

Frequently asked questions regarding SARS-CoV2 in cancer patients – recommendations for clinicians caring for patients with malignant diseases

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Introduction SARS-CoV-2:

SARS-CoV-2 is a novel betacoronavirus that has been first identified in China in winter 2019 as the cause of a severe inflammatory *coronavirus infectious disease* (CoVID-19) of the respiratory tract. Because its genome is closest related to previously identified CoVs in bats, SARS-CoV-2 was originally thought to represent a zoonosis. However, its rapid spread in the human populations suggests that SARS-CoV-2 is surprisingly well adapted to the human host hence behaving like a new member of the community-acquired respiratory viruses (CARVs). Similar to other CARVs, the clinical presentation can range from a- and oligosymptomatic to full-blown influenza-like illness and primary viral pneumonia. For the purpose of these clinical recommendations, manifestations of upper respiratory tract infectious disease (URTID) are diagnosed if there is at least one of the following: cough, coryza, sore throat, shortness of breath AND a systemic symptom/sign such as fever/malaise/myalgia AND laboratory confirmation by nucleic acid testing (NAT). Conversely, lower respiratory tract infectious disease (LRTID) is diagnosed in patients with tracheitis and bronchitis, whereby dyspnea and/or declining oxygen saturation at ambient air often predict bi-lateral ground glass infiltrates seen earliest on CT-scans, hence identifying viral pneumonia. Notably, LRTID may occur early or late in the course and may rapidly progress to life-threatening respiratory failure because of massive impairment of gas-exchange. In addition, multi-organ failure affecting renal and cardiac function have been described. This life-threatening complication is thought to be due to a hyperinflammatory process compatible with hemophagocytic lymphohistiocytosis (HLH)^{1,2}.

In general, CARVs follow a seasonality with influenza-, respiratory syncytial and parainfluenza viruses being the most prominent ones³. Influenza and RSV can be treated with specific antivirals, which is essential for the care of infected cancer patients. Importantly, cancer patients with CARV-infections are prone to co-infections and bacterial/fungal superinfections are the primary cause for CARV-associated mortality in cancer patients⁴.

Infection with SARS-CoV-2 has been described to occur after an incubation period of about 3 to 5 days, with most common symptoms being raised temperature/fever and cough⁵. Of note, the peak of clinical disease is in the second week with an increase in inflammation⁶. It is not clear if cancer is a general risk factor for infection^{5,7,8}, but old age, hypertension and diabetes

have clearly been defined as risk factors for worse outcome⁶. Cancer patients should also be assumed to have a worse prognosis⁷ and preliminary experience from Italy suggests that mortality in patients with hematological malignancy may be as high as 20% (Livio Pagano, personal communication). However, with regard to the present or upcoming outbreak of SARS-CoV-2 accurate estimates regarding mortality and spread are almost impossible to give since most factors influencing the epidemiology are still unknown⁹.

Specific aspects for hematologists and oncologists:

Clinicians caring for cancer patients during the SARS-CoV-2 pandemic face a variety of challenges including the management of cancer patients infected with SARS-CoV-2 as well as coping with a drastically changed work environment due to emergency measures, staff sicknesses and expected shortages of drugs, blood products and equipment for personal protection amongst others. In this setting it appears wise to implement center-specific standard-operating-procedures to define altered responsibilities and access to care. Depending on the magnitude of changes within a certain region, prioritization with regard to anti-cancer therapy may be necessary to ensure safe administration of potentially dangerous and toxic treatments. An example for these changed working conditions may be that centers may automatically admit all patients presenting with febrile temperature to an area dedicated to the treatment of COVID-19 patients. If, however, a cancer patient treated in the outpatient clinic presents with febrile neutropenia and is admitted to the COVID-19 dedicated area, the cancer patient may actually be at higher risk and not receive the adequate therapy within the required time frame in this emergency setting. It seems advisable to envisage the situation of delivering care in a COVID-19-dedicated area during the time of the most profound immunosuppression caused by anti-cancer treatment. Some elective therapies leading to profound immunosuppression later on may be re-evaluated under the consideration that management of complications may be hampered because of emergency measures. On the other hand, it is vital to ensure appropriate cancer therapy as much as possible, especially in patients with curative options and rapid proliferation of their disease. Therefore, the individual situation of cancer patients needs to be considered when implementing emergency measures.

We have addressed some potential questions relevant for clinicians caring for cancer patients in the following. We do not address the topic of stem cell transplantation and cell therapy, since this is the focus of guidelines prepared by the European Society for Blood and Marrow Transplantation which can be accessed under

<https://www.ebmt.org/ebmt/news/coronavirus-disease-covid-19-ebmt-recommendations-update-march-23-2020>. Also, we do not provide specific recommendations as to structural changes within departments caring for cancer patients because geographical differences are too large to make generalized statements. However, individual treatment decisions will have to take these aspects into account and clinicians may have to deviate from these recommendations due to reduced capacities or other structural impediments.

1) What is the risk for the patient to become infected with SARS-CoV2 and what is the risk for the patient to have a severe disease course?

Current available data does not show a different rate of infection in patients with a malignant disease compared to healthy members of the population^{5,6}. This is mostly due to the fact that cancer patients as well as healthy individuals are immunologically naïve to this novel pathogen. Regarding the course of the infection, underlying malignant disease has not been identified as an independent risk factor in multivariate analysis so far⁶. However, severely immunosuppressed patients generally have a higher risk of developing complications in CARV infections¹⁰ and it should be assumed that cancer patients are at risk of a more severe course of COVID-19 as well⁷. In the absence of more specific data, potential risk factors for severe course of the disease should be assumed as for other CARV-infections: severe immunodeficiency, lymphopenia, long and profound neutropenia and older age.¹⁰ As lymphopenia is a risk factor for LRTID and mortality in CARV infections in SCT-recipients and SARS-CoV2 appears to cause or be associated with lymphopenia, patients with pre-existing severe lymphopenia ($<0.2 \times 10^9/L$) may in time be shown to have an increased risk for a severe course of COVID-19 as well^{6,10}. Clinicians should also be aware that cancer patients generally shed CARV longer than immunocompetent people¹¹ and this is probably true for this novel coronavirus as well.

2) What can be done to prevent COVID 19?

The most important measures are general contact precautions including hand hygiene. Patients should be counselled regarding current recommendations of their local and national health authorities. It is strongly advised that patients with active malignant disease or currently on treatment should stay away from any social gatherings, especially in high-risk areas.⁷ Also, all symptomatic family members or those at high risk of early infection with SARS-CoV-2 should stay away from patients with active malignant disease or currently on treatment regardless of risk of corona. The aim is to prevent any infection with CARV. Face masks can be offered for situations when contact isolation is difficult, but patients should be aware of a possibly false sense of security and never rely only on them.¹²

Good general health should be reinforced in cancer patients. Patients should be advised regarding the importance of good general health: stop smoking, reduce weight loss, physiotherapy, sufficient supply of vitamins like vitamin C and D, and the treatment of any iron-deficiency.

Patients with secondary immunodeficiencies should be evaluated if they require intravenous immunoglobulins (ivlg) as recommended by EMA (recurrent infections in patients with IgG < 4g/l due to secondary immunodeficiency)¹³. Physicians need to be aware that ivlg are NOT specifically effective against SARS-CoV2 because of lack of specific antibodies within the product, but they help to generally restore a defective immune response and help to prevent additional (for example bacterial) infections. As time elapses there is a high probability that new preparations from immune donors will include protective antibodies as well.

Prophylactic antibiotics and generous implementation of G-CSF seem a logical attempt to avoid bacterial superinfections and shorten duration of severe immunosuppression. However, prior exposure to antibiotics has been associated with adverse outcome in CARV-infections in stem-cell transplant recipients¹⁴. Also, in geographical areas with a high rate of multi-drug resistant bacteria, antibiotic prophylaxis is unlikely to work. G-CSF on the other hand is known to be associated with the risk of hyperinflammation during regeneration. Thus, we strongly recommend not to implement additional antimicrobial prophylaxis on top of recent recommendations by current guidelines concerning use of antibiotics and G-CSF¹⁵⁻¹⁷. In contrast, vaccination against influenza and especially pneumococci should be recommended for all cancer patients as per current guidelines^{18,19}.

3) Who should have therapy for malignant disease deferred or interrupted?

The most relevant and urgent question of clinicians is the most difficult to answer: which anti-cancer therapies should be deferred or interrupted and which should be given or continued? We have attempted to provide a rationale regarding the deferral or interruption of therapies in fig. 1A/B. Generally, patients with controlled underlying disease have fewer infections than untreated patients²⁰, therefore, uncontrolled malignant disease should be avoided and life-threatening malignancy needs treatment, especially if there is relevant curative potential. As stated above, impairments and shortages due to the emergency situation need to be taken into account. However, active malignant disease should be treated accordingly and timely to prevent a worsening in outcome. This includes surgical procedures (for example for obstruction) as well as systemic anti-cancer therapy or radiation.

Generally, treatment in asymptomatic patients should continue as close to normal as possible. Prophylactic interruptions of continuous therapies are not generally recommended. Many continuous therapies like for example BCR-ABL targeting TKI are not associated with a clinically relevant increase in immunosuppression and discontinuation may impair control of the malignant disease. Also, clinicians should be aware of the fact that termination of some drugs, for example ruxolitinib, may have devastating effects in terms of a rebound of symptoms²¹. On the other hand, some therapies are associated with significant cytopenias and toxicities which must be assumed as risk factor for adverse outcome of COVID-19. In addition, as stated above lymphopenia is likely a specific risk factor for adverse outcome⁶. Therefore, administration of drugs inhibiting B cells like monoclonal antibodies against CD20 are possibly harmful and should be critically evaluated. Also, drugs associated with hypersensitivity-phenomena may aggravate COVID-19-induced hypersensitivity-pneumonitis²². Therefore, interruptions of some therapies may seem prudent in patients presenting with symptoms of RTID. In general, recommendations regarding the management of potential infectious complications of novel and targeted therapies should be observed^{23,24}.

4) How long should precautions last?

Precautions in individual cancer patients regarding therapy should last until there are no more clinical signs of ongoing infection and the patient has been tested negative. Clinicians need to be aware of prolonged shedding of CARV in cancer patients¹¹. General precautions in the population depend on guidance by national health authorities. Some experts assume that the critical time of the pandemic will last 2-4 months, if measures of clear-cut social distancing are effectively maintained.

5) What diagnostic measures should be taken in somebody who shows symptoms of RTID/LRTID?

In someone presenting with symptoms of RTID, broad diagnostics (ideally SARS-CoV-2 in addition to multiplex-NAT including other CARV like influenza, parainfluenza, metapneumo- and human coronaviruses and respiratory pathogens like pneumococci) is strongly recommended^{10,25}. Identification of the infectious agent, even if it is not SARS-CoV-2, has therapeutic and regulatory consequences and should thus be obtained. We are aware that national recommendations regarding testing for SARS-CoV-2 may differ and that shortages of tests may become a problem. However, we recommend that cancer patients should be generously tested since it has immediate implications.

Samples should generally be taken from the involved anatomical area. Nasopharyngeal aspirates, samples from lower respiratory tract and nasopharyngeal swabs may be used, nasal swabs alone confer a lower sensitivity²⁶. Clinicians should be aware that testing for SARS-CoV-2 may produce false negative results in asymptomatic or mildly symptomatic patients and in patients with LRTID if samples from the upper respiratory tract are tested^{27,28}. Therefore, it is very important to implement standardized sampling and to repeat tests in patients with unexpected results to avoid bias by pre-analytical mistakes. For diagnosis of LRTID in patients with CARV infection including SARS-CoV-2, CT scans should be used rather than chest X ray²⁸⁻³⁰. If LRTID is present, patients should undergo standard microbiological testing to test for bacterial or fungal superinfection since superinfection is the most dangerous complication in any CARV-infection⁴.

6) What general therapeutic measures should be taken in somebody who is infected with SARS-CoV-2?

It seems logical to reduce immunosuppression in those patients where this is possible. However, possible disadvantages should be taken into consideration like immune reconstitution syndrome¹. Therefore, in most cases it is probably not prudent to stop immunosuppression. Steroids, particularly high-dose, are generally associated with a prolonged shedding and an increased mortality in CARV-infections^{31,32}. However, recent reports on COVID-19 suggest a benefit of steroid treatment³³ and low-dose steroid (<1mg/kg/d for 3 days) has been described in an immunosuppressed patient³⁴. A randomized trial is currently underway³⁵. Thus, it seems reasonable to reduce high doses of steroids to avoid profound immunosuppression by tapering to doses <1mg/kg/d. As stated above, ivlg-preparations to date are not specifically active against SARS-CoV-2 and are therefore currently not recommended as treatment.

Recent reports support a relevant proportion of hyperinflammation in severe cases of COVID-19 and suggest the consideration of additional anti-inflammatory drugs like tocilizumab or ruxolitinib in patients fulfilling criteria of HLH^{1,36-38}.

7) How can COVID 19 be treated specifically?

There are no established standard treatments for COVID-19. Whenever possible, patients should be included into clinical trials. Infectious disease specialists should be involved in therapeutic decisions. If experimental treatment with drugs approved for other indications is considered, physicians should share the decision with the patients and inform them about the chances and risks of such strategies.

Experiences with SARS and first experiences with SARS-CoV-2 suggest efficacy of some treatment options³⁹: lopinavir/ritonavir, chloroquine and remdesivir seem most promising. Ribavirin is potentially effective based on *in silico* models, but no clinical data is available. For SARS, retrospective data with low quality of evidence suggested effectiveness of ribavirin in combination with lopinavir/ritonavir.

If specific treatment is administered it should probably be given as early as possible to be effective, similar to treatment of influenza.

8) What else should be considered?

Since cancer patients are particularly prone to severe courses of CARV-infections, clinicians should be aware of other CARV and other respiratory pathogens, which may require specific treatment.^{10,25,40} Also, co-infections are much more common in cancer patients and as stated above, cancer patients tend to take considerably longer to clear the virus than healthy controls¹¹. Often the question is raised whether blood products may confer a risk of infection – this does not seem to be the case. Therefore, blood products are safe, although they might become rare because of restrictions of donors.

Special aspects in pediatric hematology/oncology:

9) What are the symptoms in children and how similar are they to those in adult?

Clinical manifestation in healthy children has been reported to be similar to adults, with cough and fever the most frequent symptoms. Presentation is usually milder than in adults. Rarely, also gastrointestinal symptoms such as diarrhea, nausea, vomiting and feeding difficulties may be present⁴¹. In immunocompromised patients, some possible differences may be noted due to lymphopenia and pre-existing conditions (pulmonary cGVHD) (same as in the adults) resulting in a more severe presentation and rapid deterioration of the general condition.

10) What is the risk of a child getting infected?

As shown by data from China, COVID-19 seems to be uncommon in children (0.9-1.2%) compared to adults (Lee et al, *J Micr Imm Inf in press*).

11) When should a child be tested and how?

Due to the clinical evidence of frequent mild onset and evolution, only children with moderate-severe clinical condition admitted to the hospital for care are currently tested for COVID-19 infection (Italian experience, specific indications could be different according to National Authorities). Due to the atypical presentation and worse outcome in immunocompromised children, testing could be advised even with mild symptoms (local strategy) because of possible therapeutic implications. Diagnostic principles are the same as in adults including additional work-up in all patients with LRTID.

12) Should we screen all children before chemotherapy?

Because of the indeterminate onset in children, some centers may decide to screen all children prior to immunosuppressive therapy. Another option could be to screen children only if they are at high risk as defined by national health authorities (for example recent contact with COVID-19 positive person or if family members are symptomatic (cough, fever, running nose, or diarrhea).

13) Special characteristics of the pediatric infection

There seems to be a persistence of positive rectal swab even in asymptomatic children, which can lead to oral-fecal transmission^{42,43}. Also, results from imaging procedures may be moderately different^{41,44}. This should be taken into account when local policies for management of COVID-19 in the respective departments are devised.

Summary

COVID-19, caused by SARS-CoV-2, is expected to be a devastating infection in patients with active cancer. It should be taken seriously and managed rigorously without jeopardizing the curative chance of individual cancer patients. In view of the rapidly changing evidence and general situation we attempted to provide current and clinically relevant guidance on the management of cancer patients with or at risk of COVID-19.

Conflicts of interest

The authors declare no conflicts of interest. The manuscript has been published in part on the website of the European Hematology Association.

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Figure Legends

Figure 1A: proposed algorithm for the management of anti-cancer therapy in patients with active malignant disease. RTID = respiratory tract infectious disease

Figure 1B: proposed algorithm for the management of anti-cancer therapy in patients with chronic/controlled malignant disease. RTID = respiratory tract infectious disease, LRTID = lower respiratory tract infectious disease