Stichting Kinderoncologie Nederland
SKION
Dutch Childhood Oncology Group
DCOG

International recommendations to discontinue Imatinib/Glivec® in pediatric CML patients with sustained complete molecular response

A collaborative IBFM recommendation of the CML study group

Version 2 DCOG

Title	international collaborative recommendations to discontinue Imatinib/Glivec® in pediatric CML patients with **complete molecular response**.
Indicated patients	Philadelphia chromosome positive patients treated with Imatinib and with **complete molecular response**
Objectives	To be a recommendation for individual physicians and patients who decide to stop Imatinib in pediatric CML patients
Database	Following this recommendation the IBFM CML study group asks to collect the individual results in the database and describe the results in their annual meeting
Patients for this recommendation	Pediatric CML patients treated with Imatinib who have achieved and maintained complete molecular remission* for at least 2 years.
Database	Describe the individual results as IBFM CML study group added to the database (e.g rates of relapses, and duration of complete molecular response after discontinuation of Imatinib, survival and progression and efficacy of restarting Imatinib after molecular relapse.
Medication	No tyrosine kinase inhibitor such as Imatinib, dasatinib e.d.

* CMolR is defined as undetectable mRNA transcripts by RT quantitation and nested PCR with a sensitivity of at least 10^{-4} or as the ratio of BCR-ABL to ABL (or other housekeeping genes) < or = 0.01% on the international scale.

Summary and Background

Chronic myeloid leukemia is a rare disease in children; SEER databases record an incidence of 2% of all leukemias in children < 15 years (accounting for 1 case/million/year) increasing up to 9% in children aged 15-19 years (2.2 cases/million/year).
Presently treatment consists of BCR/ABL kinase inhibitors as first choice drugs, in both adults and children. Only approximately 60% of the treated children have a sibling donor or a good matched non-related donor for stem cell transplantation. All others remain on BCR/ABL kinase inhibitor such as imatinib and/or newer generations of BCR/ABL targeting kinase inhibitors. The management of pediatric CML is recently explicitly described by the international CML study group and published (de la Fuente, 2014).
Recently, several adverse long-term effects have been described in adult series and scarce case reports in children treated with BCR/ABL kinase inhibitors, such as imatinib. For instance, decreased growth development, aberrant bone composition and incomplete pubertal development are reported as a result of long-term treatment with tyrosine kinase inhibitors such as Imatinib. Due to the rareness of the disease in children, collaborating international pediatric studies are lacking.
Many adolescents already discontinue Imatinib themselves. In the meantime, promising results are described in the "STIM"study (small serie of adult CML patients) in which imatinib is stopped; 40% remained in a complete molecular response. Most patients (>90%) with molecular relapse experienced this relapse early (<7 months) after stopping Imatinib. All relapsed patients achieved a second molecular remission after restarting Imatinib. So, the international CML treating physicians of the IBFM are confronted with drug discontinuation of several patients themselves, or with reasons such as impaired growth development and/or complications or toxicity.

Therefore, this international recommendation is proposed to be a guideline for the individual physician who is confronted with patients treated for CML who on individual basis discontinuate Imatinib or who have to stop tyrosine kinase inhibitors as a result of toxicity. The international reference laboratories used for BCR/ABL analysis are board certified and good standardized methods exist internationally to follow the patients during time.

The IBFMSG CML advises that all patients in major complete response who discontinue treatment are reported to the international database at the DCOG or preferably Poitiers???. These observational observations will give insights in unforeseen results on a group level.

This recommendation is an IBFM international guideline from the CML study group. The aim of the IBFM CML study group is to offer the best standard of care to children and adolescents with CML, relying on the improved knowledge of the disease and updated research.

The IBFM CML study group:

Dr. Frederic Millot, (CHAIR)
Unité d'hémato-oncologie pédiatrique
CHU de Poitiers
86 000 Poitiers
France
Tel: 00 33 (0)5 49 44 30 78
Fax: 00 33(0)5 49 44 33 03
Email : f.millot@chu-poitiers.fr

Prof. Dr. Eveline de Bont
Pediatric oncologist/hematologist,
Head pediatric oncology/hematology
Beatrix Children's Hospital,
University Medical Center Groningen (UMCG),
Groningen,
The Netherlands
Tel: +31 50 3614213
Fax: +31 50 3614235
Email: e.s.j.m.de.bont@umcg.nl

Prof. Dr. Meinolf Suttorp
Div. Pediatric Hematology and Oncology
Dpt. of Pediatrics
Univ. Hospital Carl Gustav Carus
Fetscherstr. 74
D-01307 Dresden,
Germany
Tel.: +49 351 458 3522
FAX: +49 351 458 5864
e-mail: meinolf.suttorp@uniklinikum-dresden.de

Prof. Dr. Andrea Biondi,
Professor of Pediatrics
University of Milano-Bicocca
Director, Department of Pediatrics
Hospital S.Gerardo/Fondazione MBBM
Via Pergolesi, 33
20052 Monza (IT)
phone: +39-039-2333513
FAX: +39-039-2301646
Email: abiondi.unimib@gmail.com

Prof. Dr. Andre Baruchel,
Chef de Service
Hématologie-Immunologie Pédiatrique
Hôpital Robert Debré (AP-HP)
48 Bd Sérurier
75935 PARIS Cedex 19
Université Paris Diderot et EA 35-18
Institut Universitaire d'Hématologie
Paris
Tel: +33 1 40 03 53 88
Fax: +33 1 40 03 47 40
Email: andre.baruchel@gmail.com

Denmark: Birgitte Lausen
Div pediatric oncology/hematology
Dpt of Paediat/adolescent medicine,
University Hospital Rigshospitalet
2100 Copenhagen, Denmark
Email: birgitte.lausen@rh.regionh.dk

Canada : Kirk Schultz
Director, Childhood Cancer/ Blood Research
BC Children's Hospital
950 West 28th Avenue, Rm A5-165
Vancouver, Canada V5Z 4H4
Phone: 6048753168
Fax :6048752911
Email : kschultz@mail.ubc.ca

United Kingdom : Josu de la Fuente
Email: Josu.delafuente@imperial.nhs.uk

Belgium: Anne.Uyttenbroeck
Barbara de Moerloose
Email: Anne.uyttebroeck@UZleuven.be
Email: barbara.DeMoerloose@uzgent.be

LIST OF ABBREVIATIONS

AIEOP	Associazione Italiana Ematologia ed Oncologia Pediatrica
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
AML-BFM	AML Berlin-Frankfurt-Münster group
ANC	Absolute neutrophil count
AP	Accelerated Phase
APL	Acute promyelocytic leukemia
BC	Blast crisis
BM	Bone marrow
BSPHO	Belgian Society of Paediatric Haematology-Oncology
CCG	Children's Cancer Group (USA)
CCR	Continued complete remission
CMolR	Complete Molecular remission
CNS	Central nervous system
COG	Children's Oncology Group (USA)
CP	Chronic Phase
CR	Complete remission
CSF	Cerebrospinal fluid
DCOG	Dutch Childhood Oncology Group
DFS	Disease-free survival
EFS	Event-free survival
FAB	French American British
FISH	Fluorescent in situ hybridization
GO	Gemtuzumab ozogamicin
IBFM-SG	International Berlin-Frankfurt-Münster Study Group
ICC (APL)	International Consortium on Childhood (APL)
JMML	Juvenile myelomonocytic leukemia
MDS	Myelodysplastic syndrome
MRC	Medical research council (UK)
MRD	Minimal residual disease
MSD	HLA-matched sibling donor
MUD	HLA-matched unrelated donor
NOPHO	Nordic Society for Paediatric Haematology and Oncology
NR	No response
OS	Overall survival
POG	Pediatric Oncology Group (USA)
PR	Partial response
SCT	Stem cell transplantation
VOD	Veno-occlusive disease
WBC	White blood cell count

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1 OBJECTIVES

This international recommendation is proposed to follow as a physician is confronted with individual patients that discontinuate Imatinib or is confronted with a high morbidity and therefore wants to stop tyrosine kinase inhibitors. Adequate follow up on BCR/ABL levels in the blood will be essential in this guideline. The international reference laboratories used for BCR/ABL analysis are board certified and good standardized methods exist internationally to follow the patients during time.

The IBFMSG CML advises that all patients in major complete response who discontinue treatment are reported to the international database at the DCOG or Poitiers??? Preferences?. These observational observations will give insights in unforeseen results on a group level.

This recommendation is an IBFM international study from the CML study group. The aim of the IBFM CML study group is to offer the best standard of care to children and adolescents with CML, relying on the improved knowledge of the disease and updated research.

2 BACKGROUND AND RATIONALE

2.1 Chronic Myeloid Leukemia (CML) in children

Chronic myeloid leukemia (CML) is a clonal stem cell disorder characterized by the BCR-ABL tyrosine kinase protein; the product of the *BCR-ABL* fusion gene. In over 90% of cases a reciprocal translocation of chromosome 9 and chromosome 22, t(9;22) is found, the so called Philadelphia chromosome.
The BCR-ABL protein has a constitutive tyrosine kinase activity, resulting in an abnormal cell cycle, inhibition of apoptosis and increasing cell proliferation.

CML is a rare disease in children and is diagnosed in approximately 2% of children with leukemia. Recently, the IBFM CML study group described the management of pediatric CML patients (de la Fuente et al 2014). The diagnosis is made by cytomorphological, cytochemical, immunological, cytogenetic and molecular techniques on bone marrow aspirate and peripheral blood. The *BCR-ABL* fusion gene detected by cytogenetic and/or molecular techniques is found in over 90% of all CML cases. In less than 10% of CML patients the classical fusion gene cannot be found; however other translocations of 22q11 to different regions than 9q34 (3%) or multiple translocations involving 3 or more chromosomes (3%) can be found. In these cases molecular techniques are essential to show rearrangements of *ABL* and *BCR* genes to establish the diagnosis (Goldman et al, NEJM 2003).

It is important to realize that the *BCR-ABL* fusion gene is not exclusively found in CML patients; this fusion gene can be detected in 3-10% of childhood leukemia's. On the molecular level the classical BCR-ABL protein (210 kD) can be distinguished by molecular weight from the BCR-ABL fusion protein (190 kD) in ALL and AML. The different proteins are the results of other breakpoints. BCR-ABL (190 kD) positive acute leukemia's ought to be treated in line with ALL or AML protocols.

The disease typically follows two or three phases: (i) a **chronic phase (CP)**; without treatment this progresses within 3 to 6 years into (ii) a somewhat ill-defined **accelerated phase (AP)**, which, in turn will culminate in (iii) **blast crisis (BC)** within 3 to 6 months without treatment. Blast crisis exhibits all features of acute leukemia with either myeloid or lymphoid morphology.

2.2 Treatment protocols before the introduction of Imatinib:

Until the introduction of Imatinib allogenic hematopoietic stem cell transplantation has been recommended as first-line treatment in CML since it is considered to be the only treatment modality with curative potential. (Silver et al review Blood 1999) There is no doubt that allogenic hematopoietic stem cell transplantation (HSCT) can result in cure of CML. However, also after alloSCT very late relapses occur (Goldman JCO 2010). In the pediatric setting cure should be the goal of treatment, rather than delay of disease progression. (Ref: Lange T et al, Leukemia 2005, Cwynarski K et al, BLOOD 2003; Suttorp M et al 2009).

Besides the anti-leukemic effect of myeloablative chemo- and radio-therapeutic conditioning regimens, transplantation outcomes also depend on the alloreactive graft-versus-leukemia effect. Overall survival rates were 60-80% for CML patients transplanted in chronic phase (Pulsipher et al 2004 Kolb et al 1990) However, the procedure has a significant transplant-related morbidity and mortality (i.e. infection, bleeding, rejection, graft-versus host disease, veno-occlusive disease, sterility).

2.3 Introduction of imatinib in pediatric CML

In the 1980's Interferon α (IFN-α) was introduced as a treatment option for patients without a suitable donor. Often IFN-α was combined with cytarabine. This treatment resulted in an increased survival time of 1 to 2 years. Even major cytogenetic responses could be achieved. The introduction of Imatinib (Glivec®) dramatically changed results for patients without a suitable donor.

Imatinib (Glivec®) is a BCR-ABL tyrosine kinase inhibitor, fitting to the BCR-ABL fusion protein resulting in apoptosis and proliferation block. The results of studies with Imatinib are promising (Kantarjian et al, Blood 2003). Patients treated in accelerated phase or blast crises with Imatinib can still respond, albeit for a shorter time (Talpaz et al, Blood 2002, Kantarjian et al, Blood 2002 and Sawyers et al, Blood 2002).

Table 3: Responses of defined subpopulations of CML patients with Imatinib after initial treatment failure

	Imatinib
Chronic phase	
Complete hematological response	95%
Major Cytogenetic response	60%
Accelerated phase	
Complete hematological response	82%
Major cytogenetic response	24%
Blast crisis	
Complete hematological response	52%
Major cytogenetic response	16%

The first randomized trials with Imatinib compared to IFN-α/Ara-C showed not only hematological responses but also a great amount of major or complete cytogenetic responses in the Imatinib treatment group (Hughes et al, 2003).
Moreover, in the light of very late relapses, the study of Hehlmann et al clearly showed that allogenic stem cell transplantation cannot be recommended anymore for front-line therapy in

newly diagnosed CML patients. This published study proposes that initial treatment can consist of a trial with modern drug treatment of tyrosine kinase inhibitors (Helhmann et al, 2007). In those who fail to respond and/or develop intolerance transplantation remains an effective therapeutic solution (Pavlu et al, 2011)

Ongoing studies with Imatinib demonstrated that not only complete hematological and cytogenetic repsonses (Hughes et al, 2003) can be achieved but that in 74% of patients a complete molecular response is achieved. (Baccarani et al, 2004). It still remains unknown whether eventual cure can be reached in CML patients treated with monotherapy Imatinib. Drug resistance of CML clones is thought to result from mutations in the kinase domain of the *BCR-ABL* gene resulting in resistance to imatinib inhibition and subsequent selection advantage of such clones.

An average of 2% incidence of progression to accelerated phase or blast crisis in the first years and less than 1% thereafter over the years for patients who start with imatinib monotherapy in chronic phase has been demonstrated in adults (Druker et al 2006). Unresponsiveness to the drug has been observed more frequently in patients with less than 3 logs of reduction in BCR-ABL transcripts after 12 months of therapy. However, minimal residual disease is reported to continue to decrease over years. Therefore we are confident that achieving a 3 log reduction is an important endpoint, but failure to do so does not necessary indicate failure of therapy. Some of the patients with failure can be rescued by increasing imatinib dose or with other cytoreductive strategies (Kantarjian et al, 2003, Talpaz et al, 2002). Progression free survival is best when major cytogenetic responses are attained within 3 months of the commencement of imatinib. Moreover, patients who remained in complete cytogenetic response for at least 24 months appeared to have a low risk of subsequent cytogenetic relapse (Marin et al, 2005).
Evidence is accumulating that early therapy intensification using high doses of imatinib (800 mg/day for adults) may induce higher rates of complete molecular responses. For example, less than 4% of patients achieved complete molecular response in the IRIS study (Glivec at the standard dose of 400 mg/day), while a rate of 28% was reported in a phase II trial of newly diagnosed CML patients treated with 800 mg/day imatinib daily (Guilhot F for the IRIS study group, 2004, Kantarjian HM, 2004). Moreover, the total %-age of cytogenetic responders as well as major molecular responders is increased. Recent update of concepts and management recommendations are summarized by the European Leukemianet (Baccarani et al 2009).

Recently, recommendations for the treatment of pediatric AML patients on behalf of the IBFM CML study group are published (de la Fuente et al, 2014).

2.4 First results of withholding imatinib in CML patients

Imatinib has greatly improved survival rates in CML. However, side effects are described. Three published case reports in children with CML treated with Imatinib describe growth deceleration. After discontinuation of Imatinib (because of SCT) one patient successfully achieved accelerated growth again (Kimoto et al, 2009), while another patient at the onset of puberty experienced catch-up growth (Mariani S, et al 2008). The third patient is still prepubertal and shows ongoing growths deceleration under Imatinib. (Schmid et al 2009)

In adult series it was demonstrated that long term side effects of imatinib are aberrant bone composition, such as demonstrated in Berman et al and Grey et al (2006). A paper of Fitter et al, (2008) demonstrated an increased trabecular bone formation and a decrease in serum calcium and phosphate related to Imatinib treatment in adult CML patients. This study demonstrated that Imatinib significantly modulates bone turnover in vivo. In children case reports also suggest aberrant bone composition along with decreased growth development (Kimoto et al 2009). Preliminary data of the French pediatric CML group by Millot et al demonstrated that in 22 patients with sufficient data a significant decrease of height standard deviation scores (SDS) was observed (median: -0.37, $p<0.0001$) between start of the imatinib treatment and after 12 months Imatinib treatment (Millot et al 2009). Especially in children these (possible) long-term side-effects are of great importance for the development of the children into adults as healthy as possible.

A pilot study of the first patients (n=12) who discontinued imatinib therapy has been reported (Rousselot *et al. 2*007; Update *ASH 2009 abstract # 859*). This study describes for the first time that discontinuation of Imatinib, resulted in a sustained complete molecular response in 50% of the patients with a median follow-up of 42 (37-49) months after discontinuation. All patients were pre-treated with interferon-alpha (IFN), and most had responded to IFN before imatinib treatment. Koskenvasa et al (ASH abstract # 2008) suggested that previous interferon use was essential to have a sustained molecular response after Imatinib discontinuation in a small group of adult CML patients. Two other case reports underscored the possibility of imatinib withdrawal (Verma et al, 2008 and Guastafierra et al, 2009)

A new, multicenter study the « Stop Imatinib » (STIM) study was started in July 2007 and results were presented at recent ASH meetings (Mahon et al, 2008, 2009) and recently published in the Lancet Oncology 2010 by Mahon et al. The aim of this study was to evaluate the persistence of complete molecular remission (CMolR) after stopping imatinib in a larger cohort. The criteria for inclusion were imatinib treatment for at least 3 years and sustained CMolR. Sustained CMolR was defined as BCR-ABL/ABL levels below a detection threshold corresponding to a 5-log reduction (undetectable signal using RQ-PCR) for at least 2 years. Molecular relapse, defined as RQ-PCR positivity, was taken into account if confirmed in two successive assessments.
This prospective, multicenter, non-randomised study included 100 patients with a median age of 63 years (range 29–80 years). Median follow-up was 17 months and 69 patients had at least 12 months follow-up. Forty-two (61%) of these 69 patients relapsed (40 before 6 months, one patient at month 7 and one at month 19). At 12 months, the probability of persistent CMolR for these 69 patients was 41% (95% CI 29-52). At the time of analysis, all patients who relapsed responded to reintroduction of imatinib: 16 of these 42 patients who relapsed showed decreases in their BCR-ABL levels, and 26 achieved CMolR that was sustained after Imatinib rechallenge. So, this study concludes that imatinib can be safely discontinued in patients with a CMolR of at least 2 years duration. Imatinib discontinuation in this setting yields promising results for molecular relapse-free survival, raising the possibility that, at least in some patients, CML might be cured with tyrosine kinase inhibtors. (Mahon et al 2010)

In conclusion, long-term imatinib use has been correlated with growth disadvantages in children as one of the major side effects. Moreover, bone composition is changed due to imatinib.

Studies in adult CML patients confirm that complete molecular remission can be sustained after discontinuation of imatinib. Relapses occur almost always within 6 months after discontinuation. All relapsed patients could be rescued again with imatinib and showed a good second response upon imatinib. Physicians are confronted with patients/moreover adolescents who want to stop or already stopped this medication.

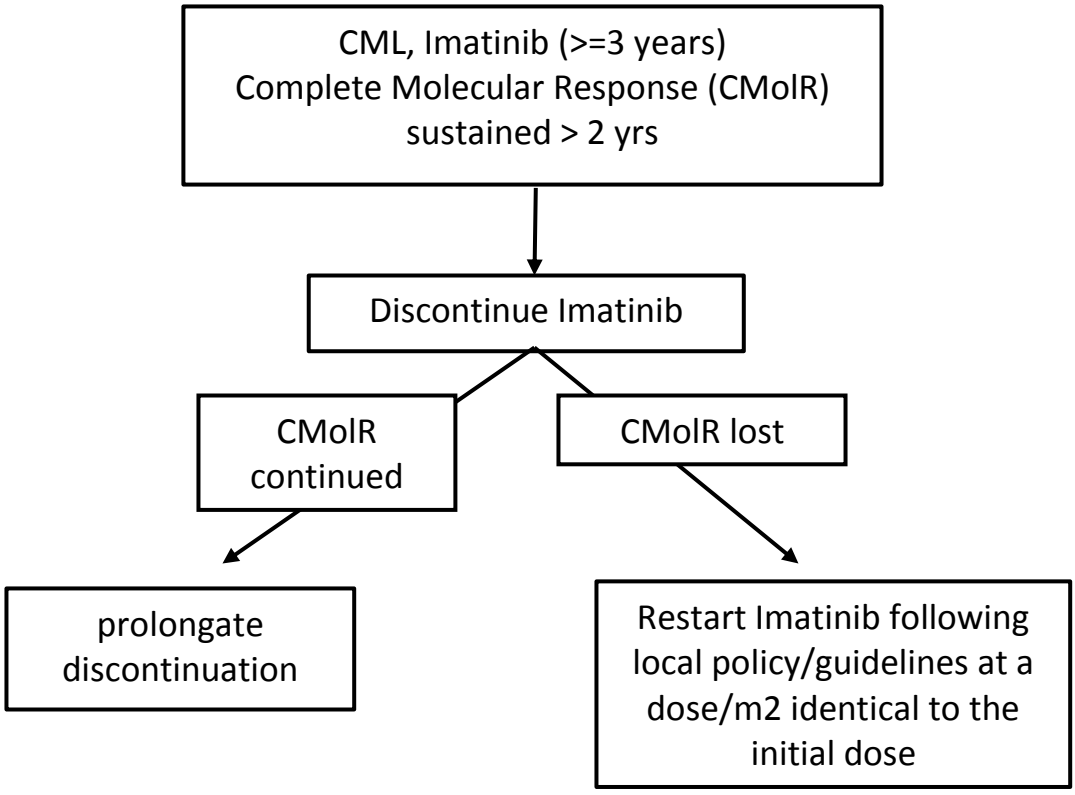
Both results prompted us to prepare recommendations for physicians treating patients who discontinue imatinib. The measurement of the BCR-ABL levels is extremely important to monitor the molecular status of the individual patients to obtain reliable and comparable BCR-ABL analysis. (Further information is given in paragraph 4 and 5.)

3 Considerations for the physicians

- Philadelphia positive CML in chronic or accelerated phase at diagnosis as defined by the diagnostic criteria
- Age $\leq$ 18 years at time of discontinuation
- Preferable sustained complete molecular response for at least 2 years measured at least 6 times during the last 2 years.
- CMolR is defined as: undetectable mRNA transpcripts by RT quantitation and nested PCR with a sensitivity of $>10^{-4}$ or the ratio of BCR-ABL to ABL (or other housekeeping genes) < or = 0.01% on the international scale

4 Guideline

4.1 Recommendation for the follow up of patients who discontinue Imatinib:



Intensive follow up is advised for 24 months after discontinuation of Imatinib. Blood samples for BCR/ABL PCR have to be evaluated at least every 4 weeks or more frequently within the local institution and/or centrally depending on the regulations for each country. When the BCR/ABL shows ongoing complete molecular remission the patient will continue without Imatinib. However, when a loss of Complete Molecular Response is encountered it is recommended that a new blood sample has to be drawn within 2 weeks and the finding of BCR/ABL positive PCR has to be confirmed.

In case of **molecular relapse**, patients should be restarted and resume the identical dose per m^2 of Imatinib or another tyrosine kinase inhibitor immediately following a complete diagnostic work-up according to local policy or following the descriptions in the management of pediatric CML patients (de la Fuente et al, 2014). In the bone marrow aspirate cytogenetic and molecular analysis for BCR/ABL needs to be performed. It is advised to measure the response on restarting treatment by molecular analysis of peripheral blood at least at 1, 3, and 6 months.

4.2 Definitions

In the latest European Leukemianet update the definition for CMolR is defined as undetectable BCR-ABL mRNA transcripts by real time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10^{-4}) (Baccarani et al JCO 2009). Definition is given in Table 1. MOST RECENT!!!!!! check

Table 1: definitions

Molecular**	
Complete (CMolR)	Undetectable BCR-ABL mRNA transcripts by real time quantitative and nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10^{-4}) or ratio of BCR-ABL to ABL (or other housekeeping genes) < or = 0.01% on the international scale.
Major (MMR)	Ratio of BCR-ABL to ABL (or other housekeeping genes) < or = 0.1% on the international scale

- **For a standardized assessment of the MolR, the conversion of each laboratory data of the international scale is mandatory to correct for the variability of the assays in different laboratories. To allow for intralaboratory variations, a fluctuation of less than one log requires confirmation. For this purpose we will use the national reference or regional laboratories collaborating in the harmonization of molecular monitoring of CML therapy in Europe (Muller MC et al, Leukemia 2009). See also Appendix 4.

At this moment there is no consensus in the adult community of CML treating physicians about the exact definition of the cut-off value for the BCR-ABL/ABL level. The abovementioned “STIM” study used as cut-off undetectable transcripts of BCR/ABL with a sensitivity of 10^{-5}. Whereas the upcoming European study concerning the discontinuation of tyrosine kinase inhibitors will use a cut-off of 10^{-4} transcripts of BCR/ABL with a sensitivity of at least 10^{-4}. The IBFM CML study group advises to ask international reference laboratories for this analysis. These laboratories are board certified and good standardized methods exist internationally to follow the patients during time.

Nearly all countries are included in the list of national reference laboratories for BCR/ABL measurements (Muller et al, 2009 (appendix 4)). When countries are not aware of such a laboratory in their neighbourhood they can contact the IBFM CML study group and discuss possibilities of collaboration with others.

Definition of Molecular relapse: that the patient has a ratio of BCR-ABL to ABL (or other housekeeping genes) > or = 0.01% on the international scale on two successive measurements. The two measurements have an interval of 2 weeks.

5 ADVISED EVALUATIONS, TESTS, AND OBSERVATIONS

First of all, it needs to be stated that it is essential to stick to the strict monitoring of the BCR/ABL status preferably every 4 weeks. In case molecular relapse is suspected upon the BCR/ABL measurement, the BCR/ABL analysis needs to be repeated in 2 weeks.

Evaluation preferred:
First year: every month physical examination including weight, height and pubertal development, blood count and **BCR/ABL status**.
Second year: every 2 months physical examination including weight, height and pubertal development, blood count and **BCR/ABL status**.
Third year: every 3 months physical examination including weight, height and pubertal development, blood count and **BCR/ABL status**.
Fourth and fifth years: every 6 months physical examination including weight, height and pubertal development, blood count and **BCR/ABL status**.
Thereafter the Guidelines of each country will be followed.

5.2 Examination during the restart of imatinib treatment at a molecular relapse

We advise to restart imatinib or another tyrosine kinase inhibitor following the published guidelines and/or good clinical practice in each country. We recommend to consult the principal investigator of the country to discuss the possibility of a stem cell transplantation after reinduction.

5.3 Laboratory tests to evaluate BCR-ABL status

The physician himself/herself will perform their molecular assays and is responsible for the adequate BCR-ABL molecular measurement in the country following the guidelines defined in Muller et al 2009.

The BCR-ABL measurement need to be determined by laboratories on the list as a laboratory that is harmonising their BCR-ABL assays internationally, and confirmed by a second analysis point, indicating the increase in relation to the first analysis point at two successive assessments with an interval of two weeks.

6 OPERATIONAL ASPECTS AND DATA COLLECTION

The UMCG and Poitiers will act as a Coordination Unit for the database and exchange of information and pooling of the data.

The archiving of all relevant documents at the local/national centers and at the UMCG and POITIERS will be handled according to national law. Each patient receives an unique patient number (UPN). All study relevant data will be stored electronically and handled confidentially.
The investigators and all members of a centre or other persons involved in the trial are obliged to keep study data and information confidential and to grant access only to individuals who are involved in the study. The database will be send to Clinical Investigation Center, Inserm, Poitiers, for statistical analyses as described before.

References

Baccarani M, Martinelli G, Rosti G et al. Imatinib and pegylated human recombinant interferon-{alpha}2b in early chronic-phase chronic myeloid leukemia. Blood. 2004;104:4245-4251.

Baccarani M, Cortes J, Pane F, Niederwieser D, Saglio G, Apperley J, Cervantes F, Deininger M, Gratwohl A, Guilhot F, Hochhaus A, Horowitz M, Hughes T, Kantarjian H, Larson R, Radich J, Simonsson B, Silver RT, Goldman J, Hehlmann R; European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009 Dec 10;27(35):6041-51.

Champagne MA, Capdeville R, Krailo M et al. Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase 1 study. Blood. 2004;104:2655-2660.

Cwynarski K, Roberts IAG, Iacobelli S et al. Stem cell transplantation for chronic myeloid leukemia in children. Blood. 2003;102:1224-1231.

Fitter S, Dewar AL, Kostakis P, To LB, Hughes TP, Roberts MM, Lynch K, Vernon-Roberts B, Zannettino AC. Long-term imatinib therapy promotes bone formation in CML patients. Blood. 2008 Mar 1;111(5):2538-47.

De la Fuente J, Baruchel A, Biondi A, de Bont E, Dresse MF, Suttorp M, Millot F. Managing children with chronic myeloid leukemia. Br J Haematology 2014; 167: 33-47.

Goldman JM, Druker BJ. Chronic myeloid leukemia: current treatment options. Blood. 2001;98:2039-2042.

Goldman JM, Melo JV. Mechanisms of disease - Chronic myeloid leukemia - Advances in biology and new approaches to treatment. New England Journal of Medicine. 2003;349:1451-1464.

Goldman JM, Majkail NS, Klein JP et al. Relapse and late mortality in 5-year survivors of myeloablative allogenic hematopoietic cell transplantation for chronic myeloid leukemia in first chronic phase. J Clin Oncol 2010; 28: 1888-1895.

Guastafierro S, Falcone U, Celentano M, Coppola M, Ferrara MG, Sica A. Is it possible to discontinue imatinib mesylate therapy in Chronic Myeloid Leukemia patients with undetectable BCR/ABL? A case report and a review of the literature. Leuk Res. 2009 Aug;33(8):1079-81.

Hughes TP, Kaeda J, Branford S et al. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. New England Journal of Medicine. 2003;349:1423-1432.

Kantarjian HM, Cortes J, O'Brien S et al. Imatinib mesylate (ST1571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase. Blood. 2002;99:3547-3553.

Kantarjian HM, Talpaz M, O'Brien S et al. Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. Blood. 2003;101:473-475.

Kantarjian HM, Cortes JE, O'Brien S et al. Imatinib mesylate therapy in newly diagnosed patients with Philadelphia chromosome-positive chronic myelogenous leukemia: high incidence of early complete and major cytogenetic responses. Blood. 2003;101:97-100.

Kantarjian HM, Schiffer CA, Sawyers CL et al. Imatinib (Gleevec (R))) maintains favorable long-term outcomes in chronic-phase chronic myeloid leukemia (CML) for patients failing interferon-alpha (IFN) - Follow-up of a phase II study. Blood. 2003;102:905A.

Karl et al Identification of genomic fusion-sites in BCR-ABL positive childhood CML Klin Padiatrie 2010; 222; 226 (abstract 52)

Kimoto T, Inoue M, Kawa K. Growth deceleration in a girl treated with imatinib. Int J Hematol. 2009 Mar;89(2):251-2.

Kolb HJ, Mittermuller J, Clemm C et al. Donor Leukocyte Transfusions for Treatment of Recurrent Chronic Myelogenous Leukemia in Marrow Transplant Patients. Blood. 1990;76:2462-2465.

Koskenvesa et al Abstract ASH 2008; 112: 2121

Lange T, Bumm T, Mueller M et al. Molecular remission to imatinib in patients with chronic myeloid leukaemia (CML) is less durable compared to patients after allografting. Blood. 2004;104:82A-83A.

Mahon, Francois-Xavier, Huguet, Francoise, Guilhot, et al: Is It Possible to Stop Imatinib in Patients with Chronic Myeloid Leukemia? An Update from a French Pilot Study and First Results from the Multicentre << Stop Imatinib >> (STIM) Study. ASH Abstracts 2008 112: 187

Mahon et al, Discontinuation of Imatinib Therapy After Achieving a Molecular Response in Chronic Myeloid Leukemia Patients. ASH abstract 2009 ; 114 : 859

Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, Legros L, Charbonnier A, Guerci A, Varet B, Etienne G, Reiffers J, Rousselot P; on behalf of the Intergroupe Français des Leucémies Myéloïdes Chroniques (FILMC). Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010 ;11:1029-1035.

Mariani S, Giona F, Basciani S, Brama M, Gnessi L. Low bone density and decreased inhibin-B/FSH ratio in a boy treated with imatinib during puberty. Lancet 2008;372: 111-2.

Marin D, Kaeda J, Szydlo R et al. Monitoring patients in complete cytogenetic remission after treatment of CML in chronic phase with imatinib: patterns of residual leukaemia and prognostic factors for cytogenetic relapse. Leukemia. 2005;19:507-512.

Merx K, Muller MC, Kreil S et al. Early reduction of BCR-ABL mRNA transcript levels predicts cytogenetic response in chronic phase CML patients treated with imatinib after failure of interferon alpha. Leukemia. 2002;16:1579-1583.

Millot F, Guilhot J, Nelken B et al. Imatinib mesylate is effective in children with chronic myelogenous leukemia in late chronic and advanced phase and in relapse after stem cell transplantation. Leukemia. 2006;20:187-192.

Millot F et al, Imatinib Is Efficient but Has a Negative Impact On Growth in Children with Previously Untreated chronic Myelogenous Leukaemia (CML) in Early Chronic Phase (CP): Results of the French National Phase IV Trial**.**ASH abstract 2009; 114: 863.

Morley, Alexander A., Bartley, Paul, Ross, David M, Latham, Sue, Martin-Harris, Henry, Budgen, Brad, Wilczek, Vicki, Branford, Susan, Hughes, Timothy: DNA-Based Monitoring of Minimal Residual Disease(MRD) in Chronic Myeloid Leukemia(CML). ASH Abstracts 2008 112: 1111

Müller MC, Cross NC, Erben P, Schenk T, Hanfstein B, Ernst T, Hehlmann R, Branford S, Saglio G, Hochhaus A. Harmonization of molecular monitoring of CML therapy in Europe. Leukemia. 2009 Nov;23(11):1957-63.

O'Brien SG, Guilhot F, Larson RA et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. New England Journal of Medicine. 2003;348:994-1004.

Olavarria E, Craddock C, Dazzi F et al. Imatinib mesylate (STI571) in the treatment of relapse of chronic myeloid leukemia after allogeneic stem cell transplantation. Blood. 2002;99:3861-3862.

Pavlu J, Szydlo R, Goldman J, Apperley J. Three decades of transplantation for chronic myeloid leukemia: what have we learned? Blood 2011; 117: 755-763.

Pulsipher MA. Treatment of CML in pediatric patients: Should imatinib mesylate (STI-571, Gleevec) or allogeneic hematopoietic cell transplant be front-line therapy? Pediatric Blood & Cancer. 2004;43:523-533.

Ross, Davi D M, Grigg, Andrew, Schwarer, Anthony, Arthur, Christopher, Loftus, Kerryn, Mills, Anthony K, Filshie, Robin, Columbus, Ruth, Reynolds, John, Seymour, John F, Branford, Susan, Hughes, Timothy: The Majority of Chronic Myeloid Leukaemia Patients Who Cease

Imatinib after Achieving a Sustained Complete Molecular Response (CMR) Remain in CMR, and Any Relapses Occur Early. ASH Abstracts 2008 112: 1102

Rousselot P, Huguet F, Rea D, Legros L, Cayuela JM, Maarek O, Blanchet O, Marit G, Gluckman E, Reiffers J, Gardembas M, Mahon FX. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. Blood. 2007 Jan 1;109(1):58-60.

Russo, Domenico, Rosti, et al: Phase II Multicentric Explorative Study of Intermittent Imatinib (IM) Treatment (INTERIM) in Elderly Patients with Ph+ Chronic Myeloid Leukemia (CML) Who Achieved a Stable Complete Cytogenetic Response (CCgR) with Standard IM Therapy. ASH Abstracts 2009 114: 860

Sawyers CL, Hochhaus A, Feldman E et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood. 2002;99:3530-3539.

Shah NP, Tran C, Lee FY et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004;305:399-401.

Schmid H, Jaeger BA, Lohse J, Suttorp M: Longitudinal growth retardation in a prepupertal girl with chronic myeloid leukemia on long-term imatinib treatment. (Letter to the editor). Haematologica; 94: 1177-1179 (2009)

Suttorp M, Claviez A, Bader P, Peters C, Gadner H, Ebell W, Dilloo D, Kremens B, Kabisch H, Führer M, Zintl F, Göbel U, Klingebiel T: Allogeneic stem cell transplantation for treatment of chronic myeloid leukemia in pediatric and adolescent patients: results of the prospective trial CML-paed I. Klin Padiatr 221:351-357 (2009)

Suttorp M, Yaniv I, Schultz K: Controversies in the treatrnent of CML in children and adolescents: TKI versus BMT? Biol Blood Marrow Transplant 17:S115-S122 (2011)

Suttorp M, Millot F: Treatment of Pediatric Chronic Myeloid Leukemia in the year 2010: Use of Tyrosine Kinase Inhibitors and Stem Cell Transplantation. Hematology - ASH Educational Program 2010; p368-376

Talpaz M, Silver RT, Druker BJ et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood. 2002;99:1928-1937.

Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002;100:2292-2302.

Verma D, Kantarjian H, Jain N, Cortes J. Sustained complete molecular response after imatinib discontinuation in a patient with chronic myeloid leukemia not previously exposed to interferon alpha. Leuk Lymphoma. 2008 Jul;49(7):1399-402.

Appendix

1. Data collection forms

2. Here attach data collection forms.

Appendix..

2. .List of reference laboratories from the Muller et al Leukemia 2009, 23: 1957-1963.

Table 3 List of participating laboratories: Country City Name Institution National reference laboratory
Austria Vienna Gerlinde Mitterbauer-Hohendanner
Ehemalige I. Medizinische Universitae tsklinik x
Austria Vienna Thomas Lion Forschungsinstitut fuer krebskranke Kinder
Belgium Brussels Hakim El Housni Erasme Hospital x
Belgium Leuven Nancy Boeckx University Hospital Gasthuisberg x
Croatia Zagreb Renata Zadro Clinical Hospital Center Zagreb x
Czech Republic Brno Jiri Mayer University Hospital Brno
Czech Republic Olomouc Peter Rohon Dept. of Hemato-oncology x (covers Slovakia)
Czech Republic Prague Jana Rulcova UHKT x
Denmark Aarhus Lykke Grubach Immunhaematologisk lab. x
Denmark Odense Niels Pallisgaard Odense University Hospital
Finland Turku Veli Kairisto Turku University Hospital Laboratories x
France Bordeaux Francois-Xavier Mahon Universite´ Victor Segalen
France Lille Claude Preudhomme Laboratoire d'Hematologie A
France Lyon Sandrine Hayette Centre hospitalier Lyon sud
France Marseille Jean Gabert Faculte´ de Medecine Nord
France Paris Jean-Michel Cayuela Hopital Saint-Louis x
Germany Dresden Christian Thiede Universitaetsklinikum Carl Gustav Carus
Germany Duesseldorf Frank Neumann Universitaetsklinikum Duesseldorf
Germany Frankfurt Heike Pfeifer Universitaetsklinikum Frankfurt
Germany Greifswald Frank Schueler Universitaet Greifswald
Germany Hamburg Philippe Schafhausen Universitaetsklinikum Hamburg-Eppendorf
Germany Hannover Nils von Neuhoff Medizinische Hochschule
Germany Jena Thomas Flohr Oncoscreen
Germany Kiel Christiane Pott Universitaetsklinik Schleswig-Holstein, Campus Kiel
Germany Leipzig Thoralf Lange Universitaetsklinikum Leipzig
Germany Mainz Georg He Johannes Gutenberg-Universitaet Mainz
Germany Mannheim Martin Muller/Andreas Hochhaus
Universitaet Heidelberg, Universitaetsmedizin Mannheim x
Germany Muenchen Susanne Schnittger Muenchner Leukaemie Labor
Germany Muenster Utz Krug Universita¨ tsklinikum Mu¨ nster
Germany Ulm Frank Stegelmann Universitaetsklinikum Ulm
Greece Athens Katerina Zoi Foundation for Biomedical Research x
Hungary Budapest Hajnalka Andrikovics National Center of Blood Transfusion Services x
Israel Tel-Hashomer Tali Tohami Chaim Sheba Medical Center x
Italy Bologna Giovanni Martinelli University of Bologna
Italy Naples Fabrizio Pane CEINGE
Italy Turin Giuseppe Saglio Ospedale Universita' di Torino x
Lithuania Vilnius Mindaugas Stoskus Vilnius University Hospital Santariskiu Clinics
Netherlands Amsterdam Jeroen Janssen VU medisch centrum, Afdeling Hematologie
Netherlands Rotterdam Peter Valk Erasmus MC, Molecular Diagnostics x
Netherlands Rotterdam Vincent van der Velden Erasmus MC, Department of Immunology
Norway Tromso/Oslo Dag Andre Nymoen SINTEF x
Poland Krakow Tomasz Sacha Katedra i Klinika Hematologii CMUJ x
Portugal Lissabon Joana Diamond Instituto Portugues de Oncologia de Lisboa x
Romania Bucharest Rodica Talmaci Fundeni Clinical Institute x
Russia Moscow Andrey Misyurin Research Center for Hematology x
Russia St. Petersburg Michael V. Dubina St. Petersburg State Pavlov Medical University
Slovenia Ljubljana Tadej Pajic University Medical Centre Ljubljana x
Spain Barcelona Dolors Colomer Unitat d'Hematopatologia, Hospital Clinic x
Spain Barcelona Josep Nomdedeu Hospital de la Santa Creu i Sant Pau
Sweden Stockholm Gisela Barbany University Hospital
Sweden Uppsala Hans Ehrencrona Uppsala University Hospital x
Switzerland Bern Elisabeth Oppliger-Leibundgut Inselspital x
Turkey Istanbul Ugur O¨ zbek I.U., DETAE x
UK Liverpool Richard E. Clark Royal Liverpool University Hospital
UK London Letizia Foroni Hammersmith Hospital
UK Salisbury Nick Cross Salisbury District Hospital x
UK Glasgow Nicola Broster Glasgow Royal Infirmary
USA Portland Rick Press Oregon Health & Science Universitys