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Hot Topic

Cancer and COVID-19: Unmasking their ties

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and its clinical manifestation, the coronavirus disease 2019 (COVID19) have rapidly spread across the globe, leading to the declaration of a pandemic. While most present mild symptoms, it appears as though nearly 20% of confirmed patients develop significant complications. These include acute respiratory distress syndrome, septic shock and multi-organ failure, with a 3–6% mortality. A plethora of treatments has been or is being assessed, but to date, none has been proven effective. Management is mainly symptomatic, with organ support for the critically ill. Several reports, mainly case series, from across the world have concluded that patients with malignancy appear more susceptible to severe infection and mortality from COVID-19. This could be attributed to immunosuppression, co-existing medical conditions and underlying pulmonary compromise which is often the case in lung malignancy. Patients with haematological cancer and those who are receiving active chemotherapy treatment may be at greatest risk due to increased immunosuppression. This pandemic tested the resilience of worldwide health-care systems in an unprecedented manner. It has forced oncologists to rethink the entire diagnostic and therapeutic process, based on the local prevalence and impact of COVID-19. In this review we will discuss the impact of COVID-19 on patients affected by cancer, their diagnosis and management, as well as the pathophysiology of COVID-19 induced acute respiratory distress symptoms and currently investigated treatment approaches.

Introduction

Since the inception of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Hubei province, China, in late 2019, it has rapidly spread across the globe [1]. On the 11th of March 2020, the World Health Organization (WHO) declared a coronavirus disease 2019 (COVID-19) pandemic, the magnitude of which has only continued to soar since [2]. While the clinical manifestations of COVID-19 are mild in the majority of those infected, it appears as though nearly 20% of confirmed patients develop significant symptoms. These include acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure. A non-negligible proportion requires oxygen therapy and admission to an Intensive Care Unit (ICU), with an overall 3–6% fatality risk for infected patients [3]. To date, many treatments have been evaluated, some still under assessment, but none has proven to be effective. Clinical management is mainly symptomatic, with organ support in the ICU for critically ill patients.

While data are limited at this stage, case series from China and Italy initially reported that patients with malignancy were more susceptible to severe infection and mortality from COVID-19 [4,5]. A higher risk could be due to immunosuppression, increased co-existing medical conditions, and, in cases of lung malignancy, underlying pulmonary compromise. Haematological cancer patients, or those that are receiving active chemotherapy treatment might be most vulnerable to complications due to increased immunosuppression.

This pandemic has strained and tested the resilience of worldwide health-care systems in an unprecedented manner, forcing hospital wards and ICUs to rapidly repurpose staff and augment intake capacity to cope with COVID-19 patients. An unavoidable consequence is the deprioritisation of elective clinical or non-emergency services. Moreover, the widespread population lockdown and fear of contracting COVID-19 has led to a reduction in the presentation and referral of symptomatic patients from primary care to hospitals. To reduce the risk of exposure for patients with cancer, many centres have set up stringent measures to limit access to their premises to patients and their caregivers. The entire diagnostic and therapeutic process in oncology has widely been reshaped based on the local prevalence and impact of COVID-19.

A number of recommendations aiming to prioritise oncological treatments has been issued [6,7], to ensure optimal cancer care in the face of ongoing stress and distress. Current projections indicate that COVID-19-related disruption of healthcare systems could potentially

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last 16–18 months, perhaps even longer, until there is an increased herd immunity due to either exposure or large-scale vaccination.

In this review we will discuss the impact of COVID-19 on cancer patients, their diagnosis and management, as well as the pathophysiology of COVID-19 induced ARDS and currently investigated treatment approaches.

SARS-CoV-2, COVID-19 and immunity

Multiple pathways are involved in triggering an infection with SARS-CoV-2. In the initial SARS-CoV, ACE2 was identified as its functional receptor, both *in vitro* and *in vivo* [8]. This is pertinent today, as SARS-CoV-2 and SARS-CoV share the same receptor binding domain. ACE2 has a critical role in viral entry into host cells. This was confirmed in mice overexpressing human ACE2 who developed more severe disease when infected with SARS-CoV [9]. ACE2 is present in multiple tissues including the heart, kidneys, blood vessels, and intestines [10–15] but is primarily expressed in alveolar epithelial type II cells. These produce surfactant and play a key role in pulmonary gas exchange [16]. Any damage to these cells could result in severe lung injury. SARS-CoV also decreases ACE2 expression levels, thereby worsening lung injury [8,17]. Therefore, ACE2 appears to play a double role, both regulating the entry of SARS-CoV into cells and protecting the lung from injury [15]. The ACE2 tissue distribution could contribute to the multi-organ failure seen in patients affected by severe COVID-19 [18,19].

Phase I-II trials testing human recombinant soluble ACE2 (hrsACE2), have been performed [20,21] and recently [22] have found that hrsACE2 can dramatically lower viral growth *in vitro*. It is too premature to speculate on the clinical efficacy of such an approach.

COVID-19 is characterized by unbridled immune cell activation. This could explain worse outcomes in elderly people and patients with active cancer. The concept of “inflamm-aging” defines the increased baseline inflammation developed as one ages [23]. This immune deregulation observed in older patients, or in lung cancer where there could be chronic pulmonary inflammation, both from the tumour microenvironment and the frequent underlying lung pathology [24], may favour a surge in pro-inflammatory cytokines and drive the severe pathogenesis of COVID-19 in these special populations.

The pathophysiology of COVID-19 is yet to be fully understood. SARS-CoV-2 appears to trigger an excessive non-effective host immune response with severe lung injury [25]. The infection can result in a cytokine storm with haemophagocytic lymphohistiocytosis (HLH), presenting with increased plasma concentrations of proinflammatory cytokines including interleukin (IL) 2, 7, and 10, granulocyte-colony stimulating factor (g-csf), interferon (IFN)-γ-inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein and tumour necrosis factor (TNF)-α [26]. The hallmark feature of HLH is an over-activation of tissue macrophages, releasing a storm of cytokines leading to rapidly progressing organ dysfunction. Pancytopenia, tissue haemophagocytosis, hepatobiliary dysfunction, disseminated intravascular coagulation, and central nervous system, dysfunction can ensue, with potentially lethal consequences. During this process, tissue macrophages can over-produce IL-1β which, through autocrine stimulation, may sustain further inflammatory cytokine release. In addition, IL-1 signalling is one of the main drivers of the acute phase response to a viral infection [27], with consequent Th17 lymphocytic differentiation [28] and the typical immuno-pathogenic picture seen in ARDS with acute lung injury [29].

Elevated serum levels of IFN-γ have been identified in patients with ARDS in COVID-19 [30,31]. IFN-γ could enhance IL-6 production in monocytes. IFN- γ is a multifunctional pleiotropic inflammatory cytokine. It can directly enhance IL-6 production in monocytes [32] but also acts via JAK1/JAK2 signalling, activating a downstream cascade [33].

Table 1
List of publications on impact of COVID-19 on cancer patients.

	Number of patients	Cancer patients	Mortality among cancer patients (%)
Garassino *et al*	NA	200	33.3
Dai *et al*	NA	154	11.4
Barlesi *et al*	NA	137	15
Liang *et al*	2007	18	50*
Metha *et al*	NA	218	28
Robilotti *et al*	NA	423	9
Luo *et al*	NA	69	24

* = Invasive ventilation or death.
NA = not available.

The implications of COVID-19 for cancer patients

Compared to the general population, patients affected by cancer harbour a higher risk of contracting infection [34]. This increased susceptibility is partially due to the cancer itself, exerting a chronic immunosuppressive state, and can exacerbated by cytotoxic therapies. Therefore, it is expected that cancer patients be at higher risk, both of infection and complications, during the COVID-19 pandemic. An infection could have direct and indirect prognostic implications. First, the former are severe or mortal complications. The latter are cancer treatment delays or hospitalizations, which could hamper the efficacy of therapy and lead to cancer-related morbidity or even death. A number of recent publications detail the possible impact of COVID-19 on cancer patients (Table 1).

Liang *et al.* [35] reported a cohort of patients with COVID-19, among whom there was an important representation (1%) of cancer patients. Unsurprisingly, given the inherent associated pulmonary fragility, lung cancer was the most frequent type (5 [28%] of 18 patients). Furthermore *Yu et al.* [36] published a retrospective analysis of 1524 patients with cancer who were admitted in Wuhan University Hospital and reported the incidence and outcome of COVID-19 among those patients. Patients with cancer had higher risk of SARS-CoV-2 infection (OR, 2.31; 95% CI, 1.89–3.02) compared to the general population. This risk appears increased in both patients with or without active anticancer treatments. The most likely to develop COVID-19 were patients with non-small cell lung cancer and those above the age of 60. Recently, Ruan *et al.* [37] showed that, among patients who died from COVID-19, 63% had underlying disease, whereas 41% of those discharged did. An early report of a subset of patients who died from COVID-19 in Italy found that 20.3% of the deceased had active cancer [38]. All of this underlines the increased risk for cancer patients, particularly lung cancer patients.

At the AACR [39], the TERAVOLT (Thoracic cancers international COVID- 19 collaboration) registry, a global collaboration involving 21 countries and endorsed by several oncology societies, was presented. It is the first large dataset for patients with COVID-19 and thoracic malignancies, regardless of therapies administered. Data were presented for the first 200 patients enrolled in the registry up to April 12, 2020. The median age was 68 years old, the vast majority had stage IV NSCLC. Most of the patients (74%) were on active anticancer treatment. The most frequent symptoms reported were fever, cough and dyspnoea and the most common complications were pneumonia, in 79.6%, and ARDS, in 26.8%. 76% of infected patients were admitted to hospitals and 33.3% of them died. Most patients were not admitted to the ICU, although the reason for this was not clearly explained. No clear association was found between any specific cancer treatment and risk of death. The multivariate analysis adjusted for the most important risk factors in the general population did not identify a risk profile for COVID-19 mortality in these patients.

Further data support the initial findings about increased mortality due to COVID-19 in patients with cancer. Dai *et al.* [40] performed a

prospective, observational multicentre study which included 105 cancer patients and 536 age-matched non-cancer controls with confirmed COVID-19. Patients with cancer had higher rates of death (OR 2.34, 95% CI [1.15, 4.77]; p = 0.03), ICU admission (OR 2.84, 95% CI [1.59; p < 0.01), developing at least one severe or critical symptom (OR 2.79, 95% CI [1.74, 4.41]; p < 0.01) and chances of needing invasive mechanical ventilation. Again, lung cancer was the most frequent cancer type (22 [20.95%] of 105 patients), followed by gastrointestinal cancer (13 [12.38%] of 105 patients), breast cancer (11 [10.48%] of 105 patients), thyroid cancer (11[10.48%] of 105 patients) and haematological cancer (9 [8.57%] of 105 patients). Moreover, patients with haematological cancer, lung cancer, or with metastatic cancer (stage IV) had the highest frequency of severe complications. Non-metastatic cancer patients experienced similar rates of severe complications to those observed in patients without cancer. Patients who received surgery had higher risks of having severe events, while patients with only radiotherapy did not demonstrate significant differences in severe events when compared to patients without cancer.

An Italian study analysed the characteristics of patients who had died from COVID-19. The infection was more likely to be fatal among elderly patients and those with more than one comorbidity. Of 355 patients whose medical charts were reviewed, 87 (24.5%) had active cancer [38]. The estimated prevalence in the general population varies between 0.3 and 13%. A recent meta-analysis has indicated that the pooled prevalence of the virus in patients with cancer is as high as 2–3% [41], suggesting that cancer patients are largely over-represented among fatalities.

Two experiences from New York, have been recently published. The first, by Metha *et al.* [42] reported on COVID-19 mortality in patients with cancer at the Montefiore Medical Center. A total of 218 COVID-19 positive patients with malignancy was identified from March 18th to April 8th, 2020. In this cohort, 61 (28%) of cancer patients died from COVID-19 with a case fatality rate of 37% (20/54) for haematological malignancies and 25% (41/164) for solid malignancies. Among solid tumours, 6/11 (55%) were lung cancer patients. Mortality was also associated with older age and the presence of multiple comorbidities.

The second series from New York was published by Robilotti *et al.* [43] at the Memorial Sloan Kettering Cancer Center. They reported the epidemiology of COVID-19 illness experienced at their centre, with an analysis of risk factors for severe infection in cancer patient populations. Roughly 40% (169/423) of the patients with cancer diagnosed with COVID-19 were admitted, 20% (85/423) developed severe respiratory illness, and 9% (38/423) died. Older age (≥65 years) and having had immune checkpoint inhibitors within the last 3 months were predictive factors associated with hospitalization and severe disease, while chemotherapy within 30 days and major surgery were not.

The only results that are an outlier regarding poor outcomes associated with cancer come from the Gustave Roussy experience, recently presented at the AACR conference [44]. It reported data on 137 COVID-19 patients with cancer, haematological cancers and breast cancer being most common. Nearly 60% had active advanced disease, while 40% were either in remission or being treated with potentially curative therapy. Within the entire cohort, 25% had worsening COVID-19 after admission, 11% were admitted to the ICU and 15% died. Patients affected by haematological cancer were more likely to have worse outcomes. Treatment with chemotherapy within the past three months, but not targeted therapy or immunotherapy, doubled the likelihood of worsening disease. However, this only applied to people with active or metastatic cancer, not those whose disease was localised or in remission. The 15% death rate among cancer patients at Gustave Roussy was comparable to that observed in the general population. Nonetheless, patients with haematological malignancies, those on chemotherapy and who are frail remained at increased risk death.

Cancer management

Such findings highlight the importance of implementing strict infection control measures and reorganising cancer care in areas in which SARS-CoV-2 is endemic. Since the outbreak, a number of management guidelines has emerged about the optimal management of patients with cancer during the COVID-19 pandemic [6,7]. All of the recommendations are to be interpreted in light of certain considerations, including the extent of the epidemic, the local healthcare structure capacity, the individual risk of infection, the status of the cancer, patient comorbidities, age and treatment characteristics. Whether to continue cancer therapy or interrupt it remains a contentious subject. In certain malignancies, a timely diagnosis and treatment are strongly warranted, with a major impact on survival. While in others, in early stages, opting for surveillance, such as in low-risk prostate cancer, postponing cancer treatment or identifying alternative treatments, such as stereotactic ablative radiotherapy instead of lung surgery, may be an option during the COVID-19 pandemic in at-risk patients.

As a general recommendation, all patients receiving curative cancer therapy should continue their treatment despite the potential risk of COVID-19 infection during anticancer therapy. Delaying treatment for patients with metastatic disease could result in performance status deterioration, admission for symptom palliation, and progressive disease and poorer outcomes.

In some circumstances, surgery could be delayed. For example, in selected early-stage hormone-positive breast cancer patients, hormonal therapy could be used as a bridge for additional months if needed, particularly in areas where ICU beds are lacking.

An essential part of the strategy to safeguard cancer patients is the implementation of strict personal precautions, social distancing, and universal masking. Another concrete step is to expand ICU capacity, ensuring that patients with cancer are not proscribed access. The set-up of a telemedicine service is also important, while ensuring treatments continue unaltered, as reducing the number of visits to the hospital is imperative to lower the risk of infection. In addition, several centres have use a triage system for all patients before entering hospital premises. It includes screening temperature checks and questionnaires, with ensuing rhino-or oro-pharyngeal swabs in case of suspicious results. Some centres even have created SARS-CoV-2 free-zones, ruling out infection in all patients, even asymptomatic ones, before admitting them to the hospital for cancer therapy or to deliver outpatient systemic chemotherapy.

The oncology community has been under increasing pressure to protect cancer patients and ensure their safety while maintaining treatments [45]. This complex task brings with it an emotional struggle as we balance the desire to cure or treat our patients, with the fear of losing them from infection [6,46].

Interaction between COVID-19 and immune-checkpoint inhibitors treatments

Given the higher risk of death due to COVID-19 in patients with cancer, there has been increasing concern about the risk related to the administration of immune-checkpoint inhibitors (ICIs). Severe autoimmune pneumonitis and COVID-19 pneumonia share similar clinical and pathological patterns. Furthermore, it has been hypothesized that initial lung injuries induced by ICI could increase the risk of developing severe COVID-19 pneumonia [47]. There is a sound biological rationale pertaining to overlapping mechanisms of cytokine release (Fig. 1).

SARS-CoV-2 induces excessive and aberrant non-effective host immune responses that are associated with potentially fatal severe lung injury [25]. In some severe cases, the infection is associated with a cytokine storm and HLH.

The resulting elevation of IL-6, IFN- γ and other cytokines, provokes symptoms, some mild such as fever, malaise and myalgia, and others more intense such as organ impairment, including lung failure.

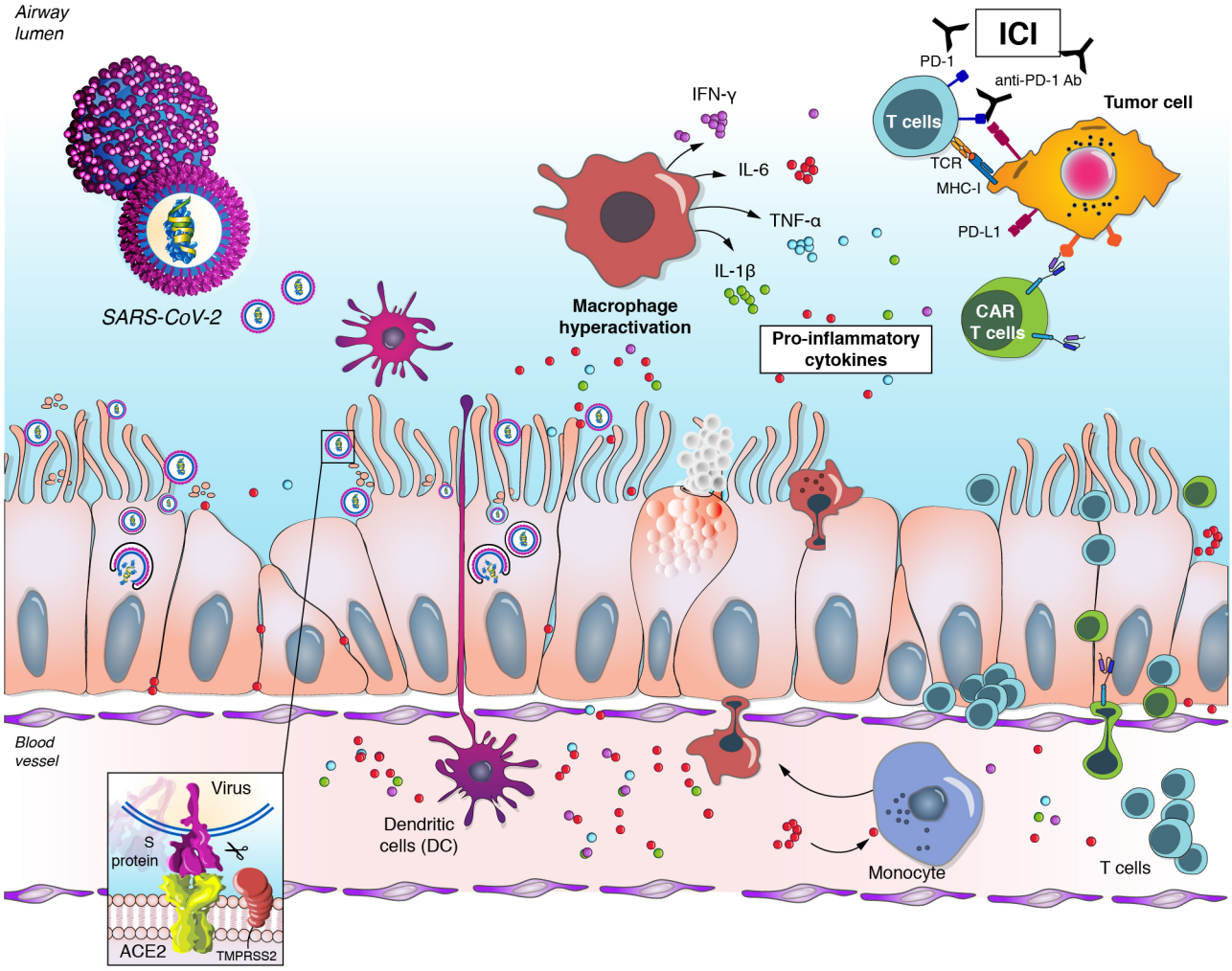

Fig. 1. Potential overlapping mechanisms of cytokine release in COVID-19, immune-checkpoint inhibitor induced pneumonitis and CAR T cell induced cytokine release syndrome.

Moreover, the pathological findings associated with ARDS in COVID-19 showed abundant interstitial mononuclear, predominantly lymphocytic, inflammatory infiltrate in the lungs, once more highlighting the key role of immune hyperactivation mechanisms in severe COVID-19 pneumonia [48]. On this basis, a synergic mechanism between ICI and COVID-19 pathogenesis, involving T lymphocyte or macrophage hyperactivation and cytokine release would not seem implausible. While the Memorial Sloan Kettering Cancer Center data support this hypothesis of increased mortality on ICI, the other series do not [44] and data are globally too scarce to corroborate this hypothesis. Finally, given the ubiquitous use of ICI in oncology today, it is important to acknowledge that we do not know if the risk of developing COVID-19 with ICI is higher than with chemotherapy.

Treatment of COVID-19

Currently, there is no standard treatment and different protocols have been adopted in hospitals. In this section, we detail some of the most used and studied options.

Steroids and immunomodulatory drugs

Corticosteroids are widely used to prevent lung injury caused by severe community-acquired pneumonia due to their excellent pharmacological effects on the suppression of exuberant and dysfunctional systematic inflammation [49]. However, the use of steroids in COVID-19 is controversial and based on limited, contradictory observational evidence.

Wu *et al.* [50] recently published their experience on the administration of methylprednisolone in patients with COVID-19 and ARDS. They reported that despite a possible efficacy of steroids, 23 out of 50 (nearly 50%) of the patients had died. The ICU mortality of critically ill patients with COVID-19 pneumonia, and receiving low-dose corticosteroids mirrors these results. In a further cohort of 46 patients in the same setting, short duration (5–7 days) steroids reduced the duration of oxygen dependence and improved disease course [51], suggesting that corticosteroids may enhance oxygen saturation and arterial oxygen tension/inspiratory oxygen fraction in the acute phase of this infection.

Two larger retrospective studies found a discordant impact of steroids on patients with COVID-19 and pneumonia. The first, with 201 patients, suggested that methylprednisolone may benefit patients who develop ARDS (n = 88), reducing mortality. The second, among 244 critically ill patients with COVID-19 [52] concluded that corticosteroid use was independent from the 28-day mortality risk. However, an increased corticosteroid dosage was significantly associated with elevated mortality risk. This suggests that if steroids are beneficial, they are of limited benefit and not a panacea, and should be administered cautiously. In the WHO [53] issued guidelines on COVID-19 therapeutic management, steroids are not recommended.

Steroid-sparing immunomodulatory approaches appear more

promising in the treatment of COVID-19. IL-6 blockade is of particular interest. It is frequently administered to patients with cancer in the context of immune checkpoint-inhibitor (ICI) induced pneumonitis [54], as well as to dampen cytokine-release syndrome in the aftermath of CAR-T cell therapy [55]. SARS-CoV-2 ARDS results from uncontrolled severe acute inflammation with possible acute lung injury and subsequent release of pro-inflammatory cytokines including IL-6, IL-1, IFN-γ and TNF-α [56].

Additionally, IL-6 stimulates T-cell proliferation and hinders the ability of pulmonary dendritic cells to prime naïve T-cells, thus downplaying the adaptive immune response [56]. A monoclonal antibody, anti-IL-6R, tocilizumab (TCZ), has been administered in a number of cases in China and Italy to patients with severe COVID-19 pneumonia. Recently, a report from the Society for Immunotherapy of Cancer [57,58] was published on the potential efficacy of TCZ in this circumstances, leading to compassionate use of TCZ in several countries. As a consequence many controlled clinical trials are ongoing (ChiCTR2000029765 and TOCIVID-19, COVACTA).

Based on a biological rationale, many other immune-modulating therapies are potential therapeutic candidates. These include agents able to alleviate activation of JAK1/2 using ruxolitinib, of IL-6/IL-6R signalling (using TCZ or an anti-IL-6 antibody such as siltuximab), of IL-1 signalling (using anakinra which is a recombinant human IL-1R antagonist or using canakinumab that is a human monoclonal anti-IL-1β antibody). IL-1 blockade has been assessed and data from a phase 3 randomised controlled trial of anakinra in septic patients with features of HLH, showed significant improvement in the 28-day survival rate, hepatobiliary dysfunction and disseminated intravascular coagulation patients, without significant adverse events [59]. In addition anti-IFN-γ (using empalumab, a human anti-IFN-γ monoclonal antibody) are promising therapeutic strategies to treat the hypercytokinemia syndrome associated with severe forms of COVID-19.

Intravenous immunoglobulins

Additional immunotherapies that could be considered for COVID-19 include immunomodulators that have broad anti-inflammatory effects such as pooled normal IgG or intravenous immunoglobulin (IVIG) therapy. IVIGs are one of the most widely used immunotherapies for a large number of autoimmune and inflammatory diseases [60,61]. They act by suppressing the immune activation and the secretion of pro-inflammatory cytokines from innate immune cells. This could, in turn inhibit inflammatory Th1 and Th17 responses, as well as favour the recruitment of T regulator cells (Tregs), which prevent inflammation-associated organ damage [62].

A recent open-label trial in three patients reported benefits of IVIG therapy (0.4 g/kg for five days) in severe COVID-19 pneumonia [63]. These results are supported by a multicentre retrospective analysis of IVIGs as therapy for critical COVID-19 patients. However, dosing and length of treatment remain unclear [64] with a greater benefit with doses > 15 g/day and administered within a week of hospitalization [65].

Efficacy data are immature, however widespread IVIG use could prove untenable due to practical considerations. IVIGs must remain available for immunodeficient patients whose survival essentially depends on them. Furthermore, their cost is prohibitive on a large scale. Finally, the ongoing pandemic will affect the collection of plasma from donors for IVIG production, further impacting the current worldwide shortage of IVIGs.

SARS-CoV-2 directed biological therapy

Using convalescent plasma from patients who were infected with SARS-CoV-2 could represent a possible treatment. Among patients infected with the previous SARS virus, there was a reduced mortality rate in those treated with plasma infusions containing antibodies to the virus. On a biological level, the patients had a sharp and rapid decline in their viral load [66]. As such, developing neutralizing monoclonal antibodies for SARS-CoV-2 may be an appealing therapeutic option and several laboratories are actively exploring this option [67]. Before any use of plasma antibody preparations; however, their neutralizing activity on SARS-CoV-2 would need to be assessed. Logistical considerations would also include the timing of plasma collection. Median seroconversion time for IgM and IgG can take up to14 days following the onset of COVID-19 [68]. Therefore, convalescent plasma likely should be collected about three weeks after infection in order to optimize the likelihood to collect a high titre of neutralizing antibodies. Preliminary data from China have shown that convalescent plasma administration was associated with clinical improvement in 91 out of 245 patients affected by COVID-19 [69]. Furthermore, in 5 critically ill patients with COVID-19, this approach appears to have resolved acute pulmonary injuries, and reduced viral loads [70]. Randomized trials are ongoing.

Antivirals

There are many potential non-immune-modulating therapies for COVID-19. Among them chloroquine and hydroxychloroquine are an important focus of investigation. These antimalarial drugs have antiviral effects against different types of viruses, *in vitro*, including in HIV. They rely on two identified mechanisms of action: inhibiting low pH-dependent viral entry into host cells and altering post-translational modifications of newly synthesized proteins by blocking glycosylation [71]. Recently, chloroquine was combined with an antiviral, remdesivir, showing promising early data in inhibiting the growth of SARS-CoV-2 *in vitro* [72] and early trials in China suggested a potential benefit of chloroquine in reducing the viral load improving the time to recovery [60]. Given these results guidelines recommend its use in China [73].

Hydroxychloroquine, which has a more favourable safety profile than chloroquine, appears more active against SARS-CoV-2 growth, *in vitro* [61]. The former's potential role seems to be enhanced by its efficacy in clearing nasopharyngeal carriage of SARS-CoV-2, reducing the mean duration of viral shedding from 15 to 20 days to 3–6 days [74]. Many hospital have adopted protocols that associate hydroxychloroquine with azithromycin, an antibiotic with a known immunomodulatory effect. This combination appears to be more effective in reducing the viral cure rate, with 100% of patients receiving the combination virus-free after six days [63]. However, while these drugs are now routinely used in some hospitals, there is no strong evidence nor randomised trials proving and supporting the efficacy of any of these molecules in COVID-19.

Numerous other antiviral studies are ongoing and but efficacy data are not yet available. Among them, remdesivir, a nucleotide analogue inhibitor of the EBOV RNA-polymerase RNA-dependent (RdRp), has shown promising *in vitro* anti-SARS-CoV-2 efficacy [72]. In clinical practice, data are less clear. Two phase 3 randomized, placebo-controlled clinical trials of remdesevir in COVID-19 showed discordant results. Preliminary analyses from the ACTT trial (NCT04280705) of over 1000 patients showed a four day improvement in recovery time. Contrarily, a Chinese study among 237 patients did not show a significant clinical benefit [75].

A combination of lopinavir and ritonavir had also been touted as a possible strategy for COVID-19; however, a randomized trial including 199 patients failed to prove any clinical benefit, highlighting the need for caution when interpreting early data [76].

Conclusion

The COVID-19 pandemic has forced healthcare systems to rethink their treatment pathways and strategies. Patients with cancer are at high risk of complications if infected with SARS-CoV-2, both directly due to their fragility, and indirectly due to treatment interruption.

While we await an effective vaccine or herd immunity, SARS-CoV-2 continues to spread, and the death-toll to rise exponentially. Advancing new therapeutic development is crucial, both to limit the number of deaths in general population and patients suffering from cancer, and to alleviate the strain on healthcare systems worldwide, already struggling to cope with the number of victims of this disease.

It is essential to better understand the role of immune dysregulation in COVID-19 and the inflammation process in order to offer an effective treatment. Several drugs alone or in combinations are being tested in clinical trials. To date, no drug has proven its clinical utility and could be labelled as standard of care.

While awaiting therapeutic progress, maximal effort should be made to protect patients with cancer from SARS-CoV-2 and to avoid any disruption to cancer care.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Al-Qahtani AA. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2): emergence, history, basic and clinical aspects. Saudi J Biol Sci 2020.
[2] WHO. Coronavirus disease 2019 (COVID19)-SITUATION REPORT 51. 2019.
[3] Baud D, Qi X, Nielsen-Saines K, Musso D, Pomar L, Favre G. Real estimates of mortality following COVID-19 infection. The Lancet Infectious Diseases.
[4] Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet. Respir Med 2020.
[5] Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. JAMA 2020.
[6] Banna G, Curioni-Fontecedro A, Friedlaender A, Addeo A. How we treat patients with lung cancer during the SARS-CoV-2 pandemic: primum non nocere. ESMO open. 2020;4:e000765.
[7] Burki TK. Cancer guidelines during the COVID-19 pandemic. Lancet Oncol 2020;21:629–30.
[8] Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005;436:112–6.
[9] Yang X-h, Deng W, Tong Z, Liu Y-x, Zhang L-f, Zhu H, et al. Mice transgenic for human angiotensin-converting enzyme 2 provide a model for SARS coronavirus infection. Comp Med 2007;57:450–9.
[10] Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature 2002;417:822–8.
[11] Danilczyk U, Penninger JM. Angiotensin-converting enzyme II in the heart and the kidney. Circ Res 2006;98:463–71.
[12] Ding Y, He L, Zhang Q, Huang Z, Che X, Hou J, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. J Pathology: A J Pathol Soc Great Britain Ireland 2004;203:622–30.
[13] Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202:415–24.
[14] Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol: A J Pathol Soc Great Britain Ireland 2004;203:631–7.
[15] Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 2020;1–5.
[16] Dobbs LG. Pulmonary surfactant. Annu Rev Med 1989;40:431–46.
[17] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Med 2005;11:875–9.
[18] Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. in China. N Engl J Med 2019;2020(382):1708–20.
[19] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497–506.
[20] Haschke M, Schuster M, Poglitsch M, Loibner H, Salzberg M, Bruggisser M, et al. Pharmacokinetics and pharmacodynamics of recombinant human angiotensin-converting enzyme 2 in healthy human subjects. Clin Pharmacokinet 2013;52:783–92.
[21] Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 2017;21:234.
[22] Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 2020.
[23] Franceschi C, Bonafè M, Valensin S, Olivieri F, de Luca M, Ottaviani E, et al. Inflamm-aging: An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2000;908:244–54.
[24] Ballaz S, Mulshine JL. The potential contributions of chronic inflammation to lung carcinogenesis. Clin Lung Cancer 2003;5:46–62.
[25] Qin C. Dysregulation of Immune Response in Patients with COVID-19 in Wuhan, China. Lancet 2020.
[26] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet.
[27] Weber A, Wasiliew P, Kracht M. Interleukin-1 (IL-1) Pathway. ScienceSignaling. 2010;3:cm1-cm.
[28] Santarlasci V, Cosmi L, Maggi L, Liotta F, Annunziato F. IL-1 and T helper immune responses. Front Immunol. 2013;4..
[29] Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev 2012;76:16–32.
[30] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Investig 2020;130.
[31] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054–62.
[32] Biondillo DE, Konicek SA, Iwamoto GK. Interferon-gamma regulation of interleukin 6 in monocytic cells. Am J Physiol-Lung Cell Mol Physiol 1994;267:L564–8.
[33] Farrara MA, Schreiber RD. The molecular cell biology of interferon-gamma and its receptor. Annu Rev Immunol 1993;11:571–611.
[34] Penn I, Starzl TE. Immunosuppression and cancer. Transplantation proceedings: NIH Public Access; 1973. p. 943.
[35] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. The Lancet Oncol 2020;21:335–7.
[36] Yu J, Ouyang W, Chua MLK, Xie C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan. JAMA Oncology: China; 2020.
[37] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020:1–3.
[38] Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA 2020.
[39] Dingenmans AC, De Toma A, Viscardi G, Pancaldi V, Mazieres J, Trama A, et al. International registry on thoracic cancer patients with COVID-19 TERAVOLT. 2020.
[40] Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-COV- 2: a multi-center study during the COVID-19 outbreak. Cancer. Discovery. 2020.
[41] Signorelli C, Scognamiglio T, Odone A. COVID-19 in Italy: impact of containment measures and prevalence estimates of infection in the general population. Acta Biomedica: Atenei Parmensis. 2020;91:175–9.
[42] Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, et al. Fatality rate of cancer patients with COVID-19 in a New York hospital system. Cancer Discovery 2020.
[43] Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of Severity in Cancer Patients with COVID-19 Illness. 2020;medRxiv. 2020(05). pp. 04.20086322.
[44] Fabrice Barlesi SF, Arnauld Bayle, Bertrand Gachot, Fanny Pommeret, Christophe Willekens, Annabelle Stoclin, Mansouria Merad, Franck GriscelliI, Jean-Baptise Micol, Roger Sun, Thomas Nihouarn, Corinne Balleygier, Fabrice André, Florian Scotte, Benjamin Besse, Jean-Charles Soria, Laurence Albiges. Outcome of cancer patients infected with COVID-19, including toxicity of cancer treatments. 2020 AACR.
[45] Addeo A, Banna GL, Weiss GJ. Tumor mutation burden—from hopes to doubts. JAMA Oncol 2019;5:934–5.
[46] Lewis MA. Between scylla and charybdis — oncologic decision making in the time of Covid-19. N Engl J Med 2020.
[47] Bersanelli M. Controversies about COVID-19 and anticancer treatment with immune checkpoint inhibitors. Future Med 2020.
[48] Tian S, Xiong Y, Liu H, Niu L, Guo J, Liao M, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol 2020.
[49] Mokra D, Mikolka P, Kosutova P, Mokry J. Corticosteroids in Acute Lung Injury: The Dilemma Continues. Int J Mol Sci 2019;20:4765.
[50] Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan. JAMA internal medicine: China; 2020.
[51] Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduction and Targeted Therapy 2020;5:1–3.
[52] Lu X, Chen T, Wang Y, Wang J, Zhang B, Li Y, et al. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. medRxiv. 2020:2020.04.07.20056390.
[53] Organization WH. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected: interim guidance, 25 January 2020. World Health Organization; 2020.
[54] Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol 2019;20:e54–64.
[55] Gardner RA, Ceppi F, Rivers J, Annesley C, Summers C, Taraseviciute A, et al. Preemptive mitigation of CD19 CAR T-cell cytokine release syndrome without attenuation of antileukemic efficacy. Blood 2019;134:2149–58.

[56] Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, et al. Anti–spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight 2019;4.
[57] Ascierto PSITC. Statement on anti-IL-6/IL-6R for COVID-19. JITC 2020.
[58] A. Addeo MO, A Friedlaender. COVID-19, lung injury in cancer patients: what we have learnt so far. Journal for ImmunoTherapy of Cancer (in press). 2020.
[59] Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. Crit Care Med 2016;44:275–81.
[60] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72–3.
[61] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020.
[62] Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol 2013;13:176–89.
[63] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;105949.
[64] Cao W, Liu X, Bai T, Fan H, Hong K, Song H, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open forum infectious diseases. Oxford University Press US; 2020. p. ofaa102.
[65] Shao Z, Feng Y, Zhong L, Xie Q, Lei M, Liu Z, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19: A multicenter retrospective cohort study. 2020.
[66] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F-M, Lim WS, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211:80–90.
[67] Chen X, Li R, Pan Z, Qian C, Yang Y, You R, et al. Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor. Cell Mol Immunol 2020;1–3.
[68] Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clin Infect Dis 2020.
[69] Casadevall A, Pirofski L-a. The convalescent sera option for containing COVID-19. J Clin Investigation 2020;130:1545–8.
[70] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323:1582–9.
[71] Rolain J-M, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. Int J Antimicrob Agents 2007;30:297–308.
[72] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269–71.
[73] [Expert recommendations on the management of patients with advanced non-small cell lung cancer during epidemic of COVID-19 (Trial version)]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases. 2020;43:E031.
[74] Zhou W, Liu Y, Tian D, Wang C, Wang S, Cheng J, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal Transduction and Targeted Therapy 2020;5:18.
[75] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet.
[76] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe covid-19. N Engl J Med 2020.