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HOT TOPIC

COVID-19 and Cancer: a Comprehensive Review

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Abstract

Purpose of Review The outbreak of the novel coronavirus disease 2019 (COVID-19) has emerged to be the biggest global health threat worldwide, which has now infected over 1.7 million people and claimed more than 100,000 lives around the world. Under these unprecedented circumstances, there are no well-established guidelines for cancer patients.

Recent Findings The risk for serious disease and death in COVID-19 cases increases with advancing age and presence of comorbid health conditions. Since the emergence of the first case in Wuhan, China, in December 2019, tremendous research efforts have been underway to understand the mechanisms of infectivity and transmissibility of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a fatal virus responsible for abysmal survival outcomes. To minimize the mortality rate, it becomes prudent to identify symptoms promptly and employ treatments appropriately. Even though no cure has been established, multiple clinical trials are underway to determine the most optimal strategy. Managing cancer patients under these circumstances is rather challenging, given their vulnerable status and the aggressive nature of their underlying disease.

Summary In this comprehensive review, we discuss the impact of COVID-19 on health and the immune system of those affected, reviewing the latest treatment approaches and ongoing clinical trials. Additionally, we discuss challenges faced while treating cancer patients and propose potential approaches to manage this vulnerable population during this pandemic.

Keywords Coronavirus · COVID-19 · Pandemic · SARS · SARS-CoV-2 · ARDS · Pneumonia · Cancer · Immune response · ACE2

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) marks the emergence of the third large-scale epidemic related to the coronavirus, after SARS-CoV in 2002 and Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012. Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China, in December 2019, among a group of individuals presenting with pneumonia of unknown etiology [1, 2]. Based on the sequencing and evolutionary data, bats are the proposed reservoir for the coronavirus [2, 3]. After its initial discovery, the spread of SARS-CoV-2 worldwide was rapid, with over 1.7 million confirmed cases globally and more than 100,000 deaths as of April 2020 [4]. The severity of this disease can range from asymptomatic disease to acute respiratory distress syndrome (ARDS) requiring aggressive measures to death [5, 6]. Current management strategies involve supportive treatment and protective measures to prevent further transmission of the virus [7, 8]. Though no potential cure has been reported, several trials are underway to determine the most appropriate treatment regimen.

Providing care to immunocompromised patients and those suffering from cancer, amidst this pandemic, has been extremely challenging. Data from China thus far have shown that cancer patients infected with COVID-19 are at 3.5 times the risk of requiring mechanical ventilation or ICU admission, compared to the general population [9•]. Additionally, the limitation of resources in outpatient settings, including administrative staff and specialists, has hindered the routine care of these patients [10•]. This review aims to evaluate current literature on the diagnosis and management of COVID-19 patients,

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and discuss approaches to managing cancer patients in this pandemic.

What Is SARS-CoV-2?

Coronaviruses (CoVs) were first identified by Tyrell and Bynoe in 1966, in patients with viral-like upper respiratory illness [11]. CoVs are enveloped, positive single-stranded RNA viruses that can infect both humans and animals. Their spherical morphology with core shell and glycoprotein projections from their envelope, as seen under an electron microscopy, makes them appear "crown-like," hence termed coronaviruses [12]. Some human CoVs can cause self-limiting upper respiratory infections in immunocompromised individuals, whereas other CoVs of beta-CoVs subgroup, such as SARS-CoV, SARS-CoV-2 (COVID-19), and MERS-CoV, can result in epidemics with increased mortality [13].

COVID-19 and the Immune Response

The fatality rate for infected cancer patients in China is 28.6% [14•], compared to a 2.3% fatality rate for all COVID-19 patients [15]. ACE2 is the common binding site for both the SARS-CoV of the 2002–2003 SARS epidemic and, reportedly, also for the SARS-CoV-2 strain underlying the current COVID-19 epidemic [16].

SARS-CoV-2 interaction with the renin–angiotensin–aldosterone system (RAAS) through angiotensin-converting enzyme-2 (ACE2) is a key factor for infectivity [17]. ACE2 physiologically counters RAAS activation and also serves as a receptor for SARS-CoV-2 [16]. ACE2 is expressed broadly in numerous tissues; however, lung alveolar epithelial cells are considered the primary targets [17]. Once CoV-2 gains entry into the target cell, the host response is a major determinant of severity of the ensuing pathogenesis (Fig. 1) [18]. The bronchial mucosa is lined by mucosal associated invariant T (MAIT) cells and γδ T cells [19]. These innate-like lymphocytes respond rapidly to pathogen invasion and trigger a cytokine response essential for microbial killing [19]. The critical role of the host immune system in patients with severe COVID-19 infection is highlighted by the characteristics of patients who have died [15]. Clinical outcomes are dependent upon factors such as age, ACE2 expression, and comorbidities. Thus, cancer patients by virtue of being older (median age of a cancer diagnosis is 66 years in the USA) [20] and having higher ACE2 expression (ACE2 tends to increase with increasing age) [21] and more comorbidities [22] are at a higher risk of adverse outcomes when infected with SARS-CoV-2. Figure 2 highlights the case-fatality rate by age group in the general population diagnosed with COVID-19 in China along with possible roles of mentioned factors.

After the initial innate response, a specific adaptive immune response is required to eliminate CoV-2 [23]. However, in cancer patients on active treatment or even during watchful observation, lymphopenia (an independent poor prognostic indicator in COVID-19 patients) [24] is common [25], and hence, the required immune response is impaired. Persistent cytokine release (likely mediated by leukocytes other than T lymphocytes) [23] may then lead to "cytokine storm" and cause significant lung damage. In addition to this damage, subpar specific immune response allows viral propagation, destruction of tissues, and progression to severe stages especially in ACE2-rich tissues, e.g., lung, intestine, and kidneys [23]. Therefore, strategies that augment immune response at this stage, e.g., immunoadjuvant therapies (IFNα or convalescent plasma) [14•, 19], block cytokines (IL-6, IL-1, or tumor necrosis factor alpha, TNFα) or early institution of antiviral agents may prove beneficial.

Less immunocompromised and nonlymphopenic cancer patients may mount an adequate response, with cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells being crucial for the control of viral infection. Persistent adaptive immune activation leading to lymphocyte exhaustion is well described in cases of chronic infections, tumorigenesis [26], and reportedly, even with SARS-CoV-1 infection [27]. Functional exhaustion of CTLs and NK cells is now reported with CoV-2 infection with significantly higher levels of exhaustion markers, e.g., programmed death-1 (PD-1), as compared to healthy controls [27, 28]. Functional exhaustion of CTLs correlates to [29] and likely results in viral disease progression and rapid decompensation [27]. Reports of successful use of anti-PD-1 drugs to reinvigorate exhausted T cells by blocking PD-1 in cases of viral, bacterial, and fungal infections are becoming common [19]. Foreseeably, clinical trials to study the use of anti-PD1 agent against COVID-19 are underway (Table 1).

Tremendous efforts are underway for vaccine development targeting CoV-2 [74]. However, virus eliminating immune response may be difficult to illicit in immunocompromised cancer patients. Vaccine effectiveness in general tends to be lower in patients with cancer, much lower for those with hematologic malignancies [75]. Utilization of long-term immune memory from convalescent individuals may provide alternate strategies for patients with hematological malignancies.

Clinical Manifestations and Diagnosis

The most common clinical symptoms of COVID-19 range from fever, cough, dyspnea, fatigue, and in rare cases diarrhea and vomiting [76]. Based on current evidence, cancer patients also present with similar symptoms, though are at much higher risk of serious outcomes resulting in death

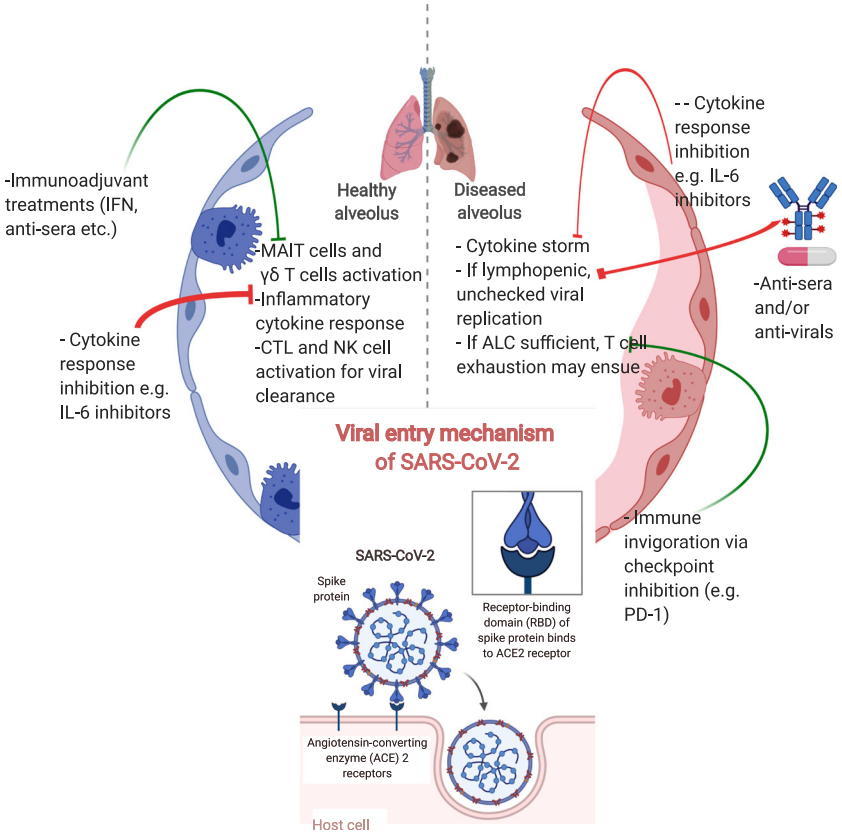

Fig. 1 Entry mechanism of SARS-CoV-2 into host cell and subsequent inflammatory and immune cascade. SARS-CoV-2 gains entry into host cell when receptor-binding domain (RBD) of viral spike protein binds with host ACE2 receptors. Mucosal associated invariant T (MAIT) cells and γδ T cells respond to invasion releasing inflammatory cytokines. Early responding immune effector cells, including CTL and NK cells, are activated against virus. If persistent cytokine release continues, significant lung damage can occur ("cytokine storm"). Specific cytokine inhibitors, e.g., IL-6 inhibitors, help reduce lung damage. Protracted disease course can result in immune exhaustion (exhausted T cells) and anti-programmed death-1 (PD-1) inhibitors can help reinvigorate immune system. ALC, absolute lymphocyte count; CTL, cytotoxic T lymphocytes; IFN, interferon; IL-6, interleukin-6; NK, natural killer; PD, programmed death-1. * Created with BioRender

when compared to the general population [9•, 10•, 14•]. Emerging data highlighting concerns of coagulopathy in COVID-19 patients is becoming available, but it is too early to infer if these are more or less common in cancer patients [77]. Some of the common laboratory findings seen in COVID-19 patients are cytopenias, specifically lymphocytopenia, along with elevation in lactate dehydrogenase (LDH) [14, 76]. COVID-19 patients should additionally be screened for secondary hemophagocytic lymphohistiocytosis (sHLH) via HScore [78]. This is an often under-recognized hyperinflammatory syndrome characterized by a severe cytokine storm often with multiorgan failure. This is to identify the subgroup of patients who may benefit from immunomodulatory treatment.

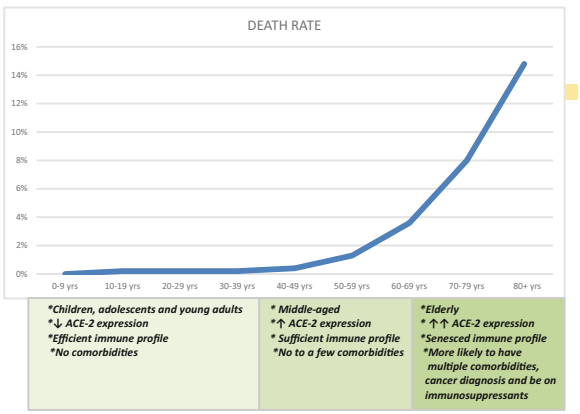

Fig. 2 Case-fatality rate by age group in general population diagnosed with COVID-19 in China [15] along with probable roles of factors: age, ACE2 expression, immune profile, and comorbidities. ACE2, angiotensin-converting enzyme-2; yrs, years

Given general upper respiratory infection symptoms, diagnosis of COVID-19 often entails ruling out other common respiratory viral infection (RVI) etiologies. Nasopharyngeal swab is usually a collection method employed to obtain specimen for testing via polymerase chain reaction (PCR). Increasing frequency of false negatives is being reported; as a result, hospitals are either repeating the test or treating patients empirically, if one presents with classical symptoms of fever, fatigue, and dyspnea of unknown etiology [79].

Table 1 Investigational therapies for COVID-19

Drug	Type	Trials*	Ref
Anakinra	Recombinant human interleukin-1 (IL-1) receptor antagonist	NCT04339712 NCT04330638 NCT04341584 NCT04324021	[30]
Arbidol hydrochloride (umifenovir)	Fusion inhibitor	NCT04252885 NCT04255017 NCT04260594	[31]
Bevacizumab	Vascular endothelial growth factor (VEGF) inhibitor	NCT04305106 NCT04275414	[32]
Camostat mesylate (+/− hydroxychloroquine)	Transmembrane protease, serine 2 (TMPRSS2) inhibitor	NCT04321096 NCT04338906	[33]
CD24Fc	Recombinant fusion protein	NCT04317040	[34]
Chloroquine or hydroxychloroquine (+/− azithromycin)	4-Aminoquinoline Endosomal acidification fusion inhibitor	NCT04321993 NCT04323527 NCT04329832 NCT04329923 NCT04334382 NCT04341870 NCT04334382 NCT04332094 NCT04329572 NCT04331600 NCT04315896 NCT04336332 NCT04338698 NCT04307693 NCT04328012 NCT04315948 NCT04342169 NCT04335552 NCT04321616 NCT04321278 NCT04341493 NCT04341727 NCT04333654 NCT04322123	[35–37]
Colchicine	Microtubule inhibitor	NCT04322565 NCT04322682	[38]
Convalescent plasma	Passive immunotherapy	NCT04343755 NCT04333355 NCT04342182 NCT04323800 NCT04340050 NCT04343261 NCT04332380 NCT04332835 NCT04333251	[39]
Darunavir and cobicistat	Protease inhibitor	NCT04252274	[40]
DAS181	Sialidase fusion protein	NCT04324489 NCT04298060 NCT03808922	[41]
Deferoxamine	Iron chelator	NCT04333550	[42]
ECMO	Extracorporeal membrane oxygenation	NCT04341285 NCT04324528 NCT04340414	[43]
EK1C4	Fusion inhibitor against SARS-CoV-2 S protein-mediated membrane fusion		[44]
Emapalumab (+/− anakinra)	Anti-interferon-gamma (IFNγ) antibody	NCT04324021	[45]
Favipiravir	RNA polymerase inhibitors	NCT04310228	[46]
Fingolimod (FTY720)	Sphingosine 1-phosphate (S1P) receptor modulator	NCT04280588	[47]
IFX-1	Anti-C5a monoclonal antibody	NCT04333420	[48]
Interferon alfa-2b	Recombinant cytokine	NCT04293887	[49]
IV immunoglobulin	Passive immunotherapy	NCT04261426 NCT04264858	[50]
Lisinopril		NCT04330300	[17]

Table 1 (continued)

Drug	Type	Trials*	Ref
Losartan Valsartan	Angiotensin-converting enzyme inhibitor (ACEi) or the angiotensin receptor blocker (ARBs)	NCT04335786 NCT04328012 NCT04312009 NCT04311177	
Leronlimab	CCR5 antagonist	NCT04343651	[51]
Lopinavir/ritonavir	Protease inhibitors	NCT04321993 NCT04295551 NCT04330690 NCT04307693 NCT04328012 NCT04255017 NCT04315948 NCT04261907 NCT04276688	[52]
Meplazumab	Anti-CD147	NCT04275245	[53]
Mesenchymal stem cells	Cell-based therapy	NCT04299152 NCT04252118 NCT04288102 NCT04269525 NCT04339660 NCT04336254 NCT04315987 NCT04313322 NCT04288102 NCT04302519 NCT04252118 NCT04273646 NCT04333368	[54–56]
Methylprednisolone Dexamethasone	Corticosteroids	NCT04343729 NCT04323592 NCT04244591 NCT04273321 NCT04329650 NCT04325061 NCT04327401	[57]
Nitric oxide	Vasodilator	NCT04306393 NCT04305457 NCT04338828 NCT04337918	[58]
Nivolumab	Programmed death receptor-1 (PD-1) blocking antibody	NCT04343144 NCT04333914	[27]
NK cells	Natural killer cell therapy	NCT04280224	[27]
Olumiant (baricitinib) Jakafi (ruxolitinib)	Janus-associated kinase (JAK) inhibitor	NCT04320277 NCT04340232 NCT04337359 NCT04331665, NCT04334044, NCT04338958	[59]
Oseltamivir	Neuraminidase inhibitors	NCT04255017 NCT04338698 NCT04303299 NCT04255017 NCT04261270	[60]
Pembrolizumab	Programmed death receptor-1 (PD-1) blocking antibody	NCT04335305	[27]
Remdesivir (GS-5734)	Adenosine nucleotide analogs	NCT04292730 NCT04252664 NCT04315948 NCT04280705 NCT04321616 NCT04257656	[61]
Ribavirin	Nucleoside analogs	NCT04319900 NCT04310228 NCT04303299 NCT04333589 NCT04336904 NCT04276688	[62]

Table 1 (continued)

Drug	Type	Trials*	Ref
Ritonavir	HIV protease inhibitors	NCT04261270	
ASC09		NCT04261907	
Sarilumab (Kevzara)	Recombinant human interleukin-6 (IL-6) receptor antagonist	NCT04315298	[63, 64]
Tocilizumab (Actemra)		NCT04324073	
Siltuximab (Sylvant)		NCT04322773	
		NCT04327388	
		NCT04339712	
		NCT04331808	
		NCT04330638	
		NCT04341870	
		NCT04331795	
		NCT04332094	
		NCT04329650	
		NCT04320615	
		NCT04317092	
		NCT04310228	
		NCT04335305	
Sirolimus	mTOR inhibitor	NCT04341675	[65]
T89	Traditional Chinese medicine	NCT04285190	[66]
Xiyanping injection		NCT04295551	
		NCT04251871	
		NCT04323332	
Tacrolimus	Calcineurin inhibitor	NCT04341038	[67]
		NCT04341675	
Thalidomide	Immunomodulatory agent	NCT04273581	[68]
		NCT04317092	
		NCT04273529	
Thymosin alpha-1 (Ta1)	Alpha thymosin peptide	NCT04320238	[69]
TJ003234	Anti-GM-CSF monoclonal antibody	NCT04341116	[70]
Mavrilimumab		NCT04337216	
Tradipitant	Neurokinin-1 (NK-1) receptor antagonist	NCT04326426	[71]
Tranexamic acid	Antifibrinolytic	NCT04338126	[72]
Vitamin C	Ascorbic acid	NCT04264533	[73]
		NCT04323514	
		NCT03680274	

NCT, national clinical trial; *Ref*, references

*Some trials include a combination of multiple different agents. For more details, please visit https://clinicaltrials.gov

Treatment of SARS-CoV-2

There are no current FDA-approved therapeutic drugs or vaccines for SARS-CoV-2. Most of the treatment options have come from previous experience treating SARS-CoV and MERS-CoV. Vigorous symptomatic management remains key to treatment. This section focuses on advances in SARS-CoV-2 therapeutic development in the general population. A cancer diagnosis does portend a higher risk of acquiring severe symptoms, and as a result, prompt intervention is recommended. However, COVID-19 treatment for cancer patients is not necessarily different from the general population or other immunocompromised patients.

Antiviral Treatment

Remdesivir is a nucleotide analog that inhibits viral RNA polymerases and has shown activity against SARS-CoV-2 in vitro [61]. In a cohort of 53 patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, clinical improvement was seen in 36 (68%) patients [80]. This suggests that remdesivir may have clinical benefit in patients with severe disease, although the lack of a control group precludes definitive conclusions. A randomized controlled trial (RCT) is currently underway (NCT04257656).

Lopinavir–ritonavir (Kaletra) is a human immunodeficiency virus (HIV) medication that has shown inhibitory activity against SARS-CoV in vitro. LOTUS-a RCT in China showed no benefit with lopinavir–ritonavir treatment compared to standard care among 199 patients with severe COVID-19 [81]. Trials with drug combinations to enhance the antiviral effects of this drug are underway (NCT04276688, NCT04252885).

Hydroxychloroquine sulfate and chloroquine phosphate, historically, anti-malaria drugs, have been shown to be safe and efficacious against COVID-19 in clinical trials conducted

in China [35, 82] and France [36]. The data from France showed a synergistic effect of azithromycin with hydroxychloroquine [36]. However, evidence of efficacy is limited given there are only few small human trials with methodological limitations [37]. Additionally, there is limited safety data available for the use of these drugs in the context of COVID-19, especially in the setting of liver and renal impairment, which may increase the risk of toxicity from these agents [83]. Therefore, at present time, there is insufficient evidence to support the routine use of these drugs outside the context of a clinical trial.

Immunomodulators

Several studies have indicated a "cytokine storm syndrome" in patients with severe COVID-19, with the release of interleukin IL-1, IL-6, IL-12, and IL-18; TNFα); granulocyte-macrophage colony stimulating factor (GM-CSF); IFNγ; and other inflammatory mediators [63]. Immunomodulators decrease the pulmonary inflammatory response, thereby improving the alveolar-capillary gas exchange (which tends be impaired due to cytokine-mediated hyperinflammation), and thus, can improve oxygenation and survival.

Cytokine Inhibitors

IL-1 and IL-6 inhibitors may ameliorate severe damage to lung tissue caused by cytokine release in patients with serious COVID-19 infections [64, 84]. One clinical trial using tocilizumab, an IL-6 inhibitor, reported improvement in clinical outcomes in 21 patients with severe COVID-19 [64]. Several interleukin inhibitors are being investigated, including a phase III RCT, COVACTA (NCT04320615), to evaluate the efficacy of tocilizumab in severe COVID-19 patients, and another double-blind, adaptive phase II/III RCT (NCT04327388) to evaluate the safety and efficacy of sarilumab (IL-6 inhibitor) has almost completed accrual.

Bruton Tyrosine Kinase Inhibitor

Acalabrutinib (Calquence) is a next-generation, highly selective Bruton tyrosine kinase inhibitor (BTKi) used to treat mantle cell lymphoma and CLL, now being tested for use in COVID-19 patients. The Bruton's tyrosine kinase pathway has a role in the production of inflammatory cytokines [85], and early clinical findings showed that acalabrutinib may ameliorate the severity of respiratory distress caused by COVID-19 infection through inflammation control. The CALAVI trial will be initiated as a randomized global clinical trial to assess the potential of acalabrutinib in the treatment of the cytokine storm associated with severely ill COVID-19 patients [86]. Additionally, other trials are being considered with different BTKi, specifically ibrutinib, to reduce the inflammatory response [87].

Janus Kinase Inhibitors

Baricitinib, fedratinib, and ruxolitinib are selective Janus-associated kinase (JAK)-STAT inhibitors that could potentially have anti-inflammatory effects in COVID-19 patients with elevated cytokine levels [59]. Baricitinib is a JAK inhibitor as well as an AAK1 (AP2-associated protein kinase 1) inhibitor that can interrupt the entry of the virus into cells in addition to an anti-inflammatory effect [88]. Several clinical trials are ongoing to confirm the efficacy of these agents.

Anti-GM-CSF

GM-CSF is a pro-inflammatory cytokine found to be elevated in the serum of COVID-19 patients. There is evidence that GM-CSF enhances the expression of pro-inflammatory cytokines in addition to promoting the differentiation of Th1 cells and polarization of macrophages to M1-like phenotype, resulting in pulmonary immunopathology and detrimental clinical manifestations in COVID-19 patients [70]. Therefore, targeting GM-CSF seems to be a promising strategy in ameliorating lung damage while allowing time for the virus to clear.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) exert anti-inflammatory effects and promote endogenous repair of alveolar epithelium [54]. A recent pilot study in seven COVID-19 patients who received donor MSC in China showed that the intervention was safe and may improve patient outcomes [55]. The FDA has approved MSC treatments for use in critically ill COVID-19 patients under the expanded access compassionate use.

Glucocorticoids

There is still controversy about the efficacy of glucocorticoids in treating COVID-19-associated pneumonia. The rationale is that steroids prolong the viral shedding time and maintain a systemic anti-inflammatory state that will minimize the precipitation of ARDS, dyspnea, and severe pneumonia. However, steroid therapy did not improve clinical outcomes for patients with SARS or MERS [89, 90]. A small observational study ($n = 31$) done in Wuhu, China, showed no association between corticosteroids and outcomes in patients with mild disease [91]. Another study conducted in Wuhan, China ($n = 201$), showed that methylprednisolone decreased the risk of death from COVID-19-associated ARDS (HR 0.38; 95% CI 0.20–0.72) [57]. Multiple prospective RCTs to explore the

effectiveness and safety of glucocorticoids in the treatment of novel coronavirus pneumonia are ongoing.

Convalescent Plasma

Convalescent plasma originates from patients who have previously recovered from the viral infection and are now able to donate their anti-SARS-CoV-19 immunoglobulin-containing blood. Once transfused into the patient, the antibodies from the convalescent plasma are thought to neutralize the virus and limit its replication. This treatment has been used to treat prior SARS-CoV. An exploratory meta-analysis of 32 studies showed evidence of reduced mortality after receiving various doses of convalescent plasma in patients with severe acute respiratory infections of viral etiology [92]. Recent experience and data from China showed that human convalescent plasma is a potential therapeutic option to lessen the severity and/or shorten the length of illness caused by COVID-19 [93]. The true clinical effect of this intervention is being verified through several ongoing RCTs. In addition, the FDA is supporting a national expanded treatment protocol to provide convalescent plasma to COVID-19 patients across the country, with the help from the Red Cross to identify prospective donors and manage the distribution of these products to hospitals.

Renin–Angiotensin–Aldosterone System Inhibitors

ACE2 has been identified as the functional receptor for SARS-CoV invasion into the human body [94]. This led to concerns about the use of RAAS inhibitors in COVID-19 patients; however, published data in humans is inadequate to support or refute this concern [17]. Vaduganathan et al. proposed an alternative hypothesis that ACE2 may be beneficial rather than harmful in patients with lung injury from SARS-CoV [17]. Clinical trials using RAAS modulators including losartan are currently underway (NCT04311177, NCT04312009, NCT04330300).

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) can be a life-saving intervention for COVID-19 patients with refractory respiratory failure in the setting of ARDS. While this intervention has been used successfully in some patients [43, 95], concerns were raised about the potential harms of ECMO therapy including elevation in IL-6 levels and decrease in the number of functioning lymphocytes [96]. As a result, the immunological status needs to be considered when selecting patients for ECMO, especially in cancer patients who are on treatments that often result in lymphopenia.

Tissue Plasminogen Activator

ARDS with concomitant DIC was observed in 70% of those who die of COVID-19 [97]. There is evidence that fibrin deposition in the pulmonary microvasculature is a contributing factor for ARDS and fibrinolytic therapy was shown to improve survival in ARDS patients. Three case reports of intravenous administration of tissue plasminogen activator (tPA) in critically ill, mechanically ventilated COVID-19 patients show an improvement in their PaO_2/FiO_2 ratio from 38 to 100% [97]. Formal studies are planned to determine the efficacy of this agent [98].

Low Molecular Weight Heparin

Prior evidence has shown that low molecular weight heparin (LMWH) has anti-inflammatory properties and reduces the biological activity and levels of IL-6 [99]. A retrospective study looked at 449 patients with severe COVID-19, of whom 99 patients received heparin (mainly LMWH). Results show that the heparinized group had lower mortality among patients who had an elevated sepsis-induced coagulopathy score and D-dimer [77]. A smaller retrospective study looked at 42 patients with COVID-19 and analyzed the efficacy of LMWH in slowing their inflammatory response [100]. The 21 patients who received LMWH during hospitalization had significantly lower levels of IL-6, higher lymphocyte levels, and less coagulopathy compared to the 21 patients who did not receive LMWH. No difference was seen in the duration of hospitalization between both groups. This data is promising; however, prospective studies are needed prior to its use in clinical practice.

Traditional Chinese Medicine

Chinese medicine has played a key role in the treatment of several prior epidemic diseases including COVID-19 pandemic [101]. *Qingfei paidu* decoction (QPD), for example, was used to treat 701 cases with COVID-19 in China. Improvement and cure was seen in 449 cases, and stability of symptoms was seen in 212 cases [101]. QPD is thought to alleviate excessive immune and inflammatory responses by regulating immune-related and cytokine action–related pathways [102]. A RCT to evaluate the effects of traditional Chinese medicine on COVID-19 patients is underway (NCT04251871).

Cancer-Specific Trials

A prospective, randomized multicenter study, IMMUNONCOVID, is currently recruiting patients with advanced or metastatic cancer who have Sars-CoV-2 infection in

Europe. The study aims to compare the efficacy of a chloroquine analog (GNS561), an anti-PD-1 (nivolumab), and an IL-6 inhibitor (tocilizumab) versus standard of care in this cohort of patients (NCT04333914). More studies to evaluate the efficacy of such agents in our cancer population are needed.

Approach in Cancer Patients

Cancer patients require timely diagnosis, evaluation, and treatment even during a pandemic. However, it is important to consider that cancer patients are immunocompromised and are at increased risk of COVID-19-related serious events (intensive care admission, requirement for mechanical ventilation, or death) in comparison to the general population [9•, 10•]. Given the current evolving situation, pragmatic approaches are needed to deal with the challenges of treating cancer patients, without jeopardizing their care.

To assist healthcare facilities in these unprecedented times, oncology societies around the world, namely the European Society of Medical Oncology (ESMO), American Society of Clinical Oncology, National Comprehensive Cancer Network (NCCN), and many more, have developed guidelines to mitigate the negative effects of the COVID-19 pandemic on the diagnosis and treatment of cancer patients [103–105]. The common theme of these proposed guidelines is to categorize patients into high, medium, or low priority based on the Ontario Health Cancer Care Ontario criteria (Table 2) in order to plan their management course accordingly [106]. Figure 3 briefly outlines cancer management in the era of COVID-19 pandemic.

In addition to these suggested priority-driven guidelines, hospitals around the world have issued internal guidelines for oncologists, aiming to decrease patient exposure to COVID-19. Given the immunocompromised nature of the patient population, cancer centers have been adhering to strict infection control guidelines, in inpatient and outpatient settings. Outpatient visits, including ambulatory clinics and chemotherapy infusion visits, have been reduced [107]. Utilization of oral therapy regimens is recommended instead of parenteral anticancer therapies, if considered equivalent. This strategy can hence reduce patients' risk of exposure to SARS-CoV-2, without compromising oncological outcome, for instance, the use of capecitabine in place of 5-fluorouracil in patients receiving concurrent neoadjuvant chemoradiation therapy for rectal cancer [108]. Additionally, one must strongly consider delaying anticancer therapy in patients with stable cancer. Zhang et al. studied the outcomes of cancer patients with COVID-19 on active anticancer therapy and reported more than fourfold higher likelihood of experiencing severe events in those who received therapy in the preceding 14 days of COVID-19 diagnosis (HR = 4.079, 95% CI 1.086–15.322, p = 0.037) [14•]. However, for aggressive cancers, it is warranted to have a risk–benefit assessment and proceeding with cancer treatment if benefits outweigh risks. As precisely mentioned by Wang et al., the major risk factor for cancer patients during the COVID-19 pandemic is their inability to receive sufficient medical support [109]. To further minimize patient exposure to COVID-19, clinicians could consider the option of chemotherapy break and the possibility of performing home laboratory draws for toxicity assessment if feasible. To avoid patients' exposure to pharmaceutical departments, patients could use drive-through pick-up or hospitals could utilize a courier medication delivery service [107, 110].

Surgery is another vital component in cancer management. In the current pandemic, the Centers for Disease Control and Prevention (CDC) and the American College of Surgeons (ACS) have advised rescheduling elective surgeries if possible [111, 112]. Evidence suggests that patients who received surgery and concomitantly contracted COVID-19 were at much higher risk of severe clinical events than those who did not have surgery [9•]. Despite these advisories, it is important for clinicians and patients to have risk assessment discussions prior to making treatment decisions. Part of the discussion should also entail resource availability, as surgeries often require post-operative care in the intensive care unit (ICU). Given the current shortage of ICU beds, it is important to delegate resources efficiently. In instances, specifically early stage cancers where surgery is often the first step in management, patients could be offered neoadjuvant therapy, and surgery could be delayed without compromising patient outcomes [104]. Evidence suggests that 60-day delays in surgical intervention of early stage breast cancer has been documented without worsening oncological outcomes [113].

Unlike medical and surgical management, radiation therapy, which is another essential part of cancer management, has its unique challenges during a pandemic. Given the nature of the treatment, patients have to attend radiation therapy (RT) sessions daily and the interruption of therapy is rather unacceptable [107]. Considering varied clinical scenarios, the American Society for Radiation

Table 2 Priority levels defined by the Ontario Health Cancer Care Ontario as part of pandemic planning clinical guideline for cancer patients

Priority A	Patient's condition is life threatening, clinically unstable *(management significantly impacts overall survival (OS) or quality of life)*
Priority B	Patient's condition is noncritical but delay beyond 6–8 weeks could potentially impact OS
Priority C	Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic *(no impact on survival or quality of life)*

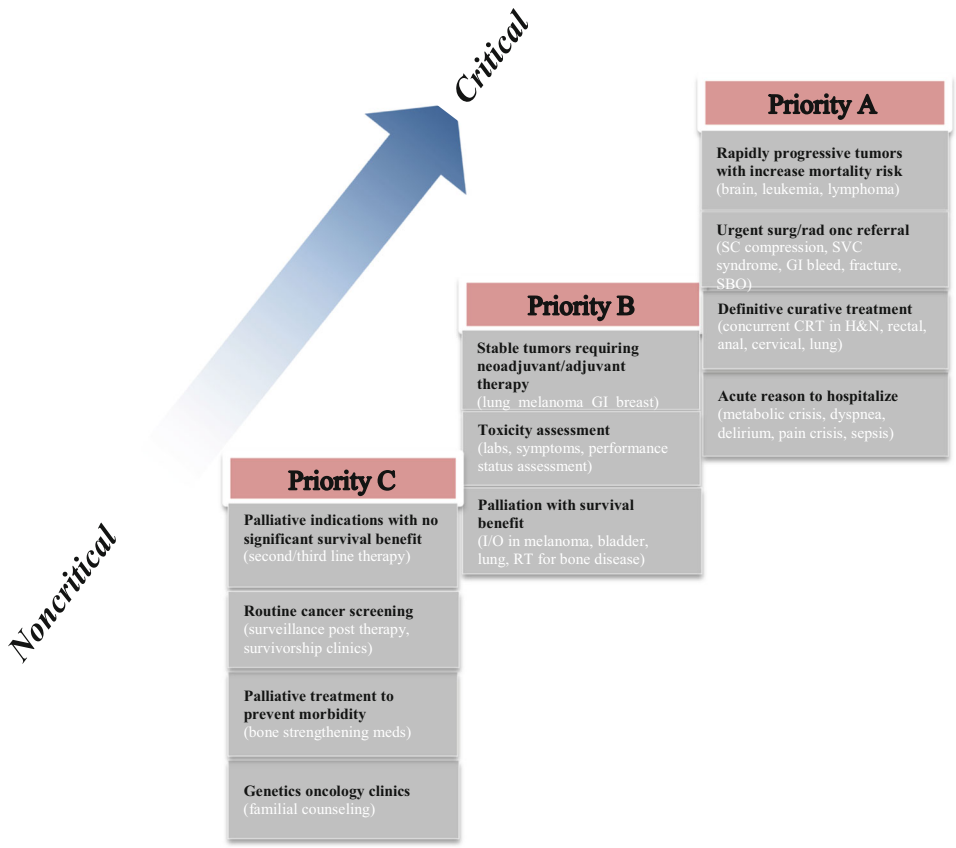

Fig. 3 Framework for prioritizing clinical management of cancer patients in COVID-19 pandemic. The prioritization-based management is adapted from the Ontario Health Cancer Care Ontario, where the patient with the lowest priority (priority C) could wait for further management until the pandemic resolves, while higher priority (specifically priority A) warrants immediate management as the benefits of the management outweigh the risks from the pandemic. Patients falling in priority B can often be slightly delayed, but usually a thorough discussion among the physician and patient further determines the course. Surg, surgery; Rad onc, radiation oncology; SBO, small bowel obstruction; SVC, superior vena cava syndrome; GI, gastrointestinal; RT, radiation therapy; CRT, chemoradiation therapy; I/O, immunotherapy

Oncology (ASTRO) recently published brief guidelines for radiation oncologists dealing with COVID-19 pandemic. As noted by ASTRO, if considered reasonable, hypofractionated schedules are encouraged [114]. Additionally, in patients with rapidly progressing disease or potentially curable tumors where RT significantly impacts survival, treatment should be prioritized as benefits outweigh risks. On the contrary, patients receiving palliative RT for symptom control or where interrupting the radiation course would not cause potential harm, one should consider delaying the treatment [104, 114].

Hematopoietic stem cell transplant (HSCT) recipients are at an increased risk of a variety of infections [107, 115]. Incidence of RVIs is seen in about 8% of allogeneic and 2% of autologous transplant recipients, with majority of patients developing nosocomial RVIs [107]. Additionally, HSCT patients receive therapies which result in prolonged cytopenia, making the transplant patients who contract COVID-19 very vulnerable for severe symptoms [116, 117]. Considering these profound implications, the European Society for Blood and Marrow Transplantation (EBMT) recommends evaluating recipients at risk closely, and in appropriate cases, deferring the transplant therapy until asymptomatic (Table 3) [118].

Clinical trials are an extremely important part of advancing medicine forward and introducing novel therapies. The Food Drug and Administration (FDA) plays a critical role in

Table 3 EBMT recommendations on managing patients pre- and post-HSCT

Patients pre-HSCT	Patients post-HSCT
Infected with COVID-19: High-risk disease: defer transplant until patient is asymptomatic and has two negative virus PCR swabs 24 h apart Low-risk disease: defer transplant for at least 3 months Close contact with COVID-19 patient: Defer procedure for at least 14 days from the last contact Confirm COVID-19 negativity with PCR	Limit risk of exposure to infected individuals and strictly adhere to infection control practices (hand hygiene, social distancing) Refrain from travel; if absolutely necessary, travel by private car instead of public means Adequate space for symptomatic patients while awaiting COVID-19 results Planned for CAR T-cell therapy should try to minimize risk by home isolation 14 days before the start of conditioning regimen

CAR, chimeric antigen receptor; *PCR*, polymerase chain reaction

conducting these clinical trials, and ensuring participants' safety is paramount in any scenario. In the midst of the current crisis, the FDA has issued guidance for the institutions to protect trial participants while administering investigational product with an altered monitoring approach [119]. At our institution, clinical trial activity during COVID-19 is tailored to the changing epidemic scenario. All nontherapeutic interventional trials that require in person specimen collection have been suspended until state "stay at home" order is lifted. Therapeutic clinical trials are prioritized by the Clinical Research Services (CRS), with weekly meetings conducted to re-prioritize with the evolving epidemic. The clinical trials that have remained open continue to obtain all tests and data points required for the primary endpoint of the study. Additionally, all correlative studies imbedded in the research plan, except questionnaires, are suspended until the state "stay at home" order is lifted. All the COVID-19-specific research studies have been prioritized and taken precedence in activation and conduct including the correlative endpoints. New studies and proposals continue to be reviewed and processed. Clinical disease teams and the scientific review committees continue to meet virtually and advance the much needed care.

Conclusions

The COVID-19 pandemic is potentially the greatest public health crisis since the influenza pandemic of 1918. This crisis has brought unprecedented challenges in the management of those who are afflicted, by overwhelming healthcare systems and causing great stress to the healthcare workforce. During such crises, generation of timely evidence for treatment options is crucial. The higher risk of COVID-19-related severe disease incurred by patients with cancer prompts the generation of a comprehensive set of pragmatic approaches specifically for cancer patients and an in-depth review of potential treatments options available to patients, including cancer patients.

Author Contribution RG, YA, and AS conceived the idea for the article; RG, YA, AS, NR, IP, and MSE performed the literature search and drafted the review; and RG, YA, AS, NR, IP, and MSE critically revised the work.

Compliance with Ethical Standards

Conflict of Interest Igor Puzanov has received compensation from Amgen for service as a consultant.

Rohit Gosain, Yara Abdou, Abhay Singh, Navpreet Rana, and Marc S. Ernstoff declare that they have no conflict of interest.

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