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1 **Favorable outcome of *de novo* advanced phases of childhood chronic myeloid leukemia.**

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35

1 **Abstract**

2 **Background.** Chronic myeloid leukemia is very rare in children. The aim of the study is to
3 report the experience within the I-CML-Ped study in children and adolescents presenting at
4 diagnosis with advanced phase disease and to describe their characteristics and outcomes.

5 **Methods.** Out of 479 children and adolescents enrolled in the International Registry for
6 Childhood Chronic Myeloid Leukemia (CML) (I-CML-Ped Study; www.clinicaltrials.gov
7 NCT01281735), 36 children (7.5%) presented at initial diagnosis with CML in advanced
8 phase according to the European LeukemiaNet criteria.

9 **Results.** Nineteen (4%) patients were diagnosed in accelerated (CML-AP) and among the 17
10 patients (3.5%) diagnosed in blastic phase (CML-BP), 70% presented with lymphoid
11 immunophenotype. Initial treatment of CML-AP/CML-BP consisted of tyrosine kinase
12 inhibitors (TKI) with or without chemotherapy leading to complete hematologic response in
13 33/36 (92%) patients. Seventeen patients proceeded to hematopoietic stem cell
14 transplantation. At last follow-up 18/19 patients with *de novo* CML-AP are alive in at least
15 major molecular response (MMR) (n=16), in progression (n=1) or in molecular relapse (n=1)
16 and 13/17 patients with *de novo* CML-BP are alive in at least MMR. Five year overall
17 survival rates are 94% (95% confidence interval [CI]: 66%-99%) and 74% (95% CI: 44%-
18 89%) for patients diagnosed in CML-AP or CML-BP, respectively.

19 **Conclusion.** Children with advanced phase at diagnosis of CML seem to have a better
20 survival rate than that reported for advanced phases evolving under TKI treatment

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22

1 **1. Introduction**

2 Chronic myeloid leukemia (CML) is characterized by the translocation t(9;22) (q34;q11.2)
3 named the Philadelphia-chromosome (Ph) leading to the production of the oncogenic BCR-
4 ABL1 transcript.^{1,2} In the absence of efficient treatment CML progresses from chronic phase
5 (CML-CP) to accelerated (CML-AP) and blastic phases (CML-BP).² CML usually presents as
6 CML-CP in adults whilst advanced phases at diagnosis represent 2.3 to 5.7% of the cases.
7 Only scant data are available regarding the outcome compared to advanced phases evolving
8 under treatment.^{3,4}

9 CML is very rare in children with an annual incidence of 1 and 2.2 cases per million in
10 children younger than 15 years and in adolescents between 15 and 19 years, respectively.⁵
11 Based on an international collaboration for collection of data, the International Registry of
12 CML in Children and Adolescents (I-CML-Ped Study; www.clinicaltrials.gov
13 NCT01281735) has provides unique and valuable data to better describe this disease in
14 pediatric cohorts.^{6,7} The increasing size of the registry now allows analysis of rare sub-
15 cohorts of pediatric CML. The aim of the present study is to report the experience within the
16 I-CML-Ped study in children and adolescents presenting at diagnosis with advanced phase
17 disease and to describe their characteristics and outcomes.

18 **2. Material and Methods**

19 The I-CML-Ped Study was set up to assess epidemiology, management and outcome of CML
20 in children and adolescents. National pediatric study groups were invited to include newly
21 diagnosed patients less than 18 years with Ph-positive (Ph+) CML whatever the phase of the
22 disease diagnosed later than January 2000. Data were collected on standardized forms. Written
23 informed consent was obtained from the children and/or their guardians. The study is registered
24 at www.clinicaltrials.gov as NCT01281735 and was open to recruitment in January 2011. From
25 January 2011 to April 2017, 479 children and adolescents with CML from 14 countries have
26 been registered. Among these 479 patients, 262 (55%) diagnosed in the time frame from 2000
27 until the end of 2010 were studied retrospectively while 217 (45%) diagnosed in the time frame
28 from 2011 until 2017 were studied prospectively. The phase of the disease was determined
29 according to the criteria of the European leukemiaNet (ELN) recommendations.⁸ The myeloid
30 or lymphoid immunophenotype was determined by flow cytometry for patients in blastic
31 phases.⁹

1 Chromosome G or Q banding analysis was performed on bone marrow metaphases as
2 previously reported.^{10,11} In case of failure of the cytogenetic analysis, fluorescence in situ
3 hybridization (FISH) was used for the diagnosis of CML.¹⁰ Determination of BCR-ABL1
4 transcript level in the blood was performed using quantitative RT-PCR as reported previously
5 and was expressed according to the International Scale (IS).¹² Conversion of local laboratory
6 BCR-ABL1 values to the International Scale was performed for assessment performed before
7 2006.¹²

8 BCR-ABL1 kinase domain mutation analysis was performed as previously reported.¹³
9 Biological assessments were performed at local laboratories. Return to CML-CP under
10 treatment was defined as <15% blasts and < 30% blasts + promyelocytes in blood or bone
11 marrow and <20% basophils according to the ELN definition (8). A complete hematologic
12 response (CHR) required the normalization of platelet and white cell differential counts, less
13 than 5% blasts in bone marrow and absence of extramedullary involvement. Cytogenetic
14 responses and molecular responses were defined as reported previously.^{8,14} Major molecular
15 response (MMR), MR4 and MR4.5 were defined as a BCR-ABL/ABL ratio of <0.1%,
16 <0.01% and <0.0032% according to the international scale (IS), respectively.¹² For patients
17 achieving CML-CP and CHR after diagnosis of CML in advanced phase, relapse was defined
18 as reappearance of blasts in peripheral blood and 5% or more of blasts in bone marrow or
19 extramedullary disease. Overall survival was assessed from the diagnosis of advanced phase
20 until the date of death or last follow-up. Survival analysis was based on the Kaplan-Meier
21 method.¹⁵

22

23 3. Results

24

25 Among 479 children and adolescents registered (median age: 12.2 years, range: 0.8- 18), 36
26 patients (7.5 %) were diagnosed in *de novo* advanced phases of CML. According to the date
27 of diagnosis (before or after the opening of the registry in 2011) 20/36 children were studied
28 retrospectively and 16/36 prospectively. The total number of patients with *de novo* CML-AP
29 at onset of the disease was 19 (4%) including 11 patients initially notified as CML-CP by the
30 local investigator who were reclassified according to the ELN criteria at the time of the
31 present analysis and were upstaged from CML-CP to CML-AP (% of blasts equal or more
32 than 15%: 4 patients; % of blasts + promyelocytes more than 30% with blasts less than 30%:
33 7 patients). Seventeen patients (3.5%) presented with CML-BP: lymphoid immunophenotype
34 (13 patients), myeloid immunophenotype (3 patients) or unknown immunophenotype (1

1 patient). Six of them (35%) had extramedullary disease: leukaemia cutis (1 patient), lymph
2 nodes with blastic infiltration assessed by biopsy (1 patient), myeloid sarcoma (2 patients),
3 central nervous system disease (2 patients). The presence of extramedullary disease was the
4 sole criteria of blastic phase in 2 of these patients (patients #5 and #13, Supplementary data).
5 The main clinical and biological characteristics of the children in advanced phases at
6 diagnosis of CML are reported in Table 1. Only 27 out of 36 patients had an analysable
7 karyotype at diagnosis: additional chromosomal aberrations (ACA) beside the Ph+
8 chromosome were observed in 3 (27%) of the 11 assessable patients in CML-AP. Among the
9 16 assessable patients in CML-BP, ACA and/or variant translocations were observed in 6
10 patients.

11
12 Data on treatment and outcome are reported in detail in Supplementary Table. Considering
13 the 19 patients in CML-AP, only one patient of the 8 patients non-upstaged from CML-CP to
14 CML-AP received a second generation TKI as first line therapy according to the
15 recommendation in children.¹⁴ Among these 19 patients, 17 achieved a CHR after first line
16 treatment including 15 patients who received imatinib alone (nine of these patients received at
17 least a second line of treatment because of loss of CHR (n=1), progression to lymphoid blastic
18 phase (n=2) or myeloid blastic phase (n=1), loss of molecular response (n=2), no achievement
19 of complete cytogenetic response (CCyR) (n=1), or because of the treating physicians' choice
20 (n=2). All but one patient achieved a CHR within a median time of 3 months (range 1-8). Six
21 patients proceeded to hematopoietic stem cell transplantation (HSCT) from an unrelated
22 donor (n=1) or a sibling donor (n=5) with a median time of 8 months (range: 4-21) after initial
23 diagnosis of CML-AP. Five of them were transplanted in CHR whilst the remaining patient
24 was transplanted in myeloid blastic phase 3 months after transformation. The reason for
25 HSCT was the occurrence of blastic phase in 2 patients, non-achievement of CCR (1 patient)
26 and choice of the treating physician for the 3 remaining patients. With a median follow up of
27 36 months (range: 5 to 117) 5/6 transplanted children are in deep molecular response and one
28 patient, who was transplanted in progression to lymphoid blastic phase, is in uncontrolled
29 disease at last follow-up.

30 Thirteen patients diagnosed with *de novo* CML-AP were not transplanted including 8 of the
31 11 patients who were initially notified as CML-CP and reclassified as CML-AP. Three events
32 (loss of CHR, loss of molecular response and progression to lymphoblastic phase leading to
33 the death of the patient) occurred in this cohort. Eleven patients are at least in MMR with a
34 median follow-up of 53 months (range, 14-114). We have limited data on the mutational

1 status of the BCR-ABL1 kinase domain before treatment and during therapy. No mutation
2 was found when mutation analyses was performed in one patient who progressed to blastic
3 phase (patient 3), in 2 slow responder patients (patients #15 and #19) and in one patient with a
4 fluctuation of BCR-ABL1 transcript level without loss of MMR (patient #11). With a median
5 follow-up of 4.3 years (range: 8 months to 13.8 years), the probability of 5-year overall
6 survival (OS) of the patients in CML-AP at diagnosis was 94% (CI 95%: 65-99%) (Figure 1).

7 For the 17 patients with *de novo* CML-BP, first-line treatment consisted of imatinib
8 (n=7) whilst 10 patients were treated according to the recommendations in children with a
9 combination of chemotherapy with either imatinib or second generation TKI.¹⁴ Sixteen out of
10 17 returned to CML-CP and achieved a CHR with a median time of 2 months (range, 1-4)
11 while one patient did not respond (presence of F317L mutation). Eleven patients in CML-BP
12 at diagnosis proceeded to HSCT with a median time of 7 months (range, 4-10 months) after
13 diagnosis as recommended in children with CML-BP.¹⁴ Donors were HLA-fully matched,
14 unrelated in 8 patients and sibling donors in 3 patients. Five of them were transplanted after
15 first line treatment (TKI in combination with chemotherapy) and 6 patients received more
16 than one line of therapy prior to transplantation because of non response (1 patient), toxicity
17 (1 patient), no achievement of CCyR (2 patients) and relapse to blastic phase (2 patients). All
18 of these patients were transplanted in chronic phase, CHR, CCyR or MMR. Relapse after
19 HSCT occurred in 5/11 patients with a median time of 5 months (range, 3-17 months). With a
20 median follow-up of 29 months (range, 5-108) after HSCT, 8 patients are alive in at least
21 MMR and 3 patients died (progressive disease, n=2; uncontrolled graft-versus-host disease,
22 n=1).

23 Six patients in CML-BP did not undergo HSCT. These patients achieved a CHR with
24 1 or 2 lines of treatment after a median time of 2 months (range, 2-3). One of them required a
25 second line of treatment in order to achieve a MMR. Among these 6 patients, one patient died
26 of relapse 7 months after diagnosis and the remaining 5 patients are alive in MMR or better
27 response with a median follow up of 28 months (range, 16-78 months). Mutation analyses of
28 the BCR-ABL 1 domain kinase was performed in 2 patients in CM-BP phase at diagnosis
29 (T315I: patient #21; no mutation found: patient #23) (Supplementary data). In 5 patients with
30 no response or loss of response or switched for toxicity of the treatment, domain kinase
31 mutation analyses were performed: mutations were found in all of them (T315I: patient #20,
32 F317L: patients #28 and #22, G250E: patient #24, and E279K: patient #27) (Supplementary
33 data). With a median follow-up of 52 months (range, 7-113 months), the probability of 5-year
34 OS of all patients in CML-BP at diagnosis was 74% (CI 95%: 44-89%) (Figure 1). For the

1 subgroup of the six non-transplanted patients the median follow-up is 25 months (range 7 –
2 78 months) with on patient dying from disease at month 7 (pt # 31, Supplementary data).

4 4. Discussion

5
6 This is the largest database analysis describing the characteristics and outcome of childhood
7 CML presenting in advanced phase of the disease. According to the EUTOS registry, 94.3%
8 of the adults presented in chronic phase at diagnosis of CML whilst the remaining 5.7 %
9 presented in accelerated (3.5%) or blastic (2.2%) phase.⁴ A quite similar proportion is
10 observed in children and adolescent according to the present study (4% and 3.5%,
11 respectively).

12 A predominance of myeloid immunophenotype is observed in adults evolving from chronic to
13 blastic phase under treatment.^{16,17} By contrast to adults with CML we previously observed a
14 majority of lymphoid blast crisis in 21 children in CML-CP at initial diagnosis who
15 transformed under TKI treatment from this CML-CP status.¹⁸ Unfortunately data regarding
16 the immunophenotype is lacking in the rare series of adults who presented as *de novo* CML-
17 BP.^{16,19,20} In the present pediatric cohort the lymphoid immunophenotype was predominantly
18 observed (76%) in *de novo* blastic phase. We cannot exclude the possibility that some patients
19 presented with a Ph+ acute lymphoblastic leukemia rather than in *de novo* CML-BP with a
20 lymphoid immunophenotype. In patients with Ph+ lymphoid blasts, the detection of the BCR-
21 ABL1 rearrangement in granulocytes by the interphase-FISH technique was recently reported
22 as a helpful decisive tool to prove the myeloid origin of the malignant clone and could be
23 used prospectively.²¹ The proportion of children (35%) in the present cohort with
24 extramedullary disease seems to be higher than in the adult population.^{16,22} This may in part
25 be explained by the higher frequency of lymphoid blast crisis in the present cohort with a
26 propensity of central nervous system disease.

27 Presentation with advanced stage of CML at diagnosis must be separated from CML-AP and
28 CML-BP evolving under treatment. Dismal outcome is reported in adults treated after
29 progression from CML-CP with a median survival in the range of 6 to 37 months and less
30 than 12 months for patients with CML-AP and CML-BP, respectively.^{17,19,22,23} HSCT can
31 significantly improve the survival of some of these patients in advanced phases compared to
32 TKI treatment alone.^{24,25} Patients exhibiting a myeloid immunophenotype of CML-BP appear
33 to have inferior survival compared with patients exhibiting the lymphoid immunophenotype
34 but this remains controversial in the adult population.^{16,22,26,27} We previously reported an

1 overall survival rate of 41% at 60 months in 21 children receiving imatinib for CP-CML who
2 progressed to predominant lymphoid blastic phase.¹⁸

3 Most of adult studies reported on advanced phases as events occurring in pretreated patients
4 diagnosed in chronic phase with only a limited proportion (15 to 20%) of *de novo* CML-AP or
5 CML-BP.^{16,19,22,23} Interestingly, patients with *de novo* CML-AP or CML-BP seem to have
6 better overall survival compared with patients who transformed from CML-CP or CML-AP.
7^{19,20,28} In one of these studies, Geelen et al reported on a cohort of 15 adult patients who
8 presented in advanced phase (8 CML-CP and 7 CML-BP) with a 5-year overall survival rates
9 of 38% and 57%, respectively.²⁰ Ohanian *et al* reported an overall survival of 87 % and 95%
10 at 36 months in 51 adult patients with *de novo* CML-AP treated with imatinib or second
11 generation TKI, respectively.²⁸ In another cohort of 71 adults with *de novo* CML-BP, the 5-
12 year overall survival rate was 34%.¹⁹ The good survival rates of pediatric patients with *de*
13 *nov*o CML-AP are consistent with these findings.

14 This analysis raised the question of compliance to our published recommendations: second
15 generation tyrosine TKI as first line therapy followed by HSCT in case of an available sibling
16 donor for children with AP-CML, second generation TKI in combination with chemotherapy
17 followed by HSCT with a sibling or an alternative donor for children with BP-CML).¹⁴
18 However, it must be kept in mind that this publication came out in the year 2014 and thus
19 could not be followed in the majority of patients analyzed in our cohort. Most of our patients
20 in advanced phase were treated upfront with TKIs alone (17/19 patients with CML-AP and
21 7/17 with CML-BP) with objective responses. Interestingly, a high rate of patients (17/19 of
22 the patients with CML-AP and 16/17 of the patients with CML-BP) achieved a CHR with the
23 first line of treatment including TKIs. Moreover, a high proportion of non-transplanted
24 patients (11/13 of the patients with CML-AP and 5/6 of the patients in CML-BP) are alive
25 with a notable follow-up including one patient treated for a myeloblastic phase at diagnosis
26 being alive in MMR with a follow-up of 28 months without HSCT. Among the 4 alive
27 patients of a recently published cohort of 10 adults with myeloid blastic phase at presentation
28 of CML, one patient is alive without transplantation with a follow up of 43.6 months (29)
29 Early HSCT could be avoided in some children with advanced phase at diagnosis and
30 restricted to second or third line of treatment. However, because of the limited number of
31 pediatric cases, further data collection is needed to determine the optimal treatment of
32 advanced phases at diagnosis of CML in children and adolescents.

33
34

1 **5. Conclusion**

2 A quite similar frequency of advanced phase at diagnosis of CML is observed in children and
3 in adults. By contrast to the adult population, a predominance of a lymphoid
4 immunophenotype is observed in pediatric patients with *de novo* CML-BP. The outcome of
5 children and adolescents in advanced phase at diagnosis seems to be favorable even without
6 HSCT in some cases. Upfront treatment recommendations for newly diagnosed CML-AP and
7 CML-BP in pediatric patients are based on TKI but the optimal treatment remains to be
8 determined. Keeping in mind the small number of pediatric cases analyzed in this study,
9 treatment approaches for advanced phases of CML diagnosed *de novo* in children might be
10 different from progress of the disease under upfront TKI treatment.

11
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24
25 Appendix A. Supplementary data

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Table 1: Clinical and biological characteristics of the children with accelerated phases and blastic phases at diagnosis of chronic myeloid leukaemia

Characteristics	Accelerated Phase (n=19)	Blastic Phase (n=17)
Age : median, years (range)	12.7 (3-18)	11.1 (5-17)
Sex : Female, (%)	7 (37)	6 (35)
Male, (%)	12 (63)	11 (65)
Splenomegaly (%)	18 (95%)	13 (76%)
Median (cm) below the costal margin (n=16; n=11 respectively)	9 (1-20)	9,5 (4-20)
Leukocytes (10 ⁹ /L)	269 (5-657)	295 (37-653)
Hemoglobin (g/dL)	8.7 (5,1-11,5)	7.4 (2,2-12,3)
Blasts in blood (%)	6 (0-23,5)	32 (0-84)
Blasts in bone marrow (%)	7 (0-28)	48 (0-96)
Immunophenotype	-	13 (76%)
lymphoid		3(18%)
myeloid		1(6%)
unknown		
Cytogenetics		
additional cytogenetic abnormalities and/or variant translocation (%)	3/11* (27%)	6/16* (37.5%)
Transcript/protein		
b2a2	3 (16%)	6 (36%)
b3a2	4 (21%)	5 (28%)
Others	0	3 (18%)
p210	8 (42%)	3 (18%)
unknonw	4 (21%)	0
Extramedullary disease (%)		6 (35%) leukaemia cutis (n=1) lymph nodes (n=1) myeloid sarcoma (n=2) central nervous system disease (n=2)

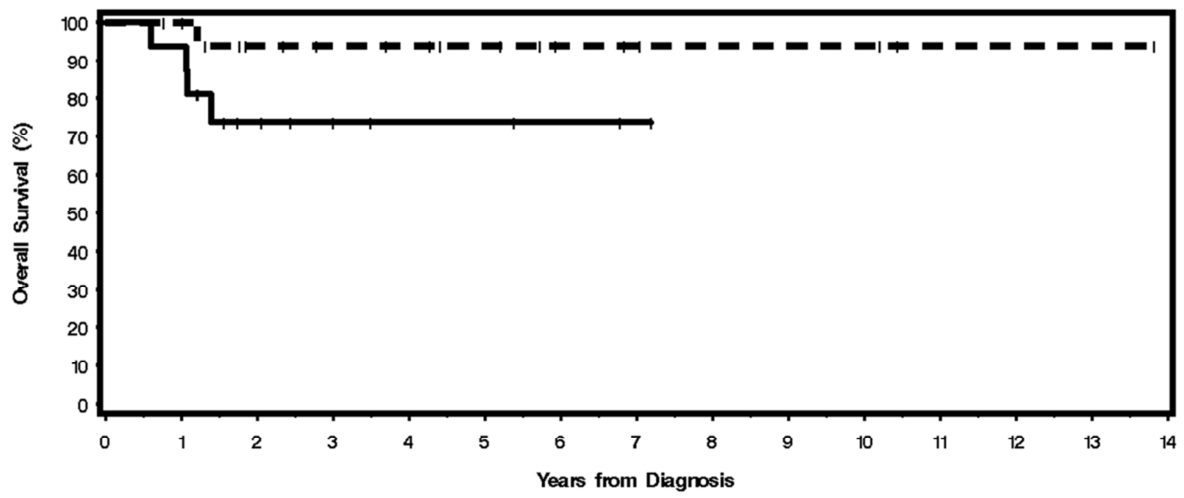


Figure 1 Overall survival curve of the children and adolescents in accelerated phase (dotted line) and in blastic phase (solid line) at initial diagnosis of chronic myeloid leukemia