



Special article

Guidelines for therapy of patients with chronic myeloproliferative neoplasms during the novel coronavirus SARS-CoV2 pandemic



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ABSTRACT

The novel coronavirus has swept across the world in 2020 and ushered a new era. In the current scenario, it is not clear how patients with myeloproliferative neoplasms (including chronic myelogenous leukemia) should be managed, considering the risk of therapy, the need for social distancing and the risk of untimely therapy discontinuation of delay. This guideline aims to give providers a sense of direction in order to better take care of patients and prioritize care.

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Introduction

In December, 2019, several cases of infection by a novel coronavirus (SARS-CoV2) started to appear in Wuhan, China.¹ This virus is highly contagious and can lead to severe pneumonia and respiratory failure. The disease caused by SARS-CoV2 (COVID-19), while initially restricted to China, quickly spread to other countries of Asia and then to the rest of the world. On March 11, 2020, the World Health Organization officially classified COVID-19 as a pandemic.^{2–4} In Brazil, the first case was

diagnosed on February 25, 2020 and since then the number of cases and deaths have grown quickly.

The virus is transmitted by respiratory droplets from infected patients. Contagion can also occur through the manipulation of a surface that contains the living virus and subsequent contact with the mouth, eyes or nose.⁵ The virus can also be found in feces, but the importance of this route for transmission is currently unknown.⁶

Symptoms of COVID-19 appear after a mean of 7 days after exposure, but may take up to two weeks to become manifest.

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Symptoms of the mild variety of the disease include dry cough, fever, nasal congestion, anosmia, headache and diarrhea.⁷ In severe forms, there is lung involvement with hypoxemia and the need for oxygen supplementation, which may lead to acute respiratory failure, making mechanical ventilation and intensive care imperative.⁷ The disease is diagnosed with virus specific RT-PCR in material collected from either a nasal swab, tracheal aspirate or bronchoalveolar lavage.⁸ At this moment, the test is only recommended for symptomatic patients and those who had contact with them.

Data from the CDC (Centers for Disease Control and Prevention) from the United States of America have demonstrated that COVID-19 has a mortality of 2–4%, depending on the age and comorbidities of the patients.⁹ Those at greater risk for an unfavorable outcome include the elderly, frail patients, patients with systemic arterial hypertension, diabetes mellitus, obesity, chronic heart and lung disorders and smoking patients.¹⁰ A recent study from China analyzed the outcomes of 1590 patients with COVID-19, including 18 patients with cancer (5 with lung cancer), and in this study, patients with cancer had a worse outcome.¹¹ There are few reports of COVID-19 in patients with hematological malignancies. A recent case report was published on a patient with CLL in therapy with chlorambucil who developed COVID-19, had the usual evolution to lung involvement and was treated with non-invasive ventilation. The incubation period was 25 days, longer than usual.¹²

As of this writing, there are no specific therapies approved for COVID-19. Several drugs are being evaluated around the world for therapy for the disease in its various manifestations. At the present time, only supportive care is recommended and in 20–30% of the cases, there is the need for hospital admission.⁹

Questions regarding the treatment of patients with myeloproliferative neoplasms

Are patients with Philadelphia-negative myeloproliferative neoplasms at an increased risk of developing infections by the novel coronavirus SARS-CoV2?

There are no published studies describing the natural history and evolution of COVID-19 in patients with Ph-negative myeloproliferative neoplasms (MPNs). The COVID-19 could have different manifestations due to the immune suppression caused by the disease and/or the medications used to treat the MPNs. Furthermore, Ph-negative MPNs are a heterogeneous group of disorders, which also needs to be taken into consideration. Patients with Polycythemia Vera (PV) and Essential Thrombocythemia (ET) are not at an increased risk of developing infections and there is minimal impact on immunity caused by the disease itself. On the contrary, patients with Myelofibrosis (MF) may have an increased risk of developing infections, particularly at later stages of disease evolution, and infections represented 11% of the causes of death in patients with MF in one large series of cases.¹³ However, it must also be remembered that SARS-CoV2 is not an opportunistic agent and it is possible that all patients with Ph-negative MPNs have an increased risk of developing the more severe varieties of COVID-19. Overall, due to lack of data and a need

for caution, we consider all patients with Ph-negative MPNs as being a high-risk group for COVID-19, particularly patients with advanced stage (Int-2/High risk by IPSS/DIPSS/DIPSS-plus) MF.

Analyzing the drugs used for treatment of Ph-negative MPNs, in regard to hydroxyurea, interferon-alpha and anagrelide, there is no evidence to suggest that these compounds increase the risk of infections, except when they lead to neutropenia. As an example, in a recently published paper of a phase III trial comparing Ropeginterferon-alfa2b versus hydroxyurea in patients with PV, there was no major increase in grade 3–4 infections in the experimental arm, versus the control arm, and most adverse events that could be classified as infections were grade 1–2 in severity.¹⁴ It is known that the Janus Kinase and Signal Transducer and Activator of Transcription (JAK-STAT) inhibitor ruxolitinib increases the risk for developing opportunistic infections, such as tuberculosis, cytomegalovirus retinitis and JC virus-induced progressive multifocal leukoencephalopathy.^{15–17} It is thus reasonable to believe that patients receiving ruxolitinib are at an increased risk of developing the more severe form of COVID-19. On the other hand, however, ruxolitinib has a potent anti-inflammatory effect and it is currently being evaluated as a potential therapy for patients with severe forms of COVID-19 (www.clinicaltrials.gov accession number NCT04337359).¹⁸ At the present time, we recommend extreme caution and that all patients with Ph-negative MPNs, particularly those with MF, follow the most restrictive recommendations for social contact and isolation, as defined by federal health authorities, with the goal of reducing the risk of contamination and the speed of disease dissemination.

Should the treatment of patients with Ph-negative MPN be modified?

In the absence of data, one should proceed with caution. It is not prudent at present time to modify therapeutic recommendations that are already underway. Measures to limit patient circulation in hospitals and healthcare facilities should be implemented and only laboratory exams and procedures that are strictly necessary should be maintained. If possible, lab samples should be collected at home. Preferably, medical appointments should use telemedicine resources, if those are available at the physicians' institution, sending medical reports and requests for exams by e-mail.

How to start therapy of newly diagnosed patients with Ph-negative MPN?

Patients with ET and PV should be treated in the usual manner, with antiplatelet agents (e.g. low-dose aspirin) and cytoreductive therapy in high-risk cases.¹⁹ For patients diagnosed with PV who have a high demand for therapeutic phlebotomy, it is reasonable to start cytoreductive therapy, even if the patients is not high-risk, with the goal of avoiding frequent trips to the local blood bank. There are few randomized trials comparing different cytoreductive therapies in PV and ET.^{14,20–23} We recommend at the present time either hydroxyurea or interferon-alpha as the initial cytoreductive therapy.¹⁹ For patients with PV who have signs of resistance or intolerance to

hydroxyurea, the best option is the JAK2 inhibitor ruxolitinib, with the caveat mentioned below.²⁴

For all PV patients and for ET patients who are at high risk for thrombosis, and in selected MF cases, the use of low-dose aspirin (ASA) is indicated as an important therapy to prevent thrombotic events. Now, there is no data showing a worsening of the clinical course in patients using ASA who are infected with SARS-CoV2. For patients with a history of thrombosis who are receiving oral anticoagulants, we advise switching to heparin in case the patient is hospitalized, as some recent data suggests that its use may be associated with a reduction in mortality.²⁵ In some patients with the more severe form of COVID-19, there may be the development of severe thrombocytopenia.²⁶ In the absence of significant thrombocytopenia or the development of hemorrhagic episodes, we recommend that the therapy be maintained.

The therapy of patients with MF should be guided by the risk of each case. Patients who have IPSS/DIPSS risk Int-2/High should receive the JAK2 inhibitor ruxolitinib.^{27,28} Ruxolitinib should also be considered in patients with Int-1 risk with large splenomegaly (greater than 10 cm from left costal border) and/or symptoms. For low-risk and Int-1 risk patients who are oligosymptomatic or without significant splenomegaly, watch and wait is the most prudent choice.¹⁹ If needed, hydroxyurea may be used for the control of moderately increased splenomegaly or leukocytosis and erythropoiesis-stimulating agents (ESAs) can be used as therapy for mild anemia.

For patients with MF or PV with the indication to receive ruxolitinib, but have not yet started therapy, considering the immunosuppressive potential of this drug, delaying therapy start until the end of the pandemic is reasonable, if the clinical conditions of the patient allow such a delay.²⁸ One should remember, however, that we do not know the duration of the COVID-19 pandemic and delaying therapy with ruxolitinib for a long period of time may lead to unfavorable outcomes.^{27,28} We recommend that this be discussed with the patient at length, so that an informed decision can be made.

If for any reason it is necessary to interrupt or discontinue therapy with ruxolitinib, we recommend tapering the drug, with the goal of avoiding the syndrome of ruxolitinib withdrawal, which may lead to respiratory failure or aggravate the clinical status of the patient.²⁹ Patients who are no longer able to swallow ruxolitinib due to endotracheal intubation should receive the drug through a nasogastric tube.³⁰

When to recommend that patients with MF have a bone marrow transplant consultation?

For patients with MF, allogeneic bone marrow transplantation is indicated if the patient has a median life expectancy equal or inferior to 60 months and has a good performance status without life-compromising comorbidities.¹⁹ In this scenario, if the patient has stable disease without a significant increase in the percentage of blasts, the transplant procedure could be delayed for 2–4 months, but this should always be discussed with the transplant center. One must keep in mind that we do not know the duration of the present pandemic and patients with advanced MF can present with rapid evolution to the blast phase of the disease, which has a very poor prognosis.^{31,32} We recommend that the patient be evaluated

frequently to detect any signs of disease worsening that would lead to a more pressing indication for allogeneic bone marrow transplantation.³¹

Questions regarding the therapy of patients with chronic myeloid leukemia

Are patients with CML at an increased risk of developing infections by the novel coronavirus SARS-CoV2?

Similar to the Ph-negative MPNs, there is no specific data available regarding COVID-19 in patients with CML treated with tyrosine kinase inhibitors (TKIs). Chronic-phase patients do not appear to have significant immunosuppression.³³ Patients in blast crisis may develop neutropenia and are considered to be patients at greater risk.³⁴ However, it is not really known whether protection against COVID-19 requires an immune status that CML or therapy with TKI may compromise. Thus, it is recommended that patients with CML receiving TKIs be extremely cautious and follow the more restrictive recommendations of social distancing.

Should therapy of patients with CML be modified?

There is no data at present recommending discontinuation of CML therapy. The therapy should be maintained and if possible, telemedicine should be used for monitoring and appointments with physicians. Essential laboratory bloodwork (complete blood cell count, BCR-ABL1 quantitative RT-PCR and biochemistry) should also be maintained, with home sample collection if possible. Frequency of appointments should be decided on a case-by-case basis.

How should one manage a patient with CML who has the diagnosis of, or is suspected for, COVID-19?

General guidelines for therapy are similar to guidelines for patients without CML, following the directives from the Brazilian Health Minister. Caution should be taken when associating drugs that may increase the corrected Q-T interval (QTc), for some TKIs are known to induce QTc prolongation, and drug interactions could potentially lead to fatal heart arrhythmias.³⁵

Patients being treated with dasatinib should be aware that one of the most common adverse events is the development of pleural effusions that can occur in up to 28% of the patients during therapy and any physician seeing such patients for respiratory symptoms should be made aware of this possibility so that the proper differential diagnosis can be made.³⁶ Temporary interruptions of TKI therapy may be needed if there is the suspicion that dasatinib is causing pleural effusions. Other measures for controlling pleural effusion include steroids and diuretics, but their efficacy is not well established.³⁷

How should one manage a newly diagnosed CML patient?

No major changes should be made in the overall approach to a newly diagnosed case of CML. Hydroxyurea can be used if there is severe leukocytosis, prior to starting the

TKI treatment, while diagnostic tests are still pending. As soon as the diagnosis is confirmed, the patients should be started on TKIs and regular monitoring should be initiated, as per the international guidelines.^{38,39} Some experts have recommended that physicians give preference to imatinib or low-dose dasatinib over nilotinib/ponatinib as first line TKIs, since thrombotic complications can occur frequently in patients who develop COVID-19 and the last two TKIs are associated with an increased rate of cardiovascular complications.^{40,41} In the first 3 months, the complete blood cell count should be monitored frequently to detect cytopenias. Temporary interruption and the use of the granulocyte cell stimulating factor (G-CSF) can be initiated to alleviate the duration of neutropenia.

When to send patients with CML to allogeneic hematopoietic stem cell transplantation?

Indications for transplant should follow the recommendations of the European LeukemiaNet. At this time, due to the risk of infection by COVID-19, urgent cases should be prioritized, mainly those who have progressed to the accelerated phase, or blast crisis, during therapy or who have reached a second chronic phase after an initial blast crisis.³⁸

Discontinuation of therapy during the COVID-19 pandemic

Although therapy discontinuation is a feasible option for those patients who have achieved a sustained and deep molecular response, as per the guidelines from the European LeukemiaNet and the National Comprehensive Cancer Network 2020, it is not recommended to stop therapy at this moment, due to the need for more frequent visits to the hospital for blood monitoring and physician consultation.^{38,39} For patients who had discontinued therapy prior to the start of the COVID-19 pandemic, monitoring should be maintained, preferably by remote clinical consultation. If the patient is unable or unwilling to proceed with the required monitoring procedures, therapy should be reinstated after prolonged discussion, in order to prevent disease progression.

How to proceed in case a patient with CML or Ph-negative myeloproliferative neoplasm develops symptoms compatible with COVID-19?

Patients who develop symptoms suggestive of COVID-19 should follow the local health authorities' recommendations on how to proceed at the present time, with the reminder that these guidelines may change from time to time. At the present time, it is recommended that patients with COVID-19 remain in quarantine, either at home or in a healthcare facility for at least 14 days, in order to reduce the risk of disease transmission to others. The same recommendations can be made for those who have contacted the patient recently.

We do not recommend that patients go to the hospital by themselves, but rather that they contact their hematologist or other healthcare provider to discuss the appropriate measures to be taken. We reiterate that drug therapy that is currently in

use should not be discontinued, except under the orientation of the treating physician.

Updated guidelines

Since information and recommendations can change rapidly in a pandemic, the authors recommend that the readers access the website of the Brazilian Hematology Association – Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH) for updated recommendations: <https://abhh.org.br/institucional/coletanea-covid19/>.

Conflicts of interest

The authors declare no conflicts of interest.

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