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Rationale and Design of a Prospective, Multicentre, Stop Tyrosine Kinase Inhibitor Trial of Paediatric Patients with Chronic Myeloid Leukaemia with Sustained Complete Molecular Response (STKI-14)

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ABSTRACT

Chronic myeloid leukaemia (CML) is a relatively rare disease in children, accounting for 2–3% of all paediatric leukaemia cases. Generally, children with CML can avoid hematopoietic stem cell transplantation and achieve molecular responses with tyrosine kinase inhibitors (TKI). However, CML stem cells are thought to survive in many patients, even after TKI treatment. Many aspects of the toxic effects of prolonged exposure to TKIs during childhood remain unclear, particularly those regarding growth impairment. This lack of clarity underscores the importance of the present clinical trial, which aims to clarify the feasibility of treatment-free remission (TFR) in children following TKI treatment. We aim to examine the long-term outcomes and complications of TKIs before and after cessation to better understand the unknown complications that could arise in adulthood. This trial targets patients who were diagnosed with CML at an age younger than 20 years, were in the chronic or accelerated phase at initial diagnosis and remained in complete molecular remission for at least 2 years after TKI administration. We will examine the utility of TKI cessation and assess the treatment results of patients who resumed TKI therapy after losing a major molecular response. We will also investigate factors related to the feasibility of a TFR after TKI cessation.

Key words: *chronic myeloid leukaemia, children, tyrosine kinase inhibitors*

Chronic myeloid leukaemia (CML) is a relatively rare disease in children, accounting for 2–3% of all paediatric leukaemia cases. Most CML patients are diagnosed during adolescence[13], and the median age at diagnosis is approximately 11–12 years. The Philadelphia chromosome (Ph) is reported to be present in 95% of all CML cases[18]. This chromosomal aberration derives from t(9;22)(q34;q11), a balanced translocation of the long arms of chromosomes 8 and 22. Consequently, the *ABL* gene at 9q34 and the *BCR* gene at 22q11 form the chimeric *BCR-ABL* gene, which expresses the constitutively active tyrosine kinase, BCR-ABL. In cells, BCR-ABL subsequently activates various downstream signalling pathways associated with the Ras/MAP, PI3/AKT, and Jak/STAT pathways and thus promotes the production of growth factor-independent cell clones. Accordingly, BCR-ABL contributes to the onset and persistence of leukaemia. At the initial onset of CML, granulocytosis (≥3% basophils) and thrombocytosis appear in the peripheral blood, whereas splenomegaly occurs as the disease pro-

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gresses. Patients younger than 20 years exhibit the following disease phases when they are first diagnosed: chronic phase (89%), accelerated phase (4%) and blastic phase (7%). In other words, most cases are diagnosed during the chronic phase[4].

The International Randomized Study of Interferon versus STI571 (IRIS) trial of adults with chronic-phase CML demonstrated the dramatic effectiveness and safety of imatinib, a tyrosine kinase inhibitor (TKI), and thus reduced the merits of allogeneic hematopoietic stem cell transplantation in patients with chronic-phase disease[3]. Although clinical trials of imatinib for paediatric CML are limited, the effects of this agent in children are expected to be similar to those observed in adults. Accordingly, imatinib is now widely used to treat chronic-phase paediatric CML.

In phase I trials of imatinib conducted by the Children's Oncology Group, the complete cytogenetic response (CCyR) rate was 83% in a 20-case cohort of patients with chronic-phase CML in whom interferon was ineffective[2]. In European phase II trials of advanced or relapsed CML, the CCyR rate was 60% among 20 cases of paediatric chronic-phase CML and 29% among 7 cases of advanced-phase CML. In contrast, no patients with advanced CML achieved a molecular response[9]. In phase IV trials for imatinib in France, the 12-month CCyR and major molecular response (MMR) rates were 62% and 34%, respectively, among 44 children with chronic-phase CML[8]. A phase IV clinical trial of imatinib for 47 children of chronic-phase CML in Berlin-Frankfurt-Munster (BFM), Germany, has preliminarily reported a 12-month CCyR rate of 93% and 18-month MMR rate of 85%[19]. In 2007, a Japanese national study of 166 cases of CML in children aged <18 years reported favourable results. In another study of 76 chronic cases treated initially with imatinib, the 12-month CCyR achievement rate was 79%, the 5-year survival rate was 92%, and the 5-year progression-free survival rate was 91% (the cutoff at time of transfer was 30 cases).

Many paediatric chronic-phase CML patients can avoid hematopoietic stem cell transplantation and achieve a molecular response with imatinib and second-generation TKIs. However, CML stem cells may survive in many patients, even after treatment with TKI[10]. Furthermore, many aspects regarding the toxic effects of prolonged exposure to TKIs during childhood remain unclear. In particular, the potential contribution of TKI use to growth impairment is concerning[17,19]. In a 2007 national study of paediatric patients with chronic-phase CML, 73% of 48 patients exhibited a decrease in their growth standard deviation scores (SDSs) during a mean imatinib treatment duration of 34 months, compared with the SDSs at the beginning of treatment (+0.01 at diagnosis vs. −0.85 after treatment). Marked growth impairment was also observed in younger children (i.e., those who initiated imatinib therapy before adolescence). Long-term follow-up data are needed to evaluate the extent of eventual growth impairment associated with TKI use. Additionally, it is important to conduct clinical trials of TKI cessation and to examine the long-term outcomes and complications of TKI use with the aim of avoiding unknown complications in adulthood.

SUBJECTS AND METHODS

Study design

This study was a multi-centre, open-label, single arm trial and has been registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN000017644).

Currently, there are limited studies that focus on the discontinuation of imatinib in children with CML. However, it is presumed that paediatric patients who sustain long-term complete molecular response (CMR) may be able to discontinue imatinib as many adult patients are able to do. This assumption may be made since molecular genetic characteristics of CML cells are similar in adults and children[20]. Furthermore, the treatment results with imatinib for children with CML are equivalent to those in adults[21]. For our research, we will conduct a study of TKI cessation in patients with CML younger than age 20 in the chronic or accelerated phase at initial diagnosis, and who remained in complete molecular remission for at least 2 years after TKI administration. Our research is based on the evidence obtained from studies that evaluated the discontinuation of imatinib in adults with CML. This study aims to assess the utility of TKI cessation by evaluating the duration of treatment-free remission (TFR) and the treatment effect in those patients who resumed TKI.

Eligibility criteria

Inclusion criteria

1) Patients with *BCR-ABL* chimeric gene-positive CML.
2) Patients who present with the chronic or accelerated phase when first diagnosed.
3) Patients younger than 20 years of age at diagnosis.
4) A total TKI treatment period of ≥3 years; in cases of stem cell rejection, the total treatment period after rejection should be ≥3 years.
5) A complete molecular response (CMR) has been maintained for ≥2 years after TKI treatment.
6) The peripheral blood concentration of major BCR-ABL/ABL messenger RNA (mRNA) ratio is <0.01% on the International Scale within 4 weeks prior to registration.
7) The Eastern Cooperative Oncology Group performance status score is 0–2 at the time of registration.
8) The patient has sufficient organ function according to laboratory data obtained within 7 days prior to registration, thus simultaneously fulfilling conditions (i) and (ii) below.
   (i) Total bilirubin: The total bilirubin concentration is no more than three times the upper limit of normal for the patient's age (Table 1).
   (ii) Creatinine: The creatinine concentration is no more than three times the upper limit of normal for the patient's age (Table 1).
9) Informed written consent from the patient or their legal representative is obtained before participation in

Table 1. Normal Laboratory Ranges by Age[22)]

Age (years)	Total bilirubin: enzymatic method	Creatinine: enzymatic method	
	Upper limit (male and female)	Upper limit (male)	Upper limit (female)
1	0.67	0.33	0.33
2	0.80	0.38	0.35
3	0.85	0.40	0.38
4	0.85	0.43	0.41
5	0.85	0.47	0.45
6	0.85	0.50	0.48
7	0.85	0.53	0.51
8	0.85	0.57	0.55
9	0.90	0.60	0.60
10	0.95	0.65	0.65
11	1.00	0.70	0.69
12	1.10	0.78	0.71
13	1.20	0.85	0.73
14	1.25	0.90	0.74
15	1.30	0.95	0.75
16	1.35	0.98	0.75
17	1.40	1.00	0.75
18	1.40	1.00	0.75
19	1.40	1.00	0.75
20	1.40	1.00	0.75

this trial.

Exclusion criteria

1) The patient has a history of progression to the blastic phase of CML.
2) The patient has a central nervous system haemorrhage of grade three or higher, based on the Common Terminology Criteria for Adverse Events, Version 4.0.
3) The patient has an uncontrolled infectious disease (including active tuberculosis and human immunodeficiency virus infection).
4) The patient is pregnant, nursing, or has a high probability of becoming pregnant.
5) The patient has a history of congenital or acquired immunodeficiency.
6) The Fridericia-revised QTc value at registration is ≥0.45 seconds according to the following formula:
   $QTc = QT/RR^{*1/3}$
7) The patient is deemed unsuitable for the trial by the attending physician(s).

Sample size

The threshold for the TFR rate has been set according to the achievements of adult chronic-phase CML patients. Japanese trials have defined a molecular relapse as >100 copies/0.5 μg RNA of Amp-CML, and the 12-month recurrence-free survival rate after imatinib cessation was 58.1% (n = 41)[7)]. In the STIM trial, TKI treatment was restarted when an MMR was lost, and the 12-month CMR maintenance rate after imatinib cessation was 41% (95% confidence interval [CI], 29–52%; n = 69)[5,6)]. The CML8 TWISTER study considered a CMR loss to be the standard criterion required for a TKI restart, and the reported 24-month TFR rate was 47% (n = 40)[15)]. With reference to these data, we set the TFR rate threshold at 40%. Furthermore, we set the expected TFR rate at 64% per the achievements reported in A-STIM, which assumed that a resumption of standard treatment indicated an MMR loss (major BCR-ABL/ABL mRNA ratio in the peripheral blood >0.1% [international scale]). The calculated sample size of 24, with a one-sided significance level of 0.05 and statistical power of 0.80, was based on the non-parametric method for survival time[1)]. We set the sample size at 25 in consideration of potentially ineligible patients.

Treatment plan

TKI treatment is ceased immediately after the registration of each patient. We then monitor the patient and maintain TKI cessation for as long as the patient remains in a state of MMR. A molecular relapse is determined to have occurred if even one MMR loss is confirmed; this depends on the amount of major BCR-ABL mRNA detected in the peripheral blood. For patients with a molecular relapse, we perform a bone marrow examination (G banding technique) and restart the same TKI that had been stopped within 7 days after the confirmation of an MMR loss. We then evaluate the treatment effectiveness by monitoring the patient after restarting TKI therapy. The study design flowchart is shown in Figure 1.

Monitoring after TKI cessation

1) The following tests will be performed for up to 12 months following TKI cessation:
   (i) The major BCR-ABL/ABL mRNA ratio in the peripheral blood will be assessed monthly. A ratio exceeding 0.1% even once will indicate a molecular relapse (MMR loss). In addition, if the concentration exceeds 0.01% after 12 months, this parameter will be re-tested during the following month.
   (ii) Immune system markers in the peripheral blood will be assessed at months 1, 3, 6, and 12.
   (iii) Natural killer (NK) cell activity will be assessed at months 6 and 12.
   (iv) A quality of life (QOL) survey will be administered at months 2, 6, and 12.

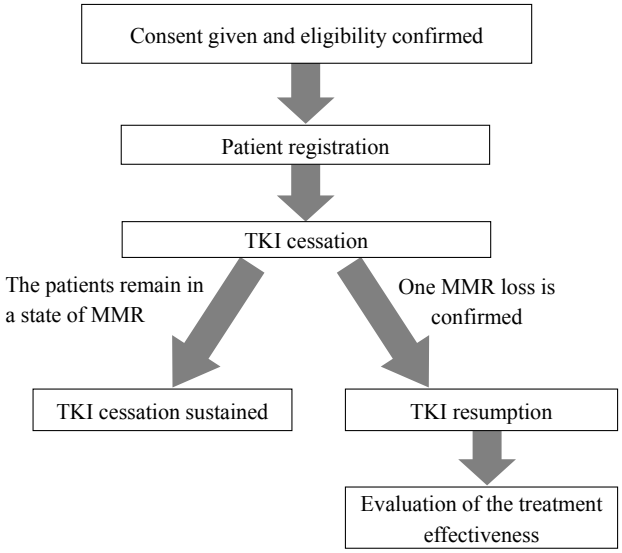

Figure 1. Study Design Flowchart

2) The following tests will be performed from 13 to 24 months after TKI cessation:
(i) The major BCR-ABL/ABL mRNA ratio in the peripheral blood will be assessed every 2 months starting from month 14. A ratio exceeding 0.1% even once will indicate a molecular relapse (MMR loss). In addition, if this concentration exceeds 0.01% after 12 months, we will re-test this parameter during the following month.

(ii) Immune system markers in the peripheral blood will be assessed at 24 months.
(iii) A QOL survey will be administered at 24 months.
3) The following tests will be performed from 25 to 36 months after TKI cessation:
(i) The major BCR-ABL/ABL mRNA ratio in the peripheral blood will be assessed every 3 months from month 27.

A ratio exceeding 0.1% even once will indicate a molecular relapse (MMR loss). In addition, if this concentration exceeds 0.01% after 12 months, we will re-test this parameter during the following month to determine whether this increase reflects a temporary exacerbation.

Monitoring after restarting TKI therapy

The following tests will be performed up to the end of the study period:

(i) The major BCR-ABL/ABL mRNA ratio in the peripheral blood will be assessed every month after resuming TKI use. The frequency of testing can be reduced to a minimum of once every 3 months if two consecutive results yield ratios <0.01%.
(ii) Immune system markers in the peripheral blood will be assessed 1, 3, and 6 months after resuming TKI.
(iii) Bone marrow examinations (G banding technique) will be performed and bone marrow markers will be assessed (only in patients with CCyR losses prior to resuming the TKI) at months 1, 3, 6, and 12 after restarting TKI. This is not required if the criteria for CCyR are met on two consecutive occasions or if the criteria for MMR are fulfilled even once.
(iv) A QOL survey will be administered 2 and 12 months after restarting TKI and 24 months after TKI cessation.

Outcomes

Primary outcome

The primary outcome of this study is the 12-month TFR rate after TKI cessation. The duration of TFR is defined from TKI withdrawal to TKI restart for any reason or to the last observation date if TKI is not resumed.

Secondary outcomes

1. The cumulative incidence of 12-month MMR loss after TKI cessation.

The MMR loss is defined as at least one peripheral blood major BCR-ABL/ABL mRNA ratio exceeding 0.1%. The duration of MMR maintenance is defined as the interval from the date of TKI cessation to the date of MMR loss. Patients who do not experience a MMR loss or death will be censored on the last observation day.

2. The cumulative 12-month incidence of CMR loss after TKI cessation.

A CMR loss is defined as two or more consecutive peripheral blood major BCR-ABL/ABL mRNA ratios of at least 0.01%; if the value exceeds 0.1%, however, the requirement for two consecutive conditions is waived. The duration of CMR maintenance is defined as the interval from the date of TKI discontinuation to the date of CMR loss. Patients who do not experience a CMR loss or death will be censored on the last observation day.

3. Factors related to TFR.
4. The cumulative incidence of MMR after TKI resumption.
5. The cumulative incidence of CMR after TKI resumption.
6. The growth rates at the time of TKI cessation, during MMR maintenance, and after TKI resumption.
7. Changes in the QOL at the time of TKI cessation, during MMR maintenance, and after TKI resumption.
8. The occurrence of adverse events at the time of TKI cessation, during MMR maintenance, and after TKI resumption.
9. Long-term toxicity.

Data collection

The registered data of the enrolled patients will be collected from participating facilities and submitted via an electronic data capture system.

Statistical analysis

Definition of the analysis datasets

1) The full analysis set comprises all registered and eligible patients who stopped TKI use, excluding cases with errors in the data, multiple entries, and ineligible data.
2) The resumed TKI analysis set consists of all patients who resumed TKI use.

The whole-study efficacy and safety analysis will use the full analysis set. The post-TKI resumption efficacy

and safety analysis will use the resumed TKI analysis set.

Primary endpoint analysis

The Kaplan–Meier method will be used to estimate the cumulative TFR curve after TKI cessation. The confidence interval for the median duration of TFR will be calculated using the Brookmeyer and Crowley method[1]. The 90% confidence interval for the 12-month TFR rate will be calculated using the Greenwood formula.

Secondary endpoint analysis

The cumulative MMR loss incidence will be calculated as the cumulative MMR loss incidence function for all patients that stopped TKI use, after considering competing risks such as TKI resumption prior to a MMR loss. The incidence of CMR loss and the cumulative incidences of MMR or CMR after TKI resumption will be determined similarly.

Factors such as the performance status score, Lansky score, duration of TKI use prior to the start of the trial, duration of CMR maintenance prior to the cessation of TKI, duration required to achieve CMR prior to the cessation of TKI, treatment history prior to the start of the trial, risk score (e.g., Sokal score, Hasford score, EUTOS score) at diagnosis, blood concentration of imatinib at TKI cessation, age at diagnosis and TKI cessation, sex, number of immunocytes including lymphocytes and level of NK activity during the trial, as well as the correlations of these factors with TFR, will be assessed using a Cox proportional hazards model.

The growth-SDS for the growth rate, the QOL, and the occurrences of adverse events will be determined at TKI cessation, during MMR maintenance, and after TKI resumption.

Ethics committee procedure and consent for the study

This trial was approved by the Clinical Research Committee of the Japanese Society of Pediatric Hematology/Oncology and the Ethics Committee of the Keio University School of Medicine.

Written informed consent was obtained from every participant and/or their legal guardian in the study.

Patient recruitment

Patients were recruited at participating institutions that were approved by the Ethics Review Committee for this study. After confirming the eligibility for registration based on the inclusion criteria, case registration was conducted in the electronic data capturing system.

Adverse events

Common Terminology Criteria for Adverse Events Version 4.0 is used for evaluation of adverse events.

Adverse events falling under any of the following are subject to emergency reporting.

(1) Unexpected non-haematological toxicity of grade 4.

(2) All deaths occurring within 30 days from start of protocol treatment to the final administration of investigational drugs.

Safety considerations

If any of the following occurs during the protocol period, the principal investigator (PI) consults the Data and Safety Monitoring Board (DSMB) on discontinuation of the study.

(1) A case of blast crisis occurs.

(2) The number of recurrence cases reaches 14.

The DSMB consists of three experts in Haematology. The DSMB reviews adverse events and recommends the review results for future response including the continuation of registration and the necessity of protocol amendment.

Organization structure

Hiroyuki Shimada is the principal investigator and Haruko Shima is the research secretariat in this study. A total of 32 institutions that belong to Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) participate in the study.

DISCUSSION

Currently, no domestic or international reports have addressed whether it is possible to cease TKI treatment in paediatric CML patients, despite the vital importance of this topic. The existing data regarding the Sokal score[5,6,15], period of interferon administration[15], treatment status prior to interferon administration[16], and period of imatinib treatment[5,6] vary significantly and were extracted from trials of imatinib cessation in adults. In addition, significantly lower levels of CD4-positive regulatory T-cells (Tregs) have been observed in CML patients who achieved a CCyR relative to those who did not achieve CCyR[14]. Moreover, patients who responded favourably to dasatinib had higher concentrations of NK cells and cytolytic T cells, compared to those with unfavourable responses[11], and patients who maintained a CMR after imatinib cessation were found to exhibit higher NK cell ratios and activity levels[12]. Taken together, these earlier findings suggest that tumour immunity is an essential component of a permanent CML cure. However, further research is needed because it is difficult to precisely extract a group in which TKI treatment can be ceased. Accordingly, the present study is based on the concept that identifying the characteristics of paediatric CML patients who can successfully cease the use of TKIs such as imatinib will greatly contribute to future treatment policies for this population.

Study status

This trial was approved by the clinical research committee of the Japanese Society of Pediatric Hematology/Oncology on April 27, 2015. We began registering patients on June 1, 2015 and concluded registration on December 31, 2016. We plan to conclude the follow-up period on December 31, 2018.

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Author contributions

Hiroyuki Shimada, Haruko Shima, Chikako Tono, Yuki Yuza, Hidemitsu Kurosawa, Akihiro Watanabe, Masaki Ito, Hideko Uryu, Kiyoko Kamibeppu, Nobutaka Kiyokawa, and Akihiko Tanizawa designed this trial and drafted the protocols. Akiko Kada conducted the statistical analysis. Akiko M. Saito assisted with drafting the protocols and with conducting the quality control procedures (data management and monitoring). Souichi Adachi provided funding to draft the protocols and finally approved the version to be published.

Competing interests

The authors declare that they have no competing interests.

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