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

Giorgia Battipaglia, MD [1,2]; Annalisa Ruggeri, MD, PhD[1]; Radwan Massoud, MD [3]; Jean El Cheikh, MD[3]; Matthieu Jestin, MD[1]; Ahmad Antar, MD[3]; Syed Osman Ahmed, MD[4]; Walid Rasheed, MD[4]; Marwan Shaheen, MD[4]; Ramdane Belhocine, MD[1]; Eolia Brissot, MD, PhD[1]; Remy Dulery, MD[1]; Sandra Eder, MD[1]; Federica Giannotti, MD[1]; Francoise Isnard, MD[1]; Simona Lapusan, MD[1]; Marie-Therese Rubio, MD[1]; Anne Vekhoff, MD[1]; Mahmoud Aljurf, MD[4]; Ollivier Legrand, MD, PhD[1]; Mohamad Mohty, MD, PhD[1,5,6]; and and Ali Bazarbachi, MD, PhD[3,7]

BACKGROUND: Sorafenib has shown encouraging results in patients with Fms-like tyrosine kinase 3 (FLT3)-positive acute myeloid leukemia. Its role after allogeneic stem cell transplantation (HSCT) has been reported in a few cases with encouraging results. **METHODS:** The authors describe the use of sorafenib as a maintenance agent after HSCT in 27 patients with FLT3-positive acute myeloid leukemia. **RESULTS:** The median age of the patients was 46 years (range, 15-57 years). Sorafenib was introduced at a median of 70 days (range, 29-337 days) after HSCT. The median treatment duration was 8.4 months (range, 0.2-46 months). Eleven patients experienced treatment toxicities, mainly of grade 1 to 2 (graded according to the National Cancer Institute Common Toxicity Criteria [version 4.0]). Dose reduction or withdrawal was required in 4 patients and 4 patients, respectively. The persistence of toxicity prompted treatment withdrawal in 1 patient. Clinical improvement followed dose modifications. Thirteen patients experienced chronic graft-versus-host disease (limited in 9 patients and extensive in 4 patients), resulting in dose reduction in 5 patients followed by withdrawal in 1 of these individuals. At a median follow-up of 18 months (range, 4-48 months), 25 patients were alive (all of whom were in complete molecular remission) and 18 were still receiving treatment, with 1-year overall survival and progression-free survival rates of 92% ± 6% and 92% ± 5%, respectively. **CONCLUSIONS:** Sorafenib treatment after HSCT appears to be feasible and highly effective with dose individualization according to patient tolerability. Further analysis is needed to evaluate the immunomodulating role of sorafenib after HSCT. The data from the current support prospective controlled trials of sorafenib after HSCT. ***Cancer* 2017;123:2867-74.**

KEYWORDS: allogeneic stem cell transplantation, acute myeloid leukemia (AML), Fms-like tyrosine kinase 3 (FLT3), maintenance, sorafenib.

INTRODUCTION

Patients diagnosed with acute myeloid leukemia (AML) with Fms-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) or with D835-activating point mutations (FLT3-TKD) have a dismal prognosis, with a high risk of disease recurrence.[1] To the best of our knowledge, no commonly accepted standard treatment has been defined to date,[2] but retrospective series have demonstrated that these patients might benefit from early allogeneic hematopoietic stem cell transplantation (HSCT) at the time of first hematologic complete response (CR).[3] Therefore, HSCT has become common practice in most centers, but long-term survival is still hampered by disease recurrence, which often is refractory to further treatment.

Several molecules against FLT3 have been developed and evaluated in clinical trials.[4,5] Sorafenib, a multitarget tyrosine kinase inhibitor approved for the treatment of patients with advanced renal cell and hepatocellular carcinoma,[6] has been studied in various AML scenarios, including as first-line therapy, for the treatment of disease recurrence, as

Correction added on 24 April 2017, after first online publication: in the 11th line of the abstract, median overall survival should be changed to 1-year overall survival.

Corresponding author: Giorgia Battipaglia, MD, Hematology and Cellular Therapy Service, Hôpital Saint Antoine, 184 Rue du Faubourg Saint Antoine, 75012 Paris, France; Fax: (011) 0033149283200; giorgia.battipaglia@aphp.fr; and Ali Bazarbachi, PhD, Bone Marrow Transplantation Program, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; Fax: (011) 9611350000, ext. 4913; bazarbac@aub.edu.lb

[1]Hematology and Cellular Therapy Service, Saint Antoine Hospital, AP-HP, Paris, France; [2]Department of Hematology and Marrow Transplantation, Federico II University, Naples, Italy; [3]Bone Marrow Transplantation Program, Department of Internal Medicine, American Universit6y of Beirut Medical Center, Beirut, Lebanon; [4]Adult Hematology/HSCT Section, Oncology Center, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [5]Hospital Saint-Antoine, Paris University UPMC, Paris, France; [6]INSERM, Paris, France; [7]Department of Cell Biology, Anatomy and Physiological Sciences, American University of Beirut, Beirut, Lebanon

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monotherapy, or in combination with conventional chemotherapeutic agents.[7,8] However, the ideal time to incorporate this drug into the treatment of patients with FLT3-positive AML remains unclear, with some reports suggesting that its use after HSCT yields promising results, allowing for long-term disease control.[9-11] Therefore, we retrospectively analyzed the outcomes of a group of patients undergoing HSCT for FLT3-positive AML who afterward received sorafenib as maintenance treatment.

MATERIALS AND METHODS

A total of 27 patients undergoing HSCT for FLT3-positive AML received sorafenib as a maintenance agent after HSCT in 3 hematology departments at 3 institutions (Hospital Saint Antoine [Paris, France], the American University of Beirut [Beirut, Lebanon], and King Faisal Specialist Hospital and Research Center [Riyadh, Saudi Arabia]). Demographic and transplantation-related information, disease recurrence-specific data, sorafenib dose, toxicity, efficacy, and duration of treatment were collected. Hematological CR was defined as previously reported.[12] Monitoring of minimal residual disease (MRD) after chemotherapy and after HSCT was performed using standard polymerase chain reaction (PCR)-based molecular techniques for nucleophosmin 1 (NPM-1) (all FLT3-positive patients), FLT3 (only in the American University of Beirut), and Wilms tumor 1 (WT1) (mainly in Hospital Saint Antoine). A positive MRD for WT1 was defined by a WT1/ABL ratio $> 0.1\%$ in peripheral blood and/or $> 1\%$ in bone marrow. A positive MRD for NPM-1 was defined as an allelic ratio of mutated NPM-1/total NPM-1 in the peripheral blood or bone marrow $>10^{-4}$. A positive MRD for FLT3 was defined as its detection on qualitative PCR. Flow cytometric analysis was used, when possible, for MRD monitoring. At the time of diagnosis, an abnormal cell population demonstrating deviation from the normal patterns of antigen expression noted on specific cell lineages at different stages of maturation compared with either normal or regenerating bone marrow was identified. The abnormal population was quantified as a percentage of the total CD45-positive white blood cell events. Subsequently, a positive MRD was defined by a homogenous cluster (>20 events) with the immunophenotype and scatter properties defined at the time of diagnosis. In the absence of molecular or flow cytometric markers allowing MRD monitoring, chimerism on CD3-negative cell fractions after HSCT was used as a surrogate. According to the threshold of sensitivity of the reverse transcriptase-PCR technique, full-donor chimerism was defined as a recipient cell percentage $<0.01\%$ (Hospital Saint Antoine) or $< 5\%$ on total bone marrow cells (the American University of Beirut and King Faisal Specialist Hospital and Research Center) and mixed chimerism as a recipient cell percentage superior to these thresholds. Neutrophil and platelet engraftments after HSCT were defined as the first of 3 consecutive days with an absolute neutrophil count $>0.5 \times 10^9$/L and a platelet count $>20 \times 10^9$/L, respectively. The conditioning regimen was defined as reduced intensity conditioning (RIC) when fludarabine and/or thiotepa were combined with a dose of intravenous busulfan of <6.4 mg/kg and as a myeloablative conditioning regimen when it contained busulfan at greater doses. Furthermore, the conditioning regimen was defined as sequential when chemotherapy was followed by an RIC regimen after a 3-day interval. Acute and chronic graft-versus-host disease (GVHD) were diagnosed and graded according to standard criteria.[13] Treatment with sorafenib was introduced after HSCT and then continued until disease progression. When side effects occurred, dose reduction and/or drug withdrawal took place as per the decision of the treating physician. The severity of adverse events was evaluated using the National Cancer Institute Common Toxicity Criteria (version 4.0).[14] Surviving patients were censored at the time of last follow-up, whereas death was considered an event in the other patients. The duration of follow-up was the time to the last assessment for survivors. Overall survival (OS) was defined as the probability of being alive, regardless of disease status, at any time point. Progression-free survival (PFS) was defined as the probability of being alive and disease free at any time point; both death and disease recurrence were considered events, and patients who were alive and in CR were censored at the time of last follow-up. OS and PFS were estimated using the Kaplan-Meier method.

RESULTS

Patient, Disease, and Transplantation Characteristics

Patient, disease, and transplantation characteristics are reported in Table 1. FLT3-ITD AML was detected in 25 patients, whereas FLT3-TKD was found in the remaining 2 patients. A total of 16 males and 11 females were included in the current report. The median age of the patients at the time of diagnosis was 46 years (range, 15-57 years). A normal karyotype was detected in all but 5 patients. Nine patients demonstrated FLT3-ITD as the sole molecular abnormality, and 13 patients had a concomitant NPM-1 mutation, which was associated with WT1 overexpression

TABLE 1. Patient, Disease, and Transplantation Characteristics

Variable	No.
Median age at diagnosis (range), y	46 (15-57)
Male/female sex	16/11
Type of FLT3 mutation	
FLT3-ITD	25
FLT3-TKD	2
Molecular abnormalities associated with	
FLT3-ITD	11
NPM-1 alone	2
NPM-1 and WT1 overexpression	2
NPM-1 and CEBPA double mutated	3
WT1 overexpression	9
None	
Molecular abnormalities associated with	2
FLT3-TKD	
NPM-1 alone	
Associated karyotype abnormalities	5
Median age at HSCT (range), y	46 (16-58)
Median time/period HSCT (range). y	2015 (2013-2016)
Median interval from CR to HSCT (range), d	53 (6-128)
First HSCT	26
Second HSCT	1
Disease status at time of HSCT	
CR1	22
CR2	3
CR3	1
Active disease	1
MRD positivity at time of HSCT	12
Type of donor	
Matched sibling	19
MUD	4
Haplo	4
Stem cell source	
BM	2
PBSC	25
Conditioning regimen	
MAC	20
RIC	5
Sequential	2
Type of conditioning	
Sequential	2
Flu-Bu	17
TBF	2
Bu-Cy	2
Bu-TBI	3
Etoposide-TBI	1
In vivo TCD	20
GVHD prophylaxis	
CsA alone	7
CsA and MMF	8
CsA and MTX	8
CsA, MMF, and PTCy	4
Median CD34 + dose (range), $\times 10^6$/kg	622 (2.74-10.13)
Median time to neutrophil engraftment, (range), d	16 (12-30)
Median time to PLT engraftment, (range), d	11 (4-30)
Chimerism at d 30	
Full donor	24
Partial donor	3
GVHD grade before sorafenib introduction	3
1-2	3
2-4	0

Abbreviations: BM, bone marrow; Bu, busulfan; CEBPA, CCAAT/enhancer binding protein (C/EBP) alpha; CR, complete remission; CsA, cyclosporine A; Cy, cyclophosphamide; FLT3, fms-like tyrosine kinase 3; Flu, fludarabine; GVHD, graft-versus-host disease; haplo, haploidentical; HSCT, hematopoietic stem cell transplantation; ITD, internal tandem duplication; MAC, myeloablative conditioning regimen; MMF, mycophenolate mofetil; MRD, minimal residual disease; MTX, methotrexate; MUD, matched unrelated donor; NPM-1, nucleophosmin 1; PBSC, peripheral blood stem cells; PLT, platelet; PTCy, posttransplant cyclophosphamide; RIC, reduced intensity conditioning regimen; TBF, thiotepa, busulfan, and fludarabine; TBI, total body irradiation; TCD, T-cell depletion; TKD, tyrosine kinase domain; WT1, Wilms tumor 1.

in 2 patients and CCAAT/enhancer binding protein (C/EBP) alpha (CEBPA) double mutation in 2 other patients. The association between FLT3-ITD and WT1 overexpression was observed in 3 patients. Both patients with FLT3-TKD presented with a concomitant NPM-1 mutation. All but 1 patient underwent their first HSCT, which was performed between 2013 and 2016. It is interesting to note that during the same period, 15 patients underwent HSCT for FLT3-positive AML, but these individuals did not receive sorafenib due to physician decision (7 patients at King Faisal Specialist Hospital and Research Center, at which only some physicians adopted this strategy), disease recurrence occurring before day 90 (3 patients), patient refusal (1 patient), GVHD (2 patients), unknown reason (1 patient), and infection (1 patient).

The median age of the patients at the time of HSCT was 46 years (range, 16-58 years). At the time of HSCT, 22 patients were in first hematologic CR, 3 were in second hematologic CR, and 1 patient was in third hematologic CR. Twelve patients in hematologic CR had a detectable MRD before HSCT. One patient presented with active disease at the time of HSCT. The median interval from CR to HSCT was 53 days (range, 6-128 days). The majority of the patients (25 patients) received peripheral blood stem cells as the stem cell source (18 from a matched sibling, 4 from a matched unrelated donor, and 3 from a haploidentical donor). The remaining 2 patients received bone marrow from a matched sibling or a haploidentical donor, respectively. A myeloablative conditioning regimen was used in 20 patients, whereas 5 patients received an RIC regimen. A sequential regimen was used in the 2 remaining patients, either for active disease or for detectable MRD before HSCT. Twenty of 27 patients received in vivo T-cell depletion with antithymocyte globulin before undergoing HSCT. The median number of CD34-positive infused stem cells was 6.22×10^6/kg (range, $2.74\text{-}10.13 \times 10^6$/kg) for peripheral blood stem cell recipients. GVHD prophylaxis consisted of cyclosporine A either alone (12 patients) or in combination with mycophenolate mofetil (8 patients) or methotrexate (7 patients). In addition, patients with a haploidentical donor also received 2 additional doses of cyclophosphamide after transplantation.

All patients achieved neutrophil engraftment within a median of 16 days (range, 12-30 days). Platelet engraftment was achieved within a median of 11 days (range, 4-30 days) in 21 of the 27 patients. In the remaining 6 patients, platelet counts were never $<20 \times 10^9$/L. Full donor chimerism at day 30 was observed in all but 3 patients. One patient presented with a chimerism loss at day 90, concomitant with disease recurrence.

Three patients experienced grade 1 to 2 acute GVHD before the introduction of sorafenib that was successfully treated with topical steroids. Six patients were out of immunosuppressive treatment (IST) at time of sorafenib introduction.

Sorafenib Treatment Details

Treatment details are reported in Table 2. Sorafenib was introduced as a single maintenance agent at a median after HSCT and after IST withdrawal of 70 days (range, 29-337 days) and 14 days (range, 4-196 days), respectively. It is interesting to note that 3 patients had already received sorafenib in association with either induction or consolidation chemotherapy. Starting doses of sorafenib were distributed as follows: 400 mg twice a day in 13 patients, 200 mg twice a day in 13 patients, or 200 mg once a day in 1 patient. Doses were then adjusted to the best tolerated dose according to side effects.

Dose Modifications, Toxicity, and Survival

Dose reduction was required in 1 patient because of financial problems. Toxicity occurred in 11 of 27 patients, and for the most part was of grade 1 to 2 and reversible in all cases. These events were mostly hematologic (2 patients), gastrointestinal (6 patients, including 1 patient with hematologic toxicity), cardiac (1 patient), cutaneous (3 patients, including 1 patient with gastrointestinal toxicity), and biochemical (amylase and lipase elevation [1 patient]). Dose reduction due to toxicity was made in 4 patients, followed by drug withdrawal in 1 of them. Direct drug withdrawal due to toxicity occurred in 4 patients. Clinical improvement followed dose reduction and/or drug withdrawal. Despite toxicity, clinicians did not consider it necessary to make dose modifications in the remaining 3 patients.

Thirteen patients experienced chronic GVHD (limited in 9 patients and extensive in 4 patients), with a median time to onset after sorafenib introduction and after HSCT of 14 days (5-56 days) and 97 days (36-152 days), respectively. A skin biopsy was performed and demonstrated GVHD in 3 patients. Of the 6 patients for whom IST had been stopped before sorafenib introduction, only 1 patient experienced GVHD. The sorafenib dose was reduced as a consequence of GVHD in 5 patients, followed by drug withdrawal in 1 of them. In 1 patient, treatment was alternatively stopped and reintroduced. Direct withdrawal was made in 2 patients who were experiencing either limited or extensive GVHD. In 1 of these 2 patients, a prophylactic treatment with azacitidine at a dose of 32 mg/m^2/day was initiated after sorafenib withdrawal, and then switched to curative doses of 75 mg/m^2/day after 2 cycles when MRD positivity was detected. This patient received a total of 9 cycles of curative azacitidine and was in persistent CR with undetectable MRD at the time of last follow-up, 20 months after HSCT.

TABLE 2. Sorafenib Treatment Details

Variable	N
Starting dose	
400 mg BID	13
200 mg BID	13
200 mg QD	1
Median time from HSCT to sorafenib start (range), mo	70 (29-337)
Toxicities	11
GI alone	4
Hematologic	1
GI plus hematologic	1
Cardiac	1
GI plus cutaneous	1
Cutaneous	2
Biochemical	1
Grade of toxicity	
1	3
2	2
3	1
4	1
Unknown	4
GVHD during sorafenib treatment	13
Limited	9
Extensive	4
Median time from sorafenib to GVHD onset (range), d	14 (5-56)
Median time from HSCT to GVHD onset (range), d	97 (36-152)
Dose modification	
None	9
Direct withdrawal	6
Dose reduction	8
Dose reduction followed by withdrawal	2
Withdrawal then resumed	1
On and off continuously	1
Reason for dose modification	
Not applicable	10
Toxicity	8
GVHD	8
Financial	1
DLI during sorafenib treatment	3
GVHD after DLI	0
Reason for DLI	
Prophylaxis	2
Recurrence	1
Treatment at time of last follow-up	
Ongoing	18
Stopped	8
Stopped at time of death	1
No. of patients alive at time of last follow-up No. of patients with undetectable MRD at time of last follow-up	25 27
Median treatment duration for all patients (range), mo Median duration of sorafenib in patients with ongoing treatment (range), mo	8.4 (0.2-46) 14 (3-46)
Median follow-up (range), mo	18 (4-48)

Abbreviations: BID, twice a day; DLI, donor lymphocyte infusion; GI, gastrointestinal; GVHD, graft-versus-host-disease; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; QD, once a day.

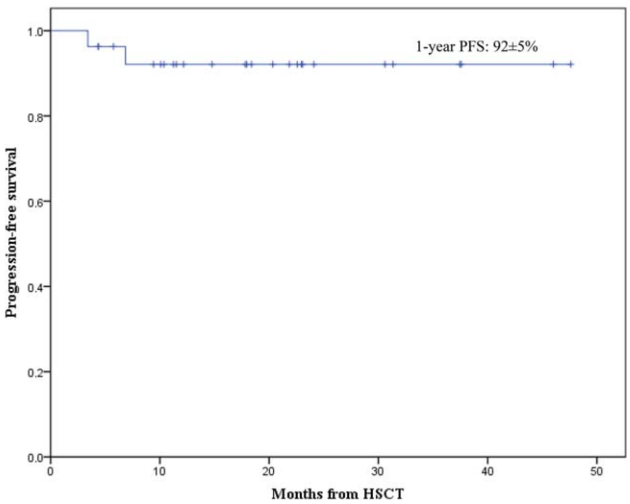

Figure 1. Progression-free survival. HSCT indicates allogeneic stem cell transplantation; PFS, progression-free survival.

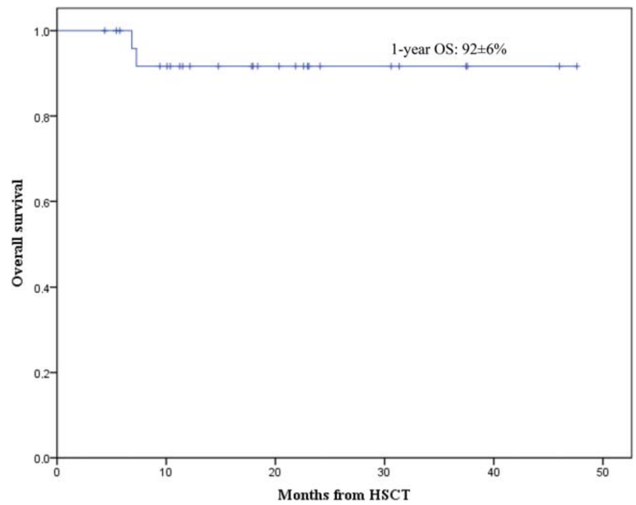

Figure 2. Overall survival. HSCT indicates allogeneic stem cell transplantation; OS, overall survival.

Three patients received donor lymphocyte infusion combined with sorafenib, none of whom experienced GVHD.

The median duration of treatment for all patients was 8.4 months (range, 0.2-46 months).

Only 1 patient who underwent HSCT while in second hematological CR experienced hematologic disease recurrence 2 months after HSCT. Salvage chemotherapy including clofarabine, cytarabine, and granulocyte colony-stimulating factor in association with sorafenib resulted in the patient achieving a third hematological CR. Maintenance treatment with sorafenib thereafter was maintained allowing disease control, but death related to GVHD occurred 7 months after HSCT.

With a median follow-up of 18 months (range, 4-48 months), the 1-year PFS rate was 92% ± 5%, whereas the 1-year OS rate was 92% ± 6% (Figs. 1 and 2) for the entire cohort. All but 2 patients were alive at the time of last follow-up, with GVHD and infection being the main causes of death, respectively. At the time of last follow-up, all surviving patients were found to have persistent undetectable MRD; 18 patients still were receiving sorafenib, with a median treatment duration of 14 months (range, 3-46 months) reported for these patients.

DISCUSSION

Nearly one-third[15] of patients newly diagnosed with AML present either with FLT3-ITD AML or FLT3-TKD AML and consequently have a poorer prognosis.[1] Similar remission rates are achieved after standard chemotherapy compared with other AML subtypes, but patients carrying a FLT3 mutation have a higher risk of early disease recurrence, and their disease often become refractory to salvage regimens. In the absence of large prospective studies investigating the best strategy to treat and maintain CR in these patients, to our knowledge there still is no standard recommendation. Retrospective studies have suggested a benefit, in terms of OS and PFS, when HSCT was performed during the first hematologic CR[3] so that these patients currently undergo HSCT in most institutions. However, even after HSCT, the risk of disease recurrence, including early disease recurrence, remains high, which calls for strategies of early maintenance prophylactic treatment after HSCT. Sorafenib is a multikinase inhibitor targeting RAF, vascular endothelial growth factor (VEGF), c-KIT, platelet-derived growth factor receptor (PDGFR), and FLT3.[6] Promising results have been reported with its use as first-line therapy in combination with induction chemotherapy or within the context of disease recurrence, used as a single agent or incorporated into standard chemotherapy regimens.[7,8,16]

In the current study, we retrospectively reported on 27 patients who received sorafenib after HSCT as a maintenance therapy. As previously reported in preliminary data from our group,[17,18] the results presented herein confirm the efficacy of this strategy, with patients experiencing long-term disease control with concomitant manageable and reversible toxicities.

In a phase 1 prospective study from Chen et al,[11] the use of sorafenib as a maintenance agent after HSCT in 22 patients with FLT3-positive AML resulted in 1-year PFS and OS rates of 95% and 100%, respectively. There were

3 instances of disease recurrence, including 1 in a patient with primary refractory AML who had achieved CR with sorafenib as a single agent before HSCT, 1 patient who experienced disease recurrence 6 months after sorafenib withdrawal due to toxicity, and 1 other patient who experienced disease recurrence while receiving sorafenib 12 months after its introduction.

More recently, Brunner et al compared the outcomes of patients undergoing HSCT for FLT3-positive AML and subsequently receiving or not receiving sorafenib as a maintenance treatment.[19] Improved 2-year PFS and OS rates of 82% and 81%, respectively, were observed in patients receiving sorafenib (vs 53% and 62%, respectively, in patients not receiving sorafenib; $P<.05$ in both cases), whereas no significant differences were observed in 1-year GVHD, although the rate of GVHD was slightly more elevated in patients receiving sorafenib compared with those who did not (55.5% vs 37.2%; $P=.28$).

Less favorable results were reported with the use of sorafenib in patients experiencing disease recurrence.[10,20] However, these studies emphasized that sustained remissions were exclusively noted when sorafenib was used after HSCT, most likely due to its capability to reduce leukemic burden and restore a graft-versus-leukemia (GVL) effect. However, these results were not confirmed by Sharma et al,[21] who reported on the use of sorafenib after HSCT, with or without additional chemotherapy, among 16 patients, none of whom achieved CR and none of whom were still alive at 1 year.

In contrast to the above cited studies, the current study also included 2 patients with FLT3-TKD mutations, despite it having been previously reported that patients harboring this mutation in association with the NPM-1 mutation have a relatively better prognosis.[22] However, in the absence of prospective randomized trials evaluating the use of sorafenib as a maintenance agent after HSCT in this category of patients, we preferred to suggest this agent to patients also presenting with FLT3-TKD AML. Our choice also was supported by data from the SORAML trial, which demonstrated that the addition of sorafenib to conventional chemotherapy in patients newly diagnosed with AML improved leukemia free survival (LFS) irrespective of FLT3 mutational status.[16]

A possible synergistic effect of sorafenib and alloreactive donor T cells in facilitating long-term disease control has been suggested,[23] and also has been proposed in murine models in which sorafenib apparently exacerbated GVHD.[24] In the current series, flare-ups of GVHD were observed early after treatment with sorafenib in 13 patients, thereby suggesting an immunomodulating effect with a possible restoration of a GVL effect. It is interesting to note that there were no cases of grade 4 or severe GVHD, and each event was manageable with immunosuppressive treatment and/or dose adaptation.

The above-mentioned studies also addressed the incidence and possible role of GVHD. Tschan-Plessl et al[23] observed GVHD in 7 of 65 patients, whereas Chen et al[11] reported a cumulative incidence of GVHD of 38%. It is interesting to note that no case of GVHD was reported in the series by Sharma et al,[21] again suggesting a synergistic effect of sorafenib and GVL/GVHD in maintaining long-term remission.

Due to the relatively limited experience with sorafenib in patients with AML after HSCT, to the best of our knowledge no standards currently exist regarding how to manage drug dose in the face of sorafenib's toxicity. In the current series, we observed side effects similar to those reported by others, with dose reductions and/or drug withdrawal being common, often without necessarily compromising the immunomodulatory drug effect. However, due to the heterogeneity of dose modification and of the starting dose, no conclusions could be reached regarding the best way to manage toxicity and the best starting dose of sorafenib. The impact of the starting dose of posttransplant maintenance treatment on patient outcome also remains unclear in other hematologic malignancies (ie, Philadelphia chromosome-positive acute lymphoblastic leukemia), in which dosing issues and toxicity management have not yet been standardized. In a retrospective series, physicians decided to initiate treatment with tyrosine kinase inhibitors after HSCT with a dose reduction of $\geq$50% from the standard pretransplant dosing to minimize toxicities and avoid treatment interruption.[25]

Moreover, in the presence of a skin rash occurring during treatment with sorafenib, it is reasonable to consider whenever possible performing a skin biopsy to differentiate between GVHD and drug toxicity, as we did in the current series in only 3 patients.

Limitations of the current study include its retrospective nature, a possible center effect, and the small number of patients. Moreover, in the current study, stratification of patients according to their FLT3 mutant-to-wild-type allelic ratio at the time of diagnosis was not possible because it was not systematically performed in the 3 centers. Recent reports have suggested that allele burden might affect prognosis in patients harboring FLT3-ITD,[26] and that its negative impact might be overcome when patients undergo HSCT at the time of first hematologic CR.[27] However, the true prognostic relevance of the allelic ratio remains to be refined further.

The results of the current study suggest that maintenance treatment with single-agent sorafenib introduced at nearly 3 months after HSCT appears efficacious, with an acceptable toxicity profile, impressive long-term disease control, and a possible synergistic effect with alloreactive donor cells. However, to the best of our knowledge, optimal disease status, starting dose of sorafenib, and the best maintenance agent to use among all the available FLT3 inhibitors remain unclear. To address these unmet clinical needs, the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) is launching BMT-CTN 1506, a multicenter, randomized, double-blind, placebo-controlled trial of gilteritinib, a FLT3 inhibitor, as a post-transplant maintenance agent for patients with FLT3-ITD AML in first hematologic CR.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Mohamad Mohty and **Ali Bazarbachi** designed the study. **Giorgia Battipaglia, Radwan Massoud**, and **Syed Osman Ahmed** collected the data (chaired by **Mahmoud Aljurf, Mohamad Mohty**, and **Ali Bazarbachi**). **Giorgia Battipaglia, Annalisa Ruggeri, Radwan Massoud, Jean El Cheikh, Matthieu Jestin, Ahmad Antar, Walid Rasheed, Marwan Shaheen, Ramdane Belhocine, Eolia Brissot, Remy Dulery, Sandra Eder, Federica Giannotti, Francoise Isnard, Simona Lapusan, Marie-Therese Rubio, Anne Vekhoff**, and **Ollivier Legrand** were in charge of patients. **Giorgia Battipaglia, Mohamad Mohty**, and **Ali Bazarbachi** analyzed and interpreted the data. **Giorgia Battipaglia, Mohamad Mohty**, and **Ali Bazarbachi** wrote or revised the article, and all authors reviewed its final version.

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