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

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The achievement of early response has been shown to predict a significantly better outcome in adults with chronic myeloid leukaemia (CML) in chronic phase (CP) treated with either imatinib (IM) or second generation tyrosine kinase inhibitors (TKIs) (Branford et al., 2012; Hanfstein et al., 2012; Marin et al., 2012; Jain et al., 2013; Jabbour et al., 2014). Recently, early molecular response (EMR) was also reported to predict a better outcome in 40 CP CML children treated with IM at a standard dose (260 mg/m2/day) (Millot et al., 2014). We hereby analysed the predictive value of the BCRABL1 transcript levels at 3 months in terms of responses and outcome in a cohort of children and adolescents with CP CML treated with high dose IM at 11 Italian centres. This study (CML Petit01) was approved by the Institutional Ethics Committees. From March 2001 to March 2014, 53 patients younger than 18 years of age with a newly diagnosed CML in CP were treated with IM at a dose of 340 mg/m2/day. Cytogenetics and quantitative reverse transcription polymerase chain reaction (qPCR) analysis were planned on bone marrow (BM) every 3 months and qPCR on peripheral blood (PB) monthly, as previously described (Giona et al., 2015). Haematological and cytogenetic response (CyR) criteria were defined according to the European LeukaemiaNet recommendations (Baccarani et al., 2009). Major molecular response (MMR) was defined as ≤0·1% BCRABL1 according to the International Scale (IS), while molecular response (MR) was considered as ≤0·01% BCRABL1 IS. Complete molecular response (CMR) was used to indicate levels of disease ≤0·0032% BCRABL1 IS or undetectable. Transcript levels ≤10% and ≤1% BCRABL1 IS at 3 months after starting IM were defined as EMR and deep EMR, respectively. Forty-four CP CML patients (27 males, 17 females; median age: 113/12 years, range 32/12 to 1510/12) who had available BCRABL1 levels at 3 months and had been followed for at least 12 months were included in this analysis. Overall, 92·5%, 85%, 56% and 39% of patients achieved a 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, BCRABL1 transcript levels >10% IS were detected in 9/44 (20·5%) patients, whereas 18/44 (41%) and 17/44 (38·5%) patients had BCRABL1 IS of >1% to ≤10% and ≤1%, respectively. In our experience, the proportions of patients who achieved an EMR and a deep EMR after 3 months of treatment were higher than those reported by Millot et al. (2014) in a comparable cohort of children and 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; Hughes et al., 2014). These findings suggest that IM exposure is an important factor influencing early treatment response in CP CML patients. To assess the association between EMR and both the response rates and disease outcome, we took into account two 3 month transcript cut-off levels, 1% and 10% BCRABL1 IS. When children were classified according to the transcript levels at 3 months using the 10% IS cut-off, those with an EMR had significantly higher response rates after 6 months of treatment compared to those with BCRABL1 IS >10%; 95% vs. 55·5%, P = 0·031 and 78% vs. 22%, P = 0·003 for CCyR and BCRABL1 IS ≤10%, respectively (Table 1). Likewise, an EMR was significantly predictive of the overall MMR rate, but not of overall CCyR, MR or CMR rates (Table 1). When patients were
classified according to the transcript levels at 3 months using the 1% IS cut-off, children with
\( BCR/ABL1 \) IS \( \leq 1\% \) had higher molecular response rates after 6 (100% vs. 46%, \( P = 0.001 \)), 9 (100% vs. 65%, \( P = 0.041 \)) and 12 months (91% vs. 50%, \( P = 0.021 \)) compared to those with values greater than 1%; nonetheless, a deep EMR was not predictive of CCyR at any time or overall MMR, MR and CMR rates (Table 1). There were no differences in baseline features and 3-month doses of IM between patients who achieved an EMR and those with higher transcript levels (Table SI). Treatment with IM was stopped in 7 patients (all but 1 with \( BCR/ABL1 \) IS \( \leq 10\% \) after 3 months of treatment) due to allogeneic haematopoietic stem cell transplantation and it was successfully discontinued in 3 patients with sustained and prolonged CMR. About one-third of patients (\( n = 13 \)) had to interrupt IM due to treatment failure; nonetheless none of our patients has died. With a median follow-up of 73.5 months (range, 15–151.3), the overall progression-free survival (PFS) probability at 10 years is 57.7% (95% confidence interval, 38.4–86.8). The estimated 5-year PFS probability for patients with \( BCR/ABL1 \) values \( \leq 10\% \) vs. those with values >10% is 85.9% vs. 76.2%, \( P = 0.4671 \) (Fig 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%, \( P = 0.3463 \)) (Fig 1B).

Recently, Millot et al (2014) reported that children with \( BCR/ABL1 \) \( \leq 10\% \) at 3 months after treatment with standard doses of IM (260 mg/m\(^2\), equal 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. In our experience the \( BCR/ABL1 \) IS values at 3 months are not predictive of overall MMR, MR and CMR rates, or 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; Hughes et al, 2014) and in children receiving standard doses of IM (Millot et al, 2014).

Table 1. Rates of cytogenetic and molecular responses according to the \( BCR/ABL1 \) transcript levels at 3 months.

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.

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Author contributions
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. analysed 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.