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de Bruijn, Clara M. A.; Millot, Frederic; Suttorp, Meinolf; Borisevich, Marina; Brons, Paul; Lausen, Birgitte; de Bont, Eveline S. J. M.

Published in:
British Journal of Haematology

DOI:
10.1111/bjh.15826

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
de Bruijn, C. M. A., Millot, F., Suttorp, M., Borisevich, M., Brons, P., Lausen, B., & de Bont, E. S. J. M. (2019). Discontinuation of imatinib in children with chronic myeloid leukaemia in sustained deep molecular remission: results of the STOP IMAPED study. *British Journal of Haematology*, *185*(4), 718-724. https://doi.org/10.1111/bjh.15826

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bjh research paper

Discontinuation of imatinib in children with chronic myeloid leukaemia in sustained deep molecular remission: results of the STOP IMAPED study

Clara M. A. de Bruijn,[1] Frédéric Millot,[2] Meinolf Suttorp,[3] Marina Borisevich,[4] Paul Brons,[5] Birgitte Lausen[6] and Eveline S. J. M. de Bont[1]

[1]Departments of Paediatric Oncology/Haematology, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands, [2]Departments of Paediatric Oncology/Haematology, Poitiers University Hospital, Poitiers, France, [3]Paediatric Haemato-Oncology, Medical Faculty, Technical University, Dresden, Germany, [4]Belarusian Research Centre for Paediatric Oncology, Haematology and Immunology, Minsk, Belarus, [5]Departments of Paediatric Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, and [6]Department of Paediatrics and Adolescent Medicine, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Received 13 October 2018; accepted for publication 4 January 2019

Correspondence: Eveline S. J. M. de Bont, Department of Paediatric Oncology/Haematology, Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, PO Box 30 001, 9700 RB Groningen, The Netherlands.
E-mail: edebont@elkerliek.nl

Summary

This international study aimed to assess the effect of imatinib discontinuation in paediatric patients with chronic myeloid leukaemia (CML) after deep molecular remission (DMR) had been achieved and maintained for at least 2 years. The primary endpoint of this analysis was the molecular relapse-free survival, estimated by the non-parametric Kaplan-Meier method. Major endpoint was the estimated rate of patients without molecular relapse at 6 months. Fourteen patients were enrolled; 4 patients maintained DMR with a follow-up of 24 (two patients), 34 and 66 months, respectively, whereas 10 patients relapsed. All molecular relapses occurred within 6 months (median 3 months, range 1–6) after imatinib discontinuation. The overall probability of maintaining DMR at 6 months was 28·6%. No parameters associated with molecular relapse could be identified. Keeping in mind the rarity of paediatric CML, which contributed to the small size of the cohort, our findings illustrate that imatinib cessation after sustained DMR is successful in only limited numbers of patients, whereas much higher rates are reported in adult patients. Further research is needed to extend the cohort of paediatric CML patients who might achieve treatment-free remission with an ideal prerequisite of predicting the occurrence of molecular relapse l after imatinib cessation.

Keywords: chronic myeloid leukaemia, paediatric CML, deep molecular remission, discontinuation of imatinib, treatment-free remission.

Imatinib (Glivec®, Gleevec®), a first generation tyrosine-kinase inhibitor (TKI), was proposed as first-line treatment for newly diagnosed paediatric patients with chronic myeloid leukaemia (CML) in December 2002 (Suttorp & Millot, 2010). The introduction of imatinib dramatically changed the prognosis of CML both in adult and paediatric patients compared to previous chemotherapeutic treatments (Millot *et al*, 2011; Suttorp *et al*, 2018). Achievement of at least major molecular remission (MMR) in a time dependent-fashion is associated with the best long-term outcome, with a duration of life comparable with that of the general population in adults (Baccarani *et al*, 2009; Bower *et al*, 2016).

Although the treatment with imatinib is well tolerated by the majority of children, there are adverse side effects associated with the drug (Millot *et al*, 2011; Steegmann *et al*, 2016; Suttorp *et al*, 2018). Besides the cardiac side effects observed in adult patients (Kerkela *et al*, 2006; Ribeiro *et al*, 2008), long-term side effects of imatinib treatment specifically described in children and young adolescents comprise longitudinal growth suppression and possible impaired fertility (Christopoulos *et al*, 2008; Mariani *et al*, 2011; Zamah *et al*,

First published online 6 March 2019
doi: 10.1111/bjh.15826

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2011; Millot *et al*, 2014a). Also, lifelong treatment with an expensive TKI, such as imatinib, one of the most successful cancer targeted therapies, poses a financial burden on health care systems (Experts in Chronic Myeloid Leukemia 2013). These physical and financial concerns highlight the importance of assessing the efficacy of stopping imatinib in patients with CML.

The promising results of the multi-centre 'Stop Imatinib' (STIM) study, which evaluated the persistence of complete molecular response after imatinib discontinuation in a large cohort of adult patients with CML was published by Mahon *et al* (2010); 41% remained in molecular response after at least 12 months of follow-up. Most cases of molecular relapse occurred within 6 months after stopping imatinib. All relapsed patients were treated again with imatinib and achieved a second molecular remission (Mahon *et al*, 2010). A more recent analysis by Saussele *et al* (2018), evaluating TKI discontinuation in 755 adult patients who had received TKI treatment for at least 3 years and maintained a confirmed deep molecular remission (DMR) for at least 1 year, reported even better results. Molecular relapse-free survival for these patients was 61% at 6 months and 50% at 24 months (Saussele *et al*, 2018). Information regarding imatinib discontinuation in paediatric patients with sustained DMR is very limited due to the small number of cases (Millot *et al*, 2011, 2014b; Moser *et al*, 2014; Suttorp *et al*, 2018). Given the rarity of paediatric CML, this analysis aimed to assess the effect of discontinuation of imatinib by analysing data from the International Paediatric CML (I-CML-ped) study arising from a large international registry of children with CML.

Methods

The international registry for paediatric CML patients is an initiative under the umbrella of the CML committee of the international Berlin-Frankfurt-Munster (I-BFM) Study Group. Paediatric patients with a confirmed diagnosis of Philadelphia chromosome-positive (Ph+) CML in chronic phase (CML-CP), treated with imatinib for at least 3 years, and maintaining DMR for at least 2 years, might discontinue treatment according the I-BFM recommendations (de la Fuente *et al*, 2014). Data was collected from September 2015 to January 2016, and retrospectively analysed. Standard treatment with imatinib 260–340 mg/m^2 was initiated after the diagnosis of CML was confirmed. Previous treatment with hydroxycarbamide or interferon alpha was allowed. Patients who had received previous allogeneic haematopoietic stem-cell transplantations were excluded. Data of 18 paediatric CML patients were collected: all patients were obtained from the international registry of CML in children and adolescents. Four patients were excluded; two due to incomplete data forms, one due to intermittent imatinib on-off treatment every 2 months because of psychological reasons, and one due to data inconsistencies. In total, 14 patients who fulfilled the eligibility criteria were statistically analysed. International recommendations applicable to the study were strictly observed (de la Fuente *et al*, 2014). Informed consent was given for all patients.

Age, sex, results of complete peripheral blood counts, bone marrow aspiration, cytogenetic features and molecular biology at time of diagnosis were retrospectively collected for patients who stopped treatment. Standard cytogenetic analysis was carried out on 20 cells in metaphase, to detect Ph+ metaphases and other possible additional chromosomal aberrations. Patients were monitored by quantitative reverse transcription polymerase chain reaction (qPCR) to detect the *BCR-ABL1* transcript. Following the internationally agreed definition of DMR in adult patients (Baccarani *et al*, 2009), DMR was defined as undetectable *BCR-ABL1* mRNA transcripts in two consecutive samples with the use of qPCR, with a sensitivity of $>10^{-4}$ or a ratio of *BCR-ABL1* to *ABL1* (or other housekeeping genes) $\leq$0·01% on the international scale (IS). Sustained DMR was defined as a remission lasting more than 2 years and confirmed with at least six *BCR-ABL1* measurements during these 2 years.

The international recommendations suggest that, after imatinib cessation, the molecular response should, preferably, be assessed every 4 weeks during the first year and every 2 months in the second year. For the third year and beyond, for indefinite time *BCR-ABL1* evaluation is recommended every 3 months. Molecular relapse was defined as detectable mRNA transcripts assessed by qPCR, with a sensitivity of $>10^{-4}$ (IS, $\geq$0·01%^{IS}) on two measurements within an interval of 2–4 weeks. In case of molecular relapse, patients had to restart and resume TKI, according to guidelines (de la Fuente *et al*, 2014). Details regarding the date of molecular relapse, date of TKI restart and type of restarted TKI were collected on standardized forms. Guidelines advised to evaluate treatment response by molecular analysis of peripheral blood at least 1, 3 and 6 months after restart of TKI (de la Fuente *et al*, 2014).

The primary analysis of the collected data consisted of an evaluation of the molecular relapse-free survival. Time to molecular relapse was measured from the date of imatinib discontinuation to the date of molecular relapse or the date of last molecular examination for patients that did not relapse. The molecular relapse-free survival was estimated by the non-parametric Kaplan-Meier method. The major endpoint was the estimated rate of patients without molecular relapse at 6 months. Secondary analyses included evaluations of prognostic factors. Prognostic factors potentially associated with persistence of DMR were age, sex, time from diagnosis to the onset of imatinib, imatinib treatment duration (overall and until the first DMR was recorded) and duration of DMR until TKI discontinuation. Quantitative factors were categorized into groups, with cut -offs set at the median value. The various parameters were firstly, investigation by univariate analyses, using the Kaplan Meier method and the two-tailed log rank-test. Secondly, all parameters with a significant

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outcome were entered into a Cox-regression model. The proportional Hazard assumption was checked individually for each prognostic factor. Statistical analyses were performed using SPSS statistical software (IBM SPSS Statistics 22, IBM Corp., Armonk, NY, USA), considered an overall alpha of 0·05 for final analyses, figures were created with the use of R (R Project for Statistical Computing® version 3.3.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

The analysed data comprised a median follow-up of 105 months (range 51–183). The patients' characteristics are summarized in Table I. Six males and eight females (ratio 0·75) were followed with a median age at time of discontinuation of imatinib of 14 years (range 9–23). Patients had been diagnosed with CML between March 2000 and August 2011 and exhibited transcript phenotypes with junctions of e13a2 (n = 1), e14a2 (n = 11) and both e13a2 and e14a2 (n = 1), whereas data of the transcript phenotype of one patient was lacking. All patients were in CML-CP at time of diagnosis; with no history of progression to accelerated phase or blast crisis. Median time between diagnosis and start of imatinib was 9 days (range 0–32) with the exception of one patient who started imatinib treatment 28 months after diagnosis in March 2000, due to the fact that imatinib was not yet approved for minors at that time. During that period this patient's treatment consisted of interferon alpha 2b in combination with cytarabine as part of a study (Millot *et al*, 2002). A total of four patients received treatment with hydroxycarbamide for a median period of 23 days (range 13–28) before imatinib initiation. Haematological remission was achieved after a median of 2 months (range 2–9) and complete cytogenetic remission was obtained after a median of 6 months (range 2–44). Patients achieved a major molecular response (MMR) within a median interval of 6 months (range 2–16) after the start of imatinib treatment. However, the precise data on the first time when MMR was achieved were missing in 5 patients. DMR was obtained in all patients after a median of 16 months (range 6–91) on imatinib. After achieving DMR, imatinib therapy was continued for a median of 49 months (range 19–92). Total median duration of imatinib therapy was 64 months (range 32–157, Table I). The reasons for imatinib discontinuation were prolonged complete molecular response (n = 13) and patient/parent decision (n = 1), which was based on stunted growth. None of the patients stopped imatinib because of toxic effects.

A confirmed molecular relapse occurred in 10 out of 14 patients after a median of 3 months (range 1–6) after discontinuing imatinib. One patient relapsed after 1 month of imatinib cessation, two patients after 2 months, two patients after 4 months, three patients after 3 months and one patient each relapsed after 5 and 6 months of imatinib cessation. TKI therapy, either imatinib (n = 7) or dasatinib (n = 3), was resumed in all patients. As assessed after restart of TKI

Table I. Patients characteristics.

Patient	Age at IM cessation (years)	Gender	Time from CML diagnosis to IM therapy (days)	Time to CCyR after start of IM (months)	Time to DMR after start of IM (months)	Duration of IM therapy after DMR (months)	Total duration of IM therapy (months)	Molecular relapse	Duration of DMR after IM cessation (months)	Achieved second DMR	Duration of TKI retreatment until second DMR (TKI, months)
1	12	Female	0	9	9	47	56	Yes	4	Yes	DAS, 15
2	13	Female	9	5	9	79	88	Yes	4	Yes	IM, 5
3	13	Female	3	7	12	19	31	Yes	1	Yes	IM, 3
4	14	Male	2	9	12	45	57	Yes	3	Yes	DAS, 2
5	19	Female	0	6	15	42	57	Yes	3	Yes	IM, 12
6	18	Male	13	6	16	27	43	Yes	3	Yes	IM, 5
7	9	Male	32	3	20	52	72	Yes	2	Yes	IM, 19
8	13	Female	632	7	21	76	97	Yes	6	Yes	DAS, 34
9	19	Female	18	3	24	48	72	Yes	5	Yes	IM, 15
10	11	Male	0	4	78	25	103	Yes	2	Yes	IM, 1
11	13	Male	27	2	12	32	45	No	66	N.A.	N.A.
12	11	Male	31	6	16	92	108	No	34	N.A.	N.A.
13	15	Female	0	5	33	47	80	No	24	N.A.	N.A.
14	23	Female	21	44	91	66	157	No	24	N.A.	N.A.

CCyR, complete cytogenetic remission; CML, chronic myeloid leukaemia; DAS, dasatinib; DMR, deep molecular remission; IM, imatinib; N.A., not applicable; NI, nilotinib; TKI, tyrosine kinase inhibitor.

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treatment by qPCR, all relapsed patients re-achieved DMR within a median time interval of 8·5 months (range 1–34). In this analysis, no cases of progression to advanced phase were seen and all patients are still alive.

With a follow-up of 24 (two patients), 34 and 66 months, respectively, four patients remained in sustained DMR translating into an overall probability of maintenance of DMR at 6 months of 28·6%. The median molecular relapse-free survival (duration of DMR) was determined to be 4 months (95% confidence interval [CI], 2·2–5·8 months), using the Kaplan-Meier method (Fig 1). Age, sex, time from diagnosis to the onset of imatinib, imatinib treatment duration (overall and until the first DMR was recorded) and duration of DMR until TKI discontinuation were not significant predictors of sustained DMR. Univariate analyses identified no significant predictive factors; consequently, no Cox regression model was performed.

Discussion

Rationale for performing this analysis

Since the introduction of imatinib treatment in 2002 for children with CML, the group of patients achieving a sustained DMR has increased. Besides financial concerns regarding treatment with an expensive and possibly life-long treatment, the risk of adverse long-term effects highlights the importance of studying the feasibility of stopping imatinib in paediatric patients. Previous studies on adult CML patients who discontinued imatinib after a sustained DMR have shown encouraging results (Mahon *et al*, 2010; Saussele *et al*, 2018). Due to the low incidence of CML in children data regarding imatinib cessation in paediatric patients is very limited (Millot *et al*, 2014b; Moser *et al*, 2014). This current study is based on an international collaboration with 13 countries, having enrolled 470 patients in the I-CML-ped registry.

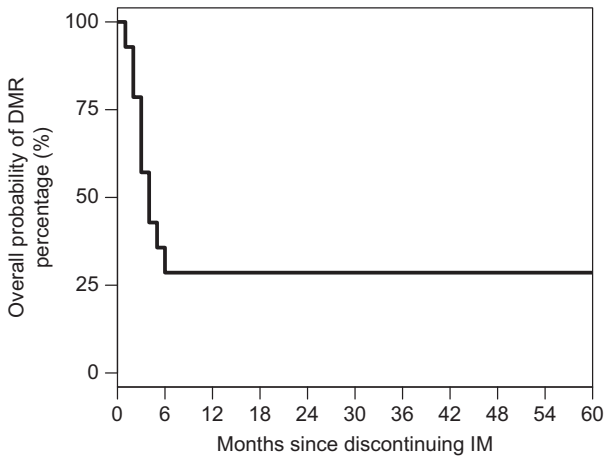

Fig 1. Kaplan-Meier estimates of DMR after stopping imatinib in children with chronic myeloid leukaemia. The estimated molecular-relapse free survival in 14 children was 28% (95% confidence interval, 2·2–5·8 months) at 6 months. Four out of fourteen patients maintained DMR with a median follow-up of 29 months (range 24–66). DMR, deep molecular remission; IM, imatinib.

Differences between this analysis and the adult stopping studies

Our study showed that the majority of paediatric patients experienced a molecular relapse after imatinib discontinuation, whereas only 28·5% remained in DMR. This rate is considerably lower than the 50% rates of sustained DMR after imatinib discontinuation in the adult STIM and EURO-SKI studies (Mahon *et al*, 2010; Saussele *et al*, 2018).

An important difference is that this paediatric stopping study design represents a retrospective analysis from data accumulated out of an international registry and was not conducted prospectively, as is the case for most adult trials. The low incidence of paediatric CML resulted in a rather long recruitment period of 8 years (2008–2015, see Table SI). Data emerging from adult stopping studies might have exerted an influence and biased decisions taken in paediatric patients (Saussele *et al*, 2016). The small number of paediatric cases must always be kept in mind. In comparison with two published paediatric trials (Millot *et al*, 2011; Suttorp *et al*, 2018), the proportion of paediatric patients with CML-CP qualifying for a stopping attempt in the current study varied between 3% and 22%, while the resulting rates of a successful drug cessation were almost identical (28–30%) (Table II).

In contrast to data from adults (Mahon *et al*, 2010; Saussele *et al*, 2018), age, sex, time from diagnosis to the onset of imatinib, imatinib treatment duration and duration of DMR until TKI discontinuation had no statistically significant impact on maintaining DMR in our cohort. These differences are probably caused by the fact that our study was not adequately powered to identify any significant changes in the parameters associated with a molecular relapse.

The definition of molecular relapse applied in this paediatric study was rigorous, as the reappearance of a positive PCR signal classified failure of a stopping TKI attempt, which had to be confirmed within a month (Table SI). This contrasts to large adult trials (e.g. EURO-SKI, STIM2, for an overview see Saussele *et al*, 2016), which mostly use loss of MMR (0·1% *BCR-ABL1/ABL1*^{IS}) to define relapse. However, only 3 out of 10 paediatric patients with failure experienced low level PCR positivity (minimal sensitivity threshold of 10^{-4} *BCR-ABL1* transcripts), which would be tolerated nowadays in most adult stopping trials, while loss of MMR, >2 log-fold increase and >1 log-fold increase of the *BCR-ABL1* transcript was observed in 3 patients, and 2 patients each, respectively (Table SI).

Comparable to the results of the adult cessation studies, all paediatric patients experienced molecular relapse within 1–6 months after treatment was stopped. Also, all relapsed

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Table II. Comparison of the sparse data available on stopping imatinib in paediatric CML controlled trials.

Cohort	Cohort size → qualified for stopping	Proportion that successfully stopped imatinib	Reference
International CML registry	470 → 14 (3%)	4/14 = 28%	Present study
CML- paediatric II study	140 → 7 (5%)	2/7% = 29%	Suttorp *et al* (2018)
French paediatric study IV	44 → 10 (22%)	3/10 = 30%	Millot *et al* (2011)

paediatric patients regained a second DMR after TKI retreatment, demonstrating that temporary imatinib cessation is safe. While the adult STIM study reported a median time of 3 months (range 1–5) necessary for DMR to recur after re-initiation of TKI treatment (Mahon *et al*, 2010), our cohort revealed that a longer period of retreatment was necessary with a median time of 8·5 months (range 1–34).

Reasons that possibly explain the differences observed

The discordance in results between our study and the adult imatinib cessation studies presently cannot be explained. Although, at diagnosis of CML, children, adolescents and young adults present with more aggressive clinical features of CML and a genomic *BCR-ABL1* breakpoint distribution pattern in the *BCR* gene in childhood that differs from adult CML, this hardly can be the reason for a poorer success rate in cessation of TKI after many years of treatment and with a DMR tumour burden comparable to adult patients (Krumbholz *et al*, 2012; Castagnetti *et al*, 2015; Saussele *et al*, 2018). Most probably, the criterion of molecular reappearance of the *BCR-ABL1* signal twice within 4 weeks without defining an upper threshold (e. g. minimum of at least 1 log increase, loss of MMR) also resulted in inclusion of cases with fluctuations in the transcript ratio on a low level. Blaming differences in the immune response between children and adults is also tempting but still speculative.

Influence on the sensitivity of the PCR-assays

As international collaboration is needed for TKI cessation studies in paediatric CML patients, problems concerning laboratory standardization arise. Apart from inter-laboratory variations, such as variations in housekeeping genes, RNA extraction, PCR platform, RT-PCR protocol and inter-operator variation, which may led to inter-centre differences in assay sensitivity, uncertainty regarding the best threshold to determine DMR still exists (Saussele *et al*, 2016). It is notable that the adult STIM study performed centralized measurements and therefore inter-laboratory variations were not applicable. Moreover, the STIM study determined the DMR with a sensitivity of log5 ($<10^{-5}$) in a large cohort (Mahon *et al*, 2010). Establishment of different sensitivity thresholds, including log4·5 ($<10^{-4{\cdot}5}$(IS)) or log5 ($<10^{-5}$(IS)), influence the quality and definition when determining DMR. Due to difficulties in the qPCR technique, not all laboratories are able to perform *BCR-ABL1* transcript detection with log5 sensitivity levels. Therefore we adhered to a minimal sensitivity of log4 ($<10^{-4\ (IS)}$) in our analysis to determine DMR. In the end, a possible discordance between the desirable threshold and the best technically-achievable threshold should be taken into account in future studies. Further research is needed to increase the database and extend the cohort of paediatric patients with CML who discontinue imatinib, with the aim to establish algorithms for a better approach for predicting occurrence of molecular relapse after imatinib cessation.

2nd generation TKIs or stepwise TKI reduction as future approaches

Furthermore, as studies on 2nd generation TKIs have also commenced in children, the proportion of patients who achieve DMR possibly will increase (Kantarjian *et al*, 2011, 2012; Gore *et al*, 2018). Further studies are needed to determine whether rates of sustained DMR after discontinuing 2nd generation TKIs in paediatric CML patients are similar to adults (Saussele *et al*, 2016, Ross *et al*, 2018). Another option for further research could include stepwise reduction in TKI therapy, as recent papers on adult patients highlight that a stepwise reduction in TKI therapy results in higher treatment-free remission rates (Abruzzese, 2017; Clark *et al*, 2017; Fassoni *et al*, 2018). So far, no experience on this approach in paediatric patients has been published. Most importantly, future research should focus on adequately powered prospective paediatric study designs, which only can be achieved by international collaboration.

Conclusions

The overall long-term health of a growing population of paediatric CML patients is the driving force behind stopping therapy. Our findings illustrate that imatinib cessation after sustained DMR was successful only in limited numbers of paediatric patients with CML. This report also highlights the differences between paediatric and adult stopping data. Future prospective trials should be conducted in arger cohorts of paediatric CML patients, in order to accumulate more data that would enable us to predict the occurrence of molecular relapse after TKI cessation. We hope that the data reported here will increase the acceptance of stopping TKI therapy in the paediatric population by clinicians as well as patients and families. Even though discontinuation in paediatric patients has not raised any reported safety issues, we recommend that TKI therapy should only be discontinued within international trials

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if strict monitoring with quality assurance and treatment of TKI withdrawal symptoms, as observed in adults, is guaranteed (Claudiani *et al*, 2016; Saussele *et al*, 2016).

Acknowledgements

The authors would like to thank the national representatives of the IBFM CML study group for participating in this study and Violaine Goyeau from the Departments of Pediatric Oncology/Haematology of Poitiers University Hospital, France, for assisting us with the data collection.

Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

FM, MS, MB, PB, BL and EB enrolled patients, revised the article and gave final approval. CB collected and analysed the data. CB and EB contributed to data interpretation. CB and MS wrote and reviewed this manuscript.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. BCR-ABL1/ABL1 ratio at the last 4 time points (calender date) before a decision of stopping was made and when molecular relapse was diagnosed and confirmed in 10 patients.

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