Special article

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

Fabio Pires de Souza Santos\textsuperscript{a,b}, Renato Sampaio Tavares\textsuperscript{c,*}, Katia Borgia Barbosa Pagnano\textsuperscript{d}

\textsuperscript{a} Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
\textsuperscript{b} Hospital BP Mirante, São Paulo, SP, Brazil
\textsuperscript{c} Hospital das Clínicas da Universidade Federal de Goiás (HC UFG), Goiânia, GO, Brazil
\textsuperscript{d} Centro de Hematologia e Hemoterapia, Universidade Estadual de Campinas (Hemocentro Unicamp), Campinas, SP, Brazil

ARTICLE INFO

Article history:
Received 20 April 2020
Accepted 15 June 2020
Available online xxx

Keywords:
Chronic myeloproliferative neoplasms
Novel coronavirus
SARS-CoV2 pandemic

ABSTRACT

The SARS-CoV2 virus 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 CML) 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.

\textcopyright 2020 Published by Elsevier Editora Ltda. 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

In December, 2019, several cases of infection by a novel coronavirus (SARS-CoV2) started to appear in Wuhan, China.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} The virus can also be found in feces, but the importance of this route for transmission is currently unknown.\textsuperscript{5}

\textsuperscript{*} Corresponding author at: Faculdade de Medicina, Hospital das Clínicas da Universidade Federal de Goiás (UFG), Avenida 1, Setor Universitário, Goiânia, GO, CEP: 74000-000, Brazil.
E-mail address: renatosampaio.tavares@gmail.com (R.S. Tavares).

2531-1579/\textcopyright 2020 Published by Elsevier Editora Ltda. 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/).

Please cite this article in press as: Santos FP, et al. Guidelines for therapy of patients with chronic myeloproliferative neoplasms during the novel coronavirus SARS-CoV2 pandemic. Hematol Transfus Cell Ther. 2020. https://doi.org/10.1016/j.htct.2020.06.005
Responses to COVID-19 symptoms may appear after a mean of 7 days after exposure, but may take up to two weeks to become manifest.

Symptoms of the mild variety of the disease include dry cough, fever, nasal congestion, anosmia, headache and diarrhea. 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. However, a recent paper 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. There are few reports of COVID-19 patients with hematological malignancies.

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.

**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 for patients diagnosed with PV who have a high demand for therapeutic phlebotomy, it is reasonable to start cytoreductive therapy, even if the patient 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. We recommend at the present time either hydroxyurea or interferon-alpha as the initial cytoreductive therapy.
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.21

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. 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. 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.

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. 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.

REFERENCES


30. ANVISA. Bula do medicamento Jakavi® (ruxolitinibe); 2018.


