Early response does not predict outcome in children and adolescents with chronic myeloid leukemia treated with high-dose imatinib

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Running title: Early response and outcome in childhood CML

Abstract

We investigated the predictive value of the 3-month *BCR-ABL1* transcript levels in terms of responses and outcome of 44 children and adolescents (<18 years at diagnosis) with chronic myeloid leukemia (CML) treated with high-dose imatinib (IM) (340 mg/m^2/day). The transcript cutoff levels of 1% and 10% *BCR-ABL1* IS were not predictive of either complete cytogenetic response at any time, overall molecular response (MR) and complete MR (CMR), and progression-free survival probabilities at 5 years. The 3-month transcript levels in children and adolescents with CML treated with high-dose IM do not appear to be informative for the prediction of outcomes.

Keywords: CML, CHILDHOOD LAEKAEMIA, TYROSINE KINASE INHIBITORS, EARLY RESPONSE, OUTCOME

Introduction

The achievement of early and/or deep response has been demonstrated to predict a significantly better outcome in adults with chronic myeloid leukemia (CML) in chronic phase (CP) treated with either imatinib (IM) or second-generation tyrosine kinase inhibitors (TKIs) (Branford *et al*, 2012; Hanfstein B *et al*, 2012; Marin *et al*, 2012; Jain *et al*, 2013; Jabbour *et al*, 2014). Consistent with this, the latest European LeukemiaNet (ELN) recommendations have updated the optimal response criteria to first-line treatment with any TKI, defining a *BCR-ABL1* transcript levels >10% and/or >1% and/or >0.1% at 3, 6 and 12 months, respectively, as a warning (Baccarani *et al*, 2013). Recently, early molecular response (EMR), defined by a BCR-ABL1 transcript level ≤10%, at 3 months has also been reported to predict a better outcome in 40 CP-CML children treated with IM at a standard dose (260 mg/m^2/day) (Millot *et al*, 2014). The aim of the present study was to analyze the predictive value of the *BCR-ABL1* transcript levels at 3 months in terms of cytogenetic and molecular responses, and the outcome in a cohort of children and adolescents with CP-CML treated with high-dose IM.

Patients and Methods

Between March 2001 and March 2014, 53 patients younger than 18 years of age with newly diagnosis of CML in CP were treated in 11 Italian pediatric centers according to the local guidelines (Giona *et al*, 2015). Treatment response of 39 of them have been recently reported (Giona *et al*, 2015). The scheduled daily dosage of IM was 340 mg/m^2/daily. Evaluations of bone marrow (BM) morphology and cytogenetics were planned before and during IM therapy every 3 months. Quantitative reverse transcription polymerase chain reaction (qPCR) on peripheral blood (PB) monthly and on BM every 3 months was scheduled for molecular monitoring. *BCR-ABL1* transcript levels were measured in a central laboratory according to a standardized method (Beillard *et al*, 2003; Gabert *et al*, 2003). Results were converted to the International Scale (IS) (White *et al*, 2010). Patients with available BCR-ABL1 transcript levels at 3 months and a minimum follow-up of 12 months were considered for landmark analyses. Hematologic and cytogenetic response (CyR) criteria were defined according to the ELN recommendations (Baccarani *et al* 2006, 2009). Major molecular response (MMR) was defined as ≤0.1% *BCR-ABL1* IS, while

molecular response (MR) was considered as ≤0.01% *BCR-ABL1* IS. Complete molecular response (CMR) was used to indicate levels of disease ≤0.0032% *BCR-ABL1* IS or undetectable. Transcript levels ≤10% and ≤1% *BCR-ABL1* IS at 3 months after starting IM were defined as EMR and deep EMR, respectively. *BCR-ABL1* transcript levels (≤10% *vs* >10%, and ≤1% *vs* >1%) at 3 months were used to perform landmark analyses to assess the association between EMR and both the response rates and outcome. Cumulative incidence of responses and progression-free survival (PFS), defined as survival without loss of either CyR or MR or evolution to blastic crisis, were estimated using the Kaplan-Meier method. Comparisons between groups were performed using the Chi-square or the Fisher's exact test and the Wilcoxon test, as appropriate. All statistical comparisons were based on two-tailed tests with a nominal significance level of 5%.

This study, named CML-Petit-01, was approved by the Institutional Ethic Committee for each participating institution.

Results and Discussion

Eight of the 53 patients had a missing *BCR-ABL1* qPCR assessment 3 months after starting treatment and 1 patient stopped IM because of severe side effects. Accordingly, 44 CP-CML patients (females: 17, males: 27) with a median age at diagnosis of 11.2 years (range: 3.1-15,8) were evaluated. Overall, 92.5%, 85%, 56% and 39% of patients achieved complete CyR (CCyR), MMR, MR and CMR after a median time of 6.2 (range 3.5-8.6), 13.4 (range 9.4-19.7), 14.9 (range 10.1-24.1) and 15 (range 10.1-24.8) months, respectively. Three months after the start of IM, *BCR-ABL1* transcript levels >10% IS were detected in 9/44 (20.5%) patients, whereas 18/44 (41%) and 17/44 (38.5%) patients had *BCR-ABL1* IS of >1% to ≤10% and ≤1%, respectively. To assess the association between EMR and disease outcome, we took into account two 3-month transcript cutoff levels, 1% and 10% *BCR-ABL1* IS. When children were classified according to the transcript level at 3 months using the 10% IS cutoff, those with EMR had significantly higher response rates after 6 months of treatment compared to those with *BCR-ABL1* IS >10%: 95% *vs* 55.5%, *P*=.031 and 78% *vs* 22%, *P*=.003 for CCyR and *BCR-ABL1* IS ≤10%, respectively (Table I). Likewise, EMR was significantly predictive of overall MMR rate (94% of patients with *BCR-ABL1* IS ≤10% *vs* 62.5% of those with higher transcript values, *P*=.041), but no for

overall CCyR, MR and CMR rates (Table I). When patients were classified according to the transcript level at 3 months using the 1% IS cutoff, children with *BCR-ABL1* IS ≤1% had higher molecular response rates after 6 (100% *vs* 46%, *P*=.001), 9 (100% *vs* 65%, *P*=.041) and 12 months (91% *vs* 50%, *P*=.021) compared to those with values greater than 1%; nonetheless, an EMR was not predictive of CCyR at any time and overall MMR, MR and CMR (Table I). The clinical and hematological features at diagnosis, as well as the dose of IM administered during the first 3 months of treatment, were similar in patients who achieved an EMR and in those with higher transcript levels (Table IS). Treatment was successfully discontinued in 3 patients with sustained and prolonged CMR; interestingly, all of them have achieved a deep EMR after 3 months of IM. In addition, 7 patients (all but 1 with *BCR-ABL1* IS ≤10% after 3 months of treatment) stopped IM to undergo allogeneic hematopoietic stem cell transplantation; whereas 13 children had to discontinue treatment because of toxicity (n= 3) or disease progression (n= 10). Although about one third of patients had to interrupt IM due to a failure, none of our patients died. With a median follow-up of 73.5 months (range, 15-151.3), the overall PFS probability at 10 years was 57.7% (95% CI, 38.4-86.8). The estimated 5-year PFS probability comparing patients with *BCR-ABL1* values ≤10% *vs* those with values >10% resulted 85.9% *vs* 76.2%, *P* = .4671 (Figure 1A). Likewise, no statistically significant differences in both 5-year and 10-year PFS probabilities were observed between patients with deep EMR and those with >1% *BCR-ABL1* IS, (92.3% *vs* 78.3% and 60.6% *vs* 67.1%, *P* =.3463) (Figure 1B).

Marin et al were the first to report that *BCR-ABL1* transcript levels >10% IS after 3 months of treatment are associated with impaired PFS and overall survival in CP-CML patients treated with standard doses of IM (400 mg/daily) (Marin *et al*, 2012). Afterwards, the predictive value of an early molecular response in outcomes of adult CP-CML patients treated with frontline IM or second-generation TKIs has been confirmed by several studies (Branford *et al*, 2012; Hanfstein *et al*, 2012; Jain *et al*, 2013; Deininger *et al*, 2014; Hughes *et al*, 2014; Jabbour *et al*, 2014). Some of these reports showed that adults starting IM frontline at higher doses (600-800 mg/daily) had a higher probability of achieving an EMR compared to patients treated with the standard dose of IM (Deininger *et al*, 2014; Hughes *et al*, 2014). Recently, Millot *et al.* reported that children with *BCR-ABL1* ≤10% 3 months after treatment with standard doses of IM (260 mg/m^2 equated to 400 mg daily in adults) had higher rates of response at 12 months and a better PFS compared with

those with greater transcript values (Millot *et al*, 2014). Our study including a cohort of children similar to that reported by Millot *et al* (2014) provide intriguing information. First at all, the proportions of patients who achieved *BCR-ABL1* transcript levels ≤10% (79.5%) and ≤1% (38.6%) after 3 months of treatment were similar to those observed in adults treated with high-dose IM (600-800 mg/daily) (Hanfstein *et al*, 2012; Jain *et al*, 2013; Deininger *et al*, 2014) and higher than those reported by Millot et al (2014). Accordingly, the low proportion of children who failed to achieve an EMR after 3 months and the high overall cytogenetic and molecular response rates obtained in our cohort of patients treated with high doses of IM suggest that IM exposure is an important factor influencing responses and outcomes. Moreover, in our experience the *BCR-ABL1* IS values at 3 months are not predictive of overall MMR, MR and CMR rates, and outcomes. Indeed, the PFS probabilities were not influenced by an EMR at 3 months, as reported both in adults treated with high-dose IM (Hanfstein *et al*, 2012; Jain *et al*, 2013; Deininger *et al*, 2014) and in children receiving standard doses of IM (Millot *et al*, 2014).

In conclusion, our study shows that the 3-month transcript cut-off levels of 1% and 10% *BCR-ABL1* IS in children and adolescents with CML treated with high doses of IM do not appear to be informative for the prediction of outcome. Cooperative studies including larger numbers of patients are required to provide definitive thresholds of the transcript levels and timing on which to base therapeutic decisions for children and adolescents with CML treated with IM.

Acknowledgments

The authors gratefully acknowledge Alfonso Piciocchi (GIMEMA Data Center) and Roberto Latagliata for the statistical data help.

Author contributions

Contribution: F.G. contributed to the study design, enrolled patients, recorded data and wrote the manuscript; G.S. coordinated molecular analyses and reviewed the manuscript; M.S. analyzed data; G.M., G.I., M.C.P., C.M., N.S., S.L., R. M, R.B., C.C., C.C., M.L.M., F.T. enrolled patients and recorded data; M.N. and AL performed cytogenetic analyses; D.D. performed molecular analysis; A.B. and F.L. review the manuscript; R.F. overviewed the study and reviewed the manuscript.

Competing interests

GS was a consultant for Bristol-Meyers-Squibb, Novartis, Ariad and Pfizer. All other authors declare no competing financial interests.

Supporting informations

Additional Supporting Information may be found in the online version of this article:

Table IS. Patient features according to the BCR-ABL1 transcript levels 3 months after starting imatinib

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Table I. Rates of cytogenetic and molecular responses according to the *BCR-ABL1* transcript levels at 3 month.

	BCR-ABL IS at 3 mo		***P***	**BCR-ABL IS at 3 mo**		***P***
	≤ 10%	**>10%**		**≤ 1%**	**>1%**	
N^ of pts (%)	**35 (79.5%)**	**9 (20.5%)**		**17 (38.6%)**	**27 61.4%)**	
CCyR						
At 6 mo, n(%)	**18/19 (95%)**	**5/9 (55.5%)**	***.003***	**10/17 (59%)**	**13/27 (48%)**	*.678*
Overall, n(%)	**29/31 (93.5%)**	**8/9 (89%)**	*.64*	**15/15 (100%)**	**24/25 (96%)**	*.433*
***BCR-ABL1* IS <1%**						
At 6 mo, n (%)	**21/27 (78%)**	**2/9 (22%)**	***.003***	**12/12 (100%)**	**11/24 (46%)**	***.001***
At 9 mo, n (%)	**20/23 (87%)**	**4/9 (44.5%)**	***.013***	**9/9 (100%)**	**15/23 (65%)**	***.041***
MMR						
At 12 mo, n (%)	**18/25 (72%)**	**3/8 (37.5%)**	*.077*	**10/11 (91%)**	**11/22 (50%)**	***.021***
At 18 mo, n(%)	**17/20 (85%)**	**3/7 (43%)**	***.029***	**10/10 (100%)**	**10/17 (59%)**	*.063*
Overall, n (%)	**30/33 (91%)**	**5/8 (62.5%)**	***.041***	**16/17 (94%)**	**18/23 (78%)**	*.165*
MR						
At 24 mo, n (%)	**12/19 (63%)**	**1/4 (25%)**	*.125*	**4/9 (44.5%)**	**11/13 (84.5%)**	*.731*
Overall, n (%)	**20/33 (61%)**	**3/8 (37.5%)**	*.237*	**11/17 (64.7%)**	**12/23 (52%)**	*.428*
CMR						
Overall, n (%)	**15/33 (45.5%)**	**1/8 (12.5%)**	*.064*	**8/17 (47%)**	**9/23 (39%)**	*.616*

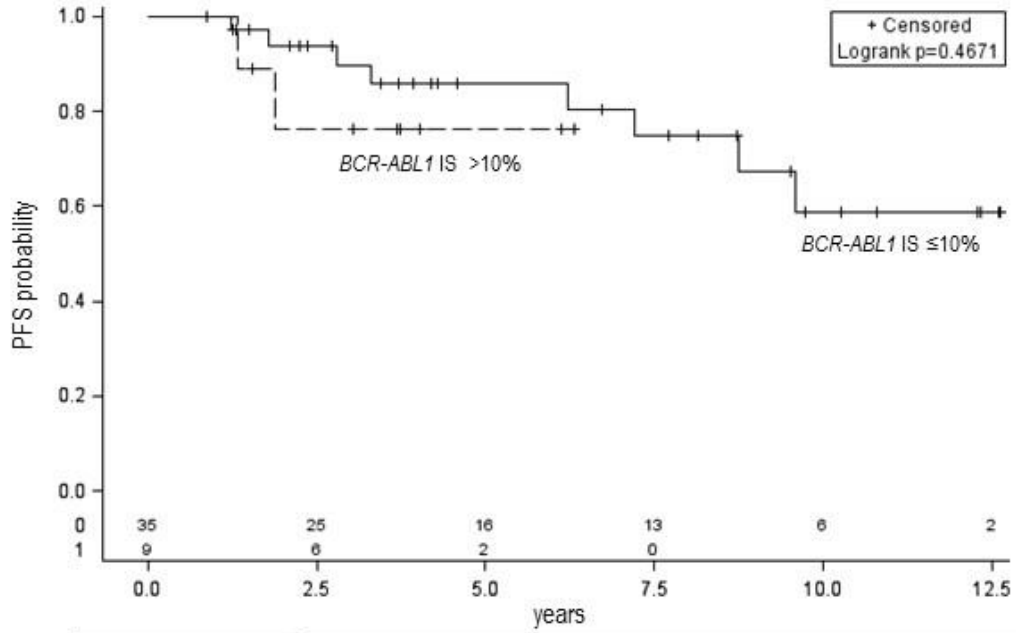
CCyR = complete cytogenetic response; MMR = major molecular response; MR = molecular response; CMR = complete molecular response.

Figure legend

Figure 1. Progression-free survival (PFS) probability according to the BCR-ABL1 transcript level cut-off at 3 month: 10% IS (A) and 1% IS (B). The number of patients at risk per period are shown. Patients lost to follow-up were censored.

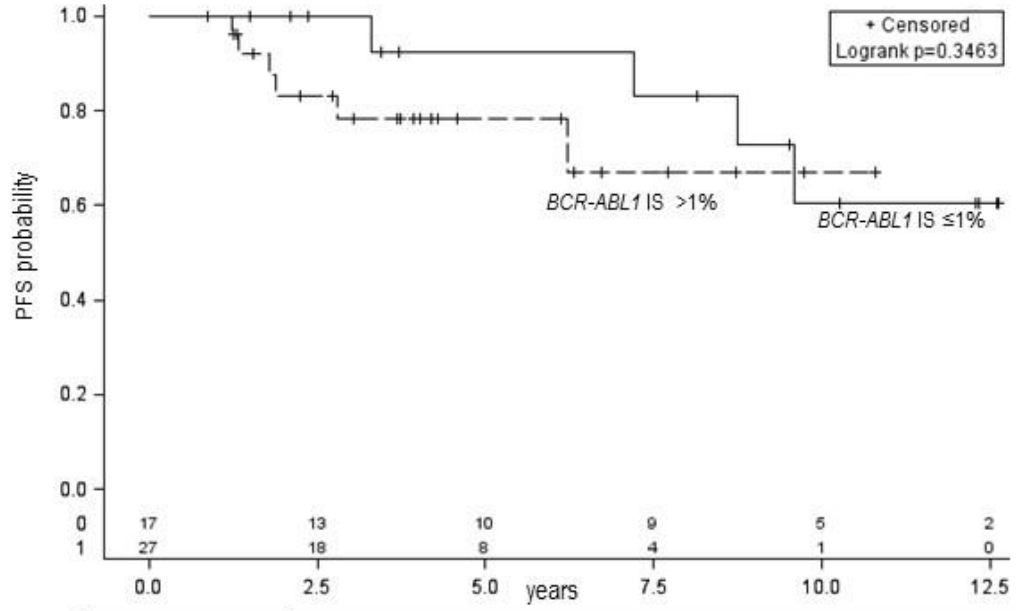
Figure 1.

A



BCR-ABL1 IS at 3 mo	PFS		
	3-year	5-year	10-year
≤10%	89.8% (95% CI, 79.4-100)	85.9% (95% CI, 73.9-99.9)	58.9% (95% CI, 38.9- 81.9)
>10%	76.2% (95% CI, 52.1-100)	76.2% (95% CI, 52.1-100)	-

B



BCR-ABL1 IS at 3 mo	PFS		
	3-year	5-year	10-year
≤1%	100% (95% CI, 100-100)	92.3% (95% CI, 78.9-100)	60.6% (95% CI, 36.2- 100)
>1%	78.3% (95% CI, 63.1-97.3)	78.3% (95% CI, 63.1-97.3)	67.1% (95% CI, 46.3-97.4)