

Children with chronic-phase chronic myeloid leukemia: characteristics and outcomes from the International Registry of Childhood CML

Frédéric Millot,¹ Joe de Keizer,¹ Markus Metzler,² Krzysztof Kalwak,³ Adalet Meral Günes,⁴ Barbara De Moerloose,⁵ Maaïke Luesink,⁶ Antonio Molines Honrubia,⁷ Petr Sedlacek,⁸ Julia Yajima,⁹ Mirella Ampatzidou,¹⁰ Michael Dworzak,¹¹ Birgitte Lausen,¹² Marina Borisevich,¹³ Chi Kong Li,¹⁴ Alexandra Kolenova,¹⁵ Gordana Jakovljevic,¹⁶ Roula Farah,¹⁷ Lisa Durocher,¹ André Baruchel¹⁸ and Meinolf Suttrop¹⁹

¹INSERM CIC 1402, University Hospital, Poitiers, France; ²Pediatric Oncology and Hematology, Department of Pediatrics and Adolescent Medicine, University Hospital Erlangen, Erlangen, Germany; ³Department of Pediatric Hematology Oncology and BMT, Wrocław Medical University, Wrocław, Poland; ⁴Pediatric Hematology and Oncology Hospital Görükle, Nilüfer/Bursa, Turkey; ⁵Department of Pediatric Hematology-Oncology, Ghent University Hospital, Ghent, Belgium; ⁶Dutch Childhood Oncology Group, Princess Maxima Center for Pediatric Oncology, Utrecht, the Netherlands; ⁷CHU Insular Materno-infantil, Las Palmas de Gran Canaria, Spain; ⁸Department of Pediatric Hematology-Oncology, University Hospital Motol, Charles University, Prague, Czech Republic; ⁹Centro Infantil Boldrini, Sao Paulo, Brazil; ¹⁰Department of Pediatric Hematology Oncology, Aghia Sophia Children's Hospital, Athens, Greece; ¹¹Children's Cancer Research Institute and St. Anna Children's Hospital, Vienna, Austria; ¹²Department of Pediatrics, Rigshospitalet, University Hospital, Copenhagen, Denmark; ¹³Belarusian Research Center for Pediatric Oncology, Hematology and Immunology, Minsk, Belarus; ¹⁴Department of Pediatrics, Prince of Wales Hospital, Hong Kong, China; ¹⁵Department of Pediatric Oncology of University Children's Hospital, Bratislava, Slovakia; ¹⁶Department of Pediatric Hematology Oncology, Children's Hospital, Zagreb, Croatia; ¹⁷Department of Pediatrics, LAU Medical Center Rizk Hospital Beirut, Beirut Lebanon; ¹⁸Department of Pediatric Hematology, Robert Debré Hospital, Paris, France and ¹⁹Pediatric Hematology and Oncology, Medical Faculty, TU Dresden, Dresden, Germany

Correspondence: F. Millot
f.millot@chu-poitiers.fr

Received: May 22, 2025.
Accepted: October 13, 2025.
Early view: October 23, 2025.

<https://doi.org/10.3324/haematol.2025.288283>

©2026 Ferrata Storti Foundation

Published under a CC BY-NC license



Abstract

Five hundred and thirty-five patients (median age 12.2 years; range, 8 months to 18 years; N=303 males, N=232 females) diagnosed with chronic myeloid leukemia (CML) in chronic phase were registered in the International Registry of Childhood CML (*clinicaltrials.gov*. Identifier: NCT01281735). Clinical signs of leukostasis or bleeding were observed in 16.5% and 20% of the patients, respectively. The spleen was palpable in 76% of patients with a median of 9 cm (range, 1-32) below the costal margin. The median leukocyte count was $222 \times 10^9/L$ (interquartile range, 95-353). First-line therapy consisted of imatinib in 482 children. Among them, 40% remained on imatinib with a median follow-up 3.8 years (95% confidence interval [CI]: 3.2-4.3 years); 3.1% died and 3.9% progressed to advanced-phase disease. The overall survival rate at 36 months was 97.4% (95% CI: 95-99%). Progression-free survival rate at 3-years was 97.1% (95% CI: 94.9-99.2%), 91.7% (95% CI: 84.5-98.3%) and 72.0% (95% CI: 59-87.9%) in the Eutos Long-Term Survival (ELTS) low-, intermediate-, and high-risk group, respectively (P log rank <0.001). Pediatric CML is characterized by bulky disease (large splenomegaly, high leukocyte counts) and the ELTS score can identify children with the poorest outcome.

Introduction

Chronic myeloid leukemia (CML) is an acquired clonal myeloproliferative malignancy characterized by the chro-

mosomal translocation $t(9;22)(q34.1;q11.2)$ resulting from the synthesis of the BCR::ABL1 oncoprotein. Pediatric CML (pCML) is a very rare disease. Clinical and biological characteristics at diagnosis of the disease have been reported

in small cohorts of children and adolescents and very few studies have reported on management and outcome.¹⁻³ The International Registry of Childhood CML (I-CML-Ped Study; *clinicaltrials.gov*. Identifier: NCT01281735) was designed with the aim to better describe the characteristics and outcome of children with CML in the tyrosine kinase inhibitors (TKI) era. In the present work we retrospectively analyzed children and adolescents with CML in chronic phase (CML-CP) registered in this International Registry which to the best of our knowledge represents the largest pCML cohort.

Methods

We selected patients registered in The International Registry of Childhood Chronic Myeloid Leukemia (I-CML-Ped Study; *clinicaltrials.gov*. Identifier: NCT01281735). Since January 2011, this registry has been recruiting prospectively and retrospectively children and adolescents less than 18 years of age at diagnosis of CML diagnosed between January 2000 and September 2020 whatever the phase of the disease. The institutional ethics committee of the University Hospital of Poitiers (Poitiers, France) reviewed and approved the I-CML-Ped Study which is being conducted in accordance with the Declaration of Helsinki. Written informed consent was provided by the children and/or their legal guardians. The phase of the disease (chronic, accelerated or blastic) was defined according to the criteria of the European LeukemiaNet (ELN) recommendation.⁴ Sokal score calculation was performed using the mathematical equation for patients aged less than 45 years.⁵ Determination of the European Treatment and Outcome Study (EUTOS) long-term survival (ELTS) score was carried out as previously reported.⁶ Karyotypes were interpreted using G- or Q-banding techniques.⁷ Complete cytogenetic response (CCyR) to treatment was defined as no Philadelphia-chromosome-positive cells in at least 20 analyzed bone marrow metaphases. *BCR::ABL1* transcript levels in the peripheral blood and bone marrow were determined by local laboratories using quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) and expressed according to the International Scale (IS).⁸ In the oldest cases, defined conversion factors were used for equivalence to tests according to IS.⁹ Responses to treatment were defined according to the European LeukemiaNet (ELN) criteria.^{4,10} Major molecular response (MMR) and deep molecular response (DMR) were defined as a ratio of *BCR::ABL1/ABL1* less than 0.1% and less than 0.01% (MR4), respectively.⁸ In the context of treatment-free remission (TFR) attempt, molecular relapse was defined as a loss of MMR at any time. Determination of transcript types and *BCR::ABL1* kinase domain mutations analysis was performed as previously reported.^{11,12}

The follow-up of children was not censored at the time of switching to other treatments including hematopoietic stem cell transplantation (HSCT). Comparisons of clinical and

biological characteristics between sexes were performed using a χ^2 test or Fisher's exact test for qualitative variables and the Wilcoxon signed-rank test for quantitative variables. Overall survival and progression-free survival (PFS, progression to advanced phase or death) were estimated by the Kaplan-Meier method and comparisons were performed using the log-rank test. The level of statistical significance was set as 0.05.

Results

Baseline characteristics

From January 2011 to March 2021, 576 patients less than 18 years old were recruited from 17 countries and among them, 535 (92.9%), 19 (3.3%) and 22 (3.8%) presented with CML in CP, in accelerated or in blastic phase, respectively. Baseline characteristics of the 535 patients with CML-CP are listed in Table 1. There was a male preponderance with a sex ratio of 1.31. Median age at diagnosis was 12.2 years (range, 8 months to 18 years).

Among the 535 children with CML-CP, the diagnosis was made incidentally in 80 (16%) children when a blood assessment was performed for medical reasons such as cough, infection, pre-operative assessment or trauma. Five hundred and eight patients (95%) presented with symptoms. Among these, the most common symptoms at presentation were asthenia, weight loss and abdominal pain (*Online Supplementary Figure S1*). Thrombosis was observed in a single patient whilst 20% of the children presented with signs of hemorrhage (multiple hematoma, retinal bleeding with blurred vision, menorrhagia, prolonged bleeding after tooth extraction). Bleeding and signs of hemorrhage were associated with a higher frequency of palpable spleen ($P=0.0007$), higher leukocyte ($P<0.0001$) and platelet ($P=0.02$) counts, and a lower hemoglobin concentration ($P=0.02$). Signs suggestive of leukostasis (priapism, central nervous abnormalities, respiratory difficulties, retinal abnormalities and visual disturbances) were observed in 88 (16%) patients. At diagnosis, the spleen was palpable in 76% of the patients with a median of 9 cm (range, 1-32) below the costal margin. The median leukocyte count was $222 \times 10^9/L$ (IQR, 4.8-1,037). There was no statistical difference between boys and girls concerning the frequency of signs of leukostasis, frequency of splenomegaly, spleen size, median of the leukocyte count and hemoglobin concentration (Table 1). However, the median platelet count was significantly higher in girls. Compared to the entire cohort, the 88 patients (16.5%) with signs of leukostasis presented with a larger spleen size ($P<0.02$) (but not with a higher frequency of palpable splenomegaly), a higher leukocyte count ($P<0.0001$) and lower hemoglobin concentration ($P<0.0001$) compared to the other patients whilst the platelet levels were not significantly different. Palpable splenomegaly was statistically associated with higher leukocyte counts ($P<0.0001$) and

Table 1. Baseline characteristics at diagnosis of children and adolescents with chronic myeloid leukemia in chronic phase.

Characteristics	All	Boys	Girls	P
Age, years, N of patients (%)	535 (100)	303 (56)	232 (44)	
0-3	35 (7)	19 (6)	16 (7)	
4-9	124 (23)	72 (24)	52 (22)	-
10-14	244 (45)	128 (42)	116 (50)	
15-18	132 (25)	84 (28)	48 (21)	
Presence of signs of leukostasis, N (%)	88 (16)	50 (9)	38 (7)	0.97
Lansky/Karnofski scales*, N	484	269	215	
100: normal, fully active, N (%)	262 (54)	146 (54)	116 (54)	-
90: minor restriction, N (%)	119 (25)	70 (26)	49 (23)	
<80: mild restriction and more, N (%)	103 (21)	53 (20)	50 (23)	
Sokal score (<45 years), N	429	236	193	<0.0001
low, N (%)	84 (20)	27 (11)	57 (30)	
intermediate, N (%)	160 (37)	86 (36)	74 (38)	
high, N (%)	185 (43)	123 (52)	62 (32)	
ELTS score, N	453	252	201	0.26
low, N (%)	304 (67)	169 (67)	135 (67)	
intermediate, N (%)	93 (21)	47 (19)	46 (23)	
high, N (%)	56 (12)	36 (14)	20 (10)	
Spleen, N	529	300	229	
Palpable spleen, N (%)	404 (76)	226 (75)	178 (78)	0.52
Spleen size, N	362	198	164	
median, cm below the costal margin (IQR)	9 (4-15)	10 (4-15)	8 (4-15)	0.28
Hb, g/dL, N	532	302	230	
median (IQR)	9.4 (7.7-11.5)	9.4 (7.7-11.6)	9.4 (7.7-11.2)	0.71
WBC, x10 ⁹ /L, N	534	302	232	
median (IQR)	222 (95-353)	223 (96-345)	216 (93-358)	0.93
Blast cells, %, N	516	288	228	
median (IQR)	0.0 (0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.77
Basophils, %, N	522	294	228	
median (IQR)	3.0 (1.8-5)	3.0 (1.5-5.6)	3.0 (1.9-5)	0.80
Eosinophils, %, N	524	296	228	
median (IQR)	3.0 (1.0-5.0)	3.0 (1.0-4.8)	3.0 (1.5-5.0)	0.39
Platelet count, x10 ⁹ /L, N	532	300	232	<0.0001
median (IQR)	494 (336-778)	462 (308-680)	552 (384-972)	
<150, N (%)	22 (4)	14 (5)	8 (3)	
150-450, N (%)	201 (38)	129 (43)	72 (31)	
450-1,000, N (%)	225 (42)	127 (42)	98 (42)	
>1,000, N (%)	84 (16)	30 (10)	54 (23)	
Karyotype, N	535	303	232	0.7481
Not done/failure, N	22	10	12	
Classical translocation, N (%)	485 (94)	277 (94)	208 (94)	
Variant translocation, N (%)	7 (2)	4 (2)	3 (2)	
ACA, N (%)	21 (4)	12 (4)	9 (4)	
Transcript type, N	379	216	163	0.1073
e14a2 (b3a2), N (%)	197 (52)	113(52)	84 (51)	
e13a2 (b2a2), N (%)	123 (33)	76 (35)	47 (29)	
combination e14a2-e13a2, N (%)	50 (13)	21 (10)	29 (18)	
atypical transcript e13a3 (b2a3), N (%)	9 (2)	6 (3)	3 (2)	
BCR::ABL1 protein, N	88	51	37	
P210 ^{BCR::ABL1} , N (%)	87 (99)	50 (99)	37 (100)	-
P190 ^{BCR::ABL1} , N (%)	1 (1)	1 (1)	0	

ACA: additional chromosomal abnormalities in Philadelphia chromosome-positive metaphases; ELTS score: Eutos Long-Term Survival score; IQR: interquartile range; Hb: hemoglobin; N: number of patients; WBC: white blood cell count. *The Karnofsky Scale is designed for patients aged 16 years and older, and the Lansky Scale for patients 1 year old to less than 16 years old.

lower hemoglobin concentration ($P < 0.0001$) compared to blood counts of patients without palpable splenomegaly. The majority (67%) of the children was allocated to the low-risk group according to the ELTS score, whereas by contrast the majority (80%) of the children was categorized as intermediate and high risk according to the Sokal system (Table 1). A significant difference was observed regarding the distribution by the Sokal system of boys and girls into the risk categories. The distribution of sexes across the three risk categories according to the ELTS scoring system did not significantly differ.

Chromosomal abnormalities in addition to the classical chromosomal translocation $t(9;22)(q34.1;q11.2)$ were found in 28 (5.5%) children among the 513 patients with available karyotypes at diagnosis (Table 1). Typical BCR::ABL1 transcripts e14a2 (b3a2) and combination of e14a2 and e13a2 (b2a2) were predominant in the 379 assessed patients while P210BCR::ABL1 protein was expressed in 87 of the remaining patients (Table 1).

Treatment and outcome

Treatment details of the 535 children diagnosed in CP are summarized in Figure 1. In brief, first-line therapy consisted of interferon α (IFN) +/- cytosine arabinoside (AraC) in 22 (4%) patients between 2000 and 2005, tyrosine kinase inhibitors (TKI) (92.3%) involving 482 patients who received imatinib between 2001 and 2020 and nine patients a second-generation TKI between 2012 and 2020 or intravenous chemotherapy (13 patients with signs of leukostasis) between 2000 and 2018, and nine (1.7%) patients underwent allogeneic HSCT between 2000 and 2002. TKI-treatment was preceded or associated with hydroxycarbamide in 228 (42.8%) patients or anagrelide or 6-mercaptopurine (2 children each) or leukapheresis (6 children). Allogeneic HSCT was performed in 131 (24.5%) children: nine as first-line treatment, 66 as second-line treatment (60 after treatment with imatinib, 4 children after IFN-AraC and 2 after chemotherapy + hydroxycarbamide) and 56 as 3rd-7th ultimate line of treatment.

Among the 535 patients in CML-CP, 24 (4.5%) deaths (11 CML-related and 13 associated with HSCT) were recorded with a median follow-up of 5.9 years (95% confidence interval [CI]: 5.4-6.6). The 5-year PFS and survival rates of the 535 patients in CML-CP were 91.6% (95% CI: 89.1-94.3%) and 94.7% (95% CI: 92.6-96.9%), respectively.

The 482 patients receiving first-line imatinib therapy were considered for analysis of the response to treatment and outcome with a median follow-up for of 5.6 years (interquartile range [IQR], 5.0-6.0 years). The median initial daily imatinib dose was 280 mg/m² (IQR, 249-319 mg/m²). Grade 3 or 4 hematological toxicity (N=69; 32%) or non-hematological toxicities (N=75; 35%) were reported in 96 (44.5%) of 216 assessable patients. Neutropenia (N=38; 55%) was the most frequently reported grade 3/4 hematological adverse events whilst musculoskeletal events (N=15; 20%) were the

most frequent grade 3/4 non-hematological side effects. Among the 469 children assessable for hematological response, 466 (99.3%) achieved complete hematological remission after a median time of 2 months (95% CI: 1.87-2.43) after the start of imatinib. CCyR was achieved with a median time of 8.2 months (95% CI: 7.4-9.0). Cumulative incidence of CCyR at 12 months and at 5 years for 478 patients with available data was 68% (95% CI: 63-72%) and 97% (95% CI: 94-98%), respectively. The ELTS score, available in 406 patients, was not correlated with the cumulative incidence of CCyR. A transcript level less than or equal to 10% at 3 months after the start of imatinib was recorded in 182 (60%) of the 302 children with an available transcript level at this time point. The rate of MMR achievement at 12 months in children with a transcript level less than or equal to 10% at 3 months was significantly higher compared to that of the 23 children with more than 10% (55% vs. 17%, respectively; $P < 0.0001$). MMR was achieved with a median time of 14.5 months (95% CI: 13.1-16.5 months). Cumulative incidence of MMR at 12 months and 5 years for 474 patients with available data was 40% (95% CI: 35-44%) and 91% (95% CI: 88-94%), respectively (Figure 2). The ELTS score showed no statistical difference in MMR achievement between the patients allocated to the low, intermediate or high-risk groups.

Among the 482 children, 195 (40%) continued receiving imatinib with a median follow-up of 3.8 years (95% CI: 3.2-4.3 years) whilst 287 (60%) patients discontinued imatinib treatment: 231 (48%) were switched to another treatment at a median of 56.2 months (95% CI: 46-75 months) after the start of imatinib and 56 (11.6%) attempted to stop at a median of (56.2 months [95% CI: 46-75 months]) after the start of imatinib. Details of second-line treatment of the 231 patients who were switched to another treatment is reported in Figure 1. The switches occurred within the first year of treatment in 90 (39%) of the 231 patients. The main reason for switching (38.1% of the switches) was a failure to achieve hematologic, cytogenetic or molecular response according to the ELN 2013 criteria (*Online Supplementary Table S1*). A mutation in the kinase domain was found in 19 of the 137 patients who switched because of progression, loss of response or a failure to achieve hematologic, cytogenetic or molecular response (*Online Supplementary Table S2*). A switch because of hematopoietic and/or extra hematopoietic toxicity occurred in 37 patients (7.6%). At last follow-up, 105 (21.7%) of the 482 patients receiving first-line imatinib therapy had undergone HSCT and 95 of them are alive.

Fifty-six (11.6%) of the 482 children discontinued imatinib in an attempt to achieve treatment-free remission between August 2007 and February 2024. The median follow-up of these 56 patients was 2.8 years (95% CI: 2.5-4.6) after discontinuation. Among them, 34 patients (group A) discontinued after at least 3 years of treatment and sustained MR4 for at least 2 years whilst 19 patients (group B) did

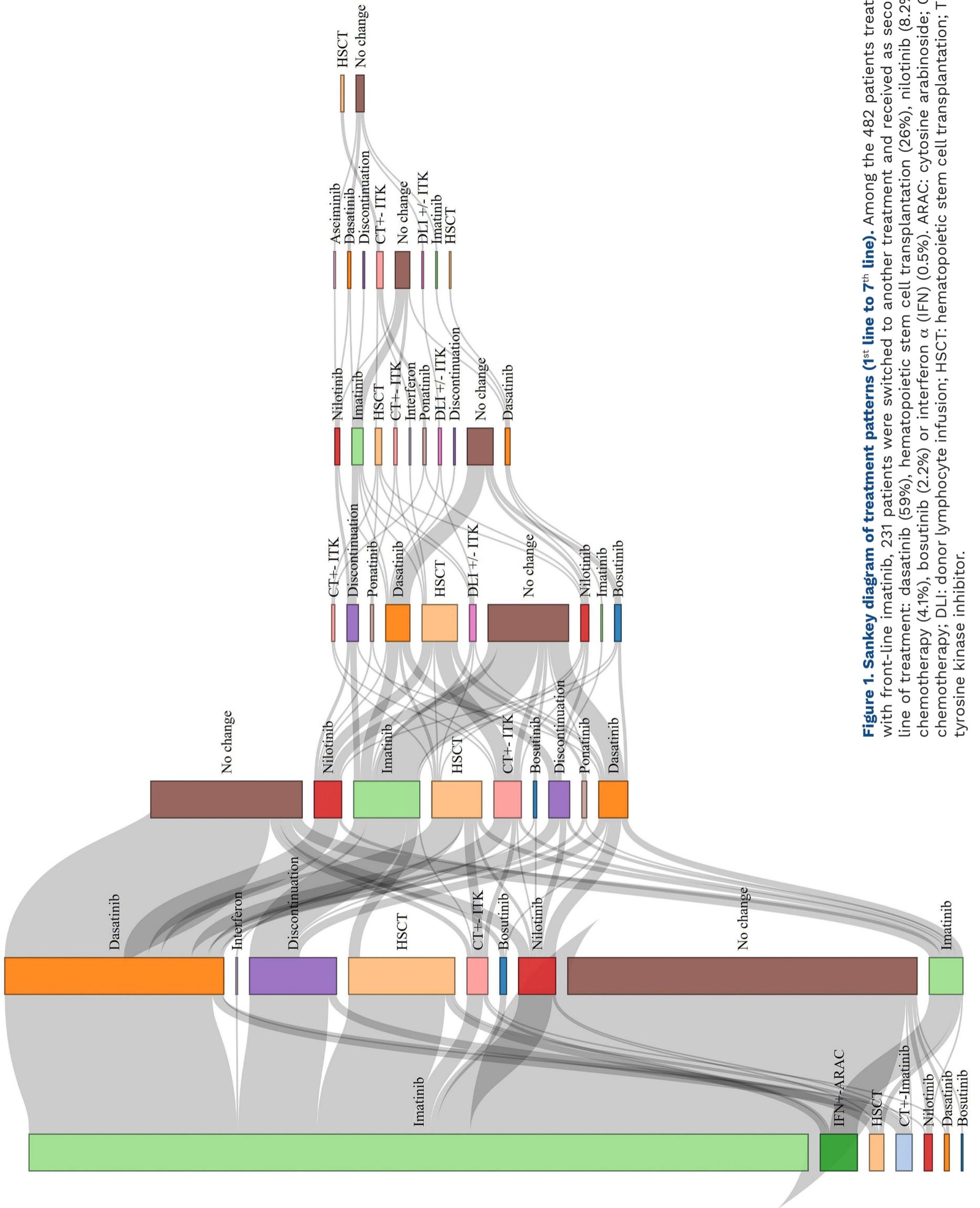


Figure 1. Sankey diagram of treatment patterns (1st line to 7th line). Among the 482 patients treated with front-line imatinib, 231 patients were switched to another treatment and received as second line of treatment: dasatinib (59%), hematopoietic stem cell transplantation (26%), nilotinib (8.2%), chemotherapy (4.1%), bosutinib (2.2%) or interferon α (IFN) (0.5%). ARAC: cytosine arabinoside; CT: chemotherapy; DLI: donor lymphocyte infusion; HSCT: hematopoietic stem cell transplantation; TKI: tyrosine kinase inhibitor.

not meet these criteria (MR4 less than 2 years, N=3; fluctuation between MR3 and MR4 N=5; no achievement of MR4, N=7; no achievement of MR4 and less than 3 years of treatment N=4) and three patients were without information. Among the 56 children who discontinue imatinib, 23 children (41%) remained treatment-free with a median time of 2.7 years (95% CI: 2.4-5.8 years) after the discontinuation of imatinib, including 18 children from group A, two children from group B and the three patients without information regarding the criteria of discontinuation. The remaining 33 patients resumed treatment with imatinib (N=18) or another TKI (N=15).

Disease progression occurred in 29 (6%) patients (accelerated phase, N=9; blast phase, N=20; lymphoid immunophenotype, N=12; myeloid, N=6; mixed, N=1; not specified, N=1).

Among them 19 (3.9%) patients progressed under imatinib treatment and ten patients progressed after switching from imatinib. PFS rate at 3-years was 97.2% (95% CI: 95.1-99.3%), 91.8% (95% CI: 85.8-98.4%) and 72.0% (95% CI: 59-87.9%) in the ELTS low-, intermediate- and high-risk groups, respectively (P log rank<0.001) (Figure 3). Among the 482 patients treated with first-line imatinib, 15 (3.1%) children died: seven children died after progression of CML (including 2 patients who relapsed after transplantation in second CP) whilst non-related CML death occurred in eight transplanted patients (transplantation in second CP after progression of CML, N=4; transplantation in first CP, N=4). Probability of overall survival at 3 years and at 5 years was 97.6% (95% CI: 96.1-99.1%) and 96.3% (95% CI: 94.4-98.2%), respectively (Figure 4). The 3-year survival rate was 98.3%

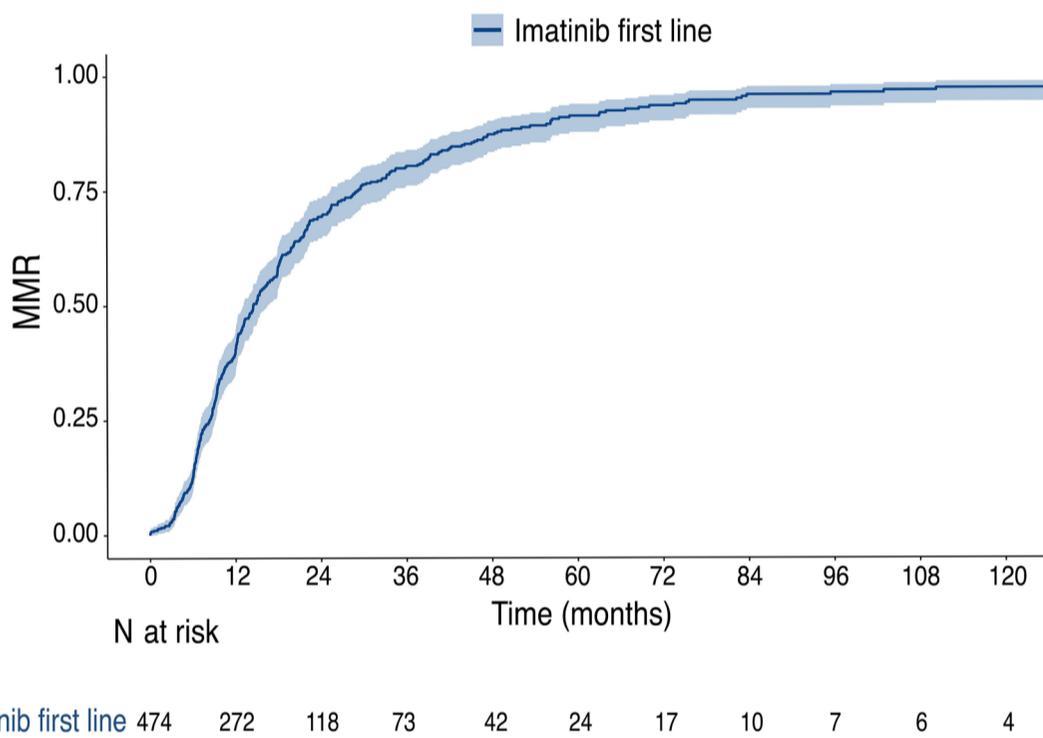


Figure 2. Cumulative incidence of major molecular response in patients receiving first-line imatinib therapy. MMR: major molecular response.

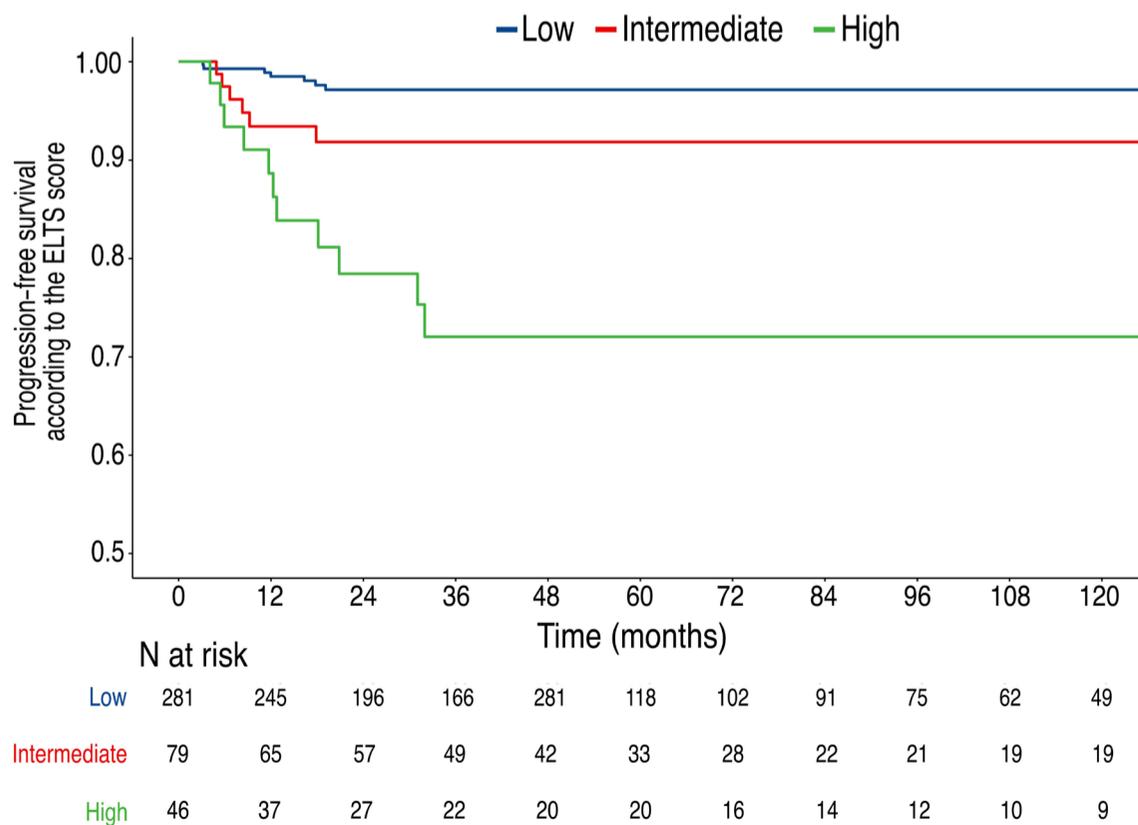


Figure 3. Progression-free survival for patients treated with first-line imatinib according to their Eutos Long-Term Survival score. ELTS: Eutos Long-Term Survival.

(95% CI: 96.6-100%), 94.5% (95% CI: 89.5-99.9%) and 95% (95% CI: 88.5-100%) in the ELTS low-, intermediate- and high-risk group, respectively (P log rank=0.0064).

Discussion

To the best of our knowledge, this report from the I-CML-Ped Study provides description, treatment and outcome data from the largest pCML cohort to date. In this study we have focused on childhood CML-CP as the characteristics and outcome of children with advanced phases at diagnosis have previously been reported.¹³ The proportion of advanced phases reported in the present work does not seem to differ to that described in adult patients.¹⁴ We found a slight male preponderance in children with CML-CP which has also been reported in adult series.¹⁴ Interestingly, 76% of the children presented with splenomegaly, contrasting with a lower frequency (less than 50%) in newly diagnosed adult patients.¹⁴ Higher leukocyte counts and lower hemoglobin levels were significantly associated with the presence of a splenomegaly. We also found that platelet counts at diagnosis were significantly higher in girls. To our knowledge, sex-related differences in platelet counts have not been previously reported either in children or adults. Despite a median leukocyte count at diagnosis in our patients about 3-fold higher than in adults, the frequency of signs of leukostasis seems to be similar (16.5% vs. 15.8%) with equivalent frequency of priapism (3.2%) in males.¹⁵ Chromosomal abnormalities in addition to the classical chromosomal translocation t(9;22)(q34.1;q11.2) were rare (5.5%). Typical BCR::ABL1 transcripts e14a2 (b3a2) including combination of e14a2 and e13a2 (b2a2) were predominant as reported in adults in whom a favorable impact on outcome was reported.^{14,16}

This registry initiated in the year 2011 provides valuable

data on the largest cohort of children treated with first-line imatinib. In the present work conducted in children diagnosed with CML between January 2000 and August 2020, only few children were treated with a second-generation TKI as first-line therapy because dasatinib, nilotinib and bosutinib were approved for minors in 2018, 2019 and 2023, respectively.¹⁷⁻¹⁹ Pediatric clinical trials of ponatinib and asciminib in children are currently underway. It was reported that children treated with first-line dasatinib or nilotinib achieved CCyR and MMR earlier than children receiving imatinib, but this did not translate into PFS or survival rates.^{16,17} Imatinib was well tolerated as previously reported in children with a similar proportion (5-6% vs. 7.6% in the present study) of children who permanently stopped imatinib because of adverse events.^{2,3} The notable proportion (48%) of patients reported here who switched from imatinib was mainly due to failure to achieve an optimal response according to the ELN criteria. However, we observed a high proportion (21.7%) of switches related to the physician's choice without taking into account the ELN failure criteria. It was reported that 24% to 30% of adults treated with imatinib for CML in clinical trials changed treatment.²⁰⁻²³ However, the proportion of switches was higher (41% and 46%, respectively) in two studies conducted in adults in a real-life setting which is the status of the present pediatric registry.^{24,25} By contrast to the data shown here, the switches reported in these two studies were mainly due to intolerance and not to failure to achieve milestones. The proportion (60%) of children with transcript levels equal to or less than 10% after 3 months of imatinib was similar to the proportion reported in adults.²⁰ We previously reported that such an early response to imatinib at 3 months predicts pCML outcome.²⁶ CCyR rates (68% and 97% at 1 and 5 years, respectively) and MMR (40% and 91% at 1 and 5 years, respectively) are in the ranges of the results from comparative trials with imatinib conducted in adults and

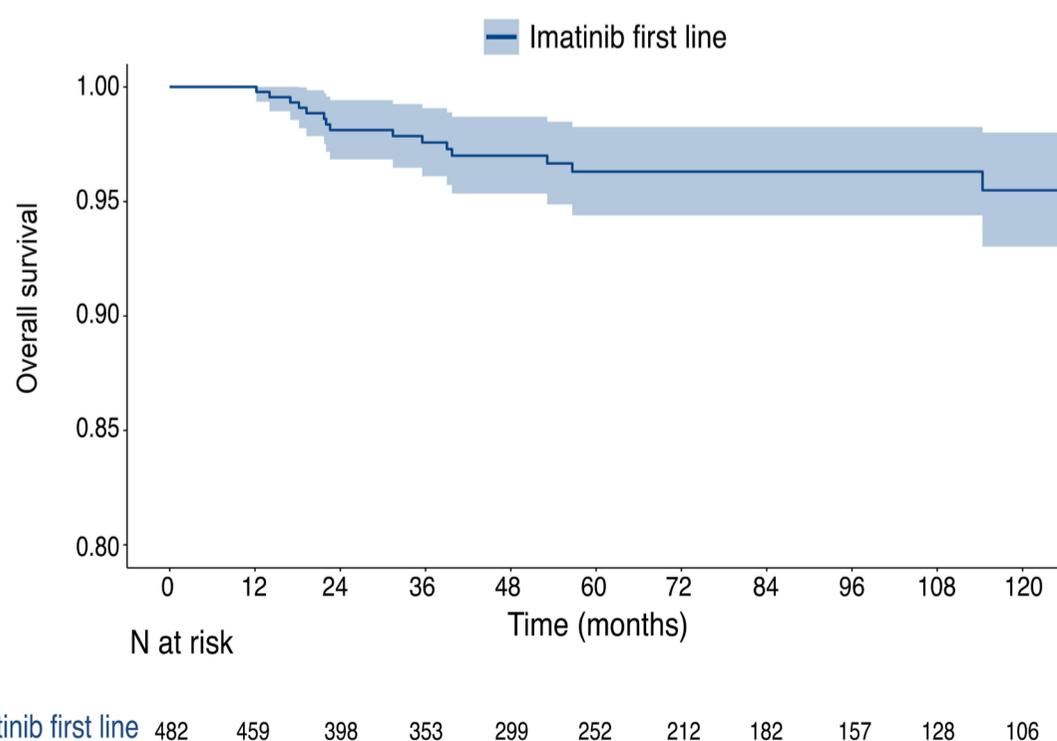


Figure 4. Overall survival for patients treated with first-line imatinib.

in prospective trials with imatinib in children.^{3,27,28,29} The overall survival rate (96.3% at 5 years) observed in our cohort of children treated with first-line imatinib compares favorably with results in adult trials with imatinib.^{21,30} There is no pediatric prognostic score to predict pCML outcome. The ELTS scoring system was set up to consider disease-specific deaths in adults with CML treated with imatinib and is relevant in predicting the long-term outcome of adults with CML-CP.³¹ As also reported in adults, we observed that as compared to the ELTS score, the Sokal score identified a higher proportion of children as high risk (43% vs. 12%) and fewer children as low risk (20% vs. 67%).⁶ Moreover, we observed that the distribution between the high-, intermediate- and low-risk groups according to the ELTS score was similar in adults and children.^{6,30,32} We also confirm that the ELTS score can identify children with a high risk of progression and can be used in the pCML treatment algorithm.³³ The treatment recommendations of our international pCML expert panel recently published are based on this finding: initial therapy with a first or second-generation TKI depends on the allocated ELTS risk group (imatinib for children allocated to the low and intermediate ELTS risk groups; second-generation TKI for those allocated to high ELTS risk group).³⁴ The proportion (41%) of our children remaining in treatment-free remission after an attempt of discontinuation of imatinib seems to be lower than the reported rate of 50% in other pediatric cohorts.^{35,36} This can be explained in several patients by neglect of the criteria (MR4 at least for 2 years with at least 3 years of treatment) which were recently defined for stopping TKI in children.³⁵ In conclusion this analysis of clinical and biological parameters of the largest cohort of children with CML in CP demonstrated that pediatric CML is characterized by a bulky disease (large splenomegaly, high leukocyte counts)

compared to adults. However, these characteristics did not translate into a lower rate of response to imatinib and the outcome was similar to that in adults receiving imatinib. While the ELTS score can identify children with a poor outcome, a refined prognostic score specific to the pediatric population needs to be established and validated.

Disclosures

No conflicts of interest to disclose.

Contributions

FM contributed to the database and wrote the manuscript. FM and MS contributed to the literature search, study design, data analysis, data interpretation, and writing. FM, MM, KK, AMG, BDM, ML, AM, PS, JY, MA, MD, BL, MB, CKL, AK, GJ, RF, AB and MS contributed to data collection, to critical revision of the article, and read and approved the final version. JDK and LD performed statistical analyses.

Acknowledgments

The authors gratefully acknowledge Professor Irene Roberts (emeritus professor of pediatric hematology, MRC Weatherall Institute of Molecular Medicine, Oxford University, Oxford, UK) and Professor François Guilhot (emeritus professor of hematology, University of Poitiers, Poitiers, France) for helpful comments on the manuscript, Violaine Goyeau and Micheline Kabore for the data monitoring. The manuscript was reread and reviewed by Jeffrey Arsham, the American medical proofreader of the University Hospital of Poitiers, Poitiers, France.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author on reasonable request.

References

1. Millot F, Traore P, Guilhot J, et al. Clinical and biological features at diagnosis in 40 children with chronic myeloid leukemia. *Pediatrics*. 2005;116(1):140-143.
2. Millot F, Baruchel A, Guilhot J, et al. Imatinib is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: results of the French national phase IV trial. *J Clin Oncol*. 2011;29(20):2827-2832.
3. Suttrop M, Schulze P, Glauche I, et al. Front-line imatinib treatment in children and adolescents with chronic myeloid leukemia: results from a phase III trial. *Leukemia*. 2018;32(7):1657-1669.
4. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia. *Blood*. 2013;122(6):872-884.
5. Sokal JE, Baccarani M, Tura S, et al. Prognostic discrimination among younger patients with chronic granulocytic leukemia: relevance to bone marrow transplantation. *Blood*. 1985;66(6):1352-1357.
6. Pffirmann M, Clark RE, Prejzner W, et al. The EUTOS long-term survival (ELTS) score is superior to the Sokal score for predicting survival in chronic myeloid leukemia. *Leukemia*. 2020;34(8):2138-2149.
7. Schoch C, Schnittger S, Bursch S, et al. Comparison of chromosome banding analysis, interphase- and hypermetaphase-FISH, qualitative and quantitative PCR for diagnosis and for follow-up in chronic myeloid leukemia: a study on 350 cases. *Leukemia*. 2002;16(1):53-59.
8. Hughes T, Deininger M, Hochhaus A, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood*. 2006;108(1):28-37.
9. Branford S, Cross NC, Hochhaus A, et al. Rationale for the recommendations for harmonizing current methodology for detecting BCR-ABL transcripts in patients with chronic myeloid

- leukaemia. *Leukemia*. 2006;20(11):1925-1930.
10. Hochhaus A, Baccarani M, Silver RT, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966-984.
 11. Cross NCP, Ernst T, Branford S, et al. European LeukemiaNet laboratory recommendations for the diagnosis and management of chronic myeloid leukemia. *Leukemia*. 2023;37(11):2150-2167.
 12. Soverini S, Colarossi S, Gnani A, et al. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on chronic myeloid leukemia. *Clin Cancer Res*. 2006;12(24):7374-7379.
 13. Millot F, Maledon N, Guilhot J, Güneş AM, Kalwak K, Suttorp M. Favourable outcome of de novo advanced phases of childhood chronic myeloid leukaemia. *Eur J Cancer*. 2019;115:17-23.
 14. Hoffmann VS, Baccarani M, Hasford J, et al. The EUTOS population-based registry: incidence and clinical characteristics of 2904 CML patients in 20 European Countries. *Leukemia*. 2015;29(6):1336-1343.
 15. Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral centre over a 16-year period. *Br J Haematol*. 1997;96(1):111-116.
 16. Jain P, Kantarjian P, Patel KP, et al. Impact of BCR-ABL transcript type on outcome in patients with chronic-phase CML treated with tyrosine kinase inhibitors. *Blood*. 2016;127(10):1269-1275.
 17. Gore L, Kearns PR, de Martino ML, et al. Dasatinib in pediatric patients with chronic myeloid leukemia in chronic phase: results from a phase II trial. *J Clin Oncol*. 2018;36(13):1330-1338.
 18. Hijiya N, Maschan A, Rizzari C, et al. Phase 2 study of nilotinib in pediatric patients with Philadelphia chromosome-positive chronic myeloid leukemia. *Blood*. 2019;134(23):2036-2045.
 19. Brivio E, Pennesi E, Willemse ME, et al. Bosutinib in resistant and intolerant pediatric patients with chronic phase chronic myeloid leukemia: results from the phase I part of study ITCC054/COG AAML1921. *J Clin Oncol*. 2023;42(7):821-831.
 20. Hehlmann R, Lauseker M, Saussele S, et al. Assessment of imatinib as first-line treatment of chronic myeloid leukemia: 10-year survival results of the randomized CML study IV and impact of non-CML determinants. *Leukemia*. 2017;31(11):2398-2406.
 21. Hoffmann VS, Baccarani M, Hasford J, et al. Treatment and outcome of 2904 CML patients from the EUTOS population-based registry. *Leukemia*. 2017;31(3):593-601.
 22. Zhang XS, Gale RP, Li ZY, et al. Predictive scoring systems for molecular responses in persons with chronic phase chronic myeloid leukemia receiving initial imatinib therapy. *Leukemia*. 2022;36(8):2042-2049.
 23. Guilhot F, Rigal-Huguet F, Guilhot J, et al. Long-term outcome of imatinib 400 mg compared to imatinib 600 mg or imatinib 400 mg daily in combination with cytarabine or pegylated interferon alpha 2a for chronic myeloid leukaemia: results from the French SPIRIT phase III randomised trial. *Leukemia*. 2021;35(8):2332-2345.
 24. Castagnetti F, Di Raimondo F, De Vivo A, et al. A population-based study of chronic myeloid leukemia patients treated with imatinib in first line. *Am J Hematol*. 2017;92(1):82-87.
 25. Geelen IGP, Thielen N, Janssen JJWN, et al. Treatment outcome in a population-based, 'real-world' cohort of patients with chronic myeloid leukemia. *Haematologica*. 2017;102(11):1842-1849.
 26. Millot F, Guilhot J, Baruchel A, et al. Impact of early molecular response in children with chronic myeloid leukemia treated in the French Glivec phase 4 study. *Blood*. 2014;124(15):2408-2410.
 27. Roy Moulik N, Keerthivasagam S, Pandey A, et al. Treatment and follow-up of children with chronic myeloid leukaemia in chronic phase (CML-CP) in the tyrosine kinase inhibitor (TKI) era—Two decades of experience from the Tata Memorial Hospital paediatric CML (pCML) cohort. *Br J Haematol*. 2024;204(4):1249-1261.
 28. Giona F, Putti MC, Micalizzi M, et al. Long-term results of high-dose imatinib in children and adolescents with chronic myeloid leukaemia in chronic phase: the Italian experience. *Br J Haematol*. 2015;170(3):398-407.
 29. Shimada H, Watanabe A, Ito M, et al. A Multicenter, prospective study for pediatric chronic myeloid leukemia in chronic phase: the JPLSG CML-08 Study. *Blood*. 2021;138 (Suppl 1):3605.
 30. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. *N Engl J Med*. 2017;376(10):917-927.
 31. Pfirrmann M, Baccarani M, Saussele S, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia*. 2016;30(1):48-56.
 32. Zhang XS, Gale RP, Huang XJ, Jiang Q. Is the Sokal or EUTOS long-term survival (ELTS) score a better predictor of responses and outcomes in persons with chronic myeloid leukemia receiving tyrosine-kinase inhibitors? *Leukemia*. 2021;36(2):482-491.
 33. Millot F, Guilhot J, Suttorp M, et al. Prognostic discrimination based on the EUTOS long-term survival score within the International Registry for Chronic Myeloid Leukemia in children and adolescents. *Haematologica*. 2017;102(10):1704-1708.
 34. Millot F, Ampatzidou M, Roy Moulik N, et al. Management of children and adolescents with chronic myeloid leukemia in chronic phase: International pediatric chronic myeloid leukemia expert panel recommendations. *Leukemia*. 2025;39(4):779-791.
 35. Millot F, Suttorp M, Ragot S, et al. Discontinuation of imatinib in children with chronic myeloid leukemia: A study from the International Registry of Childhood CML. *Cancers*. 2021;13(16):4102-4109.
 36. Shima H, Kada A, Tanizawa A, et al. Discontinuation of tyrosine kinase inhibitors in pediatric chronic myeloid leukemia. *Pediatr Blood Cancer*. 2022;69(8):e29699.