





## Atención al paciente oncológico en tiempos de COVID-19

### Cancer patient care in times of COVID-19

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Received: June 30, 2020 | Accepted: August 05, 2020 | Published: August 10, 2020

Cite as: Luna-López AE, Germán-Flores L, Zúñiga-García AE. Atención al paciente oncológico en tiempos de COVID-19. Univ Méd Pinareña [Internet]. 2021 [citado: Fecha de acceso]; 17(1):e573. Disponible en: <http://www.revgaleno.sld.cu/index.php/ump/article/view/573>

## ABSTRACT

**Introduction:** with the emergence of the new coronavirus and the wide worldwide distribution, its effects in people with some comorbidities are a global concern. Cancer is a disease with a high incidence and prevalence in society, included among the main causes of mortality.

**Objective:** to describe the management of cancer patients during COVID-19

**Method:** a literature review of articles published up to June 2020 was carried out, using the Pubmed / Medline, SCOPUS and SciELO databases. 28 references were selected for the preparation of the present.

**Development:** cancer has variable clinical and prognostic behaviors that generally lead to states of immunosuppression caused by the therapeutics used for its treatment; Therefore, they are more vulnerable to infectious diseases. The proper care of this group of people is the responsibility of the health systems. Some measures are based on social distancing, either in reducing the number of companions of the patient in the consultation or chemotherapy sessions, the prohibition of visits to hospitalized patients and the use of technologies with the use of teleconsultations for routine follow-up, as well as the change from intravenous to oral treatments

**Conclusions:** the study of the behavior of COVID-19 in cancer patients is under development. The measures that the institutions take to achieve quality care for people with cancer are varied and are based mainly on social distancing.

Keywords: Coronavirus Infections; Cancer Care Facilities; Oncology Service, Hospital.

## RESUMEN

**Introducción:** con el surgimiento del nuevo coronavirus y la amplia distribución mundial, es una preocupación global sus efectos en personas con algunas comorbilidades. El cáncer es una enfermedad con alta incidencia y prevalencia en la sociedad, incluida entre las principales causas de mortalidad.

**Objetivo:** describir el manejo del paciente oncológico durante la COVID-19

**Método:** se realizó una revisión de la literatura de artículos publicados hasta junio del 2020, utilizando las bases de datos de Pubmed/Medline, SCOPUS y SciELO. Se seleccionaron 28 referencias para la elaboración de la presente revisión.

**Desarrollo:** el cáncer posee comportamientos clínicos y pronóstico variables que generalmente conllevan a estados de inmunosupresión causada por la terapéutica empleada para su tratamiento; por lo cual presentan mayor vulnerabilidad ante enfermedades infecciosas. Es responsabilidad de los sistemas de salud la correcta atención a este grupo de personas. Algunas medidas se basan en el distanciamiento

social, ya sea en la reducción de la cantidad de acompañantes del paciente en la consulta o las sesiones de quimioterapia, la prohibición de las visitas a los pacientes hospitalizados y el empleo de las tecnologías con el uso de las teleconsultas para el seguimiento rutinario, así como el cambio de tratamientos por vía intravenosa a vía oral.

**Conclusiones:** el estudio del comportamiento de la COVID-19 en pacientes oncológicos está en desarrollo. Las medidas que tomen las instituciones para lograr una atención de calidad a las personas que poseen cáncer son variadas y se basan sobre todo en el distanciamiento social.

**Palabras Clave:** Infecciones por Coronavirus; Instituciones Oncológicas; Servicio de Oncología en Hospital

## INTRODUCTION

On December 2019, 27 patients with pneumonia of unknown etiology were reported in the city of Wuhan, China. Weeks later, the causal agent was isolated, a new type of coronavirus that was later named SARS-CoV-2 (*Severe Acute Respiratory Syndrome Coronavirus-2*), which causes COVID-19 (*coronavirus disease-2019*).<sup>(1)</sup>

COVID-19 spread rapidly around the world and was declared a pandemic by the World Health Organization (WHO) on March 2020.<sup>(2)</sup> As of June 28, 2020, COVID-19 had infected 9,843,073 people and caused the death of 495 760 and Cuba reported 2330 confirmed positive cases and 86 deaths.<sup>(3)</sup>

Cancer is among the top ten causes of death in the world. In 2018, 18 million people were diagnosed with cancer and 9,5 million people died from this disease worldwide according to WHO figures.<sup>(4)</sup> In Cuba, cancer caused the death of 25 035 people in 2019, being the second cause of death in the country.<sup>(5)</sup>

The widespread of COVID-19 dramatically impacts people with chronic diseases such as diabetes, high blood pressure and cancer. Infection rates can be significantly higher in cancer patients than in the general population. It is suggested that cancer patients infected with SARS-CoV-2 are at increased risk of developing severe forms of COVID-19 with a rapid progression to death.<sup>(6)</sup>

Cancer patients are particularly vulnerable to infections of different etiologies. The degree of physical and immunological deterioration in cancer patients is significant; and it increases with the addition of cytostatic treatments and radiotherapy. The rescheduling of consultations, the postponement of oncological surgeries, of chemotherapeutic and radio therapeutic treatments due to social distancing and the saturation of health services by the great wave of patients infected in many places all over the world, causes the oncotherapy to be delayed or interrupted in these patients.<sup>(7)</sup>

It is a challenge for health workers to deal with the consequences of the global expansion of COVID-19. Science and new discoveries need a complex process to be corroborated and therefore international cooperation in the field of health is necessary. That is why this bibliographic review is carried out with the objective of describing the management of cancer patients during COVID-19.

## METHOD

A literature review of articles published up to June 2020 was conducted using the Pubmed/Medline, SCOPUS and SciELO databases. As a search strategy, the combination of terms using logical operators was used. They used the terms “cancer”; “COVID-19”; “coronavirus”; “SARS-CoV-2”; “immune system”; “immunosuppression”; “immunotherapy”. As inclusion criteria, it was established the selection of articles published in academic magazines submitted to arbitration, as well as data from Cuban Public Health System and World Health Organization official government sites. There were chosen 28 references to explain this topic.

## DEVELOPMENT

The most common clinical manifestations of COVID-19 are: fever, cough, dyspnea, myalgia and fatigue. Other less specific symptoms that may be present are rhinorrhea, diarrhea, headache, nausea and vomiting. The most

effective diagnostic method for detecting SARS-CoV-2 is real-time polymerase chain reaction (RT-PCR) with specificity greater than 90 %. In addition, radio opacity can be observed in both lung fields in imaging studies, with radiological evidence of viral pneumonia.<sup>(1,8)</sup>

### Treatment of COVID-19 and interactions with some antineoplastic drugs

It is important to know the effects that may have the administration of drugs applied for the treatment of patients with COVID-19 and the interactions with other drugs. The adverse effects of antineoplastic drugs are varied and interactions with other drugs used for the treatment of COVID-19 are under study.

Chloroquine and hydroxychloroquine have been suggested for the treatment of COVID-19. Both are anti-malarial drugs, also used against autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. It is an essential drug for the WHO because of its antiviral activity, demonstrated in 2006, and currently proven effective against SARS-CoV-2.<sup>(2,8)</sup> Its interaction with some antineoplastic drugs (doxorubicin and trastuzumab [Herceptin]) is associated with conduction disorders, ventricular hypertrophy and valve dysfunction.<sup>(9)</sup>

In Cuba, chloroquine and hydroxychloroquine are applied in the treatment of patients who remain hospitalized in intensive care units, so it is part of the Cuban therapeutic scheme.<sup>(10)</sup> The use of hydroxychloroquine in combination with azithromycin is currently studied, because of the association of these with the lengthening of QT; as a result it is recommended to use it under the surveillance of patients with arrhythmia risk and by toxicity.<sup>(2,11)</sup> The interaction of azithromycin with vinblastine (VBL) is associated to an increase of serum levels of P-glycoprotein and an increase of this drug's toxicity.<sup>(9)</sup>

Lopinavir/ritonavir is an antiretroviral combination commonly marketed as kaletra for the treatment of HIV-1 and HIV-2 infection; and is currently used for the treatment of patients infected with SARS-CoV-2. In Cuba, it is used for the treatment of people hospitalized with a diagnosis of COVID-19.<sup>(10)</sup> Cardiotoxicity by prolongation of the QT segment in the electrocardiogram is frequent when it is combined with tyrosine kinase inhibitors, doxorubicin or ondansetron.<sup>(12)</sup>

Although antibiotic therapy does not have antiviral effects, they are used whenever bacterial co-infection is suspected due to the high risk of infection of this type in hospitalized patients, especially those in intensive care units under mechanical ventilation, it is necessary to mention it. The use of broad-spectrum antibiotics is not recommended if a bacterial infection is not suspected.<sup>(8)</sup>

Interferons (IFNs) are a group of proteins produced by the body's cells as a defensive response to viruses. They are important modulators of the immune response that interfere with viral replication by protecting cells from virus infections. They are currently applied in the treatment of patients with COVID-19. And its effectiveness has been demonstrated in combination with other drugs such as ribavirin and remdesivir.<sup>(8)</sup> In Cuba, it is manufactured by the Center of Genetic Engineering and Biotechnology, and it is used in people with risk of infection and in infected patients.<sup>(10)</sup> Interferon beta-1a has a favorable interaction profile, although some cases of autoimmune hepatitis and acute hepatic insufficiencies have been reported, for this reason it should be monitored when it is associated to hepatotoxic drugs such as crizotinib and lenalidomide. As well as avoiding the combination with tramadol in patients at risk of epilepsy (epileptic patients, with brain tumor or elderly) due to the lowering of the epileptogenic threshold.<sup>(12)</sup>

There are other types of treatment in the research phase. Passive immunotherapy using plasma from people who are recovering from the disease is useful.<sup>(8)</sup> The use of corticosteroids is controversial, especially in patients with acute respiratory distress syndrome,<sup>(8,11,13)</sup> as well as the use of peptides, monoclonal antibodies and new antivirals are under development and in research phases where effectiveness has not yet been demonstrated.<sup>(11,13)</sup> That is why there is a continuous need for updating on this subject.

### Immune system in cancer patient

Cancer itself is a complex disease. The treatments and the prognoses of people who suffer it are varied, since it does not depend only on the affected organ, but also on the histological variety, the mutated genes, among

other factors. Therefore, a wide variety of these diseases have been described, all of them with different pathophysiologies, treatments and prognoses.

With the onset of SARS-CoV-2 and the spreading of COVID-19, studies have begun to identify the vulnerability of cancer patients with some types of this disease.<sup>(10)</sup> The response of the immune system is complex and varies among individuals, and cancer patients, depending on a variety of factors.

The tumor microenvironment consists not only of malignant cells, but also of other normal cells (endothelial, pericytes, tumor-associated fibroblasts, adipocytes, stem cells, and leukocyte populations). This is generally a site of local immunosuppression. Tumor cells have demonstrated to have the ability to locally deactivate or evade the immune system by means of suppressive signals. Examples are the low antigenic expression of tumor cells, the loss of co-stimulatory molecules and the increase of immunosuppressive molecules, which promotes tumor growth and progression.<sup>(14)</sup>

Systemic immunosuppression in the cancer patient depends on a certain degree on the treatment administered. The literature reports that, cancer patients who are given cytotoxic drugs are vulnerable to infectious diseases, especially opportunistic bacteria and fungi. Advances in cancer therapy have been significant in recent years, however, it is a challenge to address the resistance of tumor cells to these therapies and the toxicity associated with the administration of these drugs.<sup>(15)</sup>

With the advance of cellular and molecular biology, research is constantly being developed to find more targeted therapies for treating cancer. Personalized medicine and immunotherapy provide the research ecosystem with new perspectives in the treatment of patients with these diseases. The combination of chemotherapy and immunotherapy has revealed novel results in the treatment of some of these diseases.<sup>(16)</sup> Some activation of the immune system has been found due to a wave of antigens released by the destruction of tumor cells damaged by chemotherapy or radiotherapy.<sup>(14,16)</sup> These treatments could translate into a better prognosis and an improvement of the immune status of the cancer patient.

### Cancer patient with COVID-19

The development of emerging infectious diseases brings new concerns for vulnerable populations, and the cancer patient is one of them. SARS-CoV-2 proves to be a virus with a high degree of infectivity, despite not having a high mortality rate in the healthy population, it is already demonstrated that it increases the complications and mortality rates in patients with some types of comorbidities.<sup>(17)</sup>

Cancer patients are considered a highly vulnerable group to COVID-19. The clinical characteristics of these patients infected with SARS-CoV-2 are under study; an example is the research developed by Zhang et al.<sup>(18)</sup> When studying the clinical manifestations of 28 patients with cancer, patients with COVID-19, 53.6% developed some kind of serious event and 28,6 % died. Patients who received some kind of anti-tumor treatment 14 days before the diagnosis of COVID-19 (chemotherapy, radiotherapy, individualized therapy and immunotherapy combined with chemotherapy) had a higher risk of developing a serious event (RR = 4,079, 95 % CI: 1,086-15,322, p=0,037). Similar results were reported by Liang, et al.<sup>(19)</sup> when studying 18 patients with cancer (OR = 5,34 95 % CI: 1,80-16,18, p=0,0026). Both studies are statistically significant, but have a very small sample size, therefore reliable results cannot be evidenced.

Yang et al,<sup>(20)</sup> in a study with a sample of 205 patients analyzed similar variables and resulted in male patients (n=96; OR = 3,86; CI 95 %:1,57-9,50; p=0,0033) and patients treated with chemotherapy 4 weeks before their diagnosis of COVID-19 (n=31; OR=3,51, CI 95% 1,16-10,59; p=0,026). In this research, as in previous ones, the sample size is considered a limitation. In Tian's research, and col.<sup>(21)</sup> they observed that cancer patients (n=232) developed the COVID-19 in a more severe state than patients with COVID-19 who did not have cancer (n=519) (OR=3,61, CI 95 %: 2,59-5,04; p<0,01).

Lung cancer is the world's leading cause of cancer death.<sup>(4)</sup> Garassino et al,<sup>(22)</sup> conducted a multicenter study where they studied a total of 200 patients with some type of thoracic malignancy infected by SARS-CoV-2. Non-small cell lung cancer was the most common affectation with 76 % of the total cases, followed by small cell

lung cancer with 29 % of the cases, and the stage in which they presented most was IV with 74 % of the total patients. Of all the patients, 84 % presented some kind of comorbidity, with high blood pressure being the most common (47 %), and patients over 65 years of age (OR 1,88, 95 % CI 1,00-3,62), a history of smoking (OR 4.24, 95 % CI 1.70-12.95), having been treated with chemotherapy (OR 2.54, 95 % CI 1.09-6.11), and the presence of some kind of comorbidity (OR 2,65, 95 % CI 1,09-7,46) were associated with the risk of dying.

However, Lee, et al.<sup>(7)</sup> studied a total of 800 cancer patients, and found no statistical significance to show that cancer patients who had received cancer treatment 4 weeks before being diagnosed with COVID-19 had a higher mortality risk than those who did not (chemotherapy (n=281 ; OR : 1,18, 95% CI:0,81-1,72; p=0,380), immunotherapy (n=44; OR 0,59, 95 % CI:0,27-1,27; p=0,177), hormonal therapy (n=64; OR=0,90, 95% CI: 0,49-1,68; p=0,744), radiotherapy (n=76; OR=0,65, 95% CI:0,36-1,18; p=0,159), and individualized therapy (n=72; OR=0,83, 95% CI:0,45-1,54; p=0,559).

The sample size in these studies may have influenced the results, which is why it is considered a limitation. The consideration of comorbidities in cancer patients such as high blood pressure and diabetes cannot be disregarded as a factor influencing the increase in mortality in cancer patients. There is still a long way to go before a conclusion can be reached; it is necessary to continue to update on this subject and the possible vulnerabilities of this group.

### Measures to protect the cancer patient

Often, patients with oncological diseases may have some state of immunosuppression due to their treatment or to the disease itself; adding other risk factors such as age and the presence of comorbidities.<sup>(23)</sup> Therefore, it is the responsibility of health systems to properly care for this group of vulnerable people when dealing with the threat of COVID-19 in order to prevent them from being infected by SARS-CoV2.

Several publications have echoed the need to protect cancer patients, especially when they are undergoing treatment.<sup>(23,24)</sup> Some specialists ask to reconsider the administration of antitumor therapies and not to delay the treatments, due to a possible deterioration of the patient because of the disease she or he suffers from.<sup>(23,25)</sup>

Some measures are based on the social distancing, either in the reduction of the number of companions of the patient in the consultation or the sessions of chemotherapy, the banning of visits to the hospitalized patients and the employment of the technologies with the use of the teleconsultations for the routine follow-up.<sup>(26)</sup> However, the modification of institutions and the organization of the system of care for these patients should be a priority for people living with these malignant diseases.

Cancer, because of its complex behavior, depends on the promptness of its diagnosis and the prompt initiation of anti-tumor treatments. The COVID-19 pandemic is causing delays in the administration of these treatments to cancer patients. In the United States, for example, many clinics have been forced to postpone surgery for these patients, or to reduce doses of chemotherapy and radiation therapy to preserve clinical capabilities in institutions that are expected to care for patients with COVID-19.<sup>(27)</sup>

The European Society of Medical Oncology has published a set of treatment guidelines to mitigate the effects of COVID-19 on cancer patients. The basis of these guidelines is social isolation, with the reduction of the number of hospital visits, the change from intravenous to oral treatments and teleconsultations. These policies allow resources to be focused, as in other countries, on caring for SARS-CoV-2 infected patients and preventing new infections. However, the reallocation of these resources often leaves oncology services without resources and could lead to new morbidity and mortality rates in these patients.<sup>(28)</sup>

It is in the hands of the institutions to create policies for the care and follow-up of these types of patients, the implementation of measures to avoid confinement in health institutions, as well as access to these institutions for the least amount of companions possible, can be an alternative. But without a doubt, the cancer patient needs to be treated under strict regimes in order to avoid the progression of the disease because of the disease she or he suffers from and the spread of SARS-CoV-2.



## CONCLUSIONS

Although there are current studies on cancer patients with COVID-19, they are inconclusive, so further research works with less bias and stronger results are needed. Health institutions are responsible for implementing strategies and policies for the care of cancer patients; currently, the basis of some of these strategies is social distancing, postponement or reduction of treatments for cancer patients.

## CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

## CONTRIBUTION OF AUTHORSHIP

The author was in charge of the conceptualization, writing of the initial draft, the writing, revision and editing.

## FINANCING

The author did not receive any type of funding to carry out this research.

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