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REVIEW

Cancer Care Management During the COVID-19 Pandemic

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Abstract: New cases of the novel coronavirus, also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are increasing around the world. Currently, health care services are mainly focused on responding to and controlling the unique challenges of the coronavirus disease 2019 (COVID-19) pandemic. These changes, along with the higher susceptibility of patients with cancer to infections, have profound effects on other critical aspects of care and pose a serious challenge for the treatment of such patients. During the COVID-19 pandemic, it is important to provide strategies for managing the treatment of patients with cancer to limit COVID-19-associated risks at this difficult time. The present study set out to summarize the latest research on epidemiology, pathogenesis, and clinical features of COVID-19. We also address some of the current challenges associated with the management of patients with cancer during the COVID-19 pandemic and provide practical guidance to clinically deal with these challenges.

Keywords: coronavirus, SARS-CoV-2, cancer, pandemic, health care

Introduction

In December 2019, the new coronavirus began quickly spread in Wuhan.[1] Since then, the World Health Organization (WHO) named the new virus "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" and announced "Coronavirus Disease 2019" (COVID-19) based on the name of the new disease on 11 February 2020.[2] COVID-19 has spread rapidly globally after it was recognized as a major international public health emergency and was declared a pandemic by WHO on March 11, 2020.[3] This zoonotic virus belongs to β – coronavirus, a large class of viruses prevalent in nature and has a phylogenetic similarity to severe acute respiratory syndrome coronavirus (SARS-CoV) that caused the severe acute respiratory syndrome (SARS) disease in 2002.[4,5] This type of respiratory disease is characterized by rapid transmission from human to human, resulting in a pandemic spread.[6] Currently, our knowledge regarding the potential mechanisms of multi-organ injury caused by this viral infection is evolving and anti-viral medications as well as vaccine developments are underway.[7] In order to control disease progression and decrease the complications and mortality of the disease, it is highly important to break the transmission cycle and use of available antiviral drugs and devices to control the progression of the disease.[7] Recent publications have suggested that patients with underlying conditions such as diabetes, hypertension, and cardiovascular disease (CVD) are at higher risk and may experience a more severe COVID-19 infection.[8] The risk of SARS-CoV-2 contracting in

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cancer patients is estimated to have twofold compared with the general population.[9] A variety of factors lead to increased infection risk and, importantly, patients with cancer commonly have several risk factors. Patients with cancer may be immunocompromised due to the underlying malignancy or cancer treatment.[10,11] Under the pandemic circumstance, oncologists should take the best treatment measures, taking into account the risks of death from COVID-19 versus the benefits and risks of continuing anticancer therapy.[12,13] In this regard, there is an urgent need to address the impact of such a pandemic on cancer patients including changes in resource allocation, clinical care, and the consent process.

The present review summarized the latest research progress of the epidemiology, pathogenesis, and clinical characteristics of COVID-19, and discussed the current treatment and scientific advancements to combat the pandemic novel coronavirus. Furthermore, we addressed some of the current challenges associated with managing cancer patients during the COVID-19 pandemic and provided some recommendations and practical approaches.

Etiology, Epidemiology, Origin, and Transmission of COVID-19

A novel virus belonging to the coronavirus (CoV) family causes COVID-19.[4] Members of this large family of viruses are distributed broadly among humans and animals and can cause respiratory, hepatic, enteric, and neurologic diseases.[14,15] In the last 20 years, several viral epidemics have been recorded, such as SARS-CoV in 2002, H1N1 flu in 2009, and Middle East coronavirus respiratory syndrome (MERS-CoV) in 2012.[14,15] These outbreaks stemmed from zoonotic coronavirus crossing the species barrier and causing high morbidity and mortality among human populations.[16] SARS-CoV-2 is highly pathogenic which led to a large-scale pandemic in the 21st-century. According to the world health organization (WHO), data updated on April 18, 2020, 213 countries, areas, or territories have reported 2,160,207 laboratory-confirmed cases, and 146,088 deaths.[17] More attention should be paid to the USA, Spain, Italy, Germany, and the UK with more severe outbreaks. USA (30.7%), Spain (8.7%), Italy (7.9%), Germany (6.3%), and UK (5.0%) are the top five countries with the highest cumulative confirmed cases in the world. Higher case-fatality rates were found in the USA (20.7%), Italy (15.0%), Spain (13.0%), and France (12.7%).[17] This worrying trend and the number of death rates are rapidly changing every. Since the first cases of COVID-19 disease were linked to direct exposure to the Huanan Seafood Wholesale Market of Wuhan, the transmission from animal to human was assumed to be the main mechanism.[18] Several studies indicated the role of bats as a possible reservoir of SARS-CoV-2.[6,19] Like other coronavirus, the virus is sensitive to heat and ultraviolet light. In addition, lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid, and chloroform except for chlorhexidine can effectively inactivate such viruses.[20] Accumulating evidence demonstrated that the virus may have an incubation period between 3 to 7 days and up to 2 weeks, while the longest incubation period was reported to be 12.5 days (95% CI, 9.2 to 18).[1] The COVID-19 outbreak is increasingly growing because of human-to-human transmission. Like other respiratory pathogens, including influenza and rhinovirus, the transmission occurs through coughing, sneezing, respiratory droplet, and contact.[15] The transmission of aerosols is also possible if victims are exposed to high aerosol concentrations in closed spaces for a long time. Data estimated that each patient transmits the infection to further 2.2 individuals (95% CI, 1.4–3.9).[21] Based on their patient pool, Wang et al estimated the case fatality rate of COVID-19 to be 2.84%.[22] In that study, the male: female mortality ratios were found to be 3.25:1.[22] The SARS-CoV-2 infection is more likely to affect individuals with basic disorders, including asthma, diabetes, high blood pressure, CVD, and cancer, presumably leading to serious and even fatal respiratory diseases.[1,23] In addition, patients with weak immunity are at a higher risk of being infected with the virus.

Genome Structure

The genome sequences of the coronavirus COVID-19 was sequenced, and have become available in the early stages of outbreak.[4] The genetic sequencing showed that this virus is a positive-sense RNA virus belongs to the β-CoV genus,[24] with 82% and 51.8% nucleotide identity to human SARS-CoV[25] and MERS-CoV,[4] respectively. The virus encodes four main structural proteins, including spike (S) glycoprotein, membrane (M) protein, small envelope (E) protein and nucleocapsid (N) protein, as well as several accessory proteins (Figure 1).[26] The virus also contains non-structural proteins (nsp) that are expressed as two long polyproteins (pp1a and pp1ab) then are cleaved into 16 mature smaller proteins (nsp1-nsp16) by the 3-chymotrypsin-like protease (3CLpro)

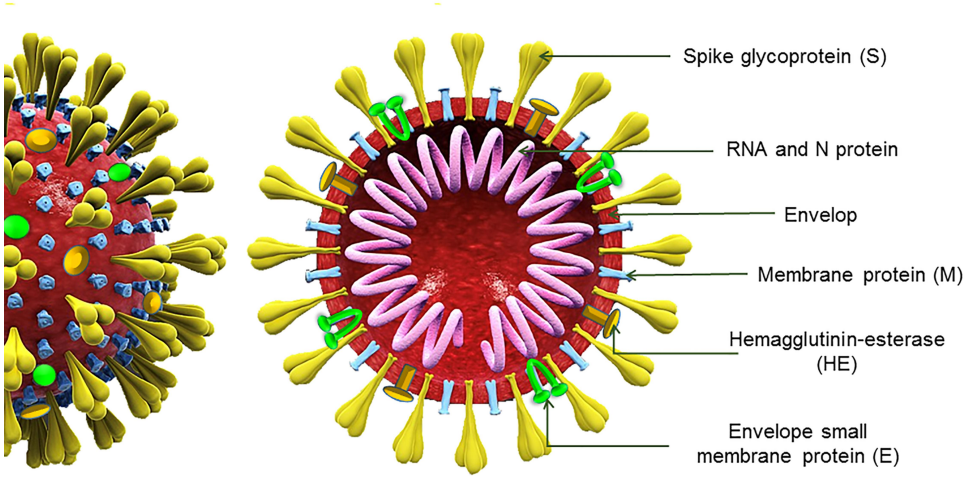

Figure 1 Schematic structure of coronavirus. The virus is an enveloped, non-segmented, positive-sense single-stranded RNA virus. The virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein, which is buried inside phospholipid bilayers and covered by the spike glycoprotein trimmer (S). The membrane (M) protein hemagglutinin-esterase (HE) and the envelope (E) protein are located among the S proteins in the virus envelope.[29]

and the papain-like protease (PLpro).[27] Some of these proteins like Nsp1, Nsp3, and Nsp15 are responsible for protein interference with the innate immune response of the host.[28]

Pathophysiology

The viral envelope plays a crucial role in virus pathogenicity, because of the fact that it facilitates viral assembly and releases.[26] The pathogenic process causing pneumonia appears to be particularly complex. The immune response is essential for control and overcoming coronavirus infections.[6] In this light, viral infection can lead to immunopathogenesis and trigger excessive uncontrolled immune responses.[6] Cytokine storm, a physiological reaction in which an uncontrolled and excessive release of cytokines injures host cells, was detected in some COVID-19-infected cases.[24] The cytokine storm-induced hyper inflammation considered a pathogenic mechanism for severe clinical scenarios of COVID-19.[30]

Chimeric antigen receptor T cell (CAR T-cell) therapy has been used increasingly for cancer treatment, especially hematological malignancies. In spite of its beneficial effects, cytokine release syndrome (CRS) is the main CAR T cell toxicity that is associated with inflammatory cytokines released by the activated CAR T cells and other immune cells such as macrophages. The disease burden and high CAR T-cell dose are associated with the severity of CRS toxicity and in the COVID-19 outbreak, treating patients with lower disease burden could decrease the CRS risk. Cancer patients are severely immunocompromised and more vulnerable to infections like COVID-19.[31,32]

Patients infected by COVID-19 exhibit increased levels of a few plasma cytokines and inflammatory factors, including interleukin 1 (IL-1), IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), monocyte chemoattractant protein-1 (MCP-1), hepatocyte growth factor (HGF), IP-10, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α).[6,33,34] Together, virus particles first attack the respiratory mucosa and then infect other cells, triggering a sequence of immune responses and developing cytokine storm in the body, which could be related to a critical condition in the patients with COVID-19.[6] Zhou et al established that the SARS-CoV-2 hijacks the angiotensin-converting enzyme 2 (ACE2) receptor, as SARS-CoV.[35] The receptor-binding capacity of SARS-CoV-2 was found to be 10 to 20 times greater than that of SARS-CoV.[36] SARS-CoV-2 binding to ACE2 induces an elevated expression of ACE2, which can result in damage to alveolar cells.[37,38] The loss of pulmonary ACE2 function can contribute to renin-angiotensin dysfunction, in turn promoting inflammation, vascular permeability and even death.[39]

Clinical Symptoms and Diagnosis of COVID-19

The major clinical symptoms resulting from SARS-CoV-2 infection include fever, cough, myalgia, and fatigue.[33] Less common signs are sputum production, runny nose,

sore throat, headache, diarrhea, vomiting, hemoptysis, and pink eye.[6] It is important to note that the severely- and critically-ill patients could present mild to weak severity even without obvious fever. Molecular approaches to detect this novel coronavirus are the first line of methods to validate suspected cases. In this regard, diagnostic tests using RT-PCR or next-generation sequencing platforms to detect the viral sequence quickly became available.[40] Concerning laboratory examinations, most patients show normal or decreased white blood cell counts and develop dyspnea and lymphopenia in the early stage of the disease.[41] In addition, there are substantially higher levels of neutrophil numbers, D-dimer, liver enzyme, LDH, blood urea, and creatinine rates in serious patients, and lymphocyte numbers continued to decrease.[6] Moreover, chest radiography or CT is an effective method used for COVID-19 diagnosis in clinical practice. Based on the current information, most patients have a good prognosis, while a few patients (especially the elderly and those with chronic underlying diseases) develop rapidly into acute respiratory distress syndrome (ARDS), septic shock, arrhythmia, acute heart injury, metabolic acidosis, secondary infection, and even death.[33]

Prevention and Management of COVID-19

There are currently no specific and effective antiviral agents or vaccines available for the treatment of SARS-CoV-2. In the absence of effective treatments, "prevention is better than cure" is the best proverb to deal with the SARS-CoV-2 pandemic. In this light, the most important strategy for the populous to undertake is cutting off the transmission route, effectively quarantining, frequently washing hands with soap and water or alcohol-based hand rub, wearing personal protective equipment such as facemask and gloves, avoiding touching eyes, nose and mouth, and observing the social distance between persons (at least 1 meter)[7,41]. The currently-available treatments for patients with COVID-19 mainly focus on symptomatic and mechanical ventilation to oxygen therapy for patients with severe infection.[6,42] Moreover, hemodynamic support is essential for managing septic shock.[43] Chloroquine is a repurposed medication that shows great potential for the treatment of the patients with COVID-19 through interfering with ACE2.[44] Chloroquine represents many interesting biochemical properties, including inhibition of pH-dependent steps in several viruses replication as well as immunomodulatory effects that suppress the production/release of IL-6 and TNF-α[6]

So far, there are several published reports on the favorable outcomes of treating patients with COVID-19 with traditional Chinese medicine, interferon, Lopinavir, Ritonavir, and short-term corticosteroids.[3,45] However, Shang et al reported that corticosteroid therapy and gamma globulin administration increased lymphocyte count, prolonged the duration of hospitalization, increased mortality, and seemed to be useful only in patients with lower lymphocyte counts.[46] Therefore, the administration of corticosteroids for COVID-19 patients' needs further investigation. The antiviral activity of Arbidol and Remdesivir against COVID-19 has been reported in vitro and in vivo, respectively. However, there is a great need for further clinical trials to confirm their effectiveness.[15,47] Besides, protease inhibitors lopinavir/ritonavir could be recommended to treat COVID-19 patients due to their effects on reducing viral loads and improving clinical symptoms.[48] It is also indicated that Ribavirin and IFN-β might inhibit the replication of SARS-CoV in vitro.[49] Apart from antiviral interferers and antibiotics, neuraminidase inhibitors and RNA synthesis inhibitors can also be used for the treatment of patients with COVID-19.[37,50] CRS, known as an uncontrolled and sharp increase in pro-inflammatory cytokine release, is common in viral infections. Different studies suggested that CRS occurs in patients with severe COVID-19, which is an important cause of death. The pivotal role of IL-6 in cytokine release syndrome can never be overstated. Therefore, inhibiting the IL-6 signal transduction pathway could be an effective treatment for COVID-19-induced CRS. Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that can effectively block the IL-6 mediated signaling. Therefore, it could possibly become an effective agent to treat severe cases of COVID-19.[51,52] Nonetheless, clinical trials are required to check the efficacy of such medications.

Immunotherapy with anti-programmed cell death 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) immune checkpoint inhibitors (ICI) could potentially restore the cellular immunocompetence.[53] US Food and Drug Administration (FDA) has approved ipilimumab as a CTLA-4–blocking antibody, nivolumab, pembrolizumab, and cemiplimab as PD-1– blocking antibodies, and atezolizumab, avelumab and durvalumab as PD-L1–blocking antibodies for the treatment of different cancers.[53,54] Such drugs mainly operate by increasing the immune response of

a patient to tumors by inhibiting negative T-cell function regulators. While patients with cancer were considered immunosuppressed because of their underlying malignancy and cytoreduction therapies, patients undergoing immunotherapy, including ICIs or CAR-T cell therapy, may have specific immunophysiologies that respond differently to COVID-19.[53] ICIs are anticancer therapies that might induce immune-related adverse events (irAEs) such as cardiotoxicity in the form of myocarditis with a high rate of morbidity and mortality.[55] Lung toxicity, especially in COVID-19 pandemic circumstance, can be life threatening. The potential overlap of ICI-associated pneumonitis/myocarditis with COVID-19-related lung or cardiac injury is a concern about the utilization of ICI during the COVID-19 pandemic. Therefore, during the current pandemic, careful decisions must be made in postponing antitumor treatment for patients receiving ICI treatment.[53]

Several studies indicate that COVID-19 demonstrates the various pattern of myocardial injury, arrhythmia, or heart failure.[55,56] In addition, elevated cardiac biomarkers in the cardio-oncology population may indicate cardiotoxicity from cancer physiology or from treatments.[56,57] Many reasons may be associated with elevated cardiac biomarkers, including receiving some drugs, invasive diagnostic/treatment strategies, CRS from CAR-T, myocarditis from ICI therapy, or heart failure from proteasome inhibitor use.[56–58] Some of these disease processes may complicate the treatment of a cancer patient who is also affected by COVID-19, so multidisciplinary evaluation by a cardio-oncologist, may be necessary to provide appropriate treatment in this high-risk population.

Management of Health Care Workers Exposed to COVID-19 Infection

During the COVID-19 outbreak, Health Care Workers (HCWs) are working long hours while being exposed to patients with COVID-19, and are vulnerable to the disease and infection. Clinicians and other support personnel may need to operate flexibly in alternative settings to promote the secure delivery of service.[10] Social distancing and separating workspaces in hospitals are critical steps to decrease the risk of infection. If HCWs are forced to self-isolate due to contact with a confirmed COVID-19 case, consider ways to continue providing care and/or supporting multidisciplinary tumor boards (eg, telephone or video consultations; virtual participation at multidisciplinary meetings; recognizing vulnerable patients and making connections to discuss changes to care and treatment).[10] The WHO considers HCWs protection to be a real concern that must be managed comprehensively. Table 1 summarizes WHO recommendations for HCWs with high and low risks for COVID-19 infection.[59,60]

COVID-19 Infection and Patients with Cancer

Cancer is one of the major causes of death and its treatment remains a challenge for the health system

Table 1 Some Recommendations for the Management of Health Care Workers (HCWs) in COVID-19 Infection[59,60]

HCWs with Low Risks for COVID-19 Infection	HCWs with High Risks for COVID-19 Infection
1. They should monitor their body temperature and respiratory symptoms daily for 14 days after the last day of exposure to COVID-19 patients. 2. HCWs should consider contact and droplet precautions when caring for all patients with acute respiratory illness and standard precautions to take care of all patients. 3. Airborne precautions for aerosol-generating procedures on all suspects and confirmed COVID-19 patients should be taken into account. 4. The application of personal protective equipment when exposed to confirmed COVID-19 patients consistently. 5. HCWs should do WHO's "My 5 Moments for Hand Hygiene" before touching a patient, before any clean or aseptic procedure, after exposure to body fluid, after touching a patient, and after touching a patient's surroundings. 6. They should practice respiratory etiquette at all times.	1. Health care interactions with patients for a period of 14 days after the last day of exposure to a confirmed COVID-19 patient should be stopped. 2. They should be tested for COVID-19 infection. 3. They should be quarantined for 14 days. 4. Providing full PPE, including disposable gown, eye protection, gloves, and either an N95 mask or a powered air-purifying respirator for staff involved in the aerosol-generating procedures like airway suctioning, intubation, and bronchoscopy. 5. Psychosocial support has to be provided for HCW during quarantine or throughout the duration of illness if an HCW is confirmed to have COVID-19. 6. A review of IPC training should be provided for the health care facility staff after a 14-day quarantine period.

Abbreviations: PPE, personal protective equipment; IPC, infection prevention and control.

worldwide.[61,62] According to evidence, patients with cancer are more susceptible to COVID-19 infection and have a higher risk of morbidity and mortality as compared with the general population.[12,46,63] In a study conducted on 1524 patients with cancer, it was estimated that these patients had a two-fold increased risk of developing COVID-19 infection compared with healthy individuals.[9] This observation correlated with a report by Kuderer et al who conducted a cohort study on patients with active or non-malignant cancer and confirmed SARS-CoV-2 infection within 30 days of COVID-19 diagnosis.[64] According to this analysis, patients who had active cancer, patients who were under anticancer treatment, and patients within both of these categories appeared to have a higher risk of mortality and severe illness due to SARS-CoV-2 infection. Therefore, the authors suggested that curative surgical resections, adjuvant chemotherapy, and maintenance chemotherapy must be continued with extreme caution during SARS-CoV-2 infection.[64] The Chinese Center for Disease Control and Prevention (China CDC) reported the case fatality of 5.6%, which is higher than the overall recorded case fatality (2.3%) from COVID-19.[65] In line with these findings, a study carried out in Italy reported that among 355 people who died due to COVID-19, 72 of these individuals (20.3%) had active cancer.[66] Furthermore, a study by Liang et al reported that 39% of COVID-19-related deaths were found in patients with cancer while only 8% of mortality was observed in patients without cancer.[67] The increased risk of death can be affected by several factors for each patient, including age, sex, and comorbidities, as well as the number of hospital visits for treatment.[63] However, this finding is not generalizable due to the small sample size (n=18), the heterogeneity of the type of cancers, and the different treatment strategies.[68] In addition, the inability of patients with cancer to receive adequate medical support, as well as the significantly higher age of patients with cancer compared with patients without cancer, could be considered as causes of higher mortality in patients with cancer during the COVID-19 pandemic.[12]

SARS-CoV-2 infection may lead to myocardial damage, more difficulty and complexity in patient management, a higher risk of infection, and worse outcomes in vulnerable patients with pre-existing comorbidities, particularly cardiovascular disease (CVD) and cancer.[55,56] Patients with cancer and COVID-19 may not exhibit typical symptoms, despite experiencing a weakened immune system and severe underlying diseases.[30,53] In order to avoid under-diagnosis of CVD and decrease the spread of infection, vigilant monitoring is required for acute myocardial infarction or heart failure in patients with COVID-19 due to similarities between respiratory and cardiac symptoms. Therefore, high awareness, hemodynamic monitoring, and supportive care are required to manage patients with cancer and CVD.[57] Importantly, physicians should make decisions on a case-by-case basis by considering cancer type, status, and overall health. Additionally, self-quarantine, replacing physical doctor visits with a telephone consultation, and deferring non-urgent procedures are strongly recommended to prevent virus transmission.[13]

However, a variety of factors, including repeated hospital visits and admissions, immunocompromised status (in particular poor immunity after surgery, radiotherapy, chemotherapy or immunotherapy), advanced age, and poor functionality, may account for a high risk of COVID-19 and consequent complications among patients with cancer.[9,12]

Strategies for Cancer Treatment During the COVID-19 Pandemic

As the COVID-19 pandemic continues, oncologists must consider the risks of death from COVID-19 versus the large benefits of cancer treatment. However, strategies should be considered to minimize interruptions to cancer care. In the current pandemic environment, patients with cancer are classed as either having confirmed infection or high-risk for COVID-19.[10,12] Patients undergoing active anticancer therapy are considered to be high-risk and should remain alert for COVID-19 symptoms.[9,10,12,63,67,68] A study revealed that patients who underwent chemotherapy or surgery in the month prior to COVID-19 diagnosis had a numerically higher risk of clinically serious events than those who did not receive chemotherapy or surgery (75% vs 43% respectively).[67] Under the current pandemic circumstances, strict preoperative screening should be performed in patients with cancer and suspected COVID-19.[69] It is recommended to establish a multidisciplinary team, including oncologists, respiratory physicians, anesthesiologists, infectious disease physicians, and infection control staff, for the management of patients with cancer and confirmed or suspected COVID-19.[10] According to the clinical guidelines found on the WHO and Centers for Disease Control and Prevention (CDC) websites, patients who have reported infection with COVID-19 should be tested for anticancer

therapy before they are considered medically stable.[2,35,37,40,46] The decision to confirm the scheduled prescription or delay treatment should be based on the biological characteristics of the tumor, the patient's clinical condition, treatment characteristics, the patient's response to current anti-tumor therapy, and the potential risks of SARS-CoV-2 infection.[10,70]

Patients undergoing active outpatient anticancer therapy are classified according to whether they receive oral or intravenous treatment, and consideration may be taken on a case-by-case basis for shifting intravenous chemotherapy to appropriate alternative oral anticancer agents.[10,71] In this setting, preventive measures should be increased for patients with or survivors of cancer. Referral of patients to the nearest medical unit for respiratory viral testing by multiplex PCR should also be considered, and postponement of routine follow-up appointments for several months is recommended.[71] Moreover, before scheduled appointments and hospitalization, patients with cancer should be asked in detail about their history of recent residence/travel, contact history and related symptoms to COVID-19.[10] As a precaution due to the COVID-19 pandemic, both the patient and family members need to measure body temperature before admission. If the body temperature is $\geq$ 37.3 °C, they need to be transferred to a clinic. Shorter course radiotherapy, delayed surgery, and transfer of intravenous to oral-systemic regimens may be the best choices to minimize the number of clinic visits and the potential risks for patients with cancer.[71] In order to promote physical distancing, and in anticipation of increased workload resulting from the pandemic, some clinical visits can also be replaced by "virtual" assessments via videoconference, telemedicine or telephone follow-up, WeChat communication, and online medical consultation.[10] These approaches could decrease in-person hospital visits during the pandemic, ensure patient safety by reducing transmission risks to vulnerable populations, improve access to care, and decrease health care costs.[10] Patients with cancer and COVID-19 must provide a mask and use hand sanitizers when arriving at hospital.[71] The confirmed case should postoperatively be transferred to isolation rooms with separate medical facilities, and all medical devices must be disposed of with caution. It is advised to delay all elective cancer surgeries or adjuvant chemotherapy and comprehensive monitoring and/or treatment of patients with cancer and COVID-19.[72]

In terms of cancer surgery, providing a safe balance between the prevention of COVID-19 transmission and the performance of surgical procedures is of paramount importance and extreme measures and restrictions are required for safe surgical strategy. Physicians have given priority to emergency cases, postponed non-essential elective surgical procedures that are not time-sensitive from a surgical point of view, and made decisions for cancer surgery based on the status of the COVID-19 pandemic, availability of resources, and patient- and tumor-related factors. Therefore, there are surgical strategies that can help make a timely surgical decision. These include (I) isolating COVID-19-specific treatment facilities to keep other facilities uncontaminated and decrease the risk of viral transmission, (II) determining the urgency of surgical cases, (III) proposing screening protocols for surgical patients based on high or low regional prevalence of COVID-19, and (IV) maintaining a safe and clean hospital environment for resuming elective surgical procedures.[73,74]

Delaying elective surgical intervention can be implemented until the spread of COVID-19 is more controlled.[10] Guidelines for triage, prioritizing, and treatment of patients with cancer during the COVID-19 pandemic have recently been released.[75] In this context, sixty-day delays in surgical operation were not associated with poor oncological results in clinical stages I or II breast cancer.[76] Patients with lung cancer, especially after radiotherapy, may have fever, dry cough, and other symptoms such as decreased white blood cell count and ground-glass opacities in CT of the chest.[63]

In light of the COVID-19 pandemic, these characteristics make it difficult to distinguish between the complications of lung cancer and those of SARS-CoV-2 infection. Moreover, patients with lung cancer might be at a higher risk of COVID-19 infection due to decreased pulmonary function.[39,63] A small cohort study conducted on 18 patients with cancer found that lung cancer was the most common type of malignancy in patients with COVID-19 (28% of patients).[67] Due to decreased lung function, low immunity in patients with lung cancer after receiving anti-tumor agents, and serious symptoms following infection, the main priority should be given to preventing and treating COVID-19.[39,63,77] Therefore, patients who do not need to be hospitalized should be treated on an outpatient basis as much as possible. In addition, follow up chest CT imaging can be delayed.[10,39,63] Patients with lung cancer who are undergoing chemotherapy and/or immunotherapy should be given regular treatment in local hospitals, and try to avoid traveling abroad. Relevant

examinations and tests can be completed in the outpatient clinic to shorten treatment time, and it is recommended to complete treatment in the daycare ward.

For patients with early-stage endometrial cancer of low and intermediate preoperative ESMO risk, hysterectomy with bilateral adnexectomy combined with a sentinel lymph node procedure is recommended.[10] For advanced ovarian cancer, the best choice would be neoadjuvant chemotherapy, even though primary cytoreduction surgery might be envisaged.

Surgical care remains the gold standard for endometrial cancer in the early stages. In the current pandemic environment, the minimally invasive laparoscopic robot-assisted or non-assisted route is the best choice. Surgery can be postponed for one to two months for low-risk endometrial cancers, and first-line medical care should be given for advanced endometrial cancers (stages III and IV). Another potential recommendation is to allow in-house chemotherapy infusion if medically and logistically feasible.[10] Under these conditions, and taking the lack of specific antiviral agents and vaccines into consideration, human convalescent serum may be an option for the prevention and treatment of COVID-19 infection in people with early symptoms.[78]

Nowadays, there is a significant global investment and effort to develop a vaccine for COVID-19. The US (NIAID) has collaborated with Moderna to develop an RNA vaccine. A safety clinical trial (ID: NCT04283461) of the candidate vaccine mRNA-1273 has started with a sample size of 45 volunteers.[79] Recently, Folegatti et al in Phase I/II clinical trial (ID: NCT04324606) reported the safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against COVID-19.[80] The investigators showed that ChAdOx1 nCoV-19 has an acceptable safety profile, and homologous boosting increases antibody responses.[80]

In this situation of emergency for health care systems, the inability to receive needed medical services as well as the shortage of human and pharmaceutical resources are additional concerns.[81] Medication shortages, primarily chemotherapy and narcotics can have a major negative effect on the provision of cancer treatment and can be life-threatening.[82,83] While drug shortages may not be immediately apparent, identifying and predicting such deficiencies can be particularly challenging during a pandemic. The American Society of Health-System Pharmacists has many guidelines for addressing drug shortages include maintaining coordination with other sites or health systems, recognizing alternative therapies, and creating criteria for prioritizing patients throughout medication shortages.[84]

The Psychological Aspect of the COVID-19 Pandemic on Cancer Patients

The negative psychological sequelae of the pandemic might be substantial for all individuals, especially patients with cancer, their families, and/or caregivers. The hard consequences of social distancing, visitor limitations and quarantine can restrict family support and advocacy opportunities, leading to disrupting a major sense of connection and a source of strength and well-being for cancer patients.[69,85,86] Most cancer patients and their families would understandably be worried about how a pandemic could affect their care and treatment. Patients also will be worried about contracting the virus and how it will affect their care and how they can continue receiving oncology services during the pandemic.[10] New patients will be concerned about whether their treatments will be postponed and what the repercussions might be for their outcome. It is necessary to remember the increased level of distress that cancer patients and their families may face during this period, beyond the distress they have encountered about their diagnosis and care and the pandemic itself. In such cases, the provision of encouragement and emotional support is essential. Bakkar et al assessed the psychological impact of delayed treatment in cancer patients on the severity of anxiety during COVID-19 by using the Hamilton anxiety rating scale (HAM-A). This scale has 14 items that measure both psychic anxiety and somatic anxiety and each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56. The score <17 presents mild severity, 18–24 mild-to moderate severity, and 25–30 moderate-to-severe. Their results indicated that patients who received delayed therapies experienced mild-to-moderate anxiety according to the HAM-A scale.[87]

Therefore, it is critical to have psychological support in each cancer center and hospital to determine the level of distress and appropriate response to the resources available. This may mean that, during this pandemic, psychosocial workers will be more needed to evaluate anxiety and will be available to meet the specific needs of patients and families.

Impact of the COVID-19 Pandemic on Cancer Research

A pandemic is likely to have an adverse impact on clinical and basic cancer research. Currently, the research on the novel coronavirus is still in the primary stage. Because

screening, evaluation, satisfaction, and commitment to a clinical trial are usually accompanied by multiple patient visits to health and research centers, as well as countless interactions between patients, physicians, and research coordinators, in pandemic situation trial initiations and accruals to be reduced.[10] During the pandemic, the workload of research teams has increased dramatically, and valuable time and resources have been devoted to COVID-19-associated tasks instead of accelerating clinical research. Moreover, if a trial patient tests positive for COVID-19, it is essential that such a person be excluded from the study. It is best to carry out academic activities, such as tumor boards or multidisciplinary conferences, through web-based systems. Teleconferences should be pursued in order to learn and explore ways for developing the approach to treatment and to encourage the sharing of information with other institutions.[71] On March 18, 2020, the FDA issued guidelines on the execution of clinical trials of medical products during the COVID-19 pandemic for industry, inspectors and institutional review boards.[88]

Conclusion

The COVID-19 pandemic has the ability to overexert existing capabilities and capacity in the health care system. Health care authorities should make critical decisions to manage the treatment of patients with cancer during the pandemic to minimize contact exposure and virus transmission. The key management approaches for patients with cancer in this COVID-19 pandemic include educating patients about using PPE, visiting health care providers online instead of in-person meetings, and deciding whether to postpone non-urgent procedures, cancer surgeries, chemotherapy, and immunotherapy. Evaluating the benefits and relative risks attributed to cancer therapies in light of the COVID-19 pandemic is crucial for continuing the safe delivery of these treatments. Moreover, promoting the patient's emotional wellbeing and providing appropriate psychosocial support services is critical during the COVID-19 pandemic in order to limit the psychological burden. Overall, particular attention should be given to the protection of patients with cancer, and further investigations are required to reduce disease severity and adverse outcomes during treatment for COVID-19.

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Disclosure

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