Dasatinib in high-risk core binding factor acute myeloid leukemia in first complete remission: a French Acute Myeloid Leukemia Intergroup trial

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ABSTRACT

Core-binding factor acute myeloid leukemia is a favorable acute myeloid leukemia subset cytogenetically defined by t(8;21) or inv(16)/t(16;16) rearrangements, disrupting *RUNX1* (previously CBFA/AML1) or *CBFB* transcription factor functions. The receptor tyrosine kinase KIT is expressed in the vast majority of these acute myeloid leukemias and frequent activating *KIT* gene mutations have been associated with a higher risk of relapse. This phase II study aimed to evaluate dasatinib as maintenance therapy in patients with core-binding factor acute myeloid leukemia in first hematologic complete remission, but at higher risk of relapse due to molecular disease persistence or recurrence. A total of 26 patients aged 18-60 years old previously included in the CBF-2006 trial were eligible to receive dasatinib 140 mg daily if they had a poor initial molecular response (n=18) or a molecular recurrence (n=8). The tolerance of dasatinib as maintenance therapy was satisfactory. The 2-year disease-free survival in this high-risk population of patients was 25.7%. All but one patient with molecular recurrence presented subsequent hematologic relapse. Patients with slow initial molecular response had a similar disease-free survival when treated with dasatinib (40.2% at 2 years) or without any maintenance (50.0% at 2 years). The disappearance of *KIT* gene mutations at relapse suggests that clonal devolution may in part explain the absence of efficacy observed with single-agent dasatinib in these patients (n. EudraCT: 2006-006555-12).

Introduction

Core binding factor acute myeloid leukemia (CBF-AML) is a favorable acute myeloid leukemia (AML) subset cytogenetically defined by t(8;21) or inv(16)/t(16;16) rearrangements, respectively responsible for *RUNX1* (formerly *CBFA)-RUNX1T1* or *CBFB-MYH11* gene fusion.[1] Both translocations are responsible for a loss-of-function of the CBF transcriptional complex involved in the regulation of numerous genes implicated in normal hematopoiesis.[2] Despite a high sensitivity to standard chemotherapy leading to high complete remission (CR) rates in both of these subgroups of AML, approximately one-third of patients subsequently relapse.[3]

Early quantification of fusion transcript by real-time quantitative polymerase reaction (RQ-PCR) to assess level of minimal residual disease (MRD) has been more recently suggested to be one of the most powerful predictors of long-term outcome.[4]

In the last decade, new prognostic factors have refined the identification of CBF-AML patients at higher risk of relapse. Frequent mutations of class III receptor tyrosine kinases (RTKs) KIT and FLT3 and also RAS genes has been shown to co-operate with the primary oncogenic event involving *RUNX1* or *CBFB*.[5-7] Among them, *KIT* and *FLT3* gene mutations have been associated with a higher risk of relapse in many retrospective studies. In the CBF-2006 study (EudraCT n. 2006-005163-26; *clinicaltrials.gov identifier: 00428558*), the French AML Intergroup prospectively assessed the respective prognostic values of RTK mutations and MRD in CBF-AML patients in a therapeutic program consisting in three consecutive high-dose AraC courses (HiDAC) as consolidation program after achievement of complete remission (CR) by anthracycline and standard dose cytarabine induction sequence.[8] A high white blood cell count (WBC), *KIT* and/or *FLT3* mutations, and a less than 3-log MRD reduction were associated with a higher risk of relapse, MRD reduction being the main prognostic factor identified by multivariate analysis.[8] The rationale for evaluating dasatinib in CBF-AML was based on the high expression level of KIT (CD117) receptor and the high incidence of adverse *KIT* mutations in this

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Table 1. Patients' characteristics.

	All patients dasa+	Molecular recurrence dasa+	Poor early molecular response		P*
			dasa+	dasa-	
Patients, n	26	8	18	25	
CBF subset (t(8;21)/inv(16) or t(16;16)), n	11/15	5/3	6/12	8/17	0.12
Median age, years (range)	44 [19-59]	44 [19-56]	44 [29-59]	43 [23-59]	0.40
Gender (M/F), n	16/10	4/4	12/6	10/15	0.54
Median WBC, 10^9/L (range)	19 [3-254]	13 [5-56]	24 [3-254]	24[5-138]	0.46
Median BM blasts, % (range)	58 [20-93]	42 [20-93]	61 [29-86]	52 [30-93]	0.11
Median fusion transcript ratio, % (range)	117 [32-947]	198 [58-588]	100 [32-947]	92 [45-623]	0.97
Additional cytogenetic abns., N**					
Loss of Y	4/11 0/15	2/5 0/3	2/6 0/12	3/8 0/17	0.99
Trisomy 8	0/11 0/15	0/5 0/3	0/6 0/12	0/8 4/17	0.13
Trisomy 22	0/11 3/15	0/5 1/3	0/6 2/12	0/8 3/17	0.99
del(9q)	3/11 0/15	2/5 0/3	1/6 0/12	0/8 0/17	0.42
del(7q)/-7	0/11 1/15	0/5 1/3	0/6 0/12	1/8 2/17	0.2
Gene mutations, N**					
KIT exon 8	1/11 3/15	0/5 0/3	1/6 3/12	1/8 1/16	0.38
KIT exon 17	2/11 1/15	1/5 0/3	1/6 1/12	2/8 2/16	0.69
KIT, all	3/11 4/15	1/5 0/3	2/6 4/12	3/8 3/16	0.73
FLT3-TKD	0/11 4/15	0/5 2/3	0/6 2/12	0/8 2/16	0.99
FLT3-ITD	3/11 0/15	3/5 0/3	0/6 0/12	2/8 1/16	0.25
FLT3, all	3/11 4/15	3/5 2/3	0/6 2/12	2/8 2/16	0.69
TKR, all	5/11 8/15	3/5 2/3	2/6 6/12	4/8 5/16	0.75
N-RAS	0/11 5/15	0/5 2/3	0/6 3/12	0/8 6/16	0.70
K-RAS	1/11 1/15	1/5 0/3	0/6 1/12	0/8 3/16	0.62
RAS, all	1/11 6/15	1/5 2/3	0/6 4/12	0/8 9/16	0.33
Minimal residual disease					
MRD2, log reduction [range]	2.7 [1.5-5.5]	3.7 [1.5-5.5]	2.5 [1.5-3.0]	2.7 [1.8-2.9]	0.07

*Comparison of dasa+ and dasa- cohorts in poor early molecular responders. **Split by CBFA/B subtype.

subtype of AML.[9] Patients with a less than 3-log MRD reduction before the second high-dose cytarabine (HiDAC) consolidation course were eligible for allogeneic hematopoietic stem cell transplantation (SCT) if they had a sibling or a matched unrelated donor. To patients without donor, the proposal was made to enter this phase II study that evaluated continuous single-agent dasatinib as a 1-year post-consolidation maintenance treatment. Patients with molecular recurrence after completing HiDAC consolidations were also eligible for this DasaCBF study. Patients continued to be monitored for MRD levels during dasatinib administration. Disease-free survival was the major end point of this academic trial by the French Acute Myeloid Leukemia Intergroup.

Methods

Patients

Between June 2008 and February 2012, 26 patients aged 18-60 years old were enrolled in the DasaCBF trial (n. EudraCT: 2006-006555-12). The study, approved by the ethic committee and by the Institutional Review Board of Angers University Hospital, was conducted in accordance with the Declaration of Helsinski.

Eligibility

Only patients previously included in the CBF-2006 trial were eligible for the phase II DasaCBF study. Briefly, CBF-AML was defined by the presence of either the t(8;21) translocation or the inv(16)/t(16;16) rearrangement by karyotype and/or FISH analysis and/or evidence of *RUNX1-RUNX1T1* or *CBFB-MYH11* fusion transcripts. In CBF-2006 trial, patients with less than 3-log MRD reduction before second consolidation course (MRD2) were eligible for allogeneic stem cell transplantation (ASCT) with a sibling or a matched unrelated donor. In the absence of a donor, these patients received the planned three HiDAC consolidation courses and were then eligible for the present DasaCBF trial. Patients with molecular recurrence defined by an MRD ratio increase of more

Table 2. Treatment-related adverse events (AEs) occurring in at least 5% of patients (n=26).

	Any grade		Grade 3/4	
	N	%	N	%
Rash	9	33	0	0
Headache	8	30	1	4
Dyspnea	7	26	0	0
Fatigue/asthenia	7	26	0	0
Myalgia	5	19	0	0
Abdominal pain	5	19	0	0
Nausea	5	19	1	4
Diarrhea	4	15	1	4
Hematuria	3	11	0	0
Edema	3	11	2	7
Constipation	2	7	0	0
Anorexia	2	7	0	0
Fever	2	7	0	0

than 1-log on two successive samples were also eligible. Eligibility also included an ECOG performance status less than 2, no uncontrolled severe infection or other malignancy, AST and ALT levels 2.5 or less times upper limit of normal (ULN), bilirubin 1.5 or less times ULN, and serum creatinine 1.5 or less ULN. Patients with QTc prolongation (>470 ms) and ongoing cardiac dysrhythmias were excluded from the study.

Drug administration

DasaCBF was an open label phase II trial. All patients were in CR1 after completion of a first induction sequence and three monthly HiDAC consolidation courses. Dasatinib was administered orally at 140 mg once daily for a total duration of 12 months. Adverse events (AE) were prospectively collected according to CTCAE v.3.0. In case of grade 3 AE, treatment was discontinuated until AE resolution to less than grade 2. In case of grade 4 AE or AE reappearance, dose reduction to 100 mg/d was allowed. Dose escalation to 90 mg bid was allowed in case of stable or increasing MRD after two months of therapy without toxicity.

Gene mutations and MRD evaluation

A systematic screening for KIT exon 8 and 17 mutations, *FLT3* internal tandem duplication (ITD), *FLT3* tyrosine kinase domain (TKD) mutation, and N/K-RAS exon 2 and 3 mutations was performed in 2 central laboratories (Lille, Reims, France), as described previously.[5,8] MRD levels were serially monitored for *RUNX1-RUNX1T1* or *CBFB-MYH11* transcripts by real-time quantitative polymerase chain reaction in 4 central laboratories (Angers, Lille, Paris Saint-Louis, Toulouse, France), as described previously.[8,10]

Statistical analysis

In these patients at high risk of relapse, the primary objective was disease-free survival. Secondary objective were: 1) complete molecular remission rate; 2) overall survival (OS) and correlation between mutation profile (*RAS, KIT, FLT3*) and response to dasatinib.

Assuming a post-dasatinib 1-year DFS of 30% in patients with poor molecular response to chemotherapy or molecular recurrence, the inclusion of 27 patients was necessary to detect an increase in 1-year DFS from 30% to 60%, with a type 1 error rate of 5% and a statistical power of 90%. To take into account potential patient withdrawal from study, 30 patients were planned to be included. Finally, 27 patients were included; one of them did not meet inclusion criteria and was thus withdrawn from the final analysis. Outcome data were up-dated in June 2012, after a median follow up of 2.9 years.

Between July 2007 and November 2012, 200 patients with newly diagnosed CBF-AML were included in the CBF-2006 trial.[8] Among the 198 eligible patients, 196 achieved complete remission and 176 were evaluated for MRD2 just before the second HiDAC consolidation course (Figure 1). Among these 176 patients, 54 presented with a less than 3-log MRD2 reduction: 2 of them experienced early relapse during consolidation therapy, 9 proceeded to ASCT, 18 were included in the DasaCBF study (dasa+ cohort) after consolidation completion and 25 received only consolidation courses without any maintenance therapy nor an SCT (dasa- cohort); these latter 25 patients were used as a control cohort. Characteristics between dasa+ and dasa- cohort patients were compared using Mann-Whitney test for continuous variables and Fisher exact test for binary variables. Outcome data were estimated by the Mantel-Byar method, considering dasatinib therapy onset as a time-dependent covariate.[11] Briefly, all patients were considered in the dasa- cohort until the time of dasatinib therapy initiation. Impact of dasatinib therapy on DFS was assessed by univariate Cox proportional hazard regression model.[12] Statistical analyses were performed on the STATA/SE 11.0 (StataCorp, College Station, TX, USA) software package.

Results

Patients' characteristics

In total, 27 patients with CBF-AML in first complete remission were included in this phase II DasaCBF study. One patient was withdrawn from the analysis because he did not meet any of the high-risk inclusion criteria (more

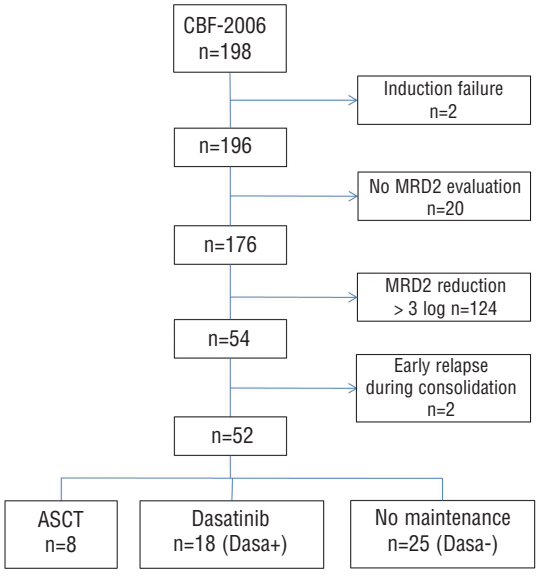


Figure 1. Flow chart of the patients. All patients were previously included in the CBF-2006 trial.[8] HSCT: allogeneic stem cell transplantation).

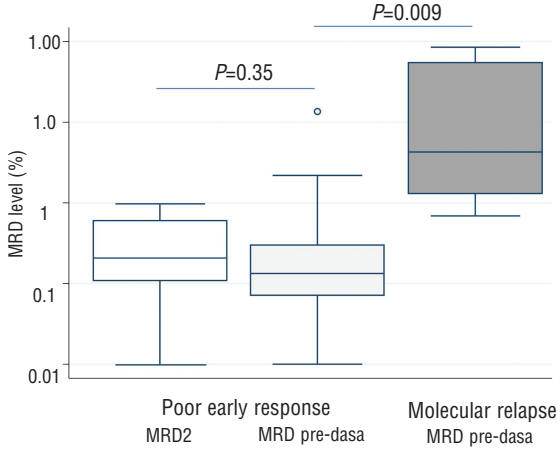


Figure 2. MRD levels in patients with poor early molecular response and in molecular relapse. In patients with poor early response (n=18, white boxes) MRD before consolidation 2 (MRD2) and before dasatinib is shown. In patients with molecular relapse (n=8, gray box), MRD before dasatinib is shown.

than 3-log reduction and no subsequent molecular recurrence). Among the 26 patients analyzed, 18 (67%) were included with less than 3-log MRD reduction after one HiDAC consolidation regimen and 8 (33%) with molecular recurrence during follow up. Patient's characteristics are summarized in Table 1. Median age was 44 years; 11 patients presented with t(8;21) and 15 patients with inv(16)/t(16;16) AML. Additional cytogenetic abnormalities were: –Y in 4 patients, +8 in one patient, +22 in 4 patients, del(9q) in 3 patients and del(7q)/-7 in one patient. All patients were screened for RTK and *RAS* gene mutations. *KIT* mutations were found in 7 of 26 patients, involving exon 8 in 4 cases and exon 17 in 3 cases. *FLT3* mutations were found in 6 of 26 patients, *FLT3*-TKD in 4 cases and *FLT3*-ITD in 2 cases.

Minimal residual disease prior to dasatinib therapy

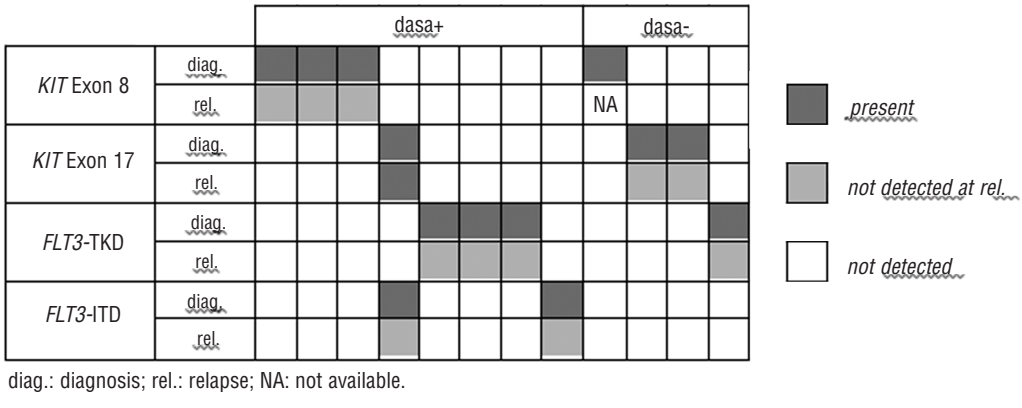
As expected, patients included for molecular recurrence had a more elevated MRD transcript level prior dasatinib initiation than patients with poor early molecular response [(4.4% (0.69-85%) *vs.* 0.11% (0%-13.6%), respectively; *P*=0.009)] (Figure 2).

Patients with poor early molecular response (n=18) were selected on pre-consolidation 2 MRD log-reduction. Despite the administration of two additional high-dose cytarabine consolidations, there was globally no difference in MRD level between pre-consolidation 2 and time of dasatinib initiation (0.22% [0%-13.6%] *vs.* 0.11% [0.1%-1%]; *P*=0.35 by a paired *t*-test) (Figure 2). The median additional log-reduction in these refractory patients was 0.3.

Safety

Most treatment-related adverse events (AEs) reached mild to moderate severity (Table 2). The most frequent AEs of any grade were rash, headache, dyspnea, and fatigue. The most frequent grade 3/4 AE was edema, found in 7% patients. Treatment-related serious AEs were reported in 5 patients (19%): one patient with edema and hypertension, one patient with edema and headache, one patient with small cell lung cancer, one pregnancy, and one with grade 4 anemia. According to trial recommendations, dasatinib doses were reduced to 100 mg QD in 5 patients and increased to 90 mg BID in 3 patients.

Table 3. Mutation profile at diagnosis and relapse in patients with TKR mutations at diagnosis (8 dasa+, 4 dasa-).



diag.: diagnosis; rel.: relapse; NA: not available.

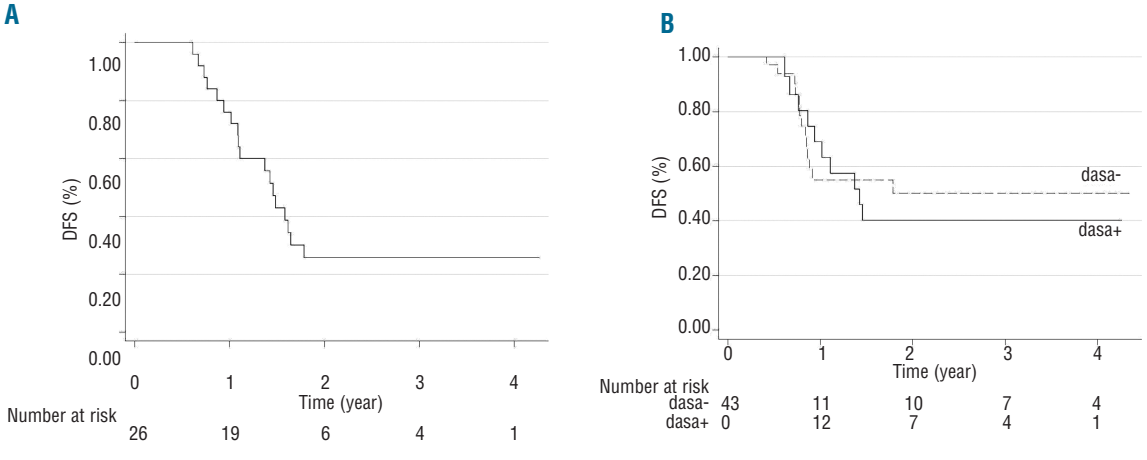


Figure 3. Minimal residual disease (MRD) levels in patients with poor early molecular response and in molecular relapse. In patients with poor early response (n=18, white boxes) MRD before consolidation 2 (MRD2) and before dasatinib is shown. In patients with molecular relapse (n=8, gray box), MRD before dasatinib is shown.

Outcome

The median follow up of this cohort of 26 patients was 2.9 years after diagnosis. Of these, 18 patients experienced hematologic relapse. According to trial design, we assumed a 1-year post-dasatinib DFS of 30% in these patients with poor molecular response to chemotherapy or molecular recurrence. For the whole cohort, post-dasatinib 1-year DFS was 31.5% [(95%CI: 14.7%-49.8%) and 2-year DFS was 25.7% (95%CI: 10.6%-44.0%)] (Figure 3A). The median time to hematologic relapse was 6.0 months after dasatinib therapy initiation.

In all patients included for molecular recurrence (n=8), hematologic relapsed occurred rapidly after dasatinib therapy initiation within a median time of 1.8 months (range 1.3-5.7).

In patients with poor initial molecular response to chemotherapy who received dasatinib as maintenance therapy (n=18, dasa+) after 2 additional cycles of HiDAC, hematologic relapse occurred in 10 patients. The median time to relapse was 11.8 months after dasatinib initiation. Using a time-dependant analysis, the outcome of this cohort was compared to the outcome of the 25 CBF-2006 patients with a similar poor initial MRD2 reduction of less than 3-log and that receive neither allogeneic SCT nor dasatinib maintenance. Among these 25 dasa- patients, 13 patients experienced hematologic relapse. The Mantel-Byar 2y-DFS estimate was 40.2% (95%CI: 17.9%-61.8%) for the dasa+ patients and 50.0% (95%CI: 29.4%-67.5%) for the dasa- patients; the difference was not significant (P=0.74) (Figure 3B).

Presence of mutations at relapse

Among the 18 patients with hematologic relapse after dasatinib therapy, 8 patients were initially diagnosed with either *KIT* and/or *FLT3* mutations: 3 with KIT exon 8, 3 with *FLT3*-TKD, one with *FLT3*-ITD and one with both KIT exon 17 and *FLT3*-ITD. In all these patients but one, *FLT3* and *KIT* mutations were not detected at relapse after dasatinib exposure. In the patient with both KIT exon 17 and *FLT3*-ITD, only *KIT* exon 17 mutation was present at relapse (Table 3).

Among the 13 dasa- patients who experienced hematologic relapse without previous dasatinib exposure, 4 patients were initially diagnosed with either *KIT* or *FLT3*-ITD mutations: 2 with *KIT* exon 17, one with *KIT* exon 8 and one with *FLT3*-D835. All but the patient with KIT exon 8 mutation have been screened for the presence of mutation at relapse. None of these 3 mutations were detected at relapse (Table 3).

Discussion

This study aimed to assess the efficacy of dasatinib in patients with CBF-AML at higher risk of relapse. Patients treated in this study were all previously included in the front-line phase III CBF-2006 study from the French AML Intergroup that defined high-risk CBF-AML as patients with MRD log-reduction of less than 3-log after induction and one HiDAC consolidation course. Patients with molecular recurrence but no hematologic relapse during follow up were also eligible. Results suggest that dasatinib alone was unable to prevent relapse in both situations of molecular primary resistance or recurrence. Clonal devolution at relapse, corresponding to the disappearance of a previous subclone, and evidenced by the frequent loss of additional RTK mutation could account for this lack of efficacy.

The rationale for evaluating dasatinib in CBF-AML was based on the high expression level of KIT (CD117) receptor and the high incidence of adverse *KIT* mutations in this subtype of AML.[9] A mutation of *KIT* gene is found in 15%-35% of CBF-AML, *KIT* mutations being more frequent in inv(16)/t(16;16) than in t(8;21).[7] *KIT* mutations have been shown to co-operate with CBF oncogenic event to induce leukemia *in vitro* and in mouse models. These mutations result in the activation of many intracellular pathways, including JAK/STAT, PI3-kinase/Akt and ERK/MAP-kinase, promoting cell growth and differentiation, but also proliferation and apoptosis inhibition. Tyrosine kinase inhibitor dasatinib has been primarily evaluated in chronic myeloid leukemia for its ability to inhibit BCR-ABL kinase, but has also been shown to inhibit wild-type KIT and juxtamembrane and activation loop mutant KIT isoforms.[13] Reported IC50 for dasatinib autophosphorylation inhibition ranged from 1-10 nmol/L in wild-type KIT to 10-100 nmol/L in D816 KIT mutants. In comparison, IC50 for BCR-ABL inhibition is around 1 nmol/L.[14] Since targeted IC50 were significantly more elevated for KIT inhibition in CBF-AML than for BCR-ABL in chronic myeloid leukemia, a dosage of 140 mg daily was chosen in this study. Administration was once daily to improve tolerance.[15]

This phase II study is the first experience of dasatinib monotherapy in CBF-AML patients. Both the German-Austrian AML Study Group (AMLSG; *clinicaltrials.gov identifier: 00850382*) and Cancer and Leukemia Group B (CALGB; *clinicaltrials.gov identifier: 01238211*) have conducted phase II trials combining dasatinib with conventional induction and consolidation therapy, followed by a 1-year dasatinib maintenance therapy in patients with CBF-AML. The results of these combined studies have not yet been published but the AMLSG group will go on with a randomized phase III study (*clinicaltrials.gov identifier: 00850382*). Unfortunately, the present phase II study was not able to detect any benefit of dasatinib as single-agent in CBF-AML patients with high risk of relapse. While we assumed a 1-year DFS of 30% in this population of patient without any treatment, the observed post dasatinib 1-year DFS was 31.5%. All patients with molecular recurrence (n=8) experienced a hematologic relapse within a short median time of 1.8 months despite dasatinib administration. These patients had relatively high MRD levels prior to dasatinib initiation. In the CBF-2006, 3-year DFS was estimated at 73% in patients who achieved a 3-log MRD2 reduction *versus* 44% in those who did not (P<0.001 by the log rank test). These patients with poor early molecular response who received dasatinib (n=18) experienced a similar relapse incidence as patients who did not receive any further therapy, with a 2-year DFS of 40.2% *versus* 50%, respectively. None of the 9 additional patients who received allogeneic SCT experienced relapse and 2-year DFS was 76% without statistical difference when compared to untransplanted patients (*data not shown*). In the absence of randomized control, and because the number of patients is quite low, these results should nonetheless be interpreted with caution. However, both cohorts were simultaneously treated with previous identical chemotherapy courses, and displayed similar characteristics. Very interestingly, by screening initial RTK mutations at leukemia relapse, we observed the disappearance of the

mutation in all but one out of 8 patients. Mutation evolution at relapse is a well-known observation. The disappearance of RTK mutations at time of relapse has been mostly reported for *FLT3*-ITD mutation, which is undetectable at relapse in approximately 20% of patients presenting the mutation at baseline.[16,17] More recently, Allen *et al*. reported the loss of *KIT* mutations in 5 of 12 (42%) patients with CBF-AML at relapse.[18] Whether the lack of dasatinib efficacy in this study is due to spontaneous loss of RTK target and/or to clonal selection induced by the tyrosine kinase inhibitor dasatinib has to be further explored. Indeed, the subclonal activity of TKI in CBF-AML has already been suggested in a patient with CBF-AML and *KIT* exon 8 mutation, in whom imatinib was able to control the subclone with *KIT* mutation without any effect on the *KIT*wt population.[19]

In conclusion, this phase II study showed that dasatinib may be safely administrated as single-agent maintenance therapy in patients in persistent hematologic CR after HiDAC consolidation. However, dasatinib did not seem to prevent relapse in these patients when they presented either poor early molecular response or molecular recurrence. The disappearance of *KIT* mutations at relapse suggests that dasatinib activity may be impaired by spontaneous and/or dasatinib-driven clonal devolution. This study does not exclude any synergic activity of dasatinib combined to standard chemotherapy in this subgroup of AML.

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Authorship and Disclosures

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