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,
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 the 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 at much higher risk of serious outcomes resulting in death.
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.

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].
| Drug | Type | Trials* | Ref |
|------|------|---------|-----|
| Anakinra | Recombinant human interleukin-1 (IL-1) receptor antagonist | NCT04339712 | [30] |
| Arbidol hydrochloride (umifenovir) | Fusion inhibitor | NCT04252885 | [31] |
| Bevacizumab | Vascular endothelial growth factor (VEGF) inhibitor | NCT04305106 | [32] |
| Camostat mesylate (+/− hydroxychloroquine) | Transmembrane protease, serine 2 (TMPRSS2) inhibitor | NCT04321096 | [33] |
| CD24Fc | Recombinant fusion protein | NCT04317040 | [34] |
| Chloroquine or hydroxychloroquine (+/− azithromycin) | 4-Aminoquinoline Endosomal acidification fusion inhibitor | NCT04335257 | [35–37] |
| Colchicine | Microtubule inhibitor | NCT04322565 | [38] |
| Convalescent plasma | Passive immunotherapy | NCT04343355 | [39] |
| Darunavir and cobicistat | Protease inhibitor | NCT04252274 | [40] |
| DAS181 | Sialidase fusion protein | NCT04324489 | [41] |
| Deferoxamine | Iron chelator | NCT04333550 | [42] |
| ECMO | Extracorporeal membrane oxygenation | NCT04341285 | [43] |
| EK1C4 | Fusion inhibitor against SARS-CoV-2 S protein-mediated membrane fusion | NCT04340414 | [44] |
| Emapalumab (+/− anakinra) | Anti-interferon-gamma (IFNγ) antibody | NCT04324021 | [45] |
| Favipiravir | RNA polymerase inhibitors | NCT04310228 | [46] |
| Fingolimod (FTY720) | Sphingosine 1-phosphate (SIP) receptor modulator | NCT04280588 | [47] |
| IFX-1 | Anti-C5a monoclonal antibody | NCT04333420 | [48] |
| Interferon alfa-2b | Recombinant cytokine | NCT04293887 | [49] |
| IV immunoglobulin | Passive immunotherapy | NCT04261426 | [50] |
| Lisinopril | | NCT04330300 | [17] |

*Trials include NCT number.
| Drug                      | Type                                           | Trials*                                                                 | Ref     |
|--------------------------|-----------------------------------------------|------------------------------------------------------------------------|---------|
| Losartan                 | Angiotensin-converting enzyme inhibitor (ACEi) or the angiotensin receptor blocker (ARBs) | NCT04335786 NCT04328012 NCT04312009 NCT04311777                      |         |
| Valsartan                |                                               | NCT04343651 NCT04321993 NCT04295551 NCT04330690 NCT04307693 NCT04328012 NCT04255017 NCT04315948 NCT04261907 | [51]    |
| Leronlimab               | CCR5 antagonist                               | NCT04330690 NCT04336254 NCT04315987 NCT04313322 NCT04288102 NCT04302519 NCT04252118 NCT04273646 NCT04333368 | [52]    |
| Lopinavir/ritonavir       | Protease inhibitors                           | NCT04330690 NCT04336254 NCT04315987 NCT04313322 NCT04288102 NCT04302519 NCT04252118 NCT04273646 NCT04333368 | [53]    |
| Meplazumab               | Anti-CD147                                    | NCT04299152 NCT04252118 NCT04288102 NCT04269525 NCT04339660 NCT04336254 NCT04313322 NCT04288102 NCT04302519 NCT04252118 NCT04273646 NCT04333368 | [54–56] |
| Mesenchymal stem cells   | Cell-based therapy                            | NCT04330690 NCT04336254 NCT04315987 NCT04313322 NCT04288102 NCT04302519 NCT04252118 NCT04273646 NCT04333368 | [57]    |
| Methylprednisolone       | Corticosteroids                               | NCT04343729 NCT04323592 NCT04244591 NCT04273321 NCT04329650 NCT04325061 NCT04327401 NCT04306393 NCT04305457 NCT04333828 NCT04337918 NCT04333914 | [58]    |
| Dexamethasone            |                                               | NCT04333368                                                          |         |
| Nitric oxide             | Vasodilator                                   | NCT04343144 NCT04333914                                              | [27]    |
| Nivolumab                | Programmed death receptor-1 (PD-1) blocking antibody | NCT04333144 NCT04333914                                              |         |
| NK cells                 | Natural killer cell therapy                   | NCT04280224 NCT04320277                                              | [27]    |
| Olumiant (baricitinib)   | Janus-associated kinase (JAK) inhibitor        | NCT04330690 NCT04336254 NCT04315987 NCT04313322 NCT04288102 NCT04302519 NCT04252118 NCT04273646 NCT04333368 | [59]    |
| Jakafi (ruxolitinib)     |                                               | NCT04333368                                                          |         |
| Oseltamivir              | Neuraminidase inhibitors                      | NCT04343144 NCT04333914                                              | [60]    |
| Ribavirin                |                                               | NCT04343144 NCT04333914                                              |         |
| Pembrolizumab            | Programmed death receptor-1 (PD-1) blocking antibody | NCT04333144 NCT04333914                                              |         |
| Remdesivir (GS-5734)     | Adenosine nucleotide analogs                  | NCT04333144 NCT04333914                                              | [27]    |
| Ribavirin                | Nucleoside analogs                            | NCT04343144 NCT04333914                                              | [61]    |
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 PaO2/FiO2 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 701 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 clinical scenario [103–105]. The table below briefly outlines cancer management in the era of COVID-19 pandemic.

| Priority Level | Clinical Scenario |
|---------------|-------------------|
| Priority A    | Patient’s condition is life threatening, clinically unstable (managing 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) |

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

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.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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