmin-1), *CEBPalfa* (CCAAT/enhancer binding protein alpha), *MLL* (mixed-lineage leukemia), and *PML-RARalfa* (promyelocytic leukemia-retinoic acid receptor alpha).[13,14]

Sorafenib was recently tested in a relatively low number of AML patients with the FLT3 mutation, and it was found to be very active also in this group of patients.[1]

With regard to the role of FLT3 minimal residual disease (MRD), Scholl et al observed that 5 out of 6 MRD-negative patients remained free of disease and 1 patient relapsed with loss of FLT3 ITD mutation.[15] Abdelhamid et al showed that high levels of MRD were predictive of disease recurrence in 17 of 20 patients examined and in 3 patients, molecular relapse took place before clinical relapse, emphasizing the importance of this marker in the MRD.[16]

Here, we report 3 consecutive cases of FLT3-mutated resistant AML patients showing that sorafenib is an effective alternative treatment for patients with relapsed or refractory FLT3-ITD–positive, alone or in combination with standard chemotherapies.

Patients and Methods

Clinical characteristics of enrolled patients are reported in Table 1.

Inclusion criteria were: (1) patients with AML, aged 18 to 75 years; (2) resistant after at least 2 lines of therapy; (3) showing FLT3-ITD mutation; and (4) eligible or not for bone marrow transplantation.

Results

Case 1

In March 2010, a 47-year-old Caucasian woman was admitted to our Department because of hyperleucocitosis (white blood cell count [WBC], 135 × 10^9/L), anemia (hemoglobin [Hb], 10.9 g/dL), and thrombocytopenia (platelet count [PLT], 94 × 10^9/L). Bone marrow was hypercellular, with subtotal myeloid blast infiltration. Myeloperoxidase activity was present in all blast cells. Using immunophenotyping, blasts resulted as positive for $CD34^{+/-}$ (33% of cells), $CD117^+$, $CD33^+$, $CD13^+$, $CD38^+$, and $CD45RA^{+/-}$ (69% of cells). Mutation of nucleophosmin was detected, and conventional karyotyping was normal. Marrow molecular analysis showed FLT3-ITD, so the patient was classified as high risk AML, according to the World Health Organization (WHO) classification.

The patient received a standard induction regimen using idarubicin and cytarabine (3+7). *Pseudomonas aeruginosa* was isolated from ear and inguinal swabs. The bone marrow evaluation performed after 15 days from the end of chemotherapy showed a partial response, with persistence of 10% to 12% of blasts. Nevertheless, 1 month later, the patient was readmitted to our Department because of an inguinal lymphadenopathy (23 mm) that was subjected to biopsy. Histological examination confirmed the diagnosis of tissutal localization of granulocytic sarcoma ($CD34^+$, $CD45^+$, MPO^+). The patient was then treated using the same induction therapy, but the final evaluation still showed a subtotal blast infiltration in the

Table 1 Patient Characteristics

Pt Number	Age, Years	Sex	Cytogenetic	FLT3	NPM	Previous Therapies	Disease Status		Adverse Event	Allo-BMT	Outcome	Cause of Death
							Before Sorafenib	After Sorafenib				
1	47	F	46, XX	ITD	Mutated	Two inductions using idarubicin with cytarabine	NR	NR; CR (after addition of cytarabine and clofarabine); molecular persistence of FLT3 ITD	Neutropenia, thrombocytopenia, elevated transaminases, diarrhea, palmar-plantar erythrodysesthesia, QT interval prolongation	Yes	Death	Acute pulmonary edema
2	24	F	47, XX, +8, t(6;9)(p23;q34)	ITD	ND	Idarubicin with cytarabine, cytarabine, cytarabine with clofarabine	Relapse	CR; molecular persistence of FLT3 ITD	Neutropenia, anemia, thrombocytopenia	No	Death	Disease progression
3	63	M	46, XY	ITD	ND	Idarubicin with etoposide with cytarabine, azacitidine	NR	CR; molecular persistence of FLT3 ITD	Fever, neutropenia, atrial fibrillation, diarrhea	No	Death	Disease progression

Abbreviations: Allo-BMT = allogeneic bone marrow transplant; F = female; FLT3 = fms related tyrosine kinase 3; ITD = internal tandem duplication; M = male; ND = not done; NPM = nucleophosmin; NR = no response; Pt = patient.