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## Lymphoblastic predominance of blastic phase in children with chronic myeloid leukaemia treated with imatinib: A report from the I-CML-Ped Study

Deborah Meyran, Arnaud Petit, Joelle Guilhot, Meinolf Suttorp, Petr Sedlacek, Eveline de Bont, Chi Kong Li, Krzysztof Kalwak, Birgitte Lausen, Srdjana Culic, et al.

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1 Title: Lymphoblastic predominance of blastic phase in children with chronic myeloid  
2 leukemia treated with imatinib: a report from the I-CML-Ped Study

3 Authors: Deborah Meyran<sup>1\*</sup>, Arnaud Petit<sup>2\*</sup>, Joelle Guilhot<sup>3</sup>, Meinolf Suttorp<sup>4</sup>, Petr  
4 Sedlacek<sup>5</sup>, Eveline De Bont<sup>6</sup>, Chi Kong Li<sup>7</sup>, Krzysztof Kalwak<sup>8</sup>, Birgitte Lausen<sup>9</sup>, Srdjana  
5 Culic<sup>10</sup>, Barbara de Moerloose<sup>11</sup>, Andrea Biondi<sup>12</sup>, and Frédéric Millot<sup>3</sup>

6 1- Department of Pediatric Hematology, Robert Debré Hospital, Paris, France

7 2- Department of Pediatric Hematology, Armand Trousseau Hospital, Paris, France

8 3- Inserm CIC 1402, University Hospital, Poitiers, France

9 4- Medical Faculty, Pediatric Hemato-Oncology, Technical University, Dresden, Germany

10 5- Department of Pediatric Hemato-Oncology, University Hospital Motol, Prague, Czech  
11 Republic

12 6- Departments of Paediatric Oncology/Haematology, Beatrix Children's Hospital, University  
13 Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

14 7- Department of Pediatrics, Prince of Wales Hospital, Hong Kong, China

15 8- Department of Pediatric Hematology Oncology and Transplantation, Wroclaw Medical  
16 University, Poland

17 9- Department of Pediatrics, Rigshospitalet, University Hospital, Copenhagen, Denmark

18 10- Department of Pediatric Hematology Oncology Immunology and Medical Genetics,  
19 Clinical Hospital Split, Croatia

20 11- Department of Pediatrics, Ghent University Hospital, Belgium

21 12- Department of Pediatrics, University of Milano-Bicocca, San Gerardo Hospital,  
22 Fondazione MBBM, Monza, Italy

23 \* Deborah Meyran and Arnaud Petit contributed equally to this study.

24 Corresponding author: Deborah Meyran

25 Hopital Robert Debré,

26 48 Boulevard Sérurier, 75019 Paris, France. Tel.: +33 1 40 03 53 88; Fax: +33 1 40 03 47 40

27 E-mail address: [deborah.meyran@hotmail.fr](mailto:deborah.meyran@hotmail.fr)

28

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31

32 **Keywords**

33 Chronic myeloid leukemia; Children; Accelerated phase; Blastic phase; Tyrosine kinase  
34 inhibitors; Hematopoietic stem cell transplantation.

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41 **Abstract**

42 **Background:** Chronic myeloid leukemia (CML) is a rare disease in children. The frequency  
43 and outcome of children evolving to accelerated phase (AP) or blastic phase (BP) under  
44 treatment with imatinib is unknown. The aim of the current study is to assess the incidence of  
45 progression from CML in chronic phase with imatinib frontline in a pediatric setting and  
46 describe the management and outcome of these patients.

47 **Patients and Methods:** In the I-CML-Ped Study database ([www.clinicaltrials.gov](http://www.clinicaltrials.gov),  
48 #NCT01281735), 19 of 339 pediatric patients in chronic phase treated with imatinib in the  
49 frontline evolved to CML-AP or CML-BP.

50 **Results:** With a median follow-up of 38 months (range: 2-190 months), the cumulative  
51 incidence of progression at one and three years was 3% (CI 95%: 1-5%) and 7% (CI 95%: 4-  
52 11%), respectively. We observed a large predominance of lymphoid-BP (70%) over myeloid-  
53 BP (30%) with imatinib in frontline therapy. Sixteen patients underwent hematopoietic stem  
54 cell transplantation and eight were treated with a tyrosine kinase inhibitor after transplant.  
55 Only the transplanted patients are alive. The five-year overall survival rate of children with  
56 CML-AP/BP is 44%, with no statistical difference between the lymphoid-BP and myeloid-BP  
57 outcome.

58 **Conclusion:** Children evolving to AP or BP under treatment with imatinib have a very poor  
59 prognosis with an OS under 50%, much worse than children with advanced phase at diagnosis.

60

## 61           **Introduction**

62           Chronic myeloid leukemia (CML) is rare in children, accounting for 2 to 3% of  
63 childhood leukemias [1], with an average annual incidence of 0.6-1.0 cases per million in  
64 children younger than 15 years [2]. At diagnosis, approximately 95% of pediatric patients are  
65 in chronic phase (CML-CP), similar to the frequency in adults [3]. In the absence of treatment,  
66 CML progresses from CML-CP to accelerated phase (CML-AP) or blastic phase (CML-BP)  
67 [4]. The frequency of progression to CML-AP or CML-BP is remarkably reduced by tyrosine  
68 kinase inhibitor (TKI) treatment, currently estimated to be in the range of 1-1.5% per year [5]  
69 *versus* more than 20% yearly in the pre-TKI era [6]. In adults, CML-BP occurring under TKI  
70 treatment expresses a predominantly myeloid phenotype (60-80%) [7]. Despite guidelines for  
71 the management of CML-BP in adult patients, their outcome is poor, with an overall survival  
72 (OS) at 12 months from 20% before TKI era to 50% after the introduction of TKI [8].  
73 Imatinib was introduced for the treatment of children with CML in the 2000s and is still the  
74 most prescribed first-line therapy for CML-CP even if the second-generation TKI (2G-TKIs)  
75 have been recently approved in this age group [9, 10]. Here, we aimed to describe the  
76 characteristics and outcome of CML-AP and CML-BP occurring under treatment with  
77 imatinib in children with CML.

78

## 79           **Materials and methods**

80

81           Patients were identified from the I-CML-Ped Study ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)  
82 #NCT01281735), a database of patients from 0-18 years old with CML from 37 centers in 14  
83 countries. The I-CML-Ped Study was set up to assess epidemiology, management and  
84 outcome of CML in children and adolescents and recorded the data retrospectively from 2000

85 until 2010 then prospectively from 2011. This study was approved by the institutional review  
86 board of the University Hospital of Poitiers, in accordance with the declaration of Helsinki.

87 A total of 445 patients were enrolled from 2001 to January 2016. At diagnosis, 376  
88 patients were in CML-CP according to the European LeukaemiaNet (ELN) criteria [11] and  
89 339 received upfront imatinib treatment. Among the 339 patients in CML-CP with imatinib  
90 frontline, 19 patients evolved from CML-CP to CML-AP or to CML-BP and represent the  
91 study cohort named as AP/BP cohort (*Supplemental Figure*). The median follow-up of the  
92 AP/BP cohort was 38 months (range: 2-190). Patient characteristics are provided in *Table 1*.  
93 The median age at diagnosis of AP/BP cohort was 13.2 years (range: 4.5 to 16.8) with a M/F  
94 sex ratio of 2.8. Progression to CML-AP or CML-BP is a time dependent variable. Therefore,  
95 to compare the characteristics at diagnosis of the AP/BP cohort to a control cohort of patients  
96 who did not progress with imatinib frontline, we took into consideration only the patients who  
97 had a follow-up above 58 months, which is the maximum delay of CML-BP onset of the  
98 AP/BP cohort. We also excluded the transplanted patients from the control cohort because  
99 hematopoietic stem cell transplantation (HSCT) could change the prognosis (*Supplemental*  
100 *Figure*). Although it is important to mention that no death was recorded in the whole cohort of  
101 patients who did not progress and have a follow-up >58 months, inclusive of both  
102 transplanted and non-transplanted patients. Overall, the control cohort includes 92 patients.  
103 The median follow-up of the control cohort was 94 months (range: 58.1-168.3 months).

104 The Sokal score was determined using the formula for patients under 45 years old [12].  
105 The diagnosis of CML was assessed by cytogenetic analysis or in case of failure by  
106 fluorescence *in situ* hybridization (FISH) [13]. BCR-ABL1 transcript level in the blood was  
107 determined by using quantitative reverse transcriptase-polymerase chain reaction as reported  
108 previously and was expressed according to the international scale (IS) [14]. The cytogenetic  
109 and molecular responses were defined according to the ELN criteria [11]. CML-AP was

110 defined by blasts in blood or bone marrow (BM) between 15-29%, or blasts cells plus  
111 promyelocytes in blood or BM > 30% with blasts cells < 30%, basophils in blood > 20%,  
112 persistent thrombocytopenia ( $<100 \times 10^9/l$ ) unrelated to therapy, cytogenetic evidence of clonal  
113 evolution. CML-BP was defined by the presence of at least 30% of blasts cells in blood or  
114 BM, or evidence of extramedullary disease [11]. The myeloid or lymphoid  
115 immunophenotype of CML-BP was determined by flow cytometry [15]. BCR-ABL1 kinase  
116 domain (KD) mutation analysis was performed as previously reported in case of suboptimal  
117 response or treatment failure. Differences in baseline characteristics between AP/BP cohort  
118 and the control cohort were tested using the Fisher's exact test for categorical data or the  
119 Wilcoxon rank sum test for continuous variables. OS was estimated using the Kaplan-Meier  
120 method [16]. In order to account for competing events, incidence of progression along time  
121 was estimated by the cumulative incidence function with the use of Fine and Gray models.  
122 Competitive events were deaths from causes other than progression. Analyses were performed  
123 using the SAS® v 9.3 (SAS Institute).

## 124 **Results**

125 In the I-CML-Ped Study database, the cumulative incidence of progression at one and  
126 three years was 3% (CI 95%: 1-5%) and 7% (CI 95%: 4-11%), respectively. Baseline  
127 characteristics of the AP/BP cohort compared with the control cohort of 92 patients who did  
128 not progress with imatinib frontline are presented in Table 1. Notably, patients in the AP/BP  
129 group had significantly more aggressive clinical and biological features with larger  
130 splenomegaly, higher white blood cells count and lower platelet count. Only ELTS score at  
131 CML-CP diagnosis was significantly discriminant to predict progression with nine (48%) of  
132 the 19 AP/BP patients who were high-risk compared to 8 (10%) in the control cohort. Eight  
133 patients had a BCR-ABL1 fusion identified by FISH only. The other AP/BP patients had a

134 karyotype showing the classical translocation t(9;22)(q34;q11) except for one who had a  
135 variant translocation t(1;9;22)(q12;q34;q11).

136 Eleven of the 19 patients (58%) received hydroxyurea before the start of TKI. Imatinib  
137 was the first-line TKI for all patients. The dose was 260 mg/m<sup>2</sup> for 12 patients and 300-340  
138 mg/m<sup>2</sup> for seven. Three patients received a concomitant additional treatment: triple intrathecal  
139 injection (n=1) for a retinal leukostasis, mitoxantrone (n=1) to reduce the leucocytes count,  
140 and cytarabine/interferon (n=1) for hemorrhagic retinopathy (*Table 2*). Because of non-  
141 achievement of cytogenetic and/or molecular responses, the dose of imatinib was increased in  
142 six patients (from 260 to 300 mg/m<sup>2</sup> or from 300 to 400-600 mg/m<sup>2</sup>), whereas eight were  
143 switched to dasatinib (60-80 mg/m<sup>2</sup>). By comparison, among the 320 patients treated with  
144 imatinib frontline who did not progress, 71 (22%) were switched to a second generation TKI  
145 due to poor response. Furthermore, three from the five patients of the AP/BP cohort who  
146 initially had a good response discontinued imatinib for toxicity (n=2) or inadequate  
147 compliance (n=1). Before the occurrence of CML-AP/CML-BP, six patients (31%) obtained a  
148 complete cytogenetic response (CCyR) after a median time of 12 months (range: 6-29) and only  
149 two (11%) achieved a major molecular response (MMR) at 18 months (*Supplemental Table 1*).

150 The median duration of TKI before the occurrence of CML-AP or CML-BP was 11.4  
151 months (range: 3-56.6). Seven patients (37%) discontinued TKI for a median duration of 40  
152 days (range: 7-130), for intolerance (n=4) and non-compliance (n=3). Among the four patients  
153 who discontinued imatinib for intolerance, imatinib was resumed in three of them at the same  
154 dose (n=1) or at a lower dose (n=2). The other patient who was initially treated with a reduced  
155 dosage of imatinib was finally switched to dasatinib. The mutational status of the BCR-ABL1  
156 kinase domain was only evaluated for 12 patients when CML-AP or CML-BP was diagnosed.  
157 Six of the 12 patients monitored (50%) acquired KD mutations (*Table 2*). In the study cohort,  
158 four patients quickly evolved to CML-AP after a median of 8.7 months (range: 3.2-18.1) from



159 the start of imatinib. For one patient, CML-AP was exclusively defined by clonal evolution  
160 with the emergence of monosomy 7. CML-AP evolved rapidly to CML-BP for two patients,  
161 after a median of 3.5 months (range: 1.8-5.3). Overall, 17 patients evolved to CML-BP,  
162 including two after CML-AP after a median of 12.3 months from diagnosis (range: 3-58).

163 Twelve (70%) of the 17 patients evolved towards lymphoid CML-BP whilst five (30%)  
164 evolved towards myeloid CML-BP, after a median of 9.8 months (range: 3-56.6) and 17.7  
165 months (range: 9.2-24.6) from the start of imatinib, respectively. At the time of CML-AP or  
166 CML-BP, 10 of 11 patients monitored (90%) acquired additional cytogenetic abnormalities  
167 (*Supplemental Table 2*).

168 CML-AP was treated by increasing the dose of imatinib from 300 to 500-600 mg/day for  
169 two of the four patients in CML-AP, whereas the others were switched to dasatinib. Sixteen of  
170 17 patients in CML-BP were treated according to acute myeloid leukemia (AML) or acute  
171 lymphoblastic leukemia (ALL) protocols, combined with imatinib or second generation TKI.  
172 Only one patient, patient 7, with lymphoid CML-BP was treated with dasatinib alone before  
173 HSCT (*Table 2*). Three patients died from progressive disease before scheduled HSCT after a  
174 median of 12.5 months (range: 6.5-19.2) from CML-AP/CML-BP diagnosis. Overall, 16  
175 patients underwent HSCT. The median interval from CML-AP/CML-BP diagnosis to HSCT  
176 was 5 months (range: 1.2-8.5). At transplant, nine of the remaining 16 patients (56%) had  
177 achieved CCyR and four (25%) MMR (*Supplemental Table 1*). Details of the HSCT  
178 procedures are given in *Table 2*. At first assessment post-HSCT, 10 patients (63%) were in  
179 CCyR and nine (56%) in MMR. Eight received a second generation TKI post-transplant.  
180 After HSCT, five patients died, three from progressive disease and two from transplant-  
181 related events. Eleven patients are still alive; 10 are in MMR, but one had a lymphoid CML-  
182 BP relapse 26 months after transplant. Five-year OS was 44% (*Figure 1A*), with no statistical  
183 difference between lymphoid-BP OS (29%) and myeloid-BP OS (40%) (*Figure 1B*).

184        **Discussion**

185        This is the first study to assess the incidence and the outcome of CML-AP and CML-BP  
186 in children treated with imatinib. Imatinib still remains the main frontline therapy in children  
187 because there is more experience with its efficacy and its toxicity than with the other TKIs  
188 [17-19]. Only few studies have evaluated the rate of progression to CML-AP or CML-BP in a  
189 population-based setting. A recent report in adults showed a rate of cumulative incidence of  
190 progression of 4.3% at two years [20]. We observed a quite similar proportion in children  
191 with cumulative incidence of progression at one and three years at 3% (CI 95%: 1-5%) and  
192 7% (CI 95%: 4-11%), respectively.

193        Many studies have previously reported that children in CP have clinical presentations with  
194 more aggressive features than adults [21-23]. However, scoring systems in CML based on  
195 clinical and biological characteristics of the disease at diagnosis, such as Sokal, Hasford, and  
196 EUTOS, have been developed within an adult setting. In children with CML, only the ELTS  
197 score at diagnosis demonstrates better differentiation of progression-free survival [24]. In our  
198 study, we used both the Sokal young score and ELTS score to define the risk groups of the  
199 patients. The vast majority (74%) of the AP/BP cohort and half of the control patients were  
200 allocated to the high-risk group according to the Sokal young score whereas the ELTS score  
201 identified a lower proportion of high-risk children in the control cohort (10%) compared to  
202 the proportion in the AP/BP cohort (48%). Sokal risk score that classifies most of the children  
203 with CML-CP in high risk group at diagnosis is therefore less discriminating for predicting  
204 progression than ELTS risk score. Until a new specific score incorporating clinical, biological  
205 and molecular features is developed in this age group to better predict progression, patients  
206 with high ELTS risk score must be closely monitored.

207        Early cytogenetic and molecular responses are reported to be the best predictors of good  
208 outcome [11]. These two parameters were clearly not satisfactory in our cohort. Non-

209 adherence is one of the most common reasons for suboptimal response and treatment failure  
210 in patients with CML treated with TKI [25]. Indeed, adolescence is a well-known challenge to  
211 compliance in pediatric patients with chronic diseases [26, 27]. In our study, the proportion of  
212 discontinuation of this pediatric AP/BP cohort is approximately the same as that reported in  
213 previous studies for adults with CML treated by oral TKI (15-30%) [28]. However, the  
214 proportion of patients who discontinued TKI for inadequate compliance and experienced  
215 CML progression remains difficult to assess because it relies on patients' declaration. At the  
216 onset of CML-AP or CML-BP, 50% of the patients who were monitored acquired KD  
217 mutations including T315I mutation. KD mutations T315I and G250E are associated with  
218 imatinib failure, which can be overcome by switching treatment to a third or fourth generation  
219 TKI [29]. However, in pediatrics, the therapeutic options are limited because ponatinib is still  
220 not approved in children. Only few cases of young patients treated by ponatinib have been  
221 reported in the literature, with no safe dose having been determined in children [30, 31]. For  
222 suboptimal responses or failure, patients have been either treated with an increased dose of  
223 imatinib or switched to a second generation TKI. Recently, a therapeutic algorithm based on  
224 pediatric hematologists' experience has been proposed to treat children in CML-CP once  
225 failure or suboptimal response has been detected [32]. Probably with this new algorithm,  
226 some of our patients would have been switched earlier to a second-generation TKI. However,  
227 it should be taken into account that the I-CML study is an international database and access to  
228 certain expensive molecules like the second-generation TKI could be more difficult in some  
229 of the countries participating in this study.

230 In adult cohorts, a predominance of myeloid immunophenotype of CML-BP (60-80%)  
231 was observed [7, 33]. In contrast to adult patients with CML, we observed predominantly  
232 lymphoid-BP (70%) in children with upfront imatinib treatment. In another report from the I-  
233 CML-Study, we have also observed a predominance of lymphoid phenotype of *de novo*

234 advanced phases of childhood CML [34]. The median time to the onset of the myeloid-BP  
235 was longer than that of lymphoid-BP, 17.7 months (range: 9.2-24.6) and 9.8 months (range: 3-  
236 56.6) respectively. Similarly, in an adult cohort, the median time from first diagnosis to  
237 myeloid-BP was also longer than that of lymphoid-BP, 39 months (range: 0-307) and 24  
238 months (range:0-161) respectively [35]. The median follow-up of 38 months is sufficiently  
239 long to limit a follow-up-dependent bias.

240 While children with *de novo* advanced phases have a favorable outcome with five-year OS  
241 rates at 94% and 74% for patients diagnosed in CML-AP and CML-BP respectively [34], the  
242 survival is poorer, less than 50%, when the transformation occurs from CML-CP to CML-AP  
243 or CML-BP while on TKI therapy. A similar outcome is observed in adults treated after  
244 progression from CML-CP with a median survival rate between 6-37 months and less than 12  
245 months for patients with CML-AP and CML-BP, respectively [7, 33]. Like adult cohorts [33],  
246 our data suggest that allo-HSCT may represent the best chance of long-term remission or cure  
247 in CML-BP. The current National Comprehensive Cancer Network guidelines suggest that  
248 patients who progress to CML-BP should receive an allo-HSCT within 3 to 6 months from  
249 diagnosis [8, 36]. However, experience in children with CML in advanced stages is very  
250 limited because of the small number of cases.

251

## 252 ***Conclusion***

253 In a pediatric setting, the cumulative incidence of progression of CML-CP with upfront  
254 imatinib treatment at one and three years is 3% and 7%, respectively, with a predominance of  
255 lymphoid progression. While children with *de novo* advanced phases have a favorable  
256 outcome, the five-year OS of progression to CML-AP or CML-BP in pediatric patients is poor,  
257 less than 50%, with no significant difference in outcome by immunophenotypic subtype.  
258 Bearing in mind the small number of pediatric patients with CML, allo-HSCT remains the

259 best therapeutic option for the young patients in CML-AP or CML-BP who progressed under  
260 treatment with imatinib.

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267

### 268 *Authorship*

269 D.M. and A.P. equally wrote the manuscript. F.M. coordinated the study. J.G. performed the  
270 statistical analysis. M.S., P.S., E.D.B., C.K.L., K.K., B.L., S.C., B.D.M., and A.B provided  
271 patients. All authors reviewed the final version of the manuscript.

272 Conflict-of-interest disclosure: The authors declare no competing financial interests.

273

274 **Figure legend:**

275 Figure 1. Outcome of CML-AP/CML-BP. Overall survival since the onset of imatinib was  
276 analyzed using Kaplan-Meier methodology. (A) for the overall population. (B) by subtype  
277 (CML-AP, lymphoid-BP, and myeloid-BP). AP, accelerated phase; BP, blastic phase.

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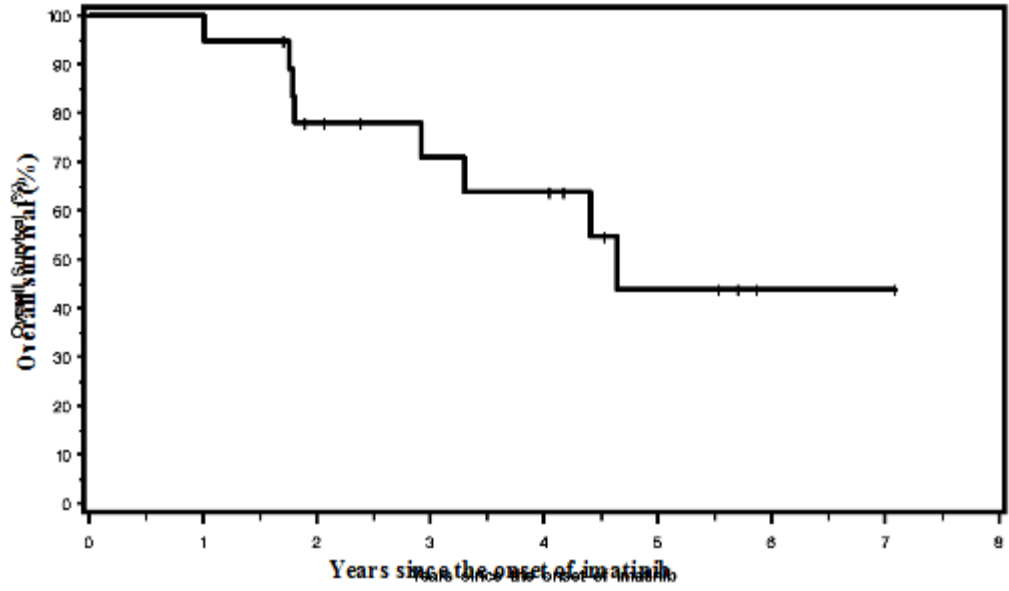
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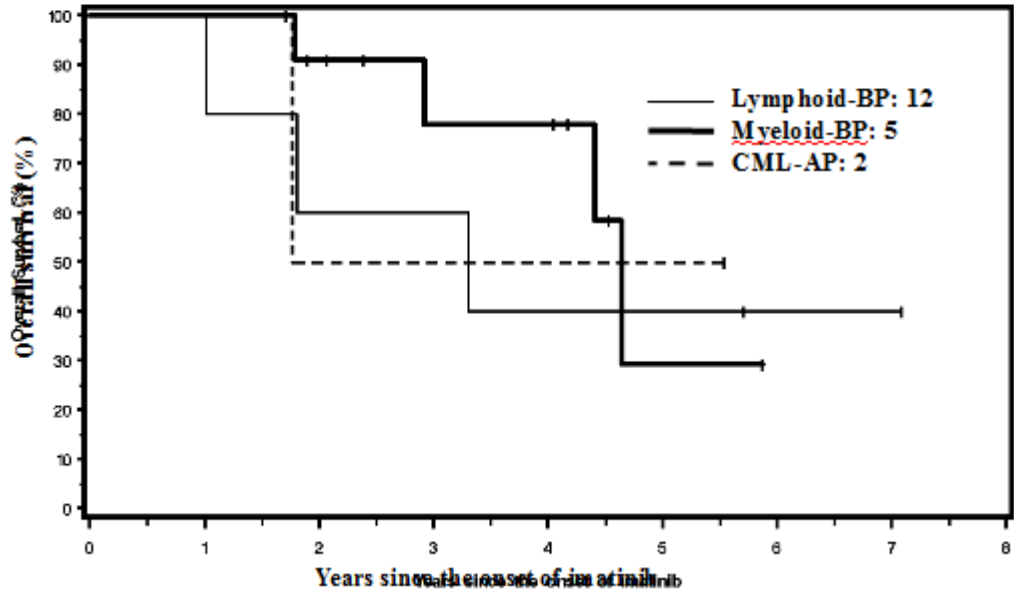
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A



B



Characteristics	<i>N</i> = 92 control patients	<i>N</i> missing	<i>N</i> = 19 AP/BP patients	<i>N</i> missing	<i>p</i>	<i>N</i> =2 AP	<i>N</i> = 12 Lymphoid- BP	<i>N</i> = 5 Myeloid- BP	<i>p</i>
<b>Gender, no. (%)</b>					> 0.05				> 0.05
Female	42 (46)		5 (26)			1	2 (17)	2 (40)	
Male	50 (54)		14 (74)			1	10 (83)	3 (60)	
<b>Age at diagnosis, ys</b>									
Median	11.4		13.2		> 0.05	14.3	12.4	11.8	> 0.05
(range)	(1.0 to 17.4)		(4.5 to 16.8)			(13.8 to 14.8)	(6 to 15.4)	(4.5 to 16.8)	
< 4 (%)	8 (9)		0 (0)			0 (0)	0 (0)	0 (0)	
4-9 (%)	22 (24)		4 (21)			0 (0)	3 (25)	1 (20)	
10-14 (%)	43 (47)		11 (58)			2 (100)	7 (58)	2 (40)	
≥ 15 (%)	19 (21)		4 (21)			0 (0)	2 (17)	2 (40)	
<b>Lansky performance (%)</b>		6		3	NA				> 0.05
100	52 (60)		10 (63)			0 (0)	7 (70)	3 (75)	
90	20 (23)		4 (25)			1 (50)	2 (20)	1 (25)	
80	10 (12)		2 (12)			1 (50)	1 (10)	0 (0)	
<80	4 (5)		0 (0)			0 (0)	0 (0)	0 (0)	
<b>Splenomegaly, no. (%)</b>	65 (71)	1	18 (95)		<b>0.0388</b>	2 (100)	11 (92)	5 (100)	> 0.05
<b>Spleen size, cm</b>		7							
Median (range)	6 (0-24)		12 (0-25)		<b>0.0003</b>				> 0.05
≤ 10	55 (65)		5 (26)			0 (0)	3 (25)	2 (40)	
>10	30 (35)		14 (74)			2 (100)	9 (75)	3 (60)	
<b>Hepatomegaly, no. (%)</b>	31 (34)	1	9 (47)		> 0.05	1 (50)	5 (42)	3 (60)	> 0.05
<b>Sokal risk score for patients. (%)</b>		10			> 0.05				> 0.05
Low (<0.8)	17(21)		1 (5)			0 (0)	1 (8)	0 (0)	
Intermediate (0.8-1.2)	24 (29)		4 (21)			0 (0)	2 (17)	2 (40)	
High (>1.2)	41 (50)		14 (74)			2 (100)	9 (75)	3 (60)	
<b>ELTS risk score. (%)</b>		10			<b>0.0003</b>				> 0.05
Low (<0.8)	54 (66)		5 (26)			0 (0)	5 (42)	0 (0)	
Intermediate (0.8-1.2)	20 (24)		5 (26)			0 (0)	2 (17)	3 (60)	
High (>1.2)	8 (10)		9 (48)			2 (100)	5 (42)	2 (40)	
<b>Median WBC count (range) x10<sup>9</sup>/L</b>	253 (5-810)		360 (70-637)		<b>0.0329</b>	411	371	225	> 0.05
<b>Median haemoglobin (range), g/L</b>	94 (40-170)		89 (68-138)		> 0.05	111	91	86	> 0.05
<b>Median Platelet count (range) x10<sup>9</sup>/L</b>	504 (51-4220)		428 (25-976)		<b>0.0107</b>	480	309	472	> 0.05
<b>BCR-ABL1 transcripts</b>		11		2	NA				NA
p210	81		17			1	12	4	
b2a2	32		4			0	2	2	
b3a2	43		4			0	3	1	
b2a2/b3a2	6		2			1	1	0	
unspecified	0		7			0	6	1	

**Table 1. Patient characteristics at the time of diagnosis in chronic phase.** AP, accelerated phase; BP, blastic phase; Ys, years; no, number; WBC, white blood cell; NA, not applicable.

Patients	Chronic phase			Accelerated phase or blastic phase								
	Age (y), sex,	First-line treatment	Stop TKI	Interval*** (m)	Type	Treatment of CML-AP/CML-BP	ABL1 KD mutations	CR before HSCT	MR before HSCT%	Donor Compatibility	Preparative regimen	Outcome
1	15, M	hydroxyurea, imatinib	Yes*	12.3	Lymphoid-BP	dasatinib for 2 weeks (stop for neutropenia), then corticosteroid+rituximab+daunorubicin/vincristine/cyclophosphamide/L-asparaginase +TIT + nilotinib	P-loop L248V	Complete	0	Unrelated cord blood, 6/6	TBI/ cyclophosphamide	Dead, sepsis from <i>Cryptococcus laurenti</i>
2	12, M	hydroxyurea, imatinib + TIT	No	24.9	Myeloid-BP	ELAM02: Induction, then consolidation 1, then half-consolidation 3 + nilotinib	F317L	Complete	3.7	Unrelated donor, BM 9/10	busulfan/ cyclophosphamide /ATG	Alive, still nilotinib post-allograft (5 years post-transplant)
3	14, M	hydroxyurea, cytarabine, interferon, imatinib	Yes**	31 (lymphoid-BP 40 (myeloid-BP))	Lymphoid-BP CNS+ then myeloid-BP	<b>Lymphoid-BP:</b> dexamethasone, HYPERCVAD (cyclophosphamide /vincristine /doxorubicin /dexamethasone) methotrexate + HD-cytarabine+ dasatinib. 12 TIT, Radiotherapy 18 Gy, 2 IT, <b>Myeloid-BP:</b> azacytidine, LD-cytarabine+nilotinib	No mutation	Complete	0.17	Unrelated cord blood (double), 5/6	cyclophosphamide/ fludarabine/TBI	Dead, relapse, dasatinib post allograft, then interferon
4	11, F	imatinib	No	9.2	Myeloid-BP	ELAM02: Induction, then consolidation 1 + dasatinib, then HD-cytarabine +gemtuzumab ozogamicin	ND	ND	ND	No transplantation	No transplantation	Dead, no remission
5	17, M	imatinib	No	21	Myeloid-BP	fludarabine-HD- cytarabine –liposomal daunorubicin-IT of cytarabine then, fludarabine - HD-cytarabine and dasatinib	No mutation	Complete	0.14	Unrelated donor BM 10/10	busulfan/ cyclophosphamide /ATG	Alive (4 years post-transplant)
6	14, F	hydroxyurea, imatinib	Yes*	11.7	CML-AP	Switch to dasatinib	No mutation	Minor	5.2	Genoid, BM	cyclophosphamide / busulfan	Alive (4 years post-transplant)
7	14, M	imatinib	Yes*	8.5	Lymphoid-BP	dasatinib	T315I, E255K	Failure	>1	Unrelated donor, PB 10/10	MD	Dead, relapse, nilotinib, then ponatinib post allograft
8	9, M	imatinib	No	4.1	Lymphoid-BP	dasatinib alone, then induction according to EsPhALL with dasatinib	ND	Complete	0.13	Unrelated donor BM 10/10	TBI/etoposide/ cyclophosphamide	Alive (4 years post-transplant), dasatinib (6 months) post allograft
9	9, M	imatinib	No	5.4	Lymphoid-BP	Dasatinib, then ALL11 protocol with dasatinib	T315I	Complete	0.016	Genoid, BM	TBI/etoposide/ cyclophosphamide	Alive, ponatinib post allograft. Relapse: ALL protocol+ ponatinib. Reject of second transplant. Waiting for a third transplant.
10	6, M	hydroxyurea, imatinib	No	31.9	Lymphoid-BP	Induction FRALLE B1+dasatinib/ EsPhALL phase 1b, bloc HR1 with dasatinib	No mutation	Complete	0.22	Unrelated donor, 10/10	TBI/etoposide/ATG	Alive (2 years post-transplant)
11	13, F	imatinib	No	5	CML-AP, lymphoid-BP	<b>CML-AP:</b> dasatinib <b>Lymphoid-BP:</b> ALL-BFM2009: 2xvincristine, 2xdaunorubicin, 1x cyclophosphamide, prednisone	E255K, PLOOP	ND	5.14	Genoid, BM	TBI/etoposide	Alive (2 years post-transplant), dasatinib post allograft
12	14, M	hydroxyurea, imatinib	No	19.1	Lymphoid-BP	ALL-BFM2009 + ALLIC-BFM2009 with dasatinib	ND	Complete	0	Genoid, BM	MD	Alive, dasatinib post allograft
13	12, M	hydroxyurea, imatinib, mitoxantrone	Yes**	58.4	Lymphoid-BP	ST JUDE TOTAL XV for ALL with dasatinib	ND	Partial	89	Genoid, BM	MD	Alive
14	11, F	hydroxyurea, imatinib,	Yes**	16.3	Lymphoid-BP	EsPhALL with imatinib	ND	ND	ND	No transplantation	No transplantation	Dead, progressive disease, aspergillosis
15	16, M	imatinib	No	17.8	Myeloid-BP	3 blocks of AML-BFM 2004 + dasatinib	ND	ND	ND	Haploidentical (mother), PB	MD	Dead, progressive disease and infection
16	15, M	hydroxyurea, imatinib,	Yes*	3	Lymphoid-BP	Induction FRALLE B2 + dasatinib, then consolidation 1b EsPhALL with dasatinib	No mutation	Complete	0.4	Genoid, BM	TBI/etoposide	Alive (2 years post-transplant), dasatinib post-allograft (1 year)
17	4, F	hydroxyurea, imatinib,	No	10.9	CML-AP then myeloid-BP	<b>CML-AP:</b> Increased dosage of imatinib (300 to 600 mg/day) + hydroxyurea <b>Myeloid-BP:</b> AML-BFM+imatinib	No mutation	ND	ND	No transplantation	No transplantation	Dead, progressive disease and opportunistic infection
18	15, M	hydroxyurea, imatinib,	No	18.1	CML-AP	Increased dosage of imatinib (300 to 500 mg/day)	ND	Partial	23	Genoid, BM	MD	Dead, post-transplant complication
19	11, M	imatinib	No	4.9	Lymphoid-BP	ALLIC-BFM2009 Ph <sup>+</sup> + imatinib	T315I	Complete	0	Genoid, PB	MD	Alive

**Table 2. Summary table of chronic phase and CML-AP or CML-BP.** TKI, tyrosine kinase inhibitor; AP, accelerated phase; BP, blastic phase; m, months; Ys, years; KD, kinase domain; CR, cytogenetic response; MR, molecular response; HSCT, hematopoietic stem cell transplantation; M, male; F, female; CNS, central nervous system; IT, intrathecal; TIT, triple intrathecal; HD, high-dose; LD, low dose; TBI, total body irradiation; ATG, anti-thymocyte globulin; BM, bone marrow, PB, peripheral blood; ND, not done; MD, missing data. \*: for intolerance, \*\*: for inadequate compliance. Interval\*\*\*: Interval from CP to transformation.