HHS Public Access

Author manuscript

Cancer Med J. Author manuscript; available in PMC 2020 May 13.

Published in final edited form as:

Cancer Med J. 2020 ; 3(1): 40–48.

COVID-19 and Cancer Patients

Rajvi Patel, **Jennifer Park**, **Ankit Shah**, **Muhammad Wasif Saif***

Department of Medical Oncology, Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra and Feinstein Institute for Medical Research, USA

Abstract

COVID-19 has now been declared a global pandemic with evolving incidence rates and fatalities. It is important to identify vulnerable populations who will be impacted most by this pandemic leading to higher mortality rates compared to the general healthy population. Although older patients and patients with co-morbidities fall into this vulnerable group, patients with hematologic and oncologic malignancies on active cytotoxic treatments are at even greater risk as they are both myelosuppressed and immunosuppressed. In addition to following the universal guidelines recommended by the Centers for Disease Control (CDC), it is important to also institute guidelines for cancer centers to help protect this vulnerable population. We review the current data, risks, and recommendations for COVID-19 in cancer patients.

Keywords

COVID-19; Cancer patients; Pneumonia; Sepsis; Influenza; Shortness of breath; Cough; Fever; Immunosuppressed

Introduction

The World Health Organization (WHO) recently declared COVID-19 to be a public health emergency of international concern due to its rapid spread. As of March 20, 2020, there are 255,811 reported cases, 10,495 deaths, and 89,918 recovered. This new virus, named 2019-nCoV by WHO is a new human-infecting Betacoronavirus that likely originated from chrysanthemum bats based on its genetic similarly to two bat-derived SARS-like coronaviruses [1]. This virus was first observed in Wuhan, China in December 2019. The virus enters the host cell using its densely glycosylated spike (S) protein, binding with high affinity to the angiotensin-converting enzyme 2 (ACE2) receptor which is expressed in type II alveolar cells, affecting the lung and airways thus causing a respiratory illness [1]. Patients with cancer are overall more susceptible to infection given their immunocompromised state due to malignancy and anticancer treatments such as chemotherapy, radiation, or surgery. Therefore, these patients may be at increased risk for contracting COVID-19 and subsequent poor prognosis.

***Corresponding author:** Muhammad Wasif Saif, Department of Medical Oncology, Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra and Feinstein Institute for Medical Research, USA, Tel: +5163212238, Fax: +5163212272; wsaif@northwell.edu.

The disease can spread from person to person through small droplets from the nose or mouth that may spread when a person coughs or sneezes. Another mode of transmission is by touching a surface that the droplets have landed on and then touching their eye, nose, or mouth. Incubation period ranges from 1 to 14 days with a median of 5 days −6 days although 24 days was reported in one study [1]. Symptoms can be mild to severe and can include fever, cough, and shortness of breath. Other symptoms may include body aches, nasal congestion, sore throat, or diarrhea. It is important recognize that some people who are infected may not develop any symptoms. There fore patients can present with varying degrees of illness but data from China show that primary symptoms were fever (87%), cough (67.8%), sputum production (34%), myalgias (14%), sore throat (13%) and diarrhea (3.8%) [1]. Chest radiographs showed bilateral patchy infiltrates and ground glass opacities on CT scan in 56.4% of patients though these studies were interpreted as normal in 17.9% of non-severe cases and 2.9% of severe cases. Lymphopenia was seen in 83.2%, prolonged prothrombin time in 58% and elevated lactate dehydrogenase in 40% of patients [1].

The role of molecular evolution of the virus from population genetic analysis looking at 103 SARS-CoV-2 genomes showed that these viruses evolved into two major types: the S type (~30%) was evolutionarily older and less aggressive and the L-type (~70%) which was more prevalent during the initial outbreak in Wuhan that demonstrated quick spread and aggressive behavior [2]. The molecular evolution in cancer patients has yet to be investigated.

Testing for COVID-19

SARS-COV-2 is the etiologic agent of COVID-19. Its viral nucleic acid is detected using real-time polymerase chain reaction (RT-PCR) and is considered the reference standard for the diagnosis [3]. Specimens should be obtained from saliva, upper respiratory tract such as nasopharyngeal and oropharyngeal swabs, lower respiratory tract, e.g. sputum, endotracheal aspirate, or bronchoalveolar lavage, urine and stool if possible [3]. In some cases, repeated testing may be required to confirm the diagnosis. If the SARS-COV-2 nucleic acid is not detected in respiratory tract samples taken on two consecutive occasions at least 24 hours apart, COVID-19 can be ruled out. It is to be noted that serology, as a diagnostic procedure, should be used only if RT-PCR is not available [3].

Other organisms responsible to cause respiratory infections, such as influenza virus A and B, adenovirus, respiratory syncytial virus, rhinovirus, human metapneumovirus, SARS-CoV, bacterial pneumonia, chlamydia, etc. should also be ruled out if clinically indicated. One should consider collecting blood cultures for bacteria that may cause pneumonia and sepsis before initiating antimicrobial therapy. It is also important to recognize key differentiating features between coronavirus, influenza, and allergies (Table 1).

A computed tomography (CT) scan of the chest without contrast is the most useful diagnostic tool to confirm or rule out viral pneumonia, and should be performed in suspected cases. In a recent report, sensitivity of chest CT in diagnosing COVID-19 was shown to be greater than that of RT-PCR (98% *vs.* 71%) [4].

Who is at highest risk for complications with COVID-19 infection?

As COVID-19 is still a relatively new disease and epidemiologic data is still emerging, there is limited data regarding which patients are at higher risk for complications. Preliminary recommendations from the CDC suggest the following groups are at higher risk for serious illness and should follow guidelines listed in (Table 2) [5,6].

- Older adults age >60.
- Patients with chronic medical conditions such as: Heart disease, lung disease, and diabetes.

This list is likely not comprehensive, however, and it is reasonable to assume that those at highest risk for complications of coronavirus are similar to those with influenza infection including the following additional groups:

- Patients that are immunocompromised either due to underlying disorder or those on chronic immunosuppressive therapy:
  - HIV/AIDS
  - Recent bone marrow transplanto
  - Bone marrow failure disorderso
  - Leukemia or Lymphoma
  - Other cancers currently receiving chemotherapy.
  - Those on chronic immunosuppressive therapy including chronic steroids for history of solid organ transplant or autoimmune illness.
- Pregnant women or those immediately postpartum (<2 weeks).
- Patients with other chronic medical conditions such as end stage renal disease, neuromuscular disorders, sickle cell disease, and cirrhosis.
- Patients who reside in nursing homes or long-term care facilities.

While children <2 years of age are typically considered a higher risk group in influenza infection, limited data thus far suggest COVID-19 appears to cause milder infection in children [7].

COVID-19 infection during pregnancy

Cancer and pregnancy, though uncommon, does exist simultaneously in patients. Moreover, caretakers and healthcare providers who are pregnant can be exposed to COVID-19 as well. Literature suggests some risk of premature rupture of membranes, preterm delivery, fetal tachycardia and fetal distress when the infection occurs in the third trimester of pregnancy. However, data on transplacental transmission is scarce and available data only comprises of amniotic fluid, cord blood, neonatal throat swab, and breast milk samples available from six of the nine patients who were found to be negative for SARS-COV-2. Similarly, at this time we do not know about the vaginal shedding of virus [8].

Why are cancer patients at a higher risk for complications?

Patients with cancer are at a higher risk in general because of myelosuppressive effects of treatment and their disease, which suppresses their immune system. Myelosuppression or bone marrow suppression is defined as a decrease in the ability of the bone marrow to produce blood cells. This may results in decreased red blood cells (anemia), white blood cells (leukopenia), and platelets (thrombocytopenia). Myelosuppression may occur when the stem cells in the bone marrow are damaged either by chemotherapy, by crowding of tumor cells or fibrosis, or due to bone marrow failure [9]. Therefore in setting of myelosuppression there will be immunosuppression since the production of white blood cells is decreased. However, immunosuppression does not always mean myelosuppression. For example, a medication may suppress white blood cells or other parts of immune system but not affect the red blood cells or platelets.

The two main types of cells in our immune sy other cancers and currently stem consist of neutrophils and lymphocytes.

- Neutrophils defend against bacterial or fungal infection and they are usually the first responders to microbial infection [10,11].
- Lymphocytes fall into three categories [10,11]:
  - B-cells make antibodies that can bind to pathogens to block pathogen invasion and activate the complement system to enhance pathogen destruction.
  - T-cells:
    - CD4+ helper cells bind antigenic peptides presented on major histocompatibility complex (MHC) class II molecules on antigen presenting cells and produce cytokines to help coordinate the immune response.
    - CD8+ cytotoxic cells bind antigens presented on MHC-I complex of virus-infected cells and kill them.
  - Natural killer cells are able to kill cells of the body that do not display MHC class-I molecules.

It is important to recognize that in addition to underlying malignancy and cytotoxic agents, COVID-19 infection in itself also causes lymphopenia, which further weakens the immune system. Therefore, if cancer patients getting chemotherapy agents that cause lymphopenia develop infection with COVID-19, then they may develop severe lymphopenia resulting in higher mortality rates. Cyclophosphamide, cisplatin, methotrexate, fludarabine, and taxanes are among the most myelosuppressive agents known to induce lymphopenia [12]. Other targeted agents known to cause lymphopenia include: mammalian target of rapamycin (mTOR) inhibitors and tyrosine-kinase receptor inhibitors targeting vascular endothelial growth factor receptor (VEGFR) [13,14]. Additionally, the combination of chemotherapy and immunotherapy may also induce severe lymphopenia [13].

A previous analysis of influenza-infected individuals requiring hospitalization suggested that patients with lung cancer and adult hematologic malignancies had longer length of stay, higher rates of mechanical ventilation, and higher case-fatality rates compared to patients with other malignancies hospitalized for influenza [15]. In general, patients with aggressive hematologic malignancies, such as acute leukemia or high-grade myelodysplastic syndrome, and bone marrow transplant recipients are felt to be at highest risk for infectious complications [15].

Patients with lung cancer represent another high-risk group as they are at increased risk for pulmonary complications from respiratory viruses. This increased risk may be due to altered anatomy and/or presence of concomitant smoking-related lung disease. Patients receiving cytotoxic chemotherapy for other solid tumor malignancies are also at increased risk for complications, though this risk is heterogeneous, depending on the extent of their disease and the anticipated bone marrow suppression of their specific chemotherapy regimen [16].

One study in China examined a prospective cohort of 18 laboratory confirmed COVID-19 patients who had a history of cancer [16]. Lung adenocarcinoma was the most frequent type of malignancy followed by colorectal, urothelial, breast, and others. 25% of cancer patients with COVID-19 had received chemotherapy or surgery within the past month while 25% were cancer survivors in routine follow up after primary resection [16]. Compared to the patients without cancer, the cancer patients with COVID-19 were older (mean age 63 years versus 47-year-old), more likely to have a history of smoking, more polypnea and had more severe baseline CT manifestations. Patients with cancer were observed to be at highest risk for severe events, defined as the composite of admission to the intensive care unit requiring invasive ventilation or death, and cancer was associated with a shorter time to development of severe events when compared to non-cancer patients [16]. Among patients with cancer, older age was the only risk factor for severe events. Patients with lung cancer did not have a higher probability of severe events compared with other cancer types and there were no significant differences in sex, other baseline symptoms, comorbidities or baseline severity of x-ray findings, though sample size was small making comparative analyses difficult.

In contrast, patients receiving single agent immunotherapy and endocrine-based therapies have a lower risk given lack of bone marrow suppression from these modalities. Lastly, patients with remote history of cancer and those who are believed to be in remission are anticipated to have a complication risk approaching that of the general population.

Case fatality rate (CFR), similar to disease illness, seems to be highly variable but increased in patients with medical comorbidities and those who developed severe respiratory symptoms. In non-cancer patients, CFR was suggested to be as high as 8% to 15% within the Hubei Province, though outside of Hubei, the CFR was no higher than 1% – 2%. Patients with cancer were observed to have a higher risk and shorter time to development of severe events that included death especially if they underwent chemotherapy or surgery within the past month [1]. Therefore, it is extremely important to prevent infection with COVID-19 in this very vulnerable patient population with hematologic and oncologic malignancies on active chemotherapy. See guidelines for cancer centers listed in (Table 3).

How to manage cancer patients during this pandemic?

We recommend more intensive screening and surveillance in cancer patients for signs and symptoms of COVID-19 infection. If the patient is found to be infected with COVID-19, cancer treatment should be postponed as long as possible if the patient's disease status is stable.

As previously discussed, there is concern that treatments such as chemotherapy or immunotherapy will cause further immunosuppression and myelosuppression causing severe events including death. Ontario guidelines recommend dividing cancer patients into priority classification groups (Table 4). Below are the treatment recommendations based on the priority classification groups A, B, or C as per the Ontario Health Pandemic Planning Clinical Guideline for Patients with Cancer [17].

- Patients already on treatment should continue therapy if possible.
- Patients in Priority A group should be treated.
- Waiting lists should be created for Priority B patients requiring treatment and should be contacted by a triage nurse to discuss and arrange treatment as soon as feasible. Treatment can be deferred for up to several weeks.
- Patients should be given a telephone number to call in the event their condition changes.
- Discussion with the patient should take place regarding the risks and benefits of delaying the initiation of treatment in addition to increased risk of contracting an infection if patient becomes immunocompromised by cancer treatment.

Currently, treatments for COVID-19 infected patients are largely supportive. WHO and its partners are launching international clinical trials that aim to generate robust data from around the world to find the most effective treatments for COVID-19. There is some preliminary data that suggests therapeutic effects of hydroxychloroquine in combination with azithromycin to reduce both the duration and symptoms of COVID-19 infection [18]. Vaccine clinical trials have been initiated as well. There is another trial exploring the efficacy of lopinavir-ritonavir in patients with COVID-19 infection [19]. This trial was a randomized, open-label trial involving 199 hospitalized adult patients with confirmed COVID-19 infection who were randomized 1:1 to receive lopinavir-ritonavir twice daily for 14 days in addition to standard care versus standard care alone. The primary end point was time to clinical improvement or discharge from the hospital [19].

99 patients were assigned to lopinavir-ritonavir group and 100 patients to standard of care group. Unfortunately, this was a negative trial where treatment with lopinavir-ritonavir was not associated with a difference from standard of care in terms of time to clinical improvement (hazard ratio 1.24, 95% confidence interval 0.90 to 1.72). In addition, mortality at 28 days was similar in both groups as well [19]. There are no known studies to date on the efficacy and toxicity of the investigational COVID-19 therapeutics in cancer patients and further studies are needed to determine efficacy in cancer patients.

Acknowledgement

This work had supported by the NIH Grant UL1TR001064.

References

1. del Rio C, Malani PN (2020) COVID-19-new insights on a rapidly changing epidemic. JAMA.
2. Tang X, Wu C, Li X, et al. (2020) On the origin and continuing evolution of SARS-CoV-2. National Science Review.
3. Cascella M, Rajnik M, Cuomo A, et al. (2020) Features, evaluation and treatment coronavirus (COVID-19) In StatPearls. StatPearls Publishing.
4. Ai T, Yang Z, Hou H, et al. (2020) Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: A report of 1014 cases. Radiology: 200642. [PubMed: 32101510]
5. CDC (2019) Coronavirus disease 2019 (COVID-19). Centers for Disease Control and Prevention.
6. CDC (2018) People at high risk of flu. Centers for Disease Control and Prevention.
7. Cai J, Xu J, Lin D, et al. (2020) A case series of children with 2019 novel coronavirus infection: Clinical and epidemiological features. Clinical Infectious Diseases.
8. Liang H, Acharya G (2020) Novel corona virus disease (COVID-19) in pregnancy: What clinical recommendations to follow?. Acta Obstetricia et. Gynecologica Scandinavica
9. Fontana L, Strasfeld L (2019) Respiratory virus infections of the stem cell transplant recipient and the hematologic malignancy patient. Infectious Disease Clinics 33(2): 523–544. [PubMed: 30940462]
10. Gamberale R, Galmarini CM, Fernández-Calotti P, et al. (2003) In vitro susceptibility of CD4+ and CD8+ T cell subsets to fludarabine. Biochemical Pharmacology 66(11): 2185–2191. [PubMed: 14609743]
11. Marshall JS, Warrington R, Watson W, et al. (2018) An introduction to immunology and immunopathology. Allergy, Asthma & Clinical Immunology 14(2): 1–10.
12. Ménétrier-Caux C, Ray-Coquard I, Blay JY, et al. (2019) Lymphopenia in cancer patients and its effects on response to immunotherapy: An opportunity for combination with cytokines?. Journal for Immunotherapy of Cancer 7(1): 85. [PubMed: 30922400]
13. Novello S, Camps C, Grossi F, et al. (2011) Phase II study of sunitinib in patients with non-small cell lung cancer and irradiated brain metastases. Journal of Thoracic Oncology 6(7): 1260–1266. [PubMed: 21610524]
14. Ray-Coquard I, Favier L, Weber B, et al. (2013) Everolimus as second-or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. British Journal of Cancer 108(9): 1771–1777. [PubMed: 23612453]
15. Cooksley CD, Avritscher EB, Bekele BN, et al. (2005) Epidemiology and outcomes of serious influenza-related infections in the cancer population. Cancer: Interdisciplinary International Journal of the American Cancer Society 104(3): 618–628.
16. Liang W, Guan W, Chen R, et al. (2020) Cancer patients in SARS-CoV-2 infection: A nationwide analysis in China. The Lancet Oncology 21(3): 335–337. [PubMed: 32066541]
17. (2020) Pandemic planning clinical guideline for patients with cancer. Ontario Health Cancer Care Ontario.
18. Gautret P, Lagier JC, Parola P, et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents: 105949. [PubMed: 32205204]
19. Cao B, Wang Y, Wen D, et al. (2020) A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine.

Table 1:

Differentiation between coronavirus, influenza and allergies.

Coronavirus	Fever
	Cough
	Shortness of breath or difficulty breathing
	Symptoms appear 2–14 days after exposure
Flu	Fever
	Cough
	Body aches
	Fatigue and weakness
	Sore throat
	Congestion
Allergies	Sneezing
	Itchy eyes and nose
	Runny or stuffy nose
	Watery, red, or swollen eyes

Table 2:

Recommendations for cancer patients.

Patients with hematologic and oncologic malignancies on active treatment should practice universal precautions recommended by the CDC:
• Social distancing by avoiding crowds (especially in poorly ventilated spaces) and minimize public transportation as much as possible.
• Wash your hands often with soap and water for at least 20 seconds (especially after blowing your nose, coughing, sneezing, or having been in a public place).
• Avoid touching your face, nose, or eyes.
• Use hand sanitizer that contains at least 60% alcohol if soap and water are not available.
• Avoid touching surfaces in public such as elevator buttons, door handles, handrails, and handshaking with people. Can use a tissue or your sleeve to cover your hands or fingers if you must touch something.
• Practice routine cleaning and disinfecting of frequently touched surfaces in your home (example: tables, doorknobs, light switches, handles, desks, toilets, faucets, sinks, and cell phones).
• Avoid any sick contacts or family members.
• Watch out for the following symptoms and emergency warning signs:
• Difficulty breathing or shortness of breath.
• New confusion or inability to arouse.
• Bluish lips or face.
• Temperature above 100.4 F with a low neutrophil count (commonly seen in patients with hematologic malignancies and on active chemotherapy).
• Consult your healthcare provider for any questions or to discuss your symptoms.

Table 3:

Recommended precautions for cancer centers.

Patients that are symptomatic and have traveled to endemic areas (within 14 days) should be masked and isolated immediately
Patients that are without symptoms and have traveled to endemic areas (within 14 days) should be masked, isolated, and assessed.
Patients with symptoms and no known travel/exposure: avoid coming to the cancer center and can be screened over the phone:
If patient has fever + cough and clinically stable: can get respiratory viral panel (RVP) testing at an urgent care center. If RVP negative, then pursue COVID testing
If fever + cough and clinically unstable: should go to the emergency room
Dispose of all magazines in the lobby and books in the treatment room and education area
Remove all courtesy telephones
No snacks or coffee openly available for self-service. They can be handed out by a staff member as requested. Wearing gloves should be recommended for any staff member distributing snacks.
There should be a designated isolation room and adjacent bathroom for any patient that needs to be isolated.
Gowns, gloves, and masks should be available for clinical teams at designated locations, especially in BMT and leukemia treatment units.
Health care providers who will be performing assessments of suspected cases should have had N-95 fit testing.
Injections that can be given without exposing patients to infusion:
• Octreotide
• Lanreotide
• Erythropoietin stimulating agents
• Growth factors

Table 4:

Priority classification of cancer patients.

Priority A: Patients who are deemed critical and require urgent services/treatment even in the event of a pandemic due to instability, unbearable suffering and/or immediate life-threatening disease. The list below is not limited to these situations.
• Rapidly progressing tumors such as brain, acute leukemia, aggressive lymphomas, cervical cancers, anal cancers and most head and neck cancers require assessment, with priority for ambulatory radiation or chemotherapy if their cancer is potentially curable.
• Spinal cord compression requiring emergency MRI and radiation oncology consultation and ongoing symptom management.
• SVC syndrome, requiring radiation oncology consultation.
• Acute pain crisis requiring assessment and pain control.
• New onset, acute delirium.
• Acute, new onset or progressive dyspnea requiring radiation, chest tube drainage, palliative chemotherapy.
• Malignant bowel obstruction or bowel perforation which may need radiation and surgical oncology services.
• Metabolic crisis assessment and care for hypo- and hypercalemia.
• Pathologic fractures requiring orthopedic assessment, radiation oncology and pain management.
Priority B: Patients who require services/treatment, including supportive care, psychosocial care and toxicity management but deemed non-critical as patient is stable without unbearable suffering and no immediate life-threatening situation. The majority of patients requiring chemotherapy will be priority B.
• IV medications/electrolyte supplementation not part of systemic treatment.
• For patients starting therapy, recognizing that there are little to no data supporting long delays, this will be a judgment call for each patient.
• Patients already receiving therapy will need to be assessed as to whether they require ongoing treatment and if it can possibly wait weeks before continuing treatment.
Priority C: Patients who are generally healthy whose condition is non-life threatening where services/treatments can be delayed without anticipated change in outcome.
• Patients receiving oral hormone therapy, especially in the adjuvant setting.
• Patients receiving follow up care.
• Patients receiving IV bisphosphonates if that is the only IV treatment required.