Additional Cytogenetic Abnormalities and Variant t(9;22) at the Diagnosis of Childhood Chronic Myeloid Leukemia: The Experience of the International Registry for Chronic Myeloid Leukemia in Children and Adolescents

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BACKGROUND: In the adult population with newly diagnosed chronic myeloid leukemia (CML), variant translocations are usually not considered to be impairing the prognosis, whereas some additional cytogenetic abnormalities (ACAs) are associated with a negative impact on survival. Because of the rarity of CML in the pediatric population, such abnormalities have not been investigated in a large group of children with CML. METHODS: The prognostic relevance of variant t(9;22) and ACAs at diagnosis was assessed in 301 children with CML in the chronic phase who were enrolled in the International Registry for Chronic Myeloid Leukemia in Children and Adolescents. RESULTS: Overall, 19 children (6.3%) presented with additional cytogenetic findings at diagnosis: 5 children (1.7%) had a variant t(9;22) translocation, 15 children (4.5%) had ACAs, and 1 had both. At 3 years, for children with a classic translocation, children with ACAs, and children with a variant t(9;22) translocation who were treated with imatinib as frontline therapy, the probability of progression-free survival (PFS) was 95% (95% confidence interval [CI], 91%-97%), 100%, and 75% (95% CI, 13%-96%), respectively, and the probability of overall survival (OS) was 98% (95% CI, 95%-100%), 100% (95% CI, 43%-98%), and 75% (95% CI, 13%-96%), respectively. No statistical difference was observed between the patients with classic cytogenetic findings and those with additional chromosomal abnormalities in terms of PFS and OS. CONCLUSIONS: In contrast to adults with CML, additional chromosomal abnormalities observed at diagnosis do not seem to have a significant prognostic impact. Cancer 2017;000:000-000. © 2017 American Cancer Society.

KEYWORDS: child, chronic myeloid leukemia, cytogenetic, imatinib, Philadelphia-positive.

INTRODUCTION
Chronic myeloid leukemia (CML) is characterized by the Philadelphia chromosome (Ph), a reciprocal balanced translocation between chromosome 9 (band q34) and chromosome 22 (band q11.2).1 Recent reports have highlighted the role of cytogenetic analysis at diagnosis and during treatment in determining the prognosis of the disease.2-4 Variant translocations (1 or more additional chromosomes involved in the translocation) or additional cytogenetic abnormalities (ACAs) have been reported in 5% to 10% of the adult population with newly diagnosed CML.3,5-7

Among these abnormalities, variant translocations are usually not considered to be impairing the prognosis of the patients.8 The ACAs, which are observed in a minority of patients (5%), were initially subdivided into major and minor...
The so-called major-route ACAs, such as trisomy 8, a second Ph, isochromosome 17q, and trisomy 19, were associated with a negative impact on survival. Minor-route ACAs were less considered. Six minor-route changes, including 5 numerical abnormalities (−7, −17, +17, +21, and −Y) and 1 structural aberration (t(3;21)(q26;q22)), were initially described by Mitelman. This classification, proposed by Mitelman, was based on the frequency of ACAs only.

Because of the rarity of CML in the pediatric population, such abnormalities have not been investigated in a large group of children and adolescents with CML. The International Registry for Chronic Myeloid Leukemia in Children and Adolescents (I-CML-Ped Study) gives us the opportunity to assess the frequency of variant translocations and ACAs and to study the potential impact of these cytogenetic abnormalities on the outcomes of children with CML treated with tyrosine kinase inhibitors.

**MATERIALS AND METHODS**

**Patients**

The I-CML-Ped Study was established to assess the epidemiology, management, and outcomes of CML in the pediatric population. The study protocol was approved by the institutional review committee. National pediatric study groups were invited to include newly diagnosed children and adolescents less than 18 years with Ph-positive CML in the chronic phase or advanced phase that was diagnosed later than January 2000. Between January 2011 and June 2016, 462 patients from 13 countries were registered retrospectively. The phase of the disease was determined according to the European LeukemiaNet recommendations. The Sokal score was calculated according to the formula for patients younger than 45 years.

The international data center is located at INSERM Clinical Investigation Centre 1402, University Hospital of Poitiers, France. The collection of the data is divided into 2 simultaneous phases. Phase A is the retrospective collection of data from patient flow charts and/or existing databases, and phase B is the prospective collection of data. New cases are reported by physicians to their national coordinating center; at regular intervals, these cases are then referred by this coordinating center to the international central data center in Poitiers, France. The data are collected from the clinical charts of the patients. The complete data are then sent to each national coordinating center and centrally at regular intervals subsequently at the international central data center. Follow-up is required twice a year. Written informed consent was obtained from the children and/or their guardians. This study is registered at ClinicalTrials.gov (NCT01281735).

**Cytogenetic Analysis**

Fifty-five laboratories performed cytogenetic analyses for their respective clinical centers. Chromosome banding analysis was performed for bone marrow metaphases after 24 or 48 hours of culture. Karyotypes were examined with G- or R-banding techniques and were interpreted according to the International System for Human Cytogenetic Nomenclature. Only cytogenetic alterations in Ph-positive cells at diagnosis were considered.

We considered all patients with an assessable cytogenetic analysis at diagnosis, whatever the number of evaluable metaphases was, to prevent the exclusion of cases with a small clone with ACAs.

**Molecular Analysis**

Fifty-five certified laboratories performed measurements of the BCR-ABL fusion transcript via a quantitative reverse transcriptase–polymerase chain reaction (qRT-PCR) assay with hybridization probes using ABL for normalization, as reported previously, and they were expressed according to the international scale.

**Definition of Response**

Only chromosome banding analyses of marrow cell metaphases were used to assess the degree of cytogenetic response. The cytogenetic response was categorized by the percentage of Ph-negative metaphases among at least 20 analyzed metaphases as follows: complete cytogenetic response (CCyR; 0% Ph-positive cells), partial cytogenetic response (≤35% Ph-positive cells), or minor cytogenetic response (36%-90% Ph-positive cells). For the definition of CCyR, only BCR-ABL1 expression determined by qRT-PCR (less than 1%) or by fluorescence in situ hybridization (less than 1% of BCR-ABL1–positive interphase cell nuclei among at least 200 nuclei) could be substituted for chromosome banding analyses of marrow cell metaphases. A major molecular response, molecular response 4.0, and molecular response 4.5 were defined as BCR-ABL1/ABL ratios ≤0.1%, ≤0.01%, and ≤0.0032%, respectively, on the international scale.

**Statistical Analysis**

Analyses were performed with SAS (version 9.3; SAS Institute, Inc, Cary, NC), and functions of R programming software (R Project for Statistical Computing) were applied. Potential differences in clinical and biological characteristics among subgroups of patients were tested with Fisher’s exact test. Progression-free survival (PFS)
was defined as survival without an accelerated phase, blast crisis, or death (whichever came first). PFS and overall survival (OS) were estimated from the diagnosis with the Kaplan-Meier method and were compared within groups with the log-rank test or the Wilcoxon test, as appropriate. The time to CCyR was calculated from the date of the start of treatment (apart from hydroxyurea). For patients treated with frontline imatinib, the cumulative incidence of CCyR was estimated from the onset of imatinib, with the Fine-Gray model accounting for competing events. Differences between groups were then explored with the Gray test.17

RESULTS
Between January 2011 and June 2016, a cytogenetic analysis at diagnosis was available for 301 patients with CML in the first chronic phase who were enrolled in the I-CML-Ped Study. The first-line treatment consisted of imatinib (268 patients), dasatinib (5 patients), nilotinib (3 patients), or other treatments such as interferon and/or cytosine arabinoside (25 patients). Patient characteristics are described in Table 1. The median age of patients with ACAs was 12 years (range, 5-16 years), 54% were girls, and all were classified as intermediate- or high-risk according to the Sokal score (33% and 67%, respectively). Among these 301 children, 282 patients (93.7%) had the classic translocation t(9;22)(q34;q11) without additional abnormalities or variants. In these 282 children, 20 metaphases or more were analyzed in 74% of the samples, and less than 20 metaphases were analyzed in 26% of the samples. Additional cytogenetic aberrations and/or variant Philadelphia translocations were identified in 19 children (6.3%): 13 patients (4.3%) had ACAs in addition to the standard translocation, a variant translocation was observed in 5 patients (1.7%), and 1 child had ACAs in addition to a variant translocation (Table 2). There were no statistically significant differences in the baseline characteristics of the patients at diagnosis between the patients with classic cytogenetic abnormalities and those with ACAs. Because of the small number of patients (n = 5), this comparison was not performed for patients with a variant Ph translocation.

Variants
At the initial diagnosis, at least 20 metaphases were examined in the 6 patients with a variant Ph translocation (unique patient numbers [UPNs] 14-19; Table 2); they included 1 patient (UPN 19) carrying ACAs in addition to the variant. Among these 6 patients, 1 additional chromosome was involved in 5 children: chromosome 1 was involved in 2 cases (UPNs 16 and 18) without evidence of recurrent breakpoints, chromosome 8 was involved in 1 case (UPN 19) in association with ACAs, and chromosomes 7 and 14 were each involved in 1 case (UPNs 14 and 17). In addition to chromosomes 9 and 22, 2 further chromosomes (chromosomes 8 and 17) were involved as the third or fourth additional chromosome in the variant Ph translocation in 1 child (UPN 15). In all the patients, the variant Ph translocation was found in all of the examined mitoses.

ACAs
Among the 13 patients with ACAs (UPNs 1-13; Table 2), at least 20 metaphases were examined at diagnosis in 7 patients, and less than 20 were examined in the remaining patients. ACAs were found in combination with t(9;22) in all the mitoses in 3 patients, whereas 10 patients had ACAs in a subclone comprising 1 to 10 metaphases (median, 2), which represented 3.3% to 91% of the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With ACAs (n = 13)</th>
<th>Patients With Variants (n = 5)</th>
<th>Patient With ACAs and Variant (n = 1)</th>
<th>Patients Without ACAs or Variants (n = 282)</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>12 y (5-16 y)</td>
<td>14 y (6-17 y)</td>
<td>16.5 y</td>
<td>12 y (8 mo to 18 y)</td>
<td>.569</td>
</tr>
<tr>
<td>Sex: male/female, %</td>
<td>46/54</td>
<td>40/60</td>
<td>100/0</td>
<td>57/43</td>
<td>.568</td>
</tr>
<tr>
<td>Palpable splenomegaly, No. (%)</td>
<td>10 (77)</td>
<td>3 (60)</td>
<td>1 (100)</td>
<td>211/279&lt;sup&gt;b&lt;/sup&gt; (76)</td>
<td>.070</td>
</tr>
<tr>
<td>Median (range), cm&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15 (0-23)</td>
<td>9.5 (0-15)</td>
<td>10</td>
<td>5 (0-32)</td>
<td></td>
</tr>
<tr>
<td>Leukocytes, median (range), g/L</td>
<td>264 (44-769)</td>
<td>334 (172-605)</td>
<td>481</td>
<td>229 (5-1037)</td>
<td>.323</td>
</tr>
<tr>
<td>Sokal score (&lt;45 y), No. (%)</td>
<td>Low</td>
<td>4/12&lt;sup&gt;b&lt;/sup&gt; (33)</td>
<td>2/4&lt;sup&gt;a&lt;/sup&gt; (50)</td>
<td>52/248&lt;sup&gt;a&lt;/sup&gt; (21)</td>
<td>.153</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>8/12&lt;sup&gt;b&lt;/sup&gt; (67)</td>
<td>2/4&lt;sup&gt;a&lt;/sup&gt; (50)</td>
<td>84/248&lt;sup&gt;a&lt;/sup&gt; (34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td></td>
<td>112/248&lt;sup&gt;a&lt;/sup&gt; (45)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ACA, additional cytogenetic abnormality.
<sup>a</sup> Comparison of patients with ACAs and patients without ACAs or variants.
<sup>b</sup> Number of assessable patients.
<sup>c</sup> Below the costal margin.
examined metaphases (median, 10%). Normal metaphases (46XY) were observed concomitantly with the aberrant clone and t(9;22) in 2 patients. The ACAs were classified as major-route ACAs (trisomy 8 and a second Ph in 2 patients), structural abnormalities (6 patients), isolated numerical abnormalities (1 patient), or a complex karyotype (4 patients).

**Outcome**
The median follow-up was 3.3 years (range, 5 months to 16 years), 3.3 years (range, 6 months to 6.5 years), and 4.5 years (range, 3-8 years) for patients with a classic translocation, patients with ACAs, and patients with a variant Ph translocation, respectively. As for events (unsatisfactory results, side effects, and physician choices) leading to a second-line therapy, the probability of still being treated with imatinib 1 year after the start of the drug was not statistically different (P = .47 overall) for children with a classic translocation (69%; 95% confidence interval [CI], 63%-75%), children with ACAs (100%), and children with a variant Ph translocation.

### TABLE 2. Cytogenetic Results and Treatment Responses of Patients With ACAs and Variants

<table>
<thead>
<tr>
<th>UPN</th>
<th>Sex/Age at Diagnosis, y</th>
<th>Karyotype at Diagnosis (No. of Mitoses)</th>
<th>Best Response by 12 mo (Time From Start of Treatment)</th>
<th>Course/Outcome (Follow-Up)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female/14</td>
<td>46,XX,t(9;22)(q34;q11) (21)/47,idem, +8 (1)</td>
<td>PCyR (12 mo)</td>
<td>Switch to dasatinib (14 mo)/alive in MR4.0 (5.5 y)</td>
</tr>
<tr>
<td>2</td>
<td>Male/9</td>
<td>46,XY,add(3)(p26),t(9;22)(q34,q11) (20)</td>
<td>CCyR (12 mo)</td>
<td>Alive in MR4.0 (6 y)</td>
</tr>
<tr>
<td>3</td>
<td>Female/15</td>
<td>46,XX,t(9;22)(q34;q11) (29)/46,idem, inv(3)(q21q26) (2)</td>
<td>Cytogenetic failure (12 mo)</td>
<td>Switch to imatinib (18 mo), progression (19 mo), chemotherapy/died in blast phase (2.5 y)</td>
</tr>
<tr>
<td>4</td>
<td>Male/12</td>
<td>46,XY,t(9;22)(q34;q11) (18)/47,XY, t(9;22)(q34;q11), +mar?der(3) (2)</td>
<td>CCyR (6 mo)</td>
<td>MMR loss (3 y)/alive (3 y)</td>
</tr>
<tr>
<td>5</td>
<td>Female/12</td>
<td>46,XX,t(2;7)(q31;q11), der(22)(t(79-22)(q34;q11) (26)</td>
<td>CCyR (12 mo)</td>
<td>Failure to achieve MMR, switch to dasatinib (18 mo) and nilotinib (45 mo)/alive without MMR (4.5 y)</td>
</tr>
<tr>
<td>6</td>
<td>Male/15</td>
<td>46,XY,t(9;22)(q34;q11) (11)/47-49,sl, del(5)(q13q35), +21, +der(22)(t(9;22)(q34;q11) (cp10)</td>
<td>CCyR (9 mo)</td>
<td>Switch to imatinib (18 mo), progression (19 mo), chemotherapy/died in blast phase (2.5 y)</td>
</tr>
<tr>
<td>7</td>
<td>Female/5</td>
<td>46,XX,t(9;22)(q34;q11) (15)/46,idem, idic(17) (11)</td>
<td>CCyR (12 mo)</td>
<td>Alive in MMR (1.5 y)</td>
</tr>
<tr>
<td>8</td>
<td>Female/13</td>
<td>46,XX,del(2)(t(2;9)(q12q21) (2;6)(q11q24), der(6)(t(2;9)(q24q11)(t(2;22)(q34;11), der(9)(t;9;p9)(t(12q24),der(22)(t(2;22)(q11q11) (15</td>
<td>Minor CyR (12 mo)</td>
<td>Switch to dasatinib (15 mo)/alive in MMR (4.5 y)</td>
</tr>
<tr>
<td>9</td>
<td>Male/11</td>
<td>46,XY (4)/46,XY,t(9;22) (26)</td>
<td>MMR (12 mo)</td>
<td>SCT (15 mo)/alive in MR5 (2.5 y)</td>
</tr>
<tr>
<td>10</td>
<td>Male/13</td>
<td>46,XY (1)</td>
<td>ND</td>
<td>Alive in MMR (2 y)</td>
</tr>
<tr>
<td>11</td>
<td>Female/5</td>
<td>46,XX,t(9;22)(q34;q11) (3)</td>
<td>MMR (12 mo)</td>
<td>Alive in MR5 (2.5 y)</td>
</tr>
<tr>
<td>12</td>
<td>Female/11</td>
<td>46,XX,t(9;22)(q34;q11) (12)</td>
<td>MMR (6 mo)</td>
<td>SCT (10 mo)/alive in MR4.0 (4.5 y)</td>
</tr>
<tr>
<td>13</td>
<td>Male/5</td>
<td>46,XY,t(9;22)(q34;q11) (7)</td>
<td>BCR-ABL1/ABL: 0.49% (12 mo)</td>
<td>BCR ABL/ABL: 0.12% (15 mo)</td>
</tr>
<tr>
<td>14</td>
<td>Male/17</td>
<td>46,XY,t(9;22;14)(q34 q11 q32) (21)</td>
<td>MMR (12 mo)</td>
<td>Alive in MR4.0 (4.5 y)</td>
</tr>
<tr>
<td>15</td>
<td>Female/9</td>
<td>46,XX,t(17;9;22;8)(q21q11q34;q11q42) (20)</td>
<td>CCyR (12 mo)</td>
<td>Failure to achieve MMR, switch to dasatinib (23 mo)/alive in MR (7 y)</td>
</tr>
<tr>
<td>16</td>
<td>Male/14</td>
<td>46,XY,t(9;22)(q12q34;11) (20)</td>
<td>CCyR (12 mo)</td>
<td>BCR-R (12 mo)</td>
</tr>
<tr>
<td>17</td>
<td>Female/6</td>
<td>46,XX,t(9;22;13q34;11) (20)</td>
<td>CCyR (4 mo)</td>
<td>BCR-R (4 mo)</td>
</tr>
<tr>
<td>18</td>
<td>Female/14</td>
<td>46,XX,t(9;22)(q34;q11;q42) (20)</td>
<td>MMR (5 mo)</td>
<td>Alive in MR5 (2.5 y)</td>
</tr>
<tr>
<td>19</td>
<td>Male/16</td>
<td>46,XY,t(9;22)(q24q34;11) (29)</td>
<td>BCR-ABL1/ABL: 3% (12 mo)</td>
<td>BCR ABL/ABL: 3% (12 mo)</td>
</tr>
</tbody>
</table>

Abbreviations: ACA, additional cytogenetic abnormality; CCyR, complete cytogenetic response; CyR, cytogenetic response; MMR, major molecular response; mo, months; MR, deep molecular response; ND, not determined; PCyR, partial cytogenetic response; SCT, stem cell transplantation; UPN, unique patient number; y, years.

Patients 1 to 13 showed ACAs, patients 14 to 18 showed variant translocations, and patient 19 showed ACAs and a variant Philadelphia chromosome translocation. All patients were initially treated with imatinib except for patients 3 and 16, who received interferon-α plus cytosine arabinoside and dasatinib, respectively, as the initial treatment.

*The follow-up period was the time from the start of the initial treatment.
(63%; 95% CI, 28%-84%). An optimal response (CCyR and/or major molecular response) to treatment was achieved within 12 months by all of the patients with a variant Ph translocation. The patient carrying ACAs in addition to a variant translocation (UPN 19) and 3 children with ACAs (UPNs 1, 3, and 19) failed to achieve a CCyR within the 12 months after the start of the treatment (Table 2). The probability of a CCyR by 15 months in patients treated with frontline imatinib (n = 268) who had a classic translocation, ACAs, and a variant Ph translocation was 83% (95% CI, 77%-88%), 77% (95% CI, 48%-97%), and 75% (95% CI, 33%-99%), respectively. With respect to the small sample size of nonclassic translocations, no statistical differences were observed over time.

With a median follow-up of 3.3 years (range, 0.1-16 years), 18 children developed CML progression: 16 patients with classic cytogenetic findings, 1 patient (patient 3) with inv(3)(q21q26) who was treated initially with a combination of interferon and cytosine arabinoside, and 1 patient (patient 16) with a variant Ph translocation who had a CCyR at 12 months with progression to the blastic phase 19 months after the achievement of a CCyR. The PFS of the 268 patients who received imatinib as first-line therapy is depicted in Figure 1A. In this cohort of children, the probability of PFS at 3 years was 95% (95% CI, 91%-97%), 100%, and 75% (95% CI, 13%-96%) for children with a classic translocation, children with ACAs, and children with a variant Ph translocation. The PFS of the 268 patients who received imatinib as first-line therapy is depicted in Figure 1A. In this cohort of children, the probability of PFS at 3 years was 95% (95% CI, 91%-97%), 100%, and 75% (95% CI, 13%-96%) for children with a classic translocation, children with ACAs, and children with a variant Ph translocation.
translocation, respectively. Seven deaths were recorded: 5 deaths occurred in patients with classic cytogenetic findings, and death also occurred in the 2 patients with non-classic cytogenetics who progressed. The probability of OS for the 268 patients who received imatinib as first-line therapy at 3 years was 98% (95% CI, 95%-100%), 100% (95% CI, 43%-98%), and 75% (95% CI, 13%-96%) for children with a classic translocation, children with ACAs, and children with a variant Ph translocation, respectively (Fig. 1B). Thus, overall, there was no difference in either PFS or OS between the patients with classic cytogenetic findings and those with ACAs (P = .34 and P = .14 overall, respectively) who were receiving imatinib as first-line therapy. Comparisons were not performed for patients with variant Ph translocations because of the small number of patients in this group. The presence of ACAs with a variant Ph translocation at diagnosis in only 1 patient did not allow us to assess the impact of such an association.

DISCUSSION
In the current study, we observed a frequency of ACAs of 4.3% for children and adolescents at the diagnosis of CML in the chronic phase; this was similar to the frequency (5.6%-6.9%) recently reported for adults. The frequency of ACAs has been reported to be higher for adults with CML in advanced phases. In contrast to the larger cohorts of adults with ACAs, our study revealed that additional abnormalities were found in a lower proportion of mitoses. In CML patients, ACAs are classified according to their frequencies as major-route abnormalities (the most common including trisomy 8, trisomy Ph [duplication of Ph; der(22)t(9;22)(q34;q11)], isochromosome 17 [i(17)(q10)], and trisomy 19) or minor-route abnormalities (less common), and they were initially described in patients with clonal evolution of the disease under treatment. According to the World Health Organization classification, the presence of ACAs at diagnosis is not considered a criterion of an advanced phase. The emergence of ACAs during the course of treatment in the imatinib era is considered to be a form of treatment failure. However, the European LeukemiaNet recommendations consider the presence of ACAs at diagnosis as a warning feature requiring close monitoring and as an adverse prognostic factor (particularly the major-route abnormalities).

Because of the limited number of patients with ACAs in the current study, the prognostic significance of each specific cytogenetic abnormality was not assessable. The proportion of optimal responses, based on the achievement of a CCyr, in children with ACAs seems to be similar to the rate observed in the group of children with classic translocations and is associated with PFS and OS rates, which did not significantly differ in the 2 groups. The 2 patients with major-route ACAs (trisomy 8 and an extra copy of Ph) were alive in deep molecular response (molecular response 4.0) after a switch to a second-generation tyrosine kinase inhibitor or stem cell transplantation. The death recorded in this group occurred in a patient with an inv(3) after failure to achieve a cytogenetic response. Wang et al recently reported a relatively good prognosis for patients with trisomy 8 and an extra copy of Ph, whereas i(17)(q10), –7/7q (–7/del7q), and 3q26.2 rearrangements were associated with adverse survival.

In the current study, variant Ph translocations were observed at the diagnosis of CML in 1.7% of children and adolescents. Such a frequency seems to be lower than the frequency of 5% to 10% observed in adults with CML. Double-fusion fluorescence in situ hybridization may be a useful tool for investigating the mechanism leading to the generation of the variant translocations. A mechanism including 1 or 2 steps leading to the variant was identified in adults with CML. However, the retrospective nature of the current study did not allow us to perform double-fusion fluorescence in situ hybridization. Similarly, we were unable to look at the frequency of der(9) deletions, which have been reported to occur more frequently in patients with variant Ph translocations, although this is not likely to affect our conclusions for children because der(9) deletions appear to have no influence on the treatment response or outcome. Five different chromosomes were involved as the third or fourth chromosomes in the variant Ph translocations in the pediatric cohort described here. Chromosomes 1 and 8 were the most involved chromosomes, but we did not identify any clusters of specific breakpoints. In the largest cohort of variant Ph translocations described in adults with CML in the chronic phase, chromosome 17 was mostly involved. Although such cytogenetic changes could be interpreted as the expression of an underlying genomic instability, the prognostic significance of such abnormalities remains controversial. In a recent study in adults treated in the imatinib era, the presence of a variant translocation had no impact on the response to the treatment or on the outcome. Based on previous studies, the latest European LeukemiaNet recommendations consider variant Ph translocations to have no value for prognosis. However, in the current study, the PFS and OS rates reported for the children with variant translocations were lower than the rates reported for adults.
ACAs and a variant Ph were observed in 1 of our patients. Among 79 adults with ACAs, Fabarius et al. reported 6 patients with such a combination. The presence of ACAs with a variant translocation at diagnosis in only 1 patient did not allow us to assess the prognostic significance of such an association.

In conclusion, with the limitation of the small number of patients, ACAs at diagnosis could not be considered an adverse prognostic factor in children and adolescents with CML in the chronic phase under imatinib. Therefore, the current work does not support a different and specific treatment for pediatric CML with ACAs or variant Ph translocations at diagnosis but suggests that careful monitoring should be performed for these children. The collection of cytogenetic data within the I-CML-Ped Study will continue to confirm or not confirm this finding. Also, in the era of qRT-PCR, conventional cytogenetics using a banding technique represents a cornerstone for diagnosis and prognostic considerations.

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CONFLICT OF INTEREST DISCLOSURES
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AUTHOR CONTRIBUTIONS
Frédéric Millot: Literature search, study design, data analysis, data interpretation, writing, collection, critical revision of the manuscript, and approval of the final manuscript. Christelle Dupraz: Data collection, critical revision of the manuscript, and approval of the final manuscript. Joelle Guilhot: Literature search, study design, data analysis, data interpretation, writing, data collection, critical revision of the manuscript, and approval of the final manuscript. Meinolf Suttorp: Literature search, study design, data analysis, data interpretation, writing, data collection, critical revision of the manuscript, and approval of the final manuscript. Christelle Dupraz: Data collection, critical revision of the manuscript, and approval of the final manuscript. Thierry Leblanc: Data collection, critical revision of the manuscript, and approval of the final manuscript. Evelyne De Bont: Data collection, critical revision of the manuscript, and approval of the final manuscript. Christelle Dupraz: Data collection, critical revision of the manuscript, and approval of the final manuscript. Srdjana Culic: Data collection, critical revision of the manuscript, and approval of the final manuscript. Michael Dworzak: Data collection, critical revision of the manuscript, and approval of the final manuscript. Emilia Kaiserova: Data collection, critical revision of the manuscript, and approval of the final manuscript. Barbara De Moerloose: Data collection, critical revision of the manuscript, and approval of the final manuscript. Farah Roula: Data collection, critical revision of the manuscript, and approval of the final manuscript. Andrea Biondi: Data collection, critical revision of the manuscript, and approval of the final manuscript. André Baruchel: Data collection, critical revision of the manuscript, and approval of the final manuscript. François Guilhot: Data collection, critical revision of the manuscript, and approval of the final manuscript.

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