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Original Research

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

Deborah Meyran [a,*,1], Arnaud Petit [b,1], Joelle Guilhot [c], Meinolf Suttorp [d], Petr Sedlacek [e], Eveline De Bont [f], Chi Kong Li [g], Krzysztof Kalwak [h], Birgitte Lausen [i], Srdjana Culic [j], Barbara de Moerloose [k], Andrea Biondi [l], Frédéric Millot [c]

[a] *Department of Pediatric Hematology, Robert Debré Hospital, APHP, Université de Paris, Paris, France*
[b] *Department of Pediatric Hematology, Armand Trousseau Hospital, APHP, Sorbonne Université, Paris, France*
[c] *Inserm CIC 1402, University Hospital, Poitiers, France*
[d] *Medical Faculty, Pediatric Hemato-Oncology, Technical University, Dresden, Germany*
[e] *Department of Pediatric Hemato−Oncology, University Hospital Motol, Prague, Czech Republic*
[f] *Departments of Paediatric Oncology/Haematology, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands*
[g] *Department of Pediatrics, Prince of Wales Hospital, Hong Kong, China*
[h] *Department of Pediatric Hematology Oncology and Transplantation, Wroclaw Medical University, Poland*
[i] *Department of Pediatrics, Rigshospitalet, University Hospital, Copenhagen, Denmark*
[j] *Department of Pediatric Hematology Oncology Immunology and Medical Genetics, Clinical Hospital Split, Croatia*
[k] *Department of Pediatrics, Ghent University Hospital, Belgium*
[l] *Department of Pediatrics, University of Milano-Bicocca, San Gerardo Hospital, Fondazione MBBM, Monza, Italy*

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KEYWORDS
Chronic myeloid leukaemia;
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Abstract ***Background:*** Chronic myeloid leukaemia (CML) is a rare disease in children. The frequency and outcome of children evolving to accelerated phase (AP) or blastic phase (BP) under treatment with imatinib is unknown. The aim of the current study is to assess the incidence of progression from CML in chronic phase with imatinib frontline in a paediatric setting and describe the management and outcome of these patients.
Patients and methods: In the I-CML-Ped Study database (www.clinicaltrials.gov, #NCT01281735), 19 of 339 paediatric patients in chronic phase treated with imatinib in the

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* *Corresponding author*: Hopital Robert Debré, 48 Boulevard Sérurier, 75019 Paris, France. Fax: +33 1 40 03 47 40.
E-mail address: deborah.meyran@hotmail.fr (D. Meyran).

[1] Deborah Meyran and Arnaud Petit contributed equally to this study.

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inhibitors;
Haematopoietic stem cell transplantation

frontline evolved to CML-AP or CML-BP.

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

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

1. Introduction

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

2. Materials and methods

Patients were identified from the I-CML-Ped Study (www.clinicaltrials.gov #NCT01281735), a database of patients from 0 to 18 years with CML from 37 centres in 14 countries. The I-CML-Ped Study was set up to assess epidemiology, management and outcome of CML in children and adolescents and recorded the data retrospectively from 2000 until 2010, then prospectively from 2011. This study was approved by the institutional review board of the University Hospital of Poitiers, in accordance with the declaration of Helsinski.

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

The Sokal score was determined using the formula for patients aged under 45 years [12]. The diagnosis of CML was assessed by cytogenetic analysis or in case of failure by fluorescence *in situ* hybridisation (FISH) [13]. BCR-ABL1 transcript level in the blood was determined by using quantitative reverse transcriptase-polymerase chain reaction as reported previously and was expressed according to the international scale [14]. The

Table 1
Patient characteristics at the time of diagnosis in chronic phase.

Characteristics	*N* = 92 Control patients	*N* missing	*N* = 19 AP/BP patients	*N* missing	*p*	*N* = 2 *AP*	*N* = 12 Lymphoid-BP	*N* = 5 Myeloid-BP	*p*
Gender, no. (%)					>0.05				>0.05
Female	42 (46)		5 (26)			1	2 (17)	2 (40)	
Male	50 (54)		14 (74)			1	10 (83)	3 (60)	
Age at diagnosis, y									
Median (range)	11.4 (1.0–17.4)		13.2 (4.5–16.8)		>0.05	14.3 (13.8–14.8)	12.4 (6–15.4)	11.8 (4.5–16.8)	>0.05
< 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)	
Lansky performance (%)		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)	
Splenomegaly, no. (%)	65 (71)	1	18 (95)		**0.0388**	2 (100)	11 (92)	5 (100)	>0.05
Spleen size, cm		7							
Median (range)	6 (0–24)		12 (0–25)		**0.0003**				>0.05
≤ 10	55 (65)		5 (26)			0 (0)	3 (25)	2 (40)	
>10	30 (35)		14 (74)			2 (100)	9 (75)	3 (60)	
Hepatomegaly, no. (%)	31 (34)	1	9 (47)		>0.05	1 (50)	5 (42)	3 (60)	>0.05
Sokal risk score for patients. (%)		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)	
ELTS risk score. (%)		10			**0.0003**				>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)	
Median WBC count (range) x10^9/L	253 (5–810)		360 (70–637)		**0.0329**	411	371	225	>0.05
Median haemoglobin (range), g/L	94 (40–170)		89 (68–138)		>0.05	111	91	86	>0.05
Median platelet count (range) x10^9/L	504 (51–4220)		428 (25–976)		**0.0107**	480	309	472	>0.05
BCR-ABL1 transcripts		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	

AP, accelerated phase; BP, blastic phase; Y, years; no, number; WBC, white blood cell; NA, not applicable.

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

3. Results

In the I-CML-Ped Study database, the cumulative incidence of progression at 1 and 3 years was 3%

Table 2
Summary table of chronic phase and CML-AP or CML-BP.

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 CNS+	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 *Cryptococcus laurenti*
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	**Lymphoid-BP:** dexamethasone, HYPERCVAD (cyclophoshamide/ vincristine/doxorubicin /dexamethasone) methotrexate + HD-cytarabine + dasatinib. 12 TIT, Radiotherapy 18 Gy, 2 IT, **Myeloid-BP:** 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)

(*continued on next page*)

Table 2 (*continued*)

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
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	**CML-AP:** dasatinib **Lymphoid-BP:** 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 Ib 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	**CML-AP:** Increased dosage of imatinib (300–600 mg/day) + hydroxyurea **Myeloid-BP:** 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 (300–500 mg/day)	ND	Partial 23	Genoid, BM	MD	Dead, post-transplant complication
19	11, M	Imatinib	No	4.9	Lymphoid-BP	ALLIC-BFM2009 Ph^++ imatinib	T315I	Complete 0	Genoid, PB	MD	Alive

TKI, tyrosine kinase inhibitor; AP, accelerated phase; BP, blastic phase; m, months; Ys, years; KD, kinase domain; CR, cytogenetic response; MR, molecular response; HSCT, haematopoietic 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.

(confidence interval [CI] 95%: 1–5%) and 7% (CI 95%: 4–11%), respectively. Baseline characteristics of the AP/BP cohort compared with the control cohort of 92 patients who did not progress with imatinib frontline are presented in Table 1. Notably, patients in the AP/BP group had significantly more aggressive clinical and biological features with larger splenomegaly, higher white blood cells count and lower platelet count. Only EUTOS long-term survival (ELTS) score at CML-CP diagnosis was significantly discriminant to predict progression with nine (48%) of the 19 AP/BP patients who were high-risk compared with 8 (10%) in the control cohort. Eight patients had a BCR-ABL1 fusion identified by FISH only. The other AP/BP patients had a karyotype showing the classical translocation t(9; 22) (q34; q11), except for one who had a variant translocation t(1; 9;22) (q12; q34; q11).

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

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

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

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

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

4. Discussion

This is the first study to assess the incidence and the outcome of CML-AP and CML-BP in children treated with imatinib. Imatinib still remains the main frontline therapy in children because there is more experience with its efficacy and its toxicity than with the other TKIs [17–19]. Only few studies have evaluated the rate of progression to CML-AP or CML-BP in a population-based setting. A recent report in adults showed a rate of cumulative incidence of progression of 4.3% at 2 years [20]. We observed a quite similar proportion in children with cumulative incidence of progression at 1 and 3 years at 3% (CI 95%: 1–5%) and 7% (CI 95%: 4–11%), respectively.

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

Early cytogenetic and molecular responses are reported to be the best predictors of good outcome [11]. These two parameters were clearly not satisfactory in our cohort. Non-adherence is one of the most common reasons for suboptimal response and treatment failure in patients with CML treated with TKI [25]. Indeed, adolescence is a well-known challenge to compliance in paediatric patients with chronic diseases [26,27]. In our study, the proportion of discontinuation of this paediatric AP/BP cohort is approximately the same as that reported in previous studies for adults with CML treated by oral TKI (15–30%) [28]. However, the proportion of patients who discontinued TKI for inadequate compliance and experienced CML progression remains difficult to assess because it relies on patients' declaration. At the onset of CML-AP or CML-BP, 50% of the patients who were monitored acquired KD mutations including T315I mutation. KD mutations T315I and G250E are associated with imatinib failure, which can be overcome by switching treatment to a third or fourth generation TKI [29]. However, in paediatrics, the therapeutic options are limited because ponatinib is still not approved in children. Only few cases of young patients treated by ponatinib have been reported in the literature, with no safe dose having been determined in children [30,31]. For suboptimal responses or failure, patients have been either treated with an increased dose of imatinib or switched to a 2G-TKI. Recently, a therapeutic algorithm based on paediatric haematologists' experience has been proposed to treat children in CML-CP once failure or suboptimal response has been detected [32]. Probably with this new algorithm, some of

our patients would have been switched earlier to a 2G-KI. However, it should be taken into account that the I-CML study is an international database and access to certain expensive molecules like the 2G-TKI could be more difficult in some of the countries participating in this study.

In adult cohorts, a predominance of myeloid immunophenotype of CML-BP (60–80%) was observed [7,33]. In contrast to adult patients with CML, we observed predominantly lymphoid-BP (70%) in children with upfront imatinib treatment. In another report from the I-CML-Study, we have also observed a predominance of lymphoid phenotype of *de novo* advanced phases of childhood CML [34]. The median time to the onset of the myeloid-BP was longer than that of lymphoid-BP, 17.7 months (range: 9.2–24.6) and 9.8 months (range: 3–56.6) respectively. Similarly, in an adult cohort, the median time from first diagnosis to myeloid-BP was also longer than that of lymphoid-BP, 39 months (range: 0–307) and 24 months (range:0–161), respectively [35]. The median follow-up of 38 months is sufficiently long to limit a follow-up dependent bias.

While children with *de novo* advanced phases have a favourable outcome with 5-year OS rates at 94% and 74% for patients diagnosed in CML-AP and CML-BP respectively [34], the survival is poorer, less than 50%, when the transformation occurs from CML-CP to CML-AP or CML-BP while on TKI therapy. A similar outcome is observed in adults treated after progression from CML-CP with a median survival rate between 6 and 37 months and less than 12 months for patients with CML-AP and CML-BP, respectively [7,33]. Like adult cohorts [33], our data suggest that allo-HSCT may represent the best chance of long-term remission or cure in CML-BP. The current National Comprehensive

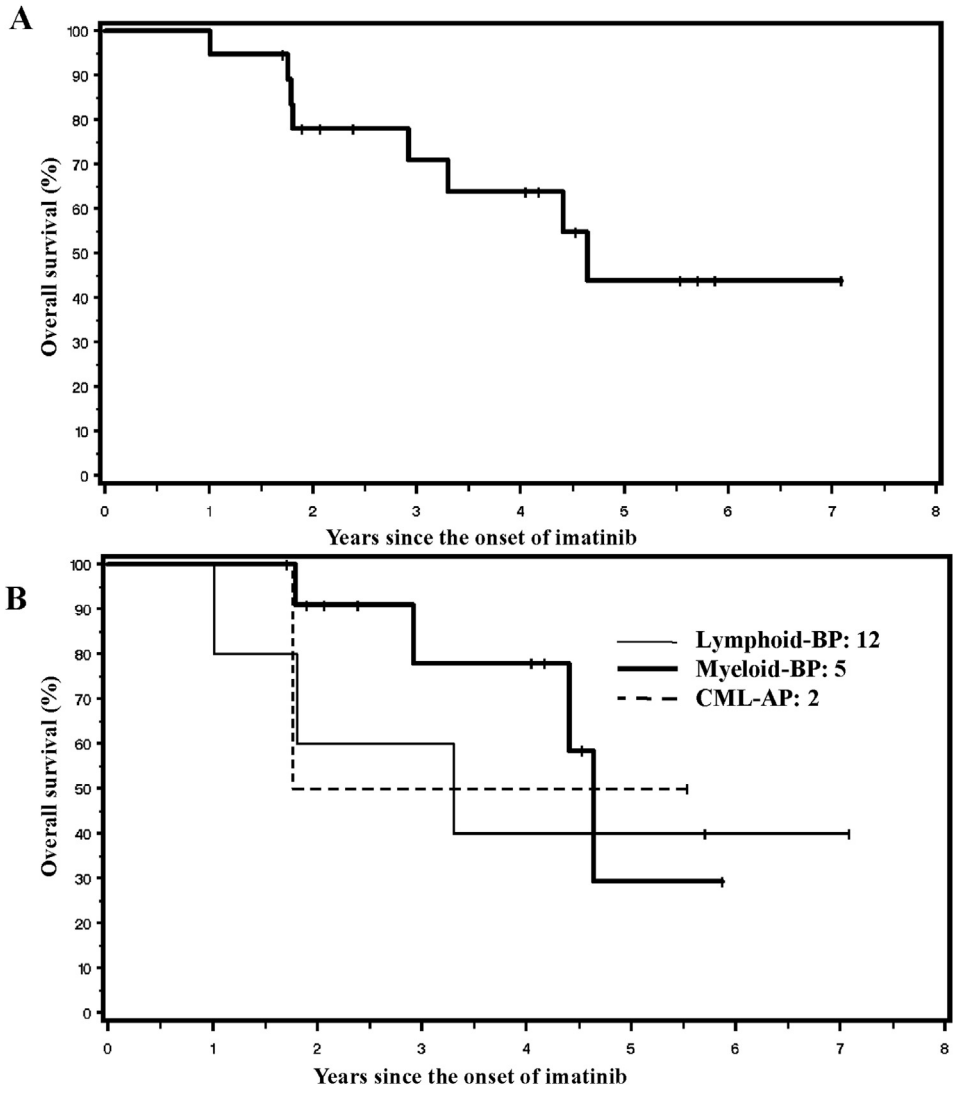

Fig. 1. Outcome of CML-AP/CML-BP. Overall survival since the onset of imatinib was analysed using Kaplan–Meier methodology (A) for the overall population and (B) by subtype (CML-AP, lymphoid-BP and myeloid-BP). AP, accelerated phase; BP, blastic phase; CML, chronic myeloid leukaemia.

Cancer Network guidelines suggest that patients who progress to CML-BP should receive an allo-HSCT within 3–6 months from diagnosis [8,36]. However, experience in children with CML in advanced stages is very limited because of the small number of cases.

5. Conclusion

In a paediatric setting, the cumulative incidence of progression of CML-CP with upfront imatinib treatment at 1 and 3 years is 3% and 7%, respectively, with a predominance of lymphoid progression. While children with *de novo* advanced phases have a favourable outcome, the 5-year OS of progression to CML-AP or CML-BP in paediatric patients is poor, less than 50%, with no significant difference in outcome by immunophenotypic subtype. Bearing in mind the small number of paediatric patients with CML, allo-HSCT remains the best therapeutic option for the young patients in CML-AP or CML-BP who progressed under treatment with imatinib.

Authorship

D.M. and A.P. equally wrote the manuscript. F.M. coordinated the study. J.G. performed the 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 patients. All authors reviewed the final version of the manuscript.

Conflict of interest statement

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.06.024.

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