COVID-19 Pandemic and Clinical Oncology Concerns

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Abstract

Purpose: The purpose of this review article is concerns on that cancer patients are regarded as a highly vulnerable group in the current Coronavirus Disease 2019 (COVID-19) pandemic.

Methods: A literature search was performed using the PubMed database and the Cochrane library. Search terms included "novel coronavirus" or "2019-nCoV" and "clinical oncology". Authors re-viewed cancer registry information, status, and treatments.

Results: COVID-19-infected cancer patients were included and the last anti-tumor treatment was within 14 days, it significantly increased the risk of developing severe events. Lung cancer was the most frequent cancer type. The common chest computed tomography (CT) findings were ground-glass opacity and patchy consolidation. A total of patients had severe events and the mortality rate was high. Furthermore, patchy consolidation on CT on admission was associated with a higher risk of developing severe events.

Conclusions: Cancer patients show deteriorating conditions and poor outcomes from the COVID-19 infection. It is recommended that cancer patients receiving anti-tumor treatments should have vigorous screening for COVID-19 infection and should avoid treatments causing im-muno suppression or have their dosages decreased in case of COVID-19 infection.

Keywords: cancer, COVID-19, cohort study, severe clinical oncology events, immune system, anti-tumor treatments

1 | INTRODUCTION

The COVID-19 pandemic has resulted in proliferation of clinical trials that are designed to lessen the spread of severe acute respiratory syndrome (SARS-CoV-2), the virus that causes COVID-19 (1–6). The overwhelming majority of cardiovascular and lung cancer patients are at increased risk for COVID-19 infection according to that the cardiovascular and pulmonary or cardio-oncology communities are playing major important role in caring for COVID-19 patients (7–10). The COVID-19 morbidity and mortality have been linked to elderly age and morbidities leading to poverty-stricken outcome to the viral infection for frail patients and more often resulting in hospi-
talization, intensive care unit admittance and need for invasive tracheal intubation (11). Among such individual cases, cancer patients represent a large subgroup at high risk of developing corona virus infection and its severe complications (12–16). The COVID-19 pandemic is disrupting clinical research in much of the world with regard to starting new trials, similar trends were observed with patient care and cancer therapy type and route of administration again on top of the list of considerations. The clinical decisions about cancer patients deserving immunotherapy in the current context of the COVID-19 pandemic should be characterized by separated reflections, avoiding generalizations and remembering their deeply different immunological status compared with that of cancer patients undergoing chemotherapy or treatment with targeted agents (17, 18). Beyond any charming scientific speculations, it is unfortunately likely that in this COVID-19 pandemic, the greatest risk for cancer patients is the unavailability of the usually high-level medical services since all our hospital resources in terms of structures, tools and healthcare professionals, are currently strongly dedicated to the outbreak management. Moreover, cancer patients who underwent recent chemotherapy or surgery had a higher risk of clinically severe events than did those not receiving treatment. With the limit of a small sample size, the authors concluded that cancer patients might have higher risk of COVID-19 and poorer outcomes than individuals without cancer. As a consequence, they recommended to consider an intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer in endemic areas. Nevertheless, the true incidence of COVID-19 in patients with cancer would be more informative in assessing whether such patients have an increased risk (and morbidity) from this viral illness as subsequently highlighted by other publications. Furthermore, the limited cancer patient population described in this first report from the literature was curiously characterized by the lack of individuals receiving anticancer immunotherapy (19, 20). Indeed, only chemotherapy and surgery were cited among treatments received by patients in the month prior to developing COVID-19. Probably, this could simply be due to the casualty of small sample otherwise, it could suggest that cancer patients receiving immunotherapy are less prone to develop COVID-19 or to be admitted in hospital due to severe coronavirus symptoms. Many of the therapeutic agents that are being used to treat patients with COVID-19 are repurposed treatments for influenza but drugs that were not effective in Ebola patients, which Remdesivir (GS-5734) is a 1′-cyano-substituted adenosine nucleotide analogue prodrug against several RNA viruses, currently under clinical development for the treatment of Ebola virus, or treatments for malaria that were developed decades ago, and are unlikely to be familiar to the oncology communities (8, 9). The oncology physicians who are on the frontline providing care to COVID-19 patients can better understand the emerging cardiovascular epidemiology of COVID-19, as well as the biological rationale for the clinical trials that are ongoing for the treatment of COVID-19 infected patient (21–23). The safety and management of cancer patients in the current COVID-19 outbreak is urgent and most cancer clinics need to establish a contingency plan. It is well established that cancer patients are more susceptible to infections because of the immunosuppressive state caused by both anticancer treatments and surgery. Generally speaking, anticancer therapy should be prior to or combined with other therapy, including anticancer treatment. Integrative cancer therapies such as blood plasma and massage involve close contact with cancer patients, and are widely used to relieve and control a variety of symptoms in cancer patients. We suggest that integrative cancer therapies involving close contact with cancer patients, and are widely used to relieve and control a variety of symptoms in cancer patients. We suggest that integrative cancer therapies involving close contact with cancer patients should be rigidly considered or forbidden in endemic areas, and stronger personal protection provisions should be made for patients. In this point of view, authors reviewed cancer registry information, status, and treatments as well as future direction during COVID-19 pandemic.

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COVID-19 PANDEMIC AND CLINICAL ONCOLOGY CONCERNS

2 | METHODS

A literature search was performed using the PubMed database and the Cochrane library. Search terms included "novel coronavirus" and "2019-nCoV". The MESH terms were: “clinical oncology” [All Fields] AND (“coronavirus”[MeSH Terms] OR (“2019-nCoV”[All Fields]) OR (“COVID-19”[All Fields]). The defined search period from November 30 2019 to May 30 2020 was selected to compare studies regarding first outbreaks and findings. Given the nature of the review, no ethics approval was required. The search was performed by two investigators and a total of 596 studies were identified (PubMed: 595, Cochrane: 1). Two investigators then reviewed these articles, initially by title and abstract and then in detail, using a customized data abstraction form. Studies were excluded if they had an incorrect subject matter, were duplications or review. Therefore, 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. Hence, univariate and multivariate analyses were carried out to assess the risk factors associated with severe events defined as a condition requiring admission to an intensive care unit, the use of mechanical ventilation, or death.

3 | RESULTS

The recent COVID-19 pandemic has overwhelmed intensive care facilities in the epicenters of infection associated with the hypoxia and profound inflammatory response (24–30). Immunotherapy of cancer stands along with and supports intensive care units (ICUs) and inpatient wards in the global effort to overcome this unprecedented pandemic.

As shown in Figure 1, COVID-19-infected cancer patients were included and the last anti-tumor treatment was within 14 days, it significantly increased the risk of developing severe events. Lung cancer was the most frequent cancer type (31–43). The common chest computed tomography (CT) findings were ground-glass opacity and patchy consolidation (31, 37, 40, 44–48). The total of patients had severe events and the mortality rate was high. Furthermore, patchy consolidation on CT on admission was associated with higher risk of developing severe events. It is becoming apparent that the ‘ground glass’ infiltrative appearance seen on CT scans from patients with COVID-19 with pneumonitis is reminiscent of imaging from patients with immune checkpoint inhibitor (ICI)-induced pneumonitis (see Figure 2 top).

As for lung cancer, keeping higher risk index of suspicion for a COVID-19 infection and protecting vulnerable patients are priorities as described in Table 1, as reported cohort studies demonstrated that lung cancer is the most type of cancer susceptible to COVID-19 infection.

Guidelines recommended by WHO are directed toward maximizing outpatient follow-up and treatment, delaying possible therapies and procedures, screening patients for COVID-19 infection even with
**TABLE 1:** Who is at highest risk for complications with COVID-19 infection?

| Category                        | Risk Factors                                                                 | Reference                           |
|---------------------------------|-----------------------------------------------------------------------------|-------------------------------------|
| Higher risk influenza infection  | Older adults age >60                                                         | CDC (2019)                          |
|                                 | Immunocompromised                                                           | Coronavirus disease 2019 (COVID-19) |
|                                 | HIV/AIDS, Recent bone marrow transplants, Bone marrow failure disorders, Leukemia or Lymphoma, Other cancers currently receiving chemotherapy, Those on chronic immunosuppressive therapy |                                     |
| Chronic medical conditions      | Pregnant women or those immediately postpartum (<2 weeks)                  | CDC (2018)                          |
|                                 | Heart disease, lung disease, and diabetes.                                  | People at high risk of flu.         |
|                                 | Chronic medical conditions                                                  |                                     |
|                                 | End stage renal disease, neuromuscular disorders, sickle cell disease, and cirrhosis. |                                     |
| Nursing homes or long-term care facilities |                                                                            |                                     |

**FIGURE 2:** Representative images of chest CT scan with histological changes: (A) image on post-operative day 1 showing post-surgery changes in right lung, and increased ground glass opacities bilaterally (arrows). (B) foci of ground glass opacity seen bilaterally (arrows).

A low index of suspicion due to similarities of symptoms with those of the underlying cancer of the treatment with adverse events. Currently, we are aware of the probably higher incidence of misdiagnosed coronavirus infections compared with that reported and updated every day. It is likely that a great portion of healthy and young population develop COVID-19 with mild symptoms, not requiring hospital admittance and thus escaping the laboratory confirmation of the disease. According to priority classification of cancer patients as listed in Table 2 undergoing treatment currently used in everyday practice to treat solid tumors such as melanoma, lung cancer, renal carcinoma, urothelial cancers and head and/or neck carcinoma constitute a growing oncological population (49–55).

Their specific susceptibility to viral infections has not been investigated. It is able to restore the cellular immunocompetence, the patient undergoing immunotherapy could be more immunocompetent than cancer patients undergoing chemotherapy. Additionally, elevated interleukin-6 (IL-6) is an hallmark inflammatory signature seen in serum of patients with severe COVID-19 acute respiratory dis-
### TABLE 2: Priority classification of cancer patients

| Patient | Classification | Examples |
|---------|----------------|----------|
| A       | Rapidly progressing tumors | brain, acute leukemia, aggressive lymphomas, cervical cancers, anal cancers |
|         | Spinal cord compression requiring emergency MRI | 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 | progressive dyspnea requiring radiation, chest tube drainage, palliative chemotherapy |
|         | Malignant bowel obstruction | bowel perforation which may need radiation and surgical oncology services. |
|         | Metabolic crisis assessment | care for hypo- and hypercalemia |
|         | • Pathologic fractures | • orthopedic assessment, radiation oncology and pain management |
| B       | IV medications/electrolyte supplementation | not part of systemic treatment |
|         | • starting therapy | little to no data supporting long delays |
|         | receiving therapy | ongoing treatment and if it can possibly wait weeks before continuing treatment. |
| C       | Oral hormone therapy | especially in the adjuvant setting |
|         | follow up care | |
|         | IV bisphosphonates | if that is the only IV treatment required |

Tress. Many of physicians have experience with the administration of immune-modulatory agents, which is why the cancer immunotherapy is poised to contribute to the current fight against COVID-19 (56, 57). Therefore, one possibility is to encourage the use of IL-6 or IL-6-receptor (IL-6R) blocking antibodies like tocilizumab (ActemraTM, Roche-Gentech) (58), sarilumab (KevzaraTM, Regeneron) and siltuximab (SylvantTM, EUSA Pharma). We expect that more detailed studies will be forthcoming on the impact of COVID-19 infection in cancer patients including the risk of infection, the clinical impact of COVID-19 and concurrent cancer, the effect on different types of cancer, and the ability to deliver appropriate and even curative cancer treatments in the setting of infection. Finally, we need to understand the heterogeneity in effectiveness of what we wish to be approved COVID-19 vaccines and antiviral agents for cancer patients. Thus, the COVID-19 infection will become just one additional factor to be taken into consideration for the comprehensive management of oncology patients eventually.

### 3.1 Clinical management for lung cancer patients during COVID-19 pandemic

With the spread of COVID-19, the routine clinical diagnosis and treatment for lung cancer patients has been disturbed. Due to the systemic immunosuppressive of lung cancer patients caused by the malignancy and anticancer treatments, lung cancer patients are more susceptible to infection than healthy individuals. Furthermore, patients with cancer had poorer prognosis from infection. Lung cancer patients should be the priority group for COVID-19.
prevention. The protection provisions and control measures aiming to protect lung cancer patients from COVID-19 have been increasingly concerned. During COVID-19 pandemic, it should be carefully differentiated for fever and respiratory symptoms for lung cancer patients receiving anti-tumor treatment, in order to evaluate the risk of COVID-19. Moreover, it is necessary to carry out meticulous and individualized clinical management for lung cancer patients to effectively protect the patients from COVID-19 (59, 60). The diagnosis and treatment of lung cancer patients have been challenged greatly because of extraordinary public health measures since the lung cancer patients are higher risk population during COVID-19 pandemic. Hence, strict protection for lung cancer patients is needed to avoid infection.

To make worse, lung cancer patients are difficult to differentiate from patients with COVID-19 in terms of clinical symptoms, which will bring great trouble to the clinical work and physical and mental health of lung cancer patients. This review will demonstrate how to apply appropriate and individual management for lung cancer patients to protect them from COVID-19. There is currently lack of pathologic data on the novel coronavirus pneumonia or COVID-19 from autopsy or biopsy. Pathologic examinations revealed that the lungs of both patients exhibited edema, proteinaceous exudate, focal reactive hyperplasia of pneumocytes with patchy inflammatory cellular infiltration apart from the tumors and multinucleated giant cells as shown in Figure 2 (bottom). Hyaline membranes were not prominent since both patients did not exhibit symptoms of pneumonia at the time of surgery and these changes likely represent an early phase of the lung pathology of COVID-19 pneumonia.

### 3.2 | Treatment strategies for lung cancer patients during COVID-19 pandemic

#### 3.2.1 | Under planning treatment strategy

The treatment strategy should be comprehensively considered according to the tumor burden and general conditions of patients. The adjuvant chemotherapy after surgery reasonable decisions should be made based on the postoperative pathology, clinical stage, genetic status, risk factors, and prognostic indicators. Additionally, epidermal growth factor receptor (EGFR) gene mutations, oral EGFR tyrosine kinase inhibitor (EGFR-TKI) treatment may be considered as the optional adjuvant treatment (61).

#### 3.2.2 | Undergoing treatment of chemotherapy strategy

A major concern in lung cancer patients is the reduction of anti-tumor efficacy due to interruption of chemotherapy. Many of them have difficulty in advancing chemotherapy due to intolerable adverse events although there is no effect of the epidemic during normal chemotherapy. Therefore, we should also regard the adjustment of chemotherapy regimen rationally while we attach importance to the adverse effects of this epidemic on chemotherapy delays in lung cancer patients. We suggest that those undergoing postoperative adjuvant chemotherapy and maintenance treatment can be postponed or switched to oral chemotherapy with targeted drug administration at home. It is also recommended that the treatment should be carried out under supervision and appropriate dosage should be chosen monitoring closely any adverse events.

#### 3.2.3 | Undergoing targeted therapy strategy

The targeted therapy to advanced lung cancer patients is recommended that the specific sensitive mutations such as EGFR, anaplastic lymphoma kinase fusion (ALK) (62) have taken into consideration in this study. It illustrates that the targeted therapy with combination of anti-vascular therapy, chemotherapy or immunotherapy may experience enhanced anti-tumor effects. However, it is necessary to be vigilant about possible increasing of adverse events due to combination therapy, which would be not controversial at the synergy effect point of view in the current epidemic situation. Therefore, the lung cancer patients with sensitive gene mutations should be treated with oral targeted drugs during COVID-19 pandemic (63). Further, the prompt consulting is necessary to lung cancer patients under proper protection for emergency symptoms or obvious disease progression.
3.2.4 | Undergoing immunotherapy strategy

One of the reasons that tumor cells can continuously replicate and proliferate in the human body is immune escape mechanism. It is involved that programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) inhibitors developed by blocking the pathway selectively in tumor cell escape (22). In addition to it, PD-1/PD-L1 have spring boarded this therapy to a new stage, which to a certain extent may maintain longer lasting anti-tumor effects. Therefore, we suggest that receiving immunotherapy on a set of data is not urgent for lung cancer patients during COVID-19 pandemic. As a consequence, immunotherapy can be suspended or postponed in lung cancer patients with stable disease considering the adverse events of potential pulmonary toxicity and injury caused by immunotherapeutic drugs. These common adverse events include myelosuppression, nausea, and vomiting. We recommend that lung cancer patients rest and maintain a reasonable diet before chemotherapy, additionally medication such as ondansetron in order to reduce the incidence of nausea and vomiting.

3.3 | Future directions of prevention for lung cancer patients during COVID-19 pandemic

It seems to play an important role in immune-related pneumonitis and could represent a possible target if there are indirect signs of high IL-6-related inflammation such as elevated C-reactive protein while the pathophysiology is multifaceted. Among cancer patients who developed ICI-induced pneumonitis with signs of high inflammation in blood tests, highly responded well to the mono-clonal anti-IL-6 receptor antibody, tocilizumab (TCZ) within a week (58). As recently published on IL-6 therapies for COVID-19, it is reported rapid improved clinical, biological and radiological out- comes, once 5 days after TCZ treatment as shown in Figure 3 Figure 3.

Furthermore, a single center experience reported that TCZ appears to be an effective treatment option in COVID-19 patients with a risk of cytokine storm. However, the result should be evaluated with caution given the combination with corticosteroids such as methylprednisolone and the small number of cases and the treatment duration. One important pathophysiological mechanism is that macrophages use the Janus kinase- signal transducer and activator of transcription proteins (JAK-STAT) system (64). Other immune-modulating therapies are potential candidates. These agents able to alleviate activation of JAK1/ JAK2 using ruxolitinib and that of IL-6/IL-6R signaling using TCZ or an anti-IL-6 antibody such as siltuximab. Additionally, it can escalate the activity of IL-1 signaling using anakinra which is a re-combinant human IL-1R antagonist or using canakinumab that is an human monoclonal anti-IL-1β antibody or anti-IFN-g using emapalumab that is an human anti-IFN-g monoclonal antibody, which are promising therapeutic strategies to treat the hyper-cytokinemia syndrome associated with severe forms of COVID-19 Figure 4 (65–67).

Several non-immune-modulating therapies are being explored. As is well known chloroquine and hydroxy-chloroquine are antimalarial drugs which...
Acute inflammation in COVID-19 and treatment strategies. These potential targets currently under investigation; DAMPS, damage-associated molecular patterns; gp, glycoprotein; IFN, interferon; IL, interleukin; JAK, Janus kinase; R, receptor; sIL-6R, soluble IL-6 receptor; TNF, tumor necrosis factor.

have shown antiviral effects against many types of viruses, in vitro, including in HIV (68–70). They rely on two identified mechanisms of action which are inhibiting low pH-dependent viral entry into host cells and altering post-translational modifications of newly synthesized proteins by blocking glycosylation. On the other hands, various recommendations have emerged about tailoring cancer therapies, including for non-small-cell lung cancer (NSCLC), to the reality of the COVID-19. The backbone of all these is to reduce unnecessary exposure, the reducing higher risk of transmission. There is no evidence suggesting patients receiving these treatments are at increased risk of severe COVID-19 complications, compared with those on other oncological therapies while ICI-induced pneumonitis may resemble COVID-19 on a pathophysiological and clinical level. This also means carefully weighing the risk-beneficiary ratio of each treatment for lung cancer patients. Similarly, no data exist about potential interaction between tyrosine kinase inhibitors and COVID-19. The COVID-19 should be ruled out even if even drug-induced pneumonitis is suspected. However, the element to keep in mind is to be reactive for all NSCLC patients. While awaiting viral swab confirmation, one should interrupt cytotoxic therapy should biological, clinical or radiological tests be suggestive of COVID-19.

**4 | DISCUSSION**

The COVID-19 has now been declared as 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 (38). The COVID-19 pandemic presents a challenge of global reach and significance which is unprecedented in the era of modern hematology and oncology (71). We present interim guidance for clinicians caring for patients with cancer who may be particularly vulnerable both to severe COVID-19 and the potential impact of the pandemic on the pro-vision of cancer investigations and treatment. This is a rapidly evolving situation and we emphasize again that clinicians must regularly review and implement institutional, local, state and national policies, modifying or adapting the suggestions provided here as needed. Finally, we propose that oncologists and hematologists advocate for the timely application of public health measures, vaccines or treatments that might contain, delay or mitigate the spread of COVID-19 based on given the potential severe impact of COVID-19 to patients with cancer. This pandemic is also going to affect recruitment and participation in clinical trials. This requires careful consideration of halting recruitment into cancer trials to divert resources to fight the pandemic may be appropriate and in certain centers is mandatory. As such, there is no easy to complicate matters universal solution to oncological care during this outbreak crisis of COVID-19 pandemic and the duration of this pandemic is hard to predict. As with all challenges, we need to adapt and evolve rapidly to treat our patients the best we can. It is important to weigh the impact of each of our decisions in these trying times rather than rely on routine automatisms, lest we forget.
5 | CONCLUSIONS

Cancer patients show deteriorating conditions and poor outcomes from the COVID-19 infection. It is recommended that cancer patients receiving anti-tumor treatments should have vigorous screening for COVID-19 infection and should avoid treatments causing immunosuppression or have their dosages decreased in case of COVID-19 infection. The clinical and biological aggressiveness of lung malignancies clearly does not allow for anticancer therapy to be withheld or postponed. Thus, while awaiting specific evidence-based guidelines, the comprehensive management of patients with lung cancer during the COVID-19 pandemic should involve specific and careful attention to their clinical and radiological pulmonary signs, more so than for patients with other types of tumor.

6 | DECLARATION OF CONFLICT

The authors declare that they have no competing interests, the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

7 | ABBREVIATION

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2; ICUs: Intensive care units; ICI: Immune checkpoint inhibitor; PD-1/PD-L1: Programmed cell death-1/programmed cell death ligand-1; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; IL-6: Interleukin-6; IL-6R: IL-6-receptor; EGFR: Epidermal growth factor receptor; EGFR-TKI: EGFR tyrosine kinase inhibitor; ALK: Anaplastic lymphoma kinase fusion; TCZ: Tocilizumab; JAK-STAT: Janus kinase–signal transducer and activator of transcription proteins; HIV: Human immunodeficiency viruses; NSCLC: Non-Small-Cell Lung Cancer

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