

MYELOID NEOPLASIA

Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study

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Key Points

- Early molecular response at 3 months can predict outcome in children treated with imatinib for CML.
- Children with CML may be less likely to achieve an early molecular response to imatinib than adults with CML.

Studies in adults have shown that an early molecular response to imatinib predicts clinical outcome in chronic myeloid leukemia (CML). We investigated the impact of the BCR-ABL1 transcript level measured 3 months after starting imatinib in a cohort of 40 children with CML. Children with a BCR-ABL1/ABL ratio higher than 10% at 3 months after the start of imatinib had a larger spleen size and a higher white blood cell count compared with those with BCR-ABL1/ABL \leq 10%. Children with BCR-ABL1/ABL \leq 10% 3 months after starting imatinib had higher rates of complete cytogenetic response and major molecular response at 12 months compared with those with BCR-ABL1/ABL $>$ 10%. With a median follow-up of 71 months (range, 22-96 months), BCR-ABL1/ABL \leq 10% correlated with better progression-free survival. Thus, early molecular response at 3 months predicts outcome in children treated with imatinib for CML. This trial was registered at www.clinicaltrials.gov as #NCT00845221. (*Blood*. 2014;124(15):2408-2410)

Introduction

Although imatinib is effective for the majority of children with chronic myeloid leukemia (CML),¹⁻³ 13% to 25% of children have a poor response.³⁻⁵ Reports in adults indicate that measurement of *BCR-ABL1* transcripts 3 months after starting imatinib can predict outcome with better overall survival in patients with a *BCR-ABL1/ABL* ratio of $<$ 10% at this time point.⁶ In order to address the relevance of this cutoff in the pediatric population in terms of cytogenetic and molecular responses and outcome, we reanalyzed the French Glivec phase 4 study data.³

Study design

This study was approved by the institutional review board of the University Hospital of Poitiers (Poitiers, France) and participants provided informed consent in accordance with the Declaration of Helsinki. Between March 2004 and December 2008, 44 consecutive patients younger than 18 years of age with newly diagnosed CML in chronic phase were enrolled in the

prospective Glivec phase 4 study from 16 French university hospitals. Patient eligibility and trial design were previously described.³ Patients received imatinib 260 mg/m² daily.¹ Bone marrow assessment including morphology, cytogenetics, and molecular analysis was performed at diagnosis, 3 months, and 12 months after the start of imatinib. Complete cytogenetic response (CCyR) was defined by the absence of Ph-positive metaphases among at least 20 analyzed metaphases in bone marrow. Determination of *BCR-ABL1* transcript level in the blood was performed at 3-month intervals using quantitative reverse transcription-polymerase chain reaction independently aligned on the International Scale (IS) by specific conversion factors as described previously.⁷⁻⁹ Major molecular response (MMR) was defined as a *BCR-ABL1* IS \leq 0.1%. molecular response (MR)^{4,0} and MR^{4,5} were defined as either detectable disease with *BCR-ABL1* IS \leq 0.01% and \leq 0.0032%, respectively, or undetectable disease with \geq 10 000 and \geq 32 000 *ABL1* copies, respectively, in the same volume of complementary DNA used to test for *BCR-ABL1*. Complete molecular response (CMR) was defined by no detectable transcripts in 2 consecutive samples, with \geq 32 000 *ABL1* copies. *BCR-ABL1* transcript levels (\leq 1%, $>$ 1% to \leq 10%, $>$ 10%) 3 months after starting imatinib were used to assess the association between early molecular response and the rates of CCyR and MMR 1 year after the start

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Table 1. Patient characteristics according to the BCR-ABL1/ABL ratio 3 months after starting imatinib

BCR-ABL1/ABL at 3 mo	≤10%	>10%	P
n (%)	25 (63)	15 (37)	
Sex, n			
Boys	14	11	
Girls	11	4	.329
Age, median (range), y	11.3 (0.8-16.7)	11.7 (1.9-17.3)	.561
Sokal risk score*			
Low	5	2	
Intermediate	7	1	
High	13	12	.170
Splenomegaly	19 (76%)	14 (93%)	
Spleen size, median (range), cm below the costal margin	5 (0-21)	13 (0-21)	.005
White blood cell count, median (range), ×10 ⁹ /L	252 (16-482)	378 (44-762)	.02

*As applied to patients younger than 45 years of age.⁹

of imatinib as well as the association between early molecular response and progression-free survival (PFS). PFS was defined by absence of accelerated phase, blast crisis, and death from any cause.¹⁰

Comparisons between groups were performed using the χ^2 test or the nonparametric Fisher exact test and Wilcoxon test, as appropriate. PFS from the onset of imatinib was estimated by the Kaplan-Meier method and was compared within groups by log-rank test. All analyses were 2-sided and were performed using SAS, version 3 (SAS Institute).

Results and discussion

Four of the 44 patients enrolled in the Glivec phase 4 study had a missing polymerase chain reaction assessment 3 months after starting imatinib and were excluded from landmark analyses performed on *BCR-ABL1* transcript levels. Hence, the patient population consisted of 40 children. Because of severe side effects, 1 of them was switched to a second-generation tyrosine kinase inhibitor (TKI) 2 months after starting imatinib and was included in the intention-to-treat analysis. Patient characteristics are reported in Table 1. A high Sokal risk score (for patients younger than 45 years of age) was observed in the majority of the patients.¹¹ Three months after the start of imatinib, a *BCR-ABL1/ABL* ratio of >10% was found in more than one-third of the patients (15 of 40; 37%) whereas 18 of 40

of the patients (45%) had a *BCR-ABL1/ABL* ratio of 1% to 10% and 7 of 40 patients (18%) had a *BCR-ABL1/ABL* ratio of ≤1%. Children and adolescents with a *BCR-ABL1/ABL* ratio >10% 3 months after starting imatinib had a similar Sokal score distribution at diagnosis but a larger spleen size and a higher white blood cell count compared with patients with a *BCR-ABL1/ABL* ratio of ≤10% (Table 1). The dose of imatinib administered within the first 3 months of treatment was similar ($P = .209$) in patients with a *BCR-ABL1/ABL* ratio >10% (median, 242 mg/m²; range, 132-381) and those with ≤10% at 3 months (median, 250 mg/m²; range, 300-342). Two children progressed to blast phase 25 months and 42 months after the start of imatinib (1 of them was switched for a second-generation TKI before onset of progression) and 1 of them died. Both children had a *BCR-ABL1/ABL* ratio of >10% at 3 months after starting imatinib. No other death was reported.

With a median follow-up of 71 months (range, 22-96 months), a transcript level ≤10% correlated with better PFS (Table 2, *BCR-ABL1/ABL* transcript level at 3 months) (supplemental Figure 1, available at the *Blood* Web site). The rate of cytogenetic response 12 months after starting imatinib was: CCyR, 72.5%; partial cytogenetic response (PCyR), 10%; less than PCyR, 12.5%. Twelve months after starting imatinib, the rates of MMR, MR^{4.0}, MR^{4.5}, and CMR were 28%, 3%, 3%, and 0%, respectively. Patients with a *BCR-ABL1/ABL* of ≤10% 3 months after starting imatinib had a higher rate of CCyR and MMR 12 months after starting imatinib compared with those with a *BCR-ABL1* transcript level >10% (Table 2, *BCR-ABL1/ABL* transcript level at 3 months). When children were classified according to the transcript level at 3 and 6 months using the 10% cutoff (Table 2, molecular response rate outcome over 12 months) according to the European Leukemia Net (ELN) response criteria,¹² those with *BCR-ABL1/ABL* of <10% at these 2 time points (60% of the patients) had a higher rate of MMR but comparison with the other 3 subgroups could not be performed because of the small number of patients.

Early molecular response defined by a *BCR-ABL1* transcript level ≤10% at 3 months has been reported to predict survival in adults treated with imatinib.^{6,13-15} Recently, Jabbour et al reported significant improvement in PFS in patients who achieved a transcript level ≤1% 6 months after starting imatinib.¹⁶ It is important to note that a *BCR-ABL1* transcript level of >10% at 3 months and/or of a level between 1% and 10% at 6 months after the start of imatinib are now considered as a warning according to the recent ELN recommendations.¹² Our data show that a high proportion (37%; 95% confidence interval [CI], 23-54) of the children in our study failed to achieve the ≤10% cutoff at 3 months. This is higher

Table 2. Rates of CCyR and MMR at 12 months and PFS at 36 and 48 months, according to the molecular response at 3 months, in 40 children with CML

BCR-ABL1/ABL at 3 mo, %	BCR-ABL1/ABL transcript level at 3 mo*					Molecular response rate outcome over 12 mo**			
	n (%)	CCyR at 12 mo (%)	MMR at 12 mo (%)	PFS at 36 mo (%)	PFS at 48 mo (%)	BCR-ABL1/ABL level*			No. of patients achieving MMR at 12 mo (%)
						at 3 mo, %	at 6 mo, %	n (%)	
≤10	25 (63)	19*** (76)	12 (48)	100	100	>10	>10	4 (10)	0
>10	15 (37)	7 (47)	1 (7)	92	61	>10	<10	11 (27.5)	1
				(95% CI, 54-99)	(95% CI, 7-91)	<10	>10	1 (2.5)	1
		P = .177	P = .0128	P = .028 (overall)		<10	<10	24 (60)	11

mo, months.

*Data from 15 highly standardized French laboratories (ie, following tightly standardized procedures, having at their disposal a conversion factor and participating in the French external quality assessment program organized by the Group of Molecular Biologists for Malignant Hemopathies which requires biannual evaluation of interlaboratory reproducibility and accuracy) were collected and centrally reviewed for updating molecular response level attribution according to the latest recommendations of the ELN.¹²

**This portion of the table shows that achieving a <10% cutoff ratio at 3 mo is in favor of a higher rate of MMR at 12 mo. However, it is also documented that a delayed cutoff ratio achievement of this <10% cutoff ratio at 6 mo with favorable outcome may exist. The small sample size of children does not allow providing robust rate estimates within subgroups.

***One patient with no conventional cytogenetic assessment at 12 mo achieved MR^{4.5} at this time point and was considered as having a CCyR.

than the 24% to 28% of adults who fail to reach the $\leq 10\%$ cutoff.^{6,14} This might be explained in part by the higher proportion of patients with bulky disease (large spleen, high leukocyte count) and a higher proportion of patients with a high Sokal risk score in our pediatric population compared with adult series.⁶ Consistent with this, Hughes et al showed that adult patients who failed to achieve a $BCR-ABL1/ABL \leq 10\%$ 3 months after the start of imatinib also had a larger median spleen size and higher Sokal risk score than those who achieve an early molecular response.¹⁷ In the present study, the dose of imatinib administered during the first 3 months of treatment was similar in children who did or did not achieve an early molecular response, suggesting that treatment exposure was not an independent influencing factor.

In summary, given the limitation of the small number of patients and events, we show that $BCR-ABL1$ transcript level 3 months after starting imatinib can identify children with a lower rate of progression who might benefit from an alternative treatment strategy. The reliability of a cutoff of 10% at 3 months after the start of imatinib as a surrogate marker of response at 1 year and PFS remains to be confirmed in a larger cohort of children.

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Authorship

Contribution: F. Millot coordinated the study and wrote the manuscript; J.G. performed statistical analysis; A.B., A.P., Y.B., F. Mazingue, P.L., C.V., C.B., C.G., N.S., K.Y., C.S., V.G., Y.R., G.C., and F. Mechinaud provided patients; and J.M. performed the molecular review.

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