Impact of the type of the BCR-ABL fusion transcript on the molecular response in pediatric patients with chronic myeloid leukemia

Response to the Original Article by: Claire M. Lucas, Robert J. Harris, Athina Giannoudis, Andrea Davies, Katy Knight, Sarah J. Watmough, Lihui Wang and Richard Clark. Chronic myeloid leukemia patients with the e13a2 BCR-ABL fusion transcript have inferior responses to imatinib compared to patients with the e14a2 transcript. Haematologica 2009, 94:1362-7.

We read with interest the article by Lucas *et al.* in this Journal focussing on the impact of the *BCR-ABL* transcript type (e13a2 *versus* e14a2) in newly diagnosed patients with chronic myeloid leukemia (CML).[1] In a series of 71 adults treated with imatinib 400mg, they demonstrated that those 39 patients expressing the e14a2 transcript type had a higher and more rapid complete cytogenetic response than the 32 patients exhibiting the e13a2 transcript. Thus, they concluded that the transcript type yields additional prognostic information to predict the long-term response to imatinib.

CML in pediatrics is rare and constitutes only approximately 2% of all childhood leukemias. Imatinib has been licensed since the year 2003 for use in children; however, its efficacy has so far been evaluated only in prospective trials with small patient numbers. Long-term experience in pediatric patients of all age groups is still very limited and the durability of responses, as well as long-term side effects of this drug, must still be determined.[2-4]

Stimulated by the article by Lucas *et al.*, we analyzed our data from children with Philadelphia-positive CML enrolled in trial CML-paed-II and questioned whether assessment of the *BCR-ABL/ABL* ratio by quantitative RT-PCR would also show a difference in molecular response with respect to the underlying transcript type.[5] Thirty pediatric patients (19 males, 11 females; age: 1 – 17 yrs, mean age: 10.5 yrs) diagnosed with CML in chronic phase were treated with imatinib at a dose of 250 mg/m^2 (equivalent to 400 mg in adults; maximum absolute dose 400 mg). Mean duration of treatment was eight months (range 1 – 15 months). Twelve patients (8 males) exhibited transcript type e13a2 and 18 pts (11 males) type e14a2. From month three to month nine after the start of the treatment the mean ratio of the *BCR-ABL/ABL* transcripts in patients exhibiting the e13a2 type was approximately twice as high as mean ratio of patients with the e14a2 type, respectively (Table 1). No difference was observed when the median values were considered. A graphical plot of all data applying the best fit mathematical model of a logarithmic decline over time showed that children exhibiting the e14a2 transcript type experienced a more rapid decline of *BCR/ABL* transcripts than children with an e13a2 transcript type (Figure 1). However, due to the small number of patients under analysis, differences of the curves cannot be considered to be significant (P≥0.05) since confidence limits overlay (SPSS statistical package, Version 14, Chicago, USA).

The molecular data accumulated in our small pediatric cohort thus confirm the findings reported by Lucas *et al.* showing that patients exhibiting the e14a2 transcript type respond better to a fixed dose of imatinib. These patients not only have a lower mean BCR/ABL transcript ratio as early as after three months of treatment but also achieved low transcript levels faster than patients with e13a2 transcript types. As published earlier by our group in more than 140 children, and confirmed in this small series of 31 individuals, the e14a2 transcript type is over-represented in children, a finding which has been also described in the majority but not in all adult cohorts.[6] This skewed distribution may weaken any statistical analysis especially in pediatrics with small cohorts due to the rarity of the diseases in this age group. Of note, Lucas *et al.* describe an almost balanced distribution of the e13a2 (n=32) and the e14a2 (n=39) transcript.

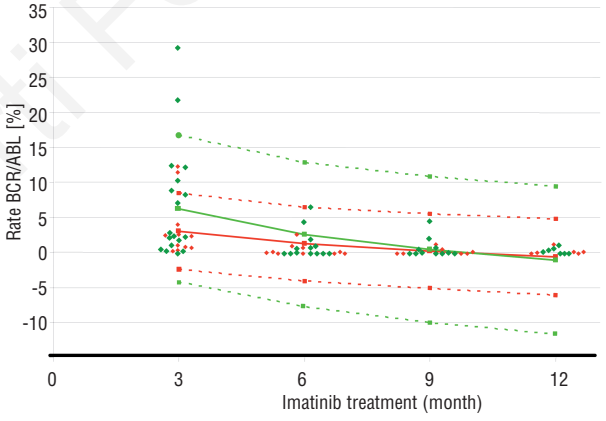

Figure 1. Time course of the transcript ratio BCR-ABL/ABL in individual patients exhibiting either the e13a2 rearrangement type (red dots) or the e14a2 type (green dots) in pediatric patients with chronic myeloid leukemia under ongoing imatinib treatment. Full lines denote the best fitted curves adapted by logarithmic function for decline over time while dotted lines show the upper and lower limits of confidence (red lines: e13a2; green lines e14a2).

Table 1. Absolute values of the BCR-ABL/ABL transcript ratio (mean, range, median) over time (three month intervals) under imatinib treatment in pediatric patients depending on the underlying transcript type e13a2 or e14a2, respectively.

		3 month	6 month	9 month	12 month
e13a2	n	12	10	7	6
	mean	3.659%	0.558%	0.337%	0.358%
	median	2.500%	0.200%	0.050%	0.200%
	range	0.420%-12.500%	0.010%-2.750%	0.020%-1.350%	0.000%-1.380%
e14a2	n	18	13	12	7
	mean	7.044%	1.260%	0.731%	0.410%
	median	2.750%	0.190%	0.085%	0.340%
	range	0.070%-29.420%	0.000%-6.730%	0.000%-4.670%	0.000%-1.210%

The authors could also show an increased pCrKL/CrKL ratio as a surrogate marker for the bcr-abl tyrosine kinase (TK) activity in patients exhibiting the e13a2 transcript type. It is tempting to speculate that patients with higher TK-activity should also be treated by either higher doses of imatinib or more potent second generation TK-inhibitors. Whether this approach would also augment recently reported side effects of imatinib on bone metabolism is of special concern in a pediatric cohort which is still in a period of growth.[7,8] We, therefore, fully agree with the suggestion by Lucas *et al.* that the analysis of the transcript type in patients with CML should be included in the analysis of response data from trials with TK inhibitors.

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Early hemorrhagic death before starting therapy in acute promyelocytic leukemia: association with high white blood cell count, late diagnosis and delayed treatment initiation

Early death is one of the major causes of failure in acute promyelocytic leukemia (APL), it occurs in approximately 5-10% of newly diagnosed cases and is most frequently due to severe intracranial or pulmonary bleeding. In the present single center study, we reviewed the clinical and biological features of patients who developed severe hemorrhagic complications before starting all-trans retinoic acid and chemotherapy, and found that late diagnosis and delayed treatment initiation, in conjunction with elevated WBC counts, are significantly associated with severe bleeding and early death.

Severe bleeding is a well known major complication of APL which leads to early death in approximately 5-10% of patients diagnosed in developed countries and in 20-30% of patients living in less privileged regions. Hemorrhages are commonly attributed in this leukemia to the frequent diffuse activation of coagulation, hyperfibrinolysis, and non-specific proteolytic activity,[1-4] and have also been reported to occur before the diagnosis of APL has been made and therapy started.[3] Systematic data on patients developing this severe complication before treatment are extremely scarce in the literature and these cases are usu-

Table 1. Comparison of clinical and biological features at diagnosis between patients with fatal hemorrhages and the remaining patients.

Features	Pts with early death	All patients	*P*
Sex m/f	4/1	49/51	ns
Age	49.9	37	ns
FAB M3/M3v	3/5 (60%)	23/100 (23%)	0.3
WBC ($\times 10^9$/L)	18	2.8	0.001
Hb (g/dL)	10	9.1	ns
Platelets ($\times 10^9$/L)	33	28	ns
Sanz's risk			
Low	1	26	
Intermediate	3	46	0.05
High	3	28	
Type of PML/RARA			
Bcr1	-	49	ns
Bcr3	5	48	
CD34+	2/5 (40%)	38/100 (38%)	ns
CD2+	2/5 (40%)	19/100 (19%)	0.04
% Pb blasts	84	70	0.04
Fever (yes/no)	3/5 (60%)	10/100 (10%)	0.03
Creatinine (mg/dL)	1.3	0.8	ns
LDH (U/L)	722	250	0.04
Alteration of coagulation parameters (y/n)	5/5 (100%)	35/100 (35%)	0.04
Median time to admission in hospital (days)	7	1.5	0.001