Sorafenib improves survival of *FLT3*-mutated acute myeloid leukemia in relapse after allogeneic stem cell transplantation: a report of the EBMT Acute Leukemia Working Party

The prognosis of acute myeloid leukemia (AML) with FMS-like tyrosine kinase 3 internal tandem duplication (*FLT3-ITD*) is generally poor and these patients are referred to allogeneic stem cell transplantation (allo-SCT) in first complete remission (CR).[1] However, long-term survival remains poor because of early relapse and lack of response to further treatment.[2] Furthermore, relapse after allo-SCT has a dismal outcome with a 1-year survival below 20%.

FLT3 tyrosine kinase inhibitors (TKI) were tested in *FLT3-ITD* AML.[3] Midostaurin improves overall survival (OS) when combined with chemotherapy, which led to its approval.[4] Because of its availability, sorafenib has been studied in various settings in *FLT3-ITD* AML, including first-line therapy, post-transplant maintenance therapy, or treatment of relapse, either alone or combined with chemotherapy or hypomethylating agents.[3,5-10] Gilteritinib was recently approved for relapsed/refractory *FLT3-ITD* AML and is currently being tested (BMT-CTN 1506; *clinicaltrials.gov identifer: 02997202*) as post-transplant maintenance. Conflicting results were reported on the use of sorafenib or other FLT3 inhibitors, either alone or combined with donor lymphocyte infusion (DLI), chemotherapy, or azacytidine, for patients in relapse after allo-SCT.[5,9,11-13]

Table 1. Patients' and transplant characteristics.

	Control N (%)	Sorafenib N (%)	*P*
Number of patients	118	34	
Female	59 (50)	13 (38)	0.226
Age at transplant; median (range)	51 (19-75)	48 (19-69)	0.792
Year of transplant (range)	2012 (2010-2015)	2013 (2010-2015)	0.05
Time from transplant to relapse; median; months (range)	3.7 (0.6-58.3)	2.8 (0.4-41.4)	0.169
Molecular profile			
NPM1	41 (40)	14 (41)	0.888
Cytogenetics			0.698
Favorable	4 (3)	0 (0)	
Intermediate	93 (79)	28 (82)	
Adverse	19 (16)	5 (15)	
N. of inductions; median (range)	1(1-8)	1.5(1-3)	0.939
CR after induction 1	74 (66)	19 (59)	0.485
Consolidation given	85 (72)	20 (61)	0.207
Follow up after relapse for alive patients; months (range)	19.74 (4.3 - 68.23)	22.69 (3.84 - 67.77)	0.49
Status at transplant			
CR1	72 (61)	18 (53)	0.676
CR2	13 (11)	4 (12)	
Active disease	33 (28)	12 (35)	
Donor type			
Matched Related Donor	50 (42)	23 (68)	0.021
Matched Unrelated Donor	59 (50)	8 (24)	
Haploidentical Donor	9 (8)	3 (9)	
Conditioning			
Myeloablative	56 (47)	23 (68)	0.038
Reduced Intensity	62 (53)	11 (32)	
In vivo TCD	67 (57)	18 (53)	0.691
Stem cell source			
BM	19 (16)	4 (12)	0.534
PBSC	99 (84)	30 (88)	
Minimal residual disease (MRD)			
MRD negative at transplant	68 (58)	11 (32)	0.009
MRD positive at transplant	50 (42)	23 (68)	
Patient CMV negative	52 (44)	7 (21)	0.013
Donor CMV negative	52 (44)	13 (38)	0.52
GvHD			
Acute GvHD grade II-IV	32 (28)	9 (28)	0.952
Chronic GvHD before relapse	18 (16)	4 (12)	0.563

N: number; CR: complete remission; TCD: T-cell depletion; BM: bone marrow; PBSC: peripheral blood stem cell; MRD: minimal residual disease; CMV: cytomegalovirus; GvHD: graft-*versus*-host disease.

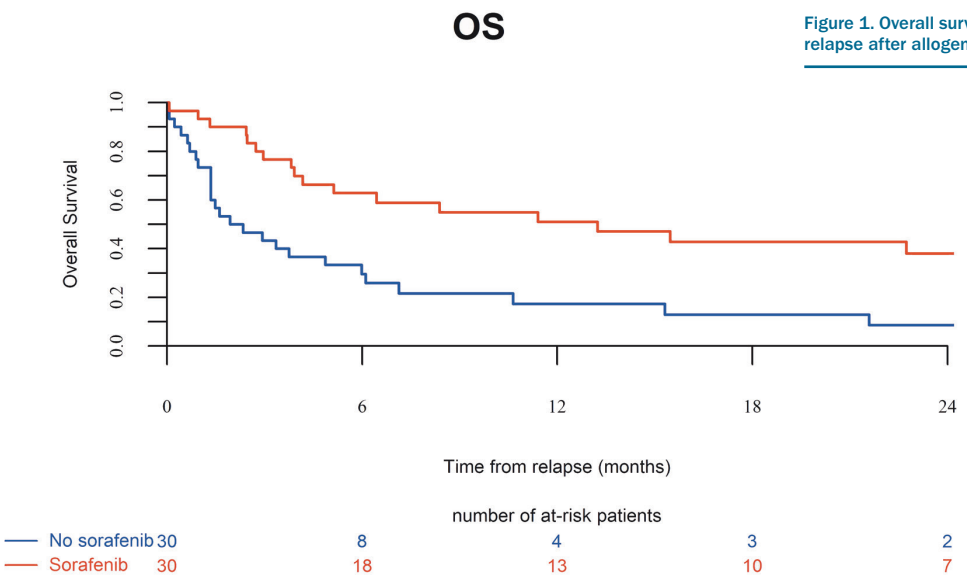

Figure 1. Overall survival (OS) (landmark analysis from relapse after allogeneic stem cell transplantation).

As structured data on the use of sorafenib for relapse after allo-SCT are very limited and lack adequate control, the purpose of the present study was to assess the safety and efficacy of sorafenib when given as salvage treatment for *FLT3-ITD* AML after allo-SCT. We compared the outcome of patients who relapsed or progressed after allo-SCT and received sorafenib salvage with that of relapsed patients who did not receive sorafenib salvage, using a large sample from the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) registry.

This is a retrospective registry-based multicenter analysis. Data were provided and approved for this study by the ALWP of the EBMT. Eligibility criteria included adult patients (age >18 years) with *FLT3*-ITD AML who relapsed or progressed after a first bone marrow (BM) or G-CSF-mobilized peripheral blood (PB) stem cell allo-SCT performed between 2010 and 2015 from an HLA matched related or unrelated or haploidentical donor. For this study, a specific questionnaire was sent to participating centers for identification of patients receiving or not receiving sorafenib, and for retrieving all information on patients', disease and treatment characteristics.

End points included response to sorafenib, acute and chronic graft-*versus*-host disease (GvHD), and OS measured from the time of relapse. OS was defined as death from any cause. The probability of OS was calculated using the Kaplan-Meier estimator. For all univariate analyses, continuous variables were categorized and the median used as a cut-off point. Univariate comparisons were by log-rank test for OS. Use of sorafenib post transplant was analyzed as a time-dependent variable, using Cox proportional hazards model. Factors differing significantly between the two groups, significantly associated with any end point in univariate analysis, and factors known to influence the outcome were included in the model. Results are expressed as Hazard Ratio (HR) with 95% Confidence Interval (CI).

A preplanned pair-matched analysis was also performed on 30 patients in the sorafenib group (the 4 remaining patients did not have a match) and 30 controls. Matching factors included age at transplant, disease status at transplant, conditioning intensity, and controls having survived at least as long as time elapsed from relapse to first infusion of sorafenib for each case, in order to avoid immortal time bias. We randomly selected one control if a case had multiple potential matches. In order to take into account correlation between case and control, comparison of case and controls was performed using Cox including a cluster term for each pair and adjusted for time interval from transplant to relapse. All tests were two-sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time-to-event outcomes. All analyses were performed using R version 3.4.1 (R Core Team, Vienna, Austria).

Altogether, 152 patients met the eligibility criteria for this study. The median time from allo-SCT to relapse was three months (range 0.4-58) and the median follow up after relapse of alive patients was 22 months (range 4-68). Thirty-four patients (22%) received sorafenib as salvage therapy for relapse/progression after allo-SCT (sorafenib group). These patients were compared with 118 patients who did not receive sorafenib salvage after allo-SCT (control group). Comparisons of patients' and transplant characteristics between the two groups are listed in Table 1. The median age at allo-SCT was 48 (range 19-69) years in the sorafenib group *versus* 51 (range 19-75) years in the control group (NS). Patients in the sorafenib group were less likely to be CMV negative or MRD negative, but more likely to have received a transplant from a matched related donor and a myeloablative conditioning. The two groups were comparable in terms of other patient, disease and transplant characteristics. Overall, 33% of patients in the sorafenib group received DLI *versus* 17% in the control group (NS). A second allo-SCT was performed in 13% and 15% of patients, respectively (NS).

The median time from relapse to any type of therapy was six days (range 1-34) in the sorafenib group *versus* eight days (range 1-245) in the control group. Sorafenib was initiated after a median of 13 days (range 1-128) from relapse at the dose of 800 mg/day in 21 patients (62%), 400 mg/day in 12 (35%), and 200 mg/day in one patient (3%), for a median duration of 79 days (range 1-1670). The sorafenib dose was modified in 35% of patients, mostly because of hematologic toxicity. In the

sorafenib group, 23 (68%) patients received sorafenib as part of the first treatment for relapse, and 11 received it after salvage chemotherapy. Sorafenib induced CR in 10 (39%) of 26 patients with available data on response.

In multivariate Cox analysis (Table 2), sorafenib given as salvage for relapse as a time dependent variable significantly improved OS [HR=0.44 (0.26-0.75); *P*=0.001]. However, older age [per 10 years, HR=1.2 (1.01-1.43); *P*=0.04], active disease at transplant [HR=2.4 (1.49-3.84); *P*=0.001], and reduced intensity conditioning [HR=1.76 (1.14-2.73); *P*=0.01] adversely affected OS. Time from transplant to relapse had no significant impact on OS [HR= 0.98 (0.96-1.01); *P*=0.17].

Thirty patients in the sorafenib group were matched with 30 controls. Patients', disease and transplant characteristics of both groups are presented in *Online Supplementary Tables S1* and *S2*. One and 2-year OS were, 51% and 38% for patients in the sorafenib group *versus* 17% and 9% for controls, respectively [HR=0.28 (0.15-0.53); *P*=0.0001] (Figure 1).

In this study, we compared outcomes of 34 patients with *FLT3-ITD* AML who relapsed or progressed after allo-SCT and received sorafenib as salvage therapy to those of 124 similar patients who did not receive sorafenib salvage. In this challenging setting, sorafenib treatment resulted in a CR rate of 39%. The one- and 2-year OS from relapse post allo-SCT, for patients in the sorafenib group, were encouraging (51% and 38%, respectively), and significantly better than those of the control group who did not receive sorafenib (17% and 9%, respectively; *P*=0.0001).

Table 2. Multivariate analysis for overall survival.

	HR (95%CI) *P*
Sorafenib given for relapse (time dependent)	0.44 (0.26-0.75) *P*=0.002
Age at allo-SCT (per 10 years)	1.2 (1.01-1.43) *P*=0.04
CR1 (reference)	
CR2	1.52 (0.81 -2.85) *P*=0.19
Active disease	2.4 (1.49-3.84) *P*<0.001
Matched related donor (reference)	
Matched unrelated donor	1.42 (0.89 -2.25) *P*=0.14
Haploidentical	0.68 (0.33-1.42) *P*=0.3
RIC *vs.* MAC	1.76 (1.14-2.73) *P*=0.01
NPM1 positive	1.34 (0.86-2.09) *P*=0.19
Time from allo-SCT to relapse (per month)	0.98 (0.96-1.01) *P*=0.17
Patient CMV positive	1.58 (1-2.5) *P*=0.051
Donor CMV positive	1.21 (0.79-1.85) *P*=0.39

HR: Hazard Ratios; CI: Confidence Intervals; allo-SCT: allogeneic stem cell transplantation; CR1: first complete remission; CR2: second complete remission; RIC: reduced intensity conditioning; MAC: myeloablative conditioning; CMV: cytomegalovirus.

Treatment of patients with *FLT3-ITD* AML who relapse or progress after allo-SCT remains a real challenge and an unmet medical need. Chemotherapy alone or combined with DLI is rarely effective in the long term.[14] A second allo-SCT can be proposed to a small percentage of patients. Currently, the most attractive treatment options for patients with *FLT3-ITD* AML failing allo-SCT are TKI with or without DLI.

Conflicting findings were previously reported on the efficacy of sorafenib salvage in *FLT3-ITD* AML relapsing after allo-SCT.[12,15] A recent report showed that six of 29 patients with *FLT3-ITD* AML, in relapse after allo-SCT and treated with sorafenib monotherapy, were alive after a median follow up of 7.5 years.[11] However, Sharma *et al.*[13] reported that none of 16 patients treated with sorafenib for relapse after allo-SCT, was still alive at one year. Besides the higher number of patients in our study, one important difference with the other reported series is our inclusion of a large control group and performance of a pair-match analysis.

In addition to the direct anti-leukemia effect of sorafenib, a possible synergistic effect with alloreactive donor T cells in facilitating long-term disease control has been suggested.[15] Interestingly, in our cohort, DLI was administered to 33% of the patients in the sorafenib group as compared to 17% of patients in the control group. DLI may therefore synergize with sorafenib to achieve sustained disease control. Nevertheless, we did not observe any increase in *de novo* GvHD in our sorafenib group, despite the higher rate of DLI in this group.

While we cannot recommend a dose of sorafenib for treatment of relapse after allo-SCT, our data indicate that the standard daily dose of 800 mg in two divided doses is safe in this setting, although dose adjustments were frequently needed.

In conclusion, sorafenib is a safe and effective salvage therapy for patients with *FLT3-ITD* AML relapsing or progressing after allo-SCT, leading to a significant improvement in OS.

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