



Novel coronavirus SARS-CoV-2 outbreak and cancer: A literature review

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Abstract

Cancer is a significant cause of death worldwide. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is spreading rapidly globally. Information on coronavirus disease 2019 (COVID-19) and its complications in cancer patients are still limited. It is relevant to consider that some chemotherapeutic agents have secondary immunosuppressive effects. Approximately 35% of hematologic cancer patients develop pneumonia caused by community respiratory viruses. People older than 65 years-old or with severe neutropenia or lymphopenia are at higher risk. Cancer patients with pneumonia infected by parainfluenza virus showed a higher risk of mortality compared to non-cancer patients ($p < 0.05$; 12.3% vs. 3.8%) or coronavirus infections ($p < 0.01$; 24% vs. 30%). Complications associated with SARS-COV2 infection in cancer patients are limited to descriptive studies, with those who received myeloablative, immunosuppressive or monoclonal antibody therapies being more susceptible.

Keywords: SARS-CoV-2. COVID-19. Cancer. Chemotherapy.

Brote del nuevo coronavirus SARS-CoV-2 y cáncer: revisión de la literatura

Resumen

El cáncer es una causa significativa de muerte en todo el mundo. La infección por el síndrome respiratorio agudo severo coronavirus-2 (SARS-CoV-2) se está propagando rápidamente a nivel mundial. La información sobre la enfermedad por coronavirus 2019 (COVID-19) y sus complicaciones en pacientes con cáncer aun es limitada. Es relevante considerar que algunos agentes quimioterapéuticos tienen efectos inmunosupresores secundarios. Aproximadamente el 35% de los pacientes con cáncer hematológico desarrolla neumonía causada por virus respiratorios comunitarios. Las personas mayores de 65 años o con neutropenia o linfopenia grave tienen un mayor riesgo. Los pacientes oncológicos con neumonía infectados por el virus parainfluenza mostraron un mayor riesgo de mortalidad en comparación con los pacientes no oncológicos ($p < 0.05$; 12.3% vs. 3.8%) o infectados por coronavirus ($p < 0.01$; 24% vs. 30%). Las complicaciones asociadas con la infección por SARS-COV2 en pacientes con cáncer se limitan a estudios descriptivos, siendo más susceptibles aquellos que recibieron terapias mieloablativas, inmunosupresoras o con anticuerpos monoclonales.

Palabras clave: SARS-CoV-2. COVID-19. Cáncer. Quimioterapia.

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Introduction

Cancer is the second leading cause of death worldwide. According to GLOBOCAN, the number of new cases in 2018 was 17,036,900¹. Cancer patients are under immunosuppression as a consequence of the malignancy as well as their cancer therapies; for this reason, they are more susceptible to infections than non-cancer patients^{2,3}.

Different kind of viruses that can affect the respiratory airway in immunocompromised patients, the most frequent described are influenza, parainfluenza, rhinovirus, respiratory syncytial virus, coronavirus, and human metapneumovirus^{4,5}. Coronavirus disease 2019 (COVID-19) was first described in the province of Wuhan, China, in late December 2019; this disease is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV2), which is a novel type of coronavirus⁶. Available information about COVID-19 and its complications in cancer patients is still limited. However, different medical societies have been working on guidelines and recommendations for this group of patients. Unlike the 2002 coronavirus contagion that affected 32 countries, COVID-19 shows a faster spread pattern than its predecessor, but with a lower mortality (2.09% for SARS-CoV2, 10.8% for SARS-CoV, and 34.77% for the acute respiratory syndrome of the middle east: MERS-CoV)^{7,8}.

Methods

An extensive systematic electronic search was undertaken of articles in electronic databases of PubMed, LILACS, EMBASE, and Scopus. The included search terms were as follows: "COVID19", "COVID-19", "SARS-Cov2", "cancer", "neoplasms", "immunotherapy", "fil-gastrim", and "G-CSF". To optimize and expand the search results, we also examined guidelines from some of the main international institutions involved with oncology and COVID-19 research: ASCO (American Society of Clinical Oncology), ESMO (European Society for Medical Oncology), NCCN (National Comprehensive Cancer Network), and IDSA (Infectious Diseases Society of America). Studies published in English or Spanish, from December 1, 2019 to October 15, 2020 were considered eligible. Entire texts of the articles reviewed were analyzed, articles which reiterated the same clinical outcomes were excluded from the study.

Cancer and respiratory viral infections

The most common pathogens isolated in lower respiratory tract infections (LRTIs) are viruses 38% (human rhinovirus (20.1%), influenza (9.9%), human coronavirus (7.4%), and others), of them⁹. LRTI in immunocompromised hosts is a significant cause of morbidity and mortality itself¹⁰. The incidence of this kind of infections is ranged between 3.5 and 29%¹¹, nevertheless, it depends on the anticancer therapy and the type of malignancy.

Cancer patients had significant higher mortality than non-cancer patients in case of pneumonia caused by parainfluenza virus ($p < 0.05$; 12.3% vs. 3.8%) and coronavirus infections ($p < 0.01$; 24% vs. 30%)¹². Approximately 35% of the hematologic cancer patients can develop pneumonia caused by community respiratory viruses; moreover, the higher risk of complications is for people older than 65 years old, severe neutropenia or lymphopenia¹³. One report identified that the main risk factors of viral infection in immunocompromised host are stem cell transplant (75%), and neutropenia (62%)¹⁴.

Clinical manifestations of COVID-19

Most of the publications reported that primarily symptoms of novel disease COVID-19 are fever (78%), cough (63%), fatigue (21%), myalgia (28%), pharyngeal pain (26%), and diarrhea (6%). Many of the cases treated in the emergency rooms may be in an incubation period, considering them highly problematic due to the high risk of contagion. Nevertheless, the meantime of exposure at the onset of symptoms was 4 days (range from 3 to 5 days)^{15,16}. The typical findings of asymptomatic SARS-CoV2 infection on chest tomography (CT) are images of ground-glass opacities (50%), stripe shadowing in the lungs (20.8%), and 29.2% had no significant changes in their CT images¹⁷. Symptomatic patients also present consolidation, nodules, pleural effusion, thoracic lymphadenopathy, lung disease such a fibrosis or emphysema or a combination of ground-glass opacities and consolidation¹⁸.

COVID-19 in cancer patients

The incidence of cancer patients with COVID-19 is between 1% and 7.1%; in spite of the provided information about this group of patients usually reports a small sample size^{2,19}. Liang et al. reported 1590 cases of COVID-16; however, just 1.13% ($n = 18$) of the patients were diagnosed with cancer before the infection, most of them had a clinical record of heavy smoking, a

history of surgical resection (72%), and half of them were considered with stable disease for more than 4 years since cancer diagnosis. These factors suggest that the state of chronic immunosuppression caused by cancer may be associated with a risk of a more severe clinical status^{2,20}, and survival is poorer among cancer patients with comorbidity such as obesity, chronic heart failure, and complications after surgery²¹.

The data available suggest that patients with lung cancer are a risk population due to their history of pulmonary illness; this situation is constant in other respiratory diseases such as asthma or chronic obstructive pulmonary disease^{22,23}. Tian et al. reported two cases which were “accidental” among a sampling of the COVID-19 in lung tumors at the time of the surgery. During the 29 days of hospital stay, one of the patients was never febrile²⁴.

A retrospective cohort in cancer patients with COVID-19 shows that lung cancer (25%) was the most frequent cancer, and all the patients had a history of anti-cancer therapy such chemotherapy, radiotherapy, or immunotherapy. Another important characteristic is that 35.7% of the patients have an advanced stage of cancer. Symptoms were like non-cancer patients reported in other studies, fever was the most prevalent symptom (23.82%), but these patients also present dry cough (22.81%) and dyspnea (14.5%). Laboratory results showed anemia in 75%, leukopenia (32.1%), low levels of serum albumin (89.3%), highly sensitive C-reactive protein levels (82.1%), and lactate dehydrogenase (50%). CT images were similar than other reports of non-cancer patients²⁵.

Clinical data for suggesting deferring chemotherapy are still limited. The toxicity of some anti-cancer drugs such as bleomycin is uncertain, also the effects of COVID-19 in patients with chemotherapy neutropenia^{26,27}.

So far, the most of the recommendations came from expert communications suggesting that maintenance schedules or non-curative chemotherapy may be postponed due to the risk of immunosuppression generated by the treatments, increasing the potential risk of COVID-19 infection. Those chemotherapies that can provide a potential cure, and if the patient is in a low-risk community of cases, can be administered; life-saving chemotherapy is still recommended^{28,29}.

In the case of gynecological cancer, it is recommended to differ the surgical management at least 15 days, however, it depends on the type of cancer. In endometrial cancer, surgery can be postponed for 2 months^{30,31}. The most recent expert consensus recommends to be careful with the decision of delaying cancer therapy; accordingly,

it is essential to consider the risk of the medical actions in light of the benefits to the patient^{32,33}.

Steroids in cancer and COVID-19

The use of steroids is still controversial, so far, a comment recently published in the Lancet concludes that although it shows a discreet benefit for the control of an inflammatory process, its chronic use and the dosage prescribed may befit as an inflammatory drug. However, it also reduces immune response, especially against viruses³⁴. Yang and collaborators identified that the use of steroids in lupus erythematosus increased the risk of various opportunistic infections 136 times, the relative risk being 2.24 (95% CI: 1.26–4.00) for cases with doses higher than 60 mg of prednisone³⁵. Other infectious processes, such as herpes zoster infection, can also increase, especially with the use of intravenous boluses of steroids or higher maintenance doses of 7.5 mg³⁶.

In patients with lymphoid neoplasia, the use of steroids is common, both in induction strategies (lymphoblastic leukemia, non-Hodgkin lymphoma, and chronic lymphocytic leukemia) and also in maintenance strategy (multiple myeloma)³⁷. A particularly vulnerable group is patients diagnosed with multiple myeloma; the evidence is still limited and most of the available information come from expert recommendations. Suspends the steroid therapy (dexamethasone and prednisone) is a main point in case of lower immunoglobulins levels and it is important to consider the administration of intravenous immunoglobulin as well as ponder the use of antiviral and prophylactic therapy against *Pneumocystis jirovecii* when we prescribed proteasome inhibitors or monoclonal antibodies (anti-CD38)³⁸.

Cancer therapies in COVID-19

As chemotherapy and steroids, the use of different types of monoclonal antibodies is debatable. The main monoclonal antibody used is Rituximab, its mechanism of action is mainly based on complement-mediated cytotoxicity, activation of apoptosis, and antibody-dependent cytotoxicity³⁹, during its administration the risk of hypogammaglobulinemia is variable. Casulo et al., in their series of 211 patients with B-cell lymphoma, reported a 38.54% incidence of hypogammaglobulinemia, the 6.6% of the cases developed symptomatic hypogammaglobulinemia after 6-month period⁴⁰. The recommendations for monoclonal therapy use in COVID-19 patients such as Rituximab, is opened for

discussion, and the real benefit of each treatment must be analyzed. For example, according to the recommendations in patients with multiple sclerosis, individuals living in regions with a high number of COVID-19 cases should be isolated at home, especially if they use strategies such as teriflunomide, Alemtuzumab, Cladribine, Rituximab, or Fingolimod, but so far the discontinuation of some of the cycles is still controversial^{41,42}.

Patients with cancer receiving immunotherapy

Immunotherapy has had an expanding presence in oncology, becoming a primary systemic treatment option in diseases such as melanoma, lung, urothelial, renal, and head-and-neck cancers. Patients receiving these treatments are faced with a unique set of treatment-related toxicities driven by an autoimmune mechanism, an overlap in the physiological insult from immunotherapy-mediated pneumonitis and SARS-CoV2-related interstitial pneumonia is hypothesized. An association between immune-related adverse events and severe COVID-19 has been raised during the current outbreak⁴³, suggesting a more severe outcome, having a higher rate of death and rate of developing critical symptoms as compared to other cancer treatment modalities⁴⁴. For this reason, the main oncology societies have published guidelines to addressing the use of cancer immunotherapy in the COVID-19 era (Table 1). Practice points for cancer immunotherapy are: use extended interval immunotherapy (nivolumab every 4 weeks and pembrolizumab every 6 weeks); individualized assessment for pausing or cessation of immunotherapy in patients with controlled low disease burden^{45,46}. These call for careful considerations on the use of dual checkpoint inhibitor therapy depending on the local prevalence of community transmission and the capacity of the local health service to cope with demand^{43,45}.

Granulocyte-colony stimulating factor (G-CSF) and COVID-19

Recombinant human granulocyte colony-stimulating factor (G-CSF, filgrastim) is widely given to oncology patients to counteract neutropenia and prevent infection. G-CSF is both a growth factor and cytokine that initiates proliferation and differentiation of mature granulocytes^{47,48}. Soon after the onset of the pandemic, a panel of experts suggested to increase the use of prophylactic G-CSF alongside chemotherapy to

Table 1. Recommendations for cancer immunotherapy during the coronavirus COVID-19 pandemic

Recommendation
Screening with a standardized questionnaire for symptoms and exposure should be performed at first visit and between hospital visits
Patients should be tested for SARS-CoV2 48-72 h before initiating treatment with cytotoxic chemotherapy, stem cell transplantation, long acting biologic therapy, cellular immunotherapy, or high-dose corticosteroids SARS-CoV2 RT-PCR testing should be done to detect infection due to SARS-CoV2 and adjust treatment. If availability of tests is limited, RT-PCR should be offered only for symptomatic patients or in case of a positive case of a family member or caregiver SARS-CoV2 serology testing should be offered to all cancer patients. If not available, limit tests to all patients undergoing chemotherapy or immunotherapy or any other active anti-cancer treatment
COVID-19 testing should be proposed to all patients undergoing chemotherapy or immunotherapy, also, in case of a positive case of a family member or caregiver
Prevention of coinfections: seasonal influenza vaccination for patients taking single-agent immune checkpoint inhibitor (the use in combination checkpoint recipients should be individualized). Pneumocystis jirovecii prophylaxis for patients receiving prolonged corticosteroid therapy for immune-mediated toxicities
Judicious use of combination anti-CTLA-4 and anti-PD-1/anti-PD-L1 immunotherapy in patients requiring high tumor response rate with good organ functional reserve. Combination checkpoint therapy is associated with higher rate for immune-related toxicities (pneumonitis), which may potentially have an adverse impact on outcomes in patients with COVID-19
Prefer oral regimens to minimize hospital visits (such as ibrutinib, acalabrutinib, and venetoclax)

SARS-CoV2: Severe acute respiratory syndrome coronavirus-2, COVID-19: Coronavirus disease 2019, RT-PCR: Reverse transcription-polymerase chain reaction.

minimize neutropenia duration⁴⁹. However, series of cases were quickly reported where G-CSF administration was associated with the development of severe disease from COVID-19⁵⁰, Morjaria et al. conducted an observational cohort of 304 hospitalized patients with cancer and COVID-19 to investigate links between concurrent neutropenia (N = 55) and G-CSF administration (N = 16) on COVID-19-associated respiratory failure and death; they found that G-CSF administration was associated with increased need for high oxygen supplementation and death (HR: 2.97, 95% CI: 1.06–8.28, p: 0.038)⁴⁷. Hence, waiting for more extensive data from prospective studies, it is probably better to avoid an extensive use of G-CSF in favor of an approach based on the use of prophylactic antibiotics, mainly driven by a thorough clinical evaluation of patients^{48,51}.

Conclusion

COVID-19 infection is currently an emergency worldwide. Actually, the spread of the virus is uncertain in each region of the world, being greater today in the United States and in Europe. For health caregivers, nurses, and surgeons, pathologist is necessary to have an adequate use of protective equipment, because biological specimens pose potential risk of infection. Cancer patients are considered as a population at risk for the acquisition of different types of infectious processes, including viral infections. We still do not know the behavior of COVID-19 infection in the different types of cancer (including hematological cancer). Therefore, recommendations can only be made according to the risk offered by each treatment regimen individually. Special care is required for those patients receiving high dosages of steroids, therapies with a high risk of immunosuppression, or the use of monoclonal antibodies due to the blockage that the innate immune response generates. We summarized the current recommendations from oncology societies (ASCO, ESMO, NCCN, and IDSA) and expert consensus as shown in [table 1](#). Until now, it is considered to defer treatment schedules as much as possible except for those situations in which chemotherapy can be curative. Finally, as the pandemic progresses, the behavior of this specific population will be known to provide more solid recommendations.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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