Treatment of FLT3-ITD-Positive Acute Myeloid Leukemia Relapsing after Allogeneic Stem Cell Transplantation with Sorafenib

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Patients with acute myeloid leukemia (AML) and internal tandem duplication of FMS-like tyrosine kinase receptor-3 gene (FLT3-ITD) mutation have poor prognoses and are often treated with allogeneic hematopoietic stem cell transplantation (HSCT). Sorafenib, an inhibitor of multiple kinases including FLT3, has shown promising activity in FLT3-ITD-positive AML. We treated 16 patients with FLT3-ITD-positive AML who relapsed after HSCT with sorafenib alone (n = 8) or in combination with cytotoxic chemotherapy (n = 8). The number of circulating blasts decreased in 80% of cases, but none of the patients achieved complete remission (CR); 3 achieved partial remission. Two patients were bridged to a second transplantation but both relapsed within 3 months of the transplantation. Median overall survival (OS) was 83 days, with none surviving more than a year. Sorafenib is not effective in the treatment of FLT3-ITD-positive AML relapsing after HSCT. Preventive strategies after HSCT may be more suitable for these high-risk patients.

Biol Blood Marrow Transplant 17: 1874-1877 (2011)

KEY WORDS: Sorafenib, FLT3, Acute myeloid leukemia, Stem cell transplantation

INTRODUCTION

FMS-like tyrosine kinase receptor-3 (FLT3) is a transmembrane protein important in proliferation and survival of hematopoietic stem cells (HSC) upon activation [1]. Internal tandem duplication of the juxtamembrane domain of the FLT3 gene (FLT3-ITD) leads to kinase activity and activation of downstream signaling pathways including the MAPK pathway [2]. FLT3-ITD has been reported in approximately a one-quarter of patients with acute myeloid leukemia (AML) and is associated with higher relapse rates and shorter survival [3-5]. As the mutation portends an increased risk of disease relapse following chemotherapy alone, allogeneic hematopoietic stem cell transplantation (HSCT) is frequently proposed if a donor is identified. Although a proportion of patients will be cured following this approach, a significant number will suffer disease recurrence following the transplantation.

Sorafenib is an oral, small-molecule, multikinase inhibitor that may restrain proliferation of leukemia cells by inhibition of the MAPK pathway through raf-1 induction of apoptosis through mcl-1 [6,7], in addition to directly targeting mutant FLT3 [8]. It was found to be active in patients with FLT3-ITD-positive AML in phase I trials [9,10]. Sorafenib has also been successfully used to treat relapsed FLT3-ITD-positive AML following allogeneic HSCT [11-16]. Here, we reviewed our experience with this drug in patients with FLT3-ITD-positive AML who relapsed after allogeneic HSCT.

MATERIALS AND METHODS

We identified all patients who received sorafenib for at least 7 days, either alone or with chemotherapy, to treat FLT3-ITD-positive AML relapse after allogeneic HSCT in our institution. The retrospective chart review protocol was approved by the institutional review board (IRB). Demographic and transplant-related information was collected, as well as relapse-specific data, sorafenib dose, and duration of treatment. Treatment

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Financial disclosure: See Acknowledgments on page 1877.

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Received May 15, 2011; accepted July 10, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.07.011

Table 1. Patient Characteristics and Response to Therapy (N = 16)

Characteristics	n (%)
Median age at diagnosis*	34 (20-63)
Antecedent hematologic history	4 (25%)
Cytogenetic risk based on AML diagnosis	
High	13 (81%)
Intermediate	2 (13%)
Unknown	1 (6%)
Sorafenib use before transplantation	6 (38%)
Complete remission at transplantation	3 (19%)
Donor type	
Matched related	5 (31%)
Mismatched related	4 (25%)
Matched unrelated	5 (31%)
Unrelated cord blood	2 (13%)
Remission duration following transplantation (months)*	3 (1-7)
Posttransplantation salvage therapy before sorafenib	7 (44%)
Number of salvage regimens before sorafenib*	0 (0-5)
Sorafenib therapy	
Alone	8 (50%)
In combination with chemotherapy	8 (50%)
Duration of sorafenib treatment in days (range)*	
Alone	39 (10-100)
In combination with chemotherapy	7 (7-32)
WBC count before sorafenib ($10^3/\mu L$)*	22.6 (0.6-119)
Peripheral blast percentage before sorafenib*	65% (0%-80%)
Median percentage decrease in circulating peripheral blasts (n = 12)*	50% (0%-88%)
Bone marrow blast percentage before sorafenib*	58.5% (12%-88%)
Median absolute decrease in bone marrow blast percentage*	0% (0-46)
CR following sorafenib	None
PR following sorafenib	3 (19%)
New or worsening GVHD following sorafenib	1 (6%)
Bridged to second transplantation	2 (13%)
Time from bridged second transplantation to relapse (days)*	(53 and 106)

WBC indicates white blood cell; CR, complete remission; PR, partial remission; GVHD, graft-versus-host disease.
*Median (range).

response was defined according to International Working Group criteria [17]. Overall survival (OS) was defined as time from sorafenib initiation to death. Actuarial survival curves were estimated according to the Kaplan-Meier method, and the significance of differences between the curves was estimated by the log-rank test.

RESULTS

Sixteen patients were treated (Table 1). Four patients had a second transplantation before sorafenib therapy, whereas 12 received sorafenib after the first transplantation. Only 3 patients (19%) were in complete remission (CR) at the time of the first transplantation. The preparative regimen was of reduced intensity (n = 7) or myeloablative (n = 9). Three patients received CD34-selected stem cells; hence, neither received graft-versus-host disease (GVHD) prophylaxis nor developed GVHD. Of the remaining 13 patients, 4 developed acute GVHD (aGVHD) of the skin before disease relapse. All 13 were receiving tacrolimus for prophylaxis or treatment of GVHD in addition to mycophenolate mofetil (n = 3) or systemic steroids (n = 1) at the time of disease recurrence. The median remission duration following transplantation was 3 months (range: 1-7 months).

Sorafenib Treatment

Six patients (38%) had received sorafenib before HSCT, either as part of the induction therapy or as a salvage regimen. In 9 patients (56%), sorafenib with or without chemotherapy was the first salvage therapy following allogeneic HSCT. The drug was given either alone or in combination with other cytotoxic therapy in 8 (50%) and 8 (50%) patients, respectively.

Sorafenib was used as a single agent orally twice daily at 400 mg (n = 6), or 600 mg (n = 2), on a 3-week cycle, either 5 days on therapy and 2 days off weekly, or 14 days on therapy and 7 days off therapy. When combined with chemotherapy, sorafenib was given as 400 mg daily (n = 4) or 400 mg twice daily (n = 4). Combined therapy included cytarabine and idarubicin (n = 7), or azacitidine (n = 1). Median duration of single-agent sorafenib treatment was 39 days, whereas median duration of sorafenib administration with chemotherapy was 7 days. Of 8 patients who received sorafenib alone, 4 developed grade $\geq$2 adverse events that included a grade 2 increase in alanine aminotransferase, grade 3 fatigue, grade 3 diarrhea, and grade 3 hyperbilirubinemia. None of the patients experienced worsening or development of GVHD after sorafenib treatment.

Response to Sorafenib

Nine patients had pre- and postsorafenib bone marrow aspirations performed: 3 patients (19%) achieved a partial remission. The responders included 2 patients who received sorafenib alone, and 1 patient received sorafenib in combination with other chemotherapy agents. A bone marrow examination was not performed in the remaining 7 patients because of disease progression (apparent from peripheral blast counts), inadequate bone marrow samples, or patient death. Peripheral blast data was available in the majority (75%) of patients (unless pancytopenic).

The median decrease in bone marrow blast percentage was 0%, whereas median absolute reduction in peripheral blood blast percentage was 50%. A reduction in the number of circulating blasts was evident in 80% of the cases, similarly distributed in the single agent versus combination therapy subgroups. Given the low response rate, no dose or schedule appeared superior. Of the 6 patients who had received sorafenib before transplantation, 1 achieved a partial remission; 3 had at least a 50% reduction in peripheral blood