

Review article

Brazilian chronic myeloid leukemia working group recommendations for discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia in clinical practice



Carla Boquimpani ^{a,b,*}, Fernanda Salles Seguro ^{c,d},
Gustavo Henrique Romani Magalhães ^e, Ingrid Luise Soares Pinto ^f,
Israel Bendit ^g, Jaisson André Pagnoncelli Bortolini ^g,
Katia Borgia Barbosa Pagnano ^h, Renato Centrone ⁱ, Vaneuza Funke ^j

^a Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti (HEMORIO), Rio de Janeiro, RJ, Brazil

^b ONCOCLÍNICA CTO, Rio de Janeiro, RJ, Brazil

^c Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, (HC FM USP), São Paulo, SP, Brazil

^d Instituto do Câncer do Estado de São Paulo (ICESP), São Paulo, SP, Brazil

^e Hospital das Clínicas da Universidade Federal de Minas Gerais (HC UFMG), Belo Horizonte, MG, Brazil

^f Instituto COI, Rio de Janeiro, RJ, Brazil

^g Centro de Pesquisas Oncológicas (CEPON), Itacurubi, Florianópolis, SC, Brazil

^h Centro de Hematologia e Hemoterapia, Universidade Estadual de Campinas, (Hemocentro Unicamp), Campinas, SP, Brazil

ⁱ Instituto Hemomed de Oncologia e Hematologia, São Paulo, SP, Brazil

^j Complexo Hospital de Clínicas, Universidade Federal do Paraná (CHC-UFPR), Curitiba, PR, Brazil

ARTICLE INFO

Article history:

Received 28 September 2021

Accepted 1 April 2022

Available online 3 May 2022

Keywords:

Practice guideline

Leukemia myelogenous chronic

BCR-ABL positive

Therapeutics

ABSTRACT

Introduction: Treatment-free remission (TFR) is a new goal of chronic myeloid leukemia (CML) therapy. TFR is feasible when the patient has achieved a deep and stable molecular response and met the criteria required to ensure its success. Treatment discontinuation should not be proposed to the CML patient if minimum conditions are not met. In Brazil, for example, molecular tests (BCR::ABL1) are not broadly available, making it difficult to monitor the patients adequately.

Objective: In this sense, providing TFR recommendations for Brazilian physicians are therefore necessary. These recommendations include the main criteria checklist to start the TKIs treatment discontinuing process in patients diagnosed with CML and the population-eligible characteristics for treatment discontinuation.

Method: Age, risk score at diagnosis, TKI treatment duration, BCR::ABL1 transcripts type, depth of the molecular response for treatment discontinuation, treatment adherence, patient monitoring and withdrawal syndrome are essential factors to consider in TFR. After TKI discontinuation, BCR::ABL1 transcripts monitoring should be more frequent. When a

* Corresponding author at: Instituto Estadual de Hematologia Arthur de Siqueira Cavalcanti (HEMORIO), Rua Frei Caneca 8, Centro, CEP 20211-030 Rio de Janeiro, RJ, Brazil.

E-mail address: carla.boquimpani@icloud.com (C. Boquimpani).

<https://doi.org/10.1016/j.htct.2022.04.002>

2531-1379/© 2022 Published by Elsevier España, S.L.U. on behalf of Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

major molecular response loss is observed during the monitoring of a patient in TFR, the TKI treatment should be resumed.

Conclusion: These recommendations should serve as a basis for medical professionals interested in proposing TKI discontinuation for CML patients in clinical practice. It is important to highlight that, despite the benefits of TFR for the patients and the health system, it should only be feasible following the minimum standards proposed in this recommendation.

© 2022 Published by Elsevier España, S.L.U. on behalf of Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The advent of tyrosine kinase inhibitors (TKIs) for the treatment of chronic myeloid leukemia (CML) has increased survival of CML patients, similar to that observed in healthy individuals.^{1,2} Despite the clear benefits of treatment with TKIs in CML, the occurrence of chronic adverse events related to the treatment may impair the quality of life of these patients.³ In clinical trials, grade 3 to 4 adverse events are considered more relevant, as they lead to treatment discontinuation, hospitalization and even death. However, in CML patients, who are treated for a long time, mild or moderate events become relevant, since these individuals will have to live with their occurrence throughout the treatment. Among the main adverse events related to the long-term TKI treatment is the occurrence of edema, diarrhea, nausea, fatigue, headache, musculoskeletal pain and dyspnea, among others.^{4,5}

The long-term treatment with TKIs can also affect different aspects related to the patient quality of life and functioning, especially due to the occurrence of low-intensity adverse events. In individuals aged between 18 and 59 treated with imatinib, worse quality of life estimates were observed and fatigue appears as a factor associated with this finding.⁶

Adherence to the proposed treatment is essential to obtain satisfactory results and it is an important predictor of disease-free survival.⁷ The estimates of adherence to treatment vary between 32.7% and 88% and the time elapsed since the start of the treatment and the occurrence of adverse events seems to negatively affect this proportion.^{7–9}

Treatment-free remission (TFR) is a new goal of CML therapy and is achieved when a patient maintains deep molecular response after TKI discontinuation. The adoption of a treatment discontinuation strategy demonstrates benefits related to safety and quality of life, in addition to being able to generate important savings for health systems in different countries.^{10–13} Considering the Brazilian data, estimates have shown that discontinuing treatment can generate savings of up to R\$ 38 million in five years.^{14,15}

Discontinuation of TKI treatment has been evaluated in several clinical trials, such as the Stop Imatinib, ENESTFreedom and ENESTop trials.^{16–19} The Stop Imatinib trial, a pioneer in the use of this strategy, has shown an estimated response maintenance of 41% after two years of

discontinuation.¹⁹ A Brazilian discontinuation trial showed a TFR rate of 60% in 30 months.²⁰ After the nilotinib discontinuation, 48.9% of patients have maintained their response at 96 weeks and 53% at 48 weeks in the ENESTFreedom and ENESTop trials, respectively.^{17,18} The 5-year updated result of the ENESTop trial demonstrated that 42.9% of the patients (54/126) were still in TFR.²¹ Other analyses corroborate these results and present a discontinuation proportion after 12 months of at least 38.5%.²² A prospective analysis conducted in Brazil shows an estimate of 54% of patients in TFR after 24 months.²³

Thus, TFR is feasible when the patient has achieved deep and stable molecular response and met the criteria required to ensure its success. In this sense, several international guidelines have established the criteria for the implementation of TFR in CML patients that can be used in the clinical practice.^{24–29}

Despite the benefits of treatment discontinuation, it should not be proposed for the CML patient if minimum conditions are not met. In Brazil, for example, the availability of molecular tests (*BCR::ABL1*) is not widespread, making it difficult to adequately monitor the patients.³⁰ In this sense, providing TFR recommendations to the Brazilian physicians is therefore necessary.

Methodology

A panel of experts was convened on July 24, 2020, gathering nine members of the Brazilian CML Working Group. A questionnaire was previously sent to the participants, addressing subjects, such as eligible population characteristics, institution characteristics, monitoring during treatment discontinuation and strategies to increase the probability of proposing TKI discontinuation and achieving TFR. The answers obtained were compiled, analyzed and debated during the panel, generating the recommendations now presented.

Summary of the key points for achieving TFR

Table 1 presents a checklist with the main criteria required to start the process of discontinuing treatment with TKIs in patients diagnosed with CML. If any of these aspects are not met, the TFR is not recommended.

Table 1 – Checklist of the main parameters for discontinuing TKIs in the clinical practice.

Required features	Confirmation
Does the patient wish and agree with treatment discontinuation?	☐
Does the patient have a typical BCR::ABL1 transcript (b3a2 and/or b2a2)?	☐
Is the patient on TKI treatment for at least 5 years?	☐
Does the patient have a stable deep molecular response $\leq$ MR4.5 (IS) for at least 2 years?	☐
Is the periodic evaluation of molecular response by real-time PCR after treatment discontinuation possible?	☐
Does the laboratory available for the test have a sensitivity $\geq$ 4.5?	☐
Real-time PCR: real-time polymerase chain reaction; TKI: tyrosine kinase inhibitors.	

Characteristics of the population eligible for treatment discontinuation

Box 2 shows a flow chart of the population eligible for TKI treatment discontinuation according to the recommendations proposed in this document.

Box 2 Mandatory requisites for eligibility for TKIs discontinuation.

Mandatory requisites

Age $\geq$ 18 years
 CML in chronic phase
 Optimal response to TKI
 $\geq$ 5 years of TKI therapy
 Deep molecular response (MR4.5 for at least 2 years)
 CML: Chronic myeloid leukemia; TKI: tyrosine kinase inhibitors.

Age

This recommendation was made for individuals aged 18 years or older as eligible for treatment discontinuation, as the majority of the trials that evaluated this strategy were conducted in this population.^{16,18,19} To date, there are few studies evaluating treatment discontinuation in the pediatric population that would support a recommendation and therefore the approach should be individualized.

The treatment discontinuation may be of greater relevance for women of childbearing age and who may still want a future pregnancy. A study conducted with the objective of evaluating the TFR achievement from the patient's perspective has shown that the desire to become pregnant, or even an unplanned pregnancy, was the main reason for considering treatment discontinuation for 10% of the analyzed

sample.³¹ The Brazilian CML population is younger at diagnosis and has a higher proportion of individuals aged between 20 and 30 years.³² Thus, despite the fact that the recommendation covers all adult patients, the age at diagnosis can be a factor to be considered for TFR future planning.

Risk score at diagnosis

The Sokal criterion should not be considered as an exclusion factor for a TFR proposal. However, the Australian recommendation has considered a high Sokal score as an alert.²⁹ Likewise, the European Society for Medical Oncology (ESMO) has included in its recommendation only patients not classified as having a high Sokal score at diagnosis.²⁵ Currently available evidence is divergent regarding the association between the Sokal score and treatment discontinuation.²² Thus, it is required to emphasize the need for frequent monitoring in this group of individuals.

TKI treatment duration

Specialists have defined the need for five years of TKI treatment duration to propose discontinuation. The same time period is recommended by the ESMO and European LeukemiaNet 2020 update.^{25,26} The TKI treatment duration proves to be an important prognostic factor for a satisfactory treatment discontinuation.²² In the EURO-SKI trial, the duration of imatinib therapy of more than 5.8 years of treatment before discontinuation increased the probability of molecular relapse-free survival to 6 months.³³

The median TKI treatment duration has ranged between 2.7 and 8.3 years in trials that assessed the discontinuation feasibility. However, when patients were treated with second-generation TKIs in the first line, the treatment duration was significantly shorter than those observed with other strategies, suggesting that these patients can discontinue treatment more quickly.²² Thus, when using second generation TKIs as a first-line strategy this time can be reduced to up to three years of treatment duration; nevertheless, deep molecular response should be achieved and maintained before discontinuation.

BCR::ABL1 transcripts type

Knowing the type of BCR::ABL1 transcripts is essential for the proposal of treatment discontinuation. Therefore, the TFR attempt is only recommended for patients with typical and measurable BCR::ABL1 transcripts (b2a2 and b3a2).^{25,26,29} Although there are successful TFR attempts in patients with atypical transcripts, there are still no standardized methods for monitoring of these transcripts in a large scale.³⁴

Depth of the molecular response for treatment discontinuation

The proportion of BCR::ABL1 transcripts should be at minimum MR4.0 (IS) or MR4.5 (BCR::ABL1 transcripts $\leq$ 0.0032% IS) in order to start the treatment discontinuation. The group decided to define the minimum value as MR4.5, considering a more conservative approach. In addition, this response should be stable for a minimum of two years. This same

Patient identifying data.....
 Transcript type

Date	Specimen no.	Source of material	BCR-ABL copy number	Control gene copy number	Ratio as %	Converted to IS (%)

Figure 1 – Suggestion for sequential reporting of results from real-time PCR assays. Extracted from Hughes et al., 2006.³⁹ IS: international scale.

criteria are considered in the recommendations proposed by Hughes et al. (2016) and ESMO.^{25,29}

The depth and the duration of molecular response are considered predictive factors for a satisfactory treatment discontinuation.²² In trials that considered MR4.5 and 2 years of deep molecular response before discontinuation, the TFR was 51.6% to 67.9%.^{16,18,35–38} In the EURO-SKI trial, each increase in the number of years of deep molecular response increased the probability of maintaining the major molecular response (MMR).³³

However, to ensure an adequate assessment of the proportion of the BCR::ABL1 transcripts, standardized tests are necessary. When a reliable test is not available, the treatment discontinuation is not recommended. Thus, the laboratories eligible to perform quantitative real-time polymerase chain reaction (real-time PCR) tests should have a sensitivity > 4.5. The importance of the availability of a high quality test is highlighted in different international guidelines.^{24–26} The results should be reported in the international scale and the reference gene copy numbers should also be available in the report (Figure 1).^{39,40} The required numbers for scoring deep molecular response are shown in Table 2.

The real-time PCR test has been widely used to monitor the treatment response in CML patients. Thus, the standardization of its interpretation is necessary. In order to standardize the monitoring of BCR::ABL1 transcript levels in CML patients, an international scale was proposed by the

National Institute of Health consensus group,³⁹ as shown in Table 3.

Treatment adherence

It is essential that the patient truly adhere to the treatment to achieve a deep molecular response, a prerequisite for treatment discontinuation. Data from a Brazilian trial has shown that patients who adhere are more likely to have a major molecular response.⁴¹ Adherence is a determining factor for obtaining satisfactory responses to the use of TKIs in CML patients, increasing the chance of obtaining a major molecular response in one year by approximately 70%.^{7,42}

In addition, patients who adhere to the treatment have better quality of life and disease impact endpoints. Lou et al. (2018) reported an absence of a significant association between adherence and the patient's desire to discontinue treatment (odds ratio [OR]: 0.92; 95% CI: 0.55 - 1.52).⁴³ Thus, the hypothesis that a future discontinuation proposal at the time of the diagnosis and the definition of a therapeutic strategy may improve the patient's adherence to the treatment still needs further investigation.

Patient monitoring

The importance of monitoring patients diagnosed with CML was shown in a Brazilian cohort of individuals in whom the real-time PCR test was performed at intervals similar to

Table 2 – Reference gene numbers required for scoring deep molecular response. Extracted from Cross et al., 2015.⁴⁰

	MR ⁴	MR ^{4,5}	MR ⁵
Minimum sum of reference gene transcripts irrespective of Whether BCR::ABL1 is detected or not ^a BCR::ABL1 ^{IS} level for positive samples ^b	10,000 ABL1 24,000 GUSB ≤0.01%	32,000 ABL1 77,000 GUSB ≤0.0032%	100,000 ABL1 240,000 GUSB ≤0.001%

IS: international scale; MR: molecular response.

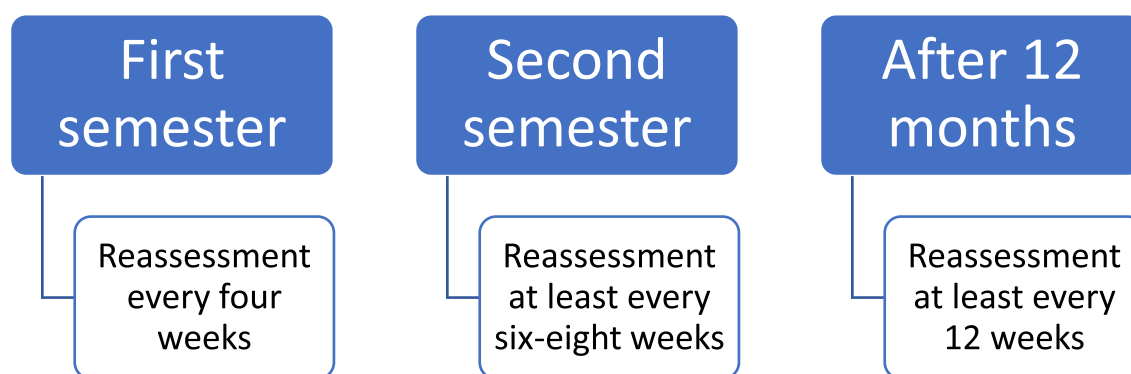
^a Numbers of reference gene transcripts in the same volume of cDNA that is tested for BCR::ABL1. The minimum number in any individual replicate should be 10,000 ABL1 or 24,000 GUSB.

^b Provided that the minimum reference gene copy numbers in the row above are fulfilled.

Table 3 – Cytogenetic and Molecular response levels.

BCR::ABL1 (%IS)	Log reduction in BCR::ABL1	Reduction in the proportion of BCR::ABL1 transcripts	Response level
10	1	1:10	Major cytogenetic response
1	2	1:100	Complete cytogenetic response
0.1	3	1:1,000	MMR
0.01	4	1:10,000	MR4.0
0.0032	4.5	1:32,000	MR4.5
0.001	5	1:100,000	MR5.0

IS: international scale.
MMR-major molecular response.
MR-molecular response.

**Figure 2 – Frequency of patient monitoring after TKI discontinuation.**

those proposed by the international guidelines. Among the patients from whom samples were available in all periods analyzed, 78.1% had an optimal response to the imatinib treatment.⁴⁴

After TKI discontinuation, BCR::ABL1 transcripts monitoring should be more frequent. These recommendations are illustrated in Figure 2. Different monitoring periods after treatment discontinuation are also proposed by other international guidelines.^{24,26} Disease recurrences are mostly observed in the first six months after discontinuation, which justifies the need for a more frequent monitoring during this period.^{19,35–38,45–48} Trials that report the time elapsed between discontinuation and failure show median periods ranging from 2 to 5 months.^{35,37,45–48}

When a loss of a major molecular response is observed at any time during the monitoring of a patient who is in TFR, the TKI treatment should be resumed.

Withdrawal syndrome

The withdrawal syndrome can be characterized by the emergence of adverse events, especially related to musculoskeletal pain, after approximately three months of TKI withdrawal.⁴⁹ This finding was first described by Richter and collaborators (2014) in approximately 30% of the patients who discontinued the drug for at least six months.⁵⁰ Since then, other authors have reported the withdrawal syndrome and its estimated

occurrence ranges from 22% to 42%.^{51–54} The presence of previous pain and a longer TKI treatment duration are among the factors related to its development.⁵⁴

The possibility of the withdrawal syndrome occurrence in this group of patients highlights the need to monitor other parameters than only those related to disease remission. Therefore, it is recommended that the emergence of adverse events and metabolic parameters continue to be evaluated after treatment discontinuation.

Second-generation TKIs as a first-line option

Second-generation TKIs were initially developed to meet medical needs not satisfied by imatinib, as approximately one-third of the patients may experience inadequate response or failure in this treatment in the long term.^{55,56} In the Brazilian public health system, nilotinib and dasatinib are available as second-line treatment for CML patients.^{57–59}

The use of second generation TKIs as a first-line strategy has shown the ability to induce a faster and deeper response, compared to imatinib.⁶⁰ Some international recommendations accept a shorter duration of treatment to discontinue these drugs.^{26,27}

The possibility of discontinuation by observing faster responses can be especially beneficial to some groups of patients, such as women of childbearing age.

Final considerations

These recommendations should serve as a basis for medical professionals interested in proposing TKI discontinuation for CML patients in clinical practice.

It is important to highlight that despite the benefits of TFR for the patients and for the health system, it should only be feasible following the minimum standards proposed in this recommendation.

Conflicts of interest

All authors received grants from Novartis to participate in the expert panel. No other competing interests were declared.

Funding

This work was supported by Novartis.

Acknowledgements

We thank ORIGIN Health Company for the support with medical writing during the development of this manuscript.

REFERENCES

1. Sasaki K, Strom SS, O'Brien S, Jabbour E, Ravandi F, Konopleva M, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol*. 2015;2(5):e186–93.
2. Mughal TI, Radich JP, Deininger MW, Apperley JF, Hughes TP, Harrison CJ, et al. Chronic myeloid leukemia: reminiscences and dreams. *Haematologica*. 2016 May 1;101(5):541–58.
3. Jiang Q, Yu L, Gale RP. Patients' and hematologists' concerns regarding tyrosine kinase-inhibitor therapy in chronic myeloid leukemia. *J Cancer Res Clin Oncol*. 2018;144(4):735–41.
4. Caldemeyer L, Dugan M, Edwards J, Akard L. Long-term side effects of tyrosine kinase inhibitors in chronic myeloid leukemia. *Curr Hematol Malig Rep*. 2016;11(2):71–9.
5. Flynn KE, Atallah E. Quality of life and long-term therapy in patients with chronic myeloid leukemia. *Curr Hematol Malig Rep*. 2016 Apr 15;11(2):80–5.
6. Efficace F, Cannella L. The value of quality of life assessment in chronic myeloid Leukemia patients receiving tyrosine Kinase Inhibitors. *Hematology*. 2016;2016(1):170–9.
7. de Almeida MH, Fogliatto L, Couto D. Importance of adherence to BCR-ABL tyrosine-kinase inhibitors in the treatment of chronic myeloid leukemia. *Rev Bras Hematol Hemoter*. 2014;36(1):54–9.
8. Geissler J, Sharf G, Bombaci F, Daban M, De Jong J, Gavin T, et al. Factors influencing adherence in CML and ways to improvement: results of a patient-driven survey of 2546 patients in 63 countries. *J Cancer Res Clin Oncol*. 2017;143(7):1167–76.
9. Anderson KR, Chambers CR, Lam N, Yau PS, Cusano F, Savoie ML, et al. Medication adherence among adults prescribed imatinib, dasatinib, or nilotinib for the treatment of chronic myeloid leukemia. *J Oncol Pharm Pract*. 2015;21(1):19–25.
10. Sauvage E, Duco J, Nizard S, Arroum S, Mahon F, Kuizenga P, et al. Modelling the economic impact of implementing treatment-free remission (TFR) in philadelphia+ (PH+) chronic myelogenous leukemia in chronic phase (CML-CP) patients treated in first line (1l) with the tyrosine kinase inhibitors (TKI): imatinib and nilotinib. *Value Heal*. 2016;19(7):A581–2.
11. Elias F, Gebran A, Said C, Beker RV, Ammar W. Budget Impact of Treatment-Free Remission in Treating Chronic-Phase Philadelphia-Positive Chronic Myeloid Leukemia in Lebanon. *J Glob Oncol*. 2019;5:1–7.
12. Shuvaev V, Abdulkadyrov K, Turkina A, Martynkevich I, Chelysheva E, Fominykh M, et al. Pharmacoeconomical analysis of chronic myelogenous leukemia treatment free remission. *Blood*. 2015 Dec 3;126(23):3293.. –3293.
13. Yamazaki K, Inagaki N, Moldaver D, Viana R, Kimura S. Budget impact analysis of treatment-free remission in nilotinib-treated Japanese chronic myeloid leukemia patients. *Cancer Sci*. 2020(January):1–10.
14. Centrone RT, Bonafe I, Miranda EC, Seguro FS, Magalhaes GH, Clementino ND, et al. Financial impact of imatinib discontinuation in brazil - a pharmoeconomic study. *Blood*. 2019 Nov 13;134(Supplement_1):5844.. –5844.
15. Abdo A, Boquimpani CM, Vivona D, Leite VS, Matsuo AL, Teich V, et al. Impact of treatment free remission (TFR) with nilotinib in 2nd line for chronic myeloid leukemia on savings that may fund all BCR-ABL tests in the brazilian public healthcare system during and after nilotinib treatment. *Blood*. 2018 Nov 29;132(Supplement 1):4760.. –4760.
16. Hochhaus A, Masszi T, Giles FJ, Radich JP, Ross DM, Gómez Casares MT, et al. Treatment-free remission following front-line nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. *Leukemia*. 2017;31(7):1525–31.
17. Ross DM, Masszi T, Gómez Casares MT, Hellmann A, Stentoft J, Conneally E, et al. Durable treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: 96-week update of the ENESTfreedom study. *J Cancer Res Clin Oncol*. 2018;144(5):945–54.
18. Mahon FX, Boquimpani C, Kim DW, Benyamini N, Clementino NCD, Shuvaev V, et al. Treatment-free remission after second-line nilotinib treatment in patients with chronic myeloid leukemia in chronic phase results from a single-group, phase 2, open-label study. *Ann Intern Med*. 2018;168(7):461–70.
19. Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, et al. 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(11):1029–35.
20. Pagnano KB, Lopes AB, Miranda EC, Delamain MT, Duarte GO, Rodrigues BR, et al. Efficacy and safety of pioglitazone in a phase 1/2 imatinib discontinuation trial (EDI-PIO) in chronic myeloid leukemia with deep molecular response. *Am J Hematol*. 2020 Dec 3;95(12).
21. Hughes TP, Clementino NC, Fominykh M, Lipton JH, Turkina AG, Moiraghi EB, et al. Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. *Leukemia*. 2021 Jun 12;35(6):1631–42.
22. Ureshino H, Kamachi K, Kimura S. Surrogate markers for treatment-free remission in patients with chronic myeloid leukemia. *Clin Lymphoma Myeloma Leuk*. 2020 Jul: 1–6.
23. Seguro FS, Maciel FV, Santos FM, Abdo ANR, Pereira TD, Nardinelli L, et al. MR 4log and low levels of NK cells are associated with higher molecular relapse after imatinib discontinuation: results of a prospective trial. *Leuk Res*. 2021 Feb;101:106516.

24. Bhatia R. Chronic myeloid leukemia. *Hematol Basic Princ Pract*. 2018; 1055–70.
25. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JJ, Hjorth-Hansen H, et al. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(November):iv41–51.
26. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. *Leukemia*. 2020;34(4):966–84.
27. Baccarani M, Abruzzese E, Accurso V, Albano F, Annunziata M, Barulli S, et al. Managing chronic myeloid leukemia for treatment-free remission: a proposal from the GIMEMA CML WP. *Blood Adv*. 2019;3(24):4280–90.
28. Almeida A, Pierdomenico F, Guerrero BP, Saraiva F, Montalvão A, Coutinho J, et al. Recommendations from a portuguese expert group for discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia patients in clinical practice. *Acta Med Port*. 2019 Aug 1;32(7–8):550.
29. Hughes TP, Ross DM. Moving treatment-free remission into mainstream clinical practice in CML. *Blood*. 2016;128(1):17–23.
30. Boquimpani CM, Abdo ANR, Martins DP, Lima LB de A, Torriani MS, Bendit I. Inclusion of molecular monitoring (BCR-ABL1) in the treatment of chronic myeloid leukemia in the Brazilian public health system (SUS): an urgent need for treatment management. *Hematol Transfus Cell Ther*. 2020(xx):1–8.
31. Sharf G, Marin C, Bradley JA, Pemberton-Whiteley Z, Bombaci F, Christensen RIO, et al. Treatment-free remission in chronic myeloid leukemia: the patient perspective and areas of unmet needs. *Leukemia*. 2020; 2102–12.
32. de Campos MG, Arantes A de M, de Oliveira JSR, LLF Chaufaille M de. Chronic myeloid leukemia: a disease of youth in Brazil. *Leuk Res*. 2010;34(4):542–4.
33. Saussele S, Richter J, Guilhot J, Gruber FX, Hjorth-Hansen H, Almeida A, et al. Discontinuation of tyrosine kinase inhibitor therapy in chronic myeloid leukaemia (EURO-SKI): a prespecified interim analysis of a prospective, multicentre, non-randomised, trial. *Lancet Oncol*. 2018 Jun;19(6):747–57.
34. Dragani M, Petiti J, Rege-Cambrin G, Gottardi E, Daraio F, Caocci G, et al. Treatment-free remission in Chronic Myeloid Leukemia harboring atypical BCR-ABL1 transcripts. *Mediterr J Hematol Infect Dis*. 2020 Aug 29;12(1):e2020066.
35. Takahashi N, Nishiwaki K, Nakaseko C, Aotsuka N, Sano K, Ohwada C, et al. Treatment-free remission after two-year consolidation therapy with nilotinib in patients with chronic myeloid leukemia: STAT2 trial in Japan. *Haematologica*. 2018;103(11):1835–42.
36. Takahashi N, Tauchi T, Kitamura K, Miyamura K, Saburi Y, Hatta Y, et al. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. *Int J Hematol*. 2018;107(2):185–93.
37. Rea D, Nicolini FE, Tulliez M, Guilhot J, Guerci-Bresler A, et al. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. *Blood*. 2017;129(7):846–54.
38. Nicolini FE, Dulucq S, Boureau L, Cony-Makhoul P, Charbonnier A, Escoffre-Barbe M, et al. Evaluation of residual disease and TKI duration are critical predictive factors for molecular recurrence after stopping imatinib first-line in chronic phase CML patients. *Clin Cancer Res*. 2019;25(22):6606–13.
39. Hughes T, Deininger M, Hochhaus A, Branford S, Radich J, Kaeda J, et al. Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: Review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. *Blood*. 2006;108(1):28–37.
40. Cross NCP, White HE, Colomer D, Ehrencrona H, Foroni L, Gottardi E, et al. Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. *Leukemia*. 2015 May 5;29(5):999–1003.
41. Almeida MH, Pagnano KBB, Vigorito AC, Lorand-Metze I, Souza CA. Adherence to tyrosine kinase inhibitor therapy for chronic myeloid leukemia: a brazilian single-center cohort. *Acta Haematol*. 2013;130:16–22.
42. Tsai YF, Huang WC, Cho SF, Hsiao HH, Liu YC, Lin SF, et al. Side effects and medication adherence of tyrosine kinase inhibitors for patients with chronic myeloid leukemia in Taiwan. *Med (United States)*. 2018;97(26).
43. Lou J, Huang J, Wang Z, Wen B, Tu C, Huang W, et al. Chronic myeloid leukemia patients and treatment-free remission attitudes: A multicenter survey. *Patient Prefer Adherence*. 2018;12:1025–32.
44. Vieira-Mion AL, Pereira NF, Funke VAM, Pasquini R. Molecular response to imatinib mesylate of Brazilian patients with chronic myeloid leukemia. *Rev Bras Hematol Hemoter*. 2017;39(3):210–5.
45. Kimura S, Imagawa J, Murai K, Hino M, Kitawaki T, Okada M, et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): a single-arm, multicentre, phase 2 trial. *Lancet Haematol*. 2020;7(3):e218–25.
46. Ross DM, Branford S, Seymour JF, Schwarzer AP, Arthur C, Yeung DT, et al. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*. 2013;122(4):515–22.
47. Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, et al. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*. 2014;32(5):424–30.
48. Yamaguchi H, Takezako N, Ohashi K, Oba K, Kumagai T, Kozai Y, et al. Treatment-free remission after first-line dasatinib treatment in patients with chronic myeloid leukemia in the chronic phase: the D-NewS Study of the Kanto CML Study Group. *Int J Hematol*. 2020;111(3):401–8.
49. Shah NP. NCCN guidelines updates: discontinuing TKI therapy in the treatment of chronic myeloid leukemia. *J Natl Compr Canc Netw*. 2019;17(55):611–3.
50. Richter J, Söderlund S, Lübking A, Dreimane A, Lotfi K, Markkvärn B, et al. Musculoskeletal pain in patients with chronic myeloid leukemia after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? *J Clin Oncol*. 2014;32(25):2821–3.
51. Petrova A, Chelysheva E, Shukhov O, Bykova A, Nemchenko I, Gusarova G, et al. Withdrawal syndrome after tyrosine kinase inhibitor discontinuation in patients with chronic myeloid leukemia in the russian prospective study RU-SKI. *Clin Lymphoma, Myeloma Leuk*. 2020;20(5):267–71.
52. Hernández-Boluda JC, Pereira A, Pastor-Galán I, Alvarez-Larrán A, Savchuk A, Puerta JM, et al. Feasibility of treatment discontinuation in chronic myeloid leukemia in clinical practice: results from a nationwide series of 236 patients. *Blood Cancer J*. 2018;8(10).
53. kang Chen K, feng Du T, sheng Xiong P, hua Fan G, Yang W. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia with losing major molecular response as a definition for molecular relapse: a systematic review and meta-analysis. *Front Oncol*. 2019;9(MAY):1–9.
54. Berger MG, Pereira B, Rousselot P, Cony-Makhoul P, Gardembas M, Legros L, et al. Longer treatment duration and history of osteoarticular symptoms predispose to tyrosine kinase

- inhibitor withdrawal syndrome. *Br J Haematol*. 2019;187(3):337–46.
55. Ward MA, Fang G, Richards KL, Walko CM, Earnshaw SR, Happe LE, et al. Comparative evaluation of patients newly initiating first-generation versus second-generation tyrosine kinase inhibitors for chronic myeloid leukemia and medication adherence, health services utilization, and healthcare costs. *Curr Med Res Opin*. 2015;31(2):289–97.
56. de Lavallade H, Apperley JF, Khorashad JS, Milojkovic D, Reid AG, Bua M, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: Incidence of sustained responses in an intention-to-treat analysis. *J Clin Oncol*. 2008;26(20):3358–63.
57. Ministério da Saúde (Brasil). Secretaria de Atenção à Saúde. Portaria no 1.219, de 4 de novembro de 2013 - Protocolo Clínico e Diretrizes Terapêuticas da Leucemia Mieloide Crônica do Adulto [Internet]. 2013. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/sas/2013/prt1219_04_11_2013.html.
58. Bristol-Myers Squibb Farmacêutica Ltda. Sprycel (Dasatinibe) [Bula]. São Paulo; 2020. p. 1–132.
59. Novartis Biociências SA. Tasigna (Nilotinibe) [Bula]. São Paulo; 2020. p. 1–59.
60. Yilmaz M, Abaza Y, Jabbour E. Selecting the best frontline treatment in chronic myeloid leukemia. *Curr Hematol Malig Rep*. 2015 Jun 29;10(2):145–57.