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REVIEW

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The impact of the SARS-CoV-2 infection, with special reference to the hematological setting

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a disease known from a few months, caused by a recently arisen virus and, consequently, it is little known. The disease has a benign course in most infected subjects (children and young adults), is often symptomatic in adults over the age of 50 and often serious and life threatening in people with comorbidities and the elderly. The few data published on coronavirus disease-2019 (COVID-19) in the blood-oncology field report a serious clinical presentation, a serious course of the disease, and a high mortality rate, as has also been reported for other cancer contexts. The current strategy for treating patients with SARS-CoV-2 includes antivirals that are effective against other viral infections and drugs that can moderate the cytokine storm. There is no specific vaccine and consequently all possible precautions must be taken to prevent SARS-CoV-2 infection in the areas of oncology, oncohematology, and bone marrow transplantation. In this reviewer's article, we report the information currently available on SARS-CoV-2 infection to help young doctors and hematologists to successfully manage patients with COVID-19.

KEYWORDS

COVID-19, hematological diseases, SARS-CoV-2

1 | INTRODUCTION

Started with an outbreak in the city of Wuhan in the Chinese province of Hubei, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its related disease (coronavirus disease-2019 [COVID-19]) invaded a wide Chinese territory around Wuhan and subsequently Italy, Germany, France, Spain, England, Sweden, the United States of America, and more recently Russia, India, Brazil, and most other countries in the World. By the end of May 2020, nearly six million people had become infected worldwide, of whom nearly 400 000 have died of COVID-19 worldwide.

The SARS-Cov-2 pandemic is characterized by a low diffusion along the meridians and a widespread along the parallels, reflecting, at least in part, the intensity of fluxes of the international trade.[1]

Cancer patients with SARS-CoV-2 infection are at a high risk to develop severe clinical events (48%-54% of infected subjects) and die (5.6%-29%).[2-4] Liang et al[2] observed 1590 COVID-19 hospitalized patients, of whom the 18 with a history of cancer developed severe events (intensive care unit admission, invasive ventilation, or death) more frequently than those without cancer (39% vs 8%, $P = .0003$). In this study, the clinical presentation was more frequently marked by polypnea in patients with cancer (47% vs 23%) who more frequently

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than patients with COVID-19 without cancer showed severe computer tomography (CT) scan findings at baseline (94% vs 71%).

Few data are available in the hematological setting. In this regard, interesting data come from a cohort study conducted in Wuhan on 128 hospitalized patients with hematologic cancer an on 126 health care providers who assisted them. The study showed that patients with hematologic cancers had a similar rate of SARS-CoV-2 infection as that of health care providers, but, once infected, they presented a more serious disease and a significantly higher mortality rate.[5] These example data, together with the data from few small other studies, suggest that the exposure of patients with cancer to SARS-CoV-2 is very risky, and that every possible precaution must be put in place to prevent this from happening.[6-12] These considerations also apply to the context of bone marrow transplantation.[13-15]

We have prepared this review article for all doctors who have not had the opportunity to investigate the different aspects of COVID-19 sufficiently, including young infectious disease specialists, hematologists, and general practitioners, who for more than one reason may meet patients with COVID-19, having to make a first diagnosis and the first decisions about it.

2 | CLINICAL PRESENTATION AND COURSE OF COVID-19

Human-to-human SARS-CoV-2 transmission through respiratory droplets or close contacts are the main transmission pathways,[10] whereas the fecal-oral transmission plays a secondary role since SARS-CoV-2 may be detected in fecal samples of only in 2%-10% of patients with diarrhea.[16,17]

After an incubation period usually ranging from 2 to 14 days,[18] SARS-CoV-2 infection leads to a wide range of clinical presentations, from an asymptomatic infection or mild form (81% of cases) to moderate/severe forms (14%-20%), and to critical disease requiring oxygen therapy (5% of symptomatic cases).[19,20]

Fever, fatigue, dry cough, and dyspnea are the most frequent symptoms, sometimes, announced by palpitation, myalgia, headache, or diarrhea. Dyspnea is reported at 2 to 5 days since symptoms and, in this case, CT may reveal infiltrations in unilateral or bilateral lung fields, ground glass appearance, interstitial infiltration, or multiple patchy consolidations in both lung fields. When all this occur, the symptoms worsen rapidly and the assistance of a ventilator become mandatory.[21,22] Nasal congestion, runny nose, sore throat, aqueous diarrhea, vomiting, abdominal pain, and myalgia are less frequently observed.[23,24] Myocardial, liver, and kidney injuries and secondary bacterial infection may also occur.[25] The presence of comorbidities (cardiovascular disease, hypertension, diabetes, chronic lung disease, renal failure, cerebrovascular disease, or malignancy) are the major risk factors for the development of the acute respiratory distress syndrome (ARDS) and the need for intensive care in 20% to 30% of cases, with a mortality rate around 10%, that, however, may reach 50% in adult aged more than 60 in some report.[26] The estimated symptomatic case-fatality risk among cases observed in Wuhan was 1.4%, but elder patients (>59 years) had 5.1 times more likely to die than those 30 to 59 year old.[27] Mortality rates around 13% have been observed in other countries, like Italy, Spain, France, England, and USA.[27]

He et al[5] carried out a cohort study in Wuhan, China, on 128 hospitalized subjects with hematologic cancers, of whom 13 developed COVID-19. Among these 128, the probability of acquiring SARS-CoV-2 infection was not associated to a type of tumor nor to the stage of the neoplastic disease nor to the number of anticancer cycles performed. The rate of cases with COVID-19 were similar in the hematologic cancer group and in a group of 226 normal health care providers used as control. The data of the 13 patients with and COVID-19 were compared with those of the 115 subjects with hematologic cancers without COVID-19 and no baseline significant difference was observed; lung CT scans showed typical findings of COVID-19 in all infected patients. The 13 patients with hematologic cancer and COVID-19 were also compared with 11 health care providers (out of the 226) hospitalized for COVID-19. The clinical presentation and course of the disease of COVID-19 were more severe in the 13 patients with hematologic cancers than in the 11 health care providers: more coinfections more complications including acute ARDS, acute renal dysfunction, and sepsis; none health care providers and eight patients with hematologic cancers had died at the end of observation ($P = .001$).

The increased severity of COVID-19 in patients with hematological cancer is also supported by anecdotal clinical cases that are published day-by-day.[28-30]

3 | LABORATORY TESTS TO DETECT SARS-CoV-2 RNA AND SPECIFIC ANTIBODIES

A reverse-transcription polymerase chain reaction (RT-PCR) assay is performed to detect SARS-CoV-2 RNA on throat or nasopharyngeal swabs or tracheal aspirate or bronchoalveolar lavage specimens.[31] Due to the low number of false-negative results, this RT-PCR assay is considered the gold standard to identify SARS-CoV-2 infection.

The detection of specific IgM and IgG antibodies with a serological immunoassay (ELISA) offers the advantage of a rapid diagnosis of having already come into contact with the virus and to avoid the infrequent false-negative cases that might had occurred with the RT-PCR assay.[32] In SARS-CoV-2 infection, IgM could be detected in patients' blood after 3 to 9 days after the infection in nearly 85% of cases but they became undetectable after 2 weeks, while IgG could be detected after 8 days in nearly 78% of cases and remain detectable for 3 weeks or longer.[33] The detection of these antibodies may also have a prognostic value since delayed and weak antibody response was found associated with a more severe clinical course.

4 | DIAGNOSTIC IMAGING

In the first stages of the disease, the instrumental diagnosis in patients with COVID-19 includes chest X-ray examination at the

patient's bed, mainly to avoid bacterial superinfection, and the lung ultrasound examination. In some cases, due to organizational difficulties or sterilization protocols,[34,35] chest radiographs may not be performed at the patient's bed. The use of High Resolution Computed Tomography (HRCT) is always indicated in clinical conditions of medium or severe gravity, in cases of clinical worsening and when the nasopharyngeal swab for the search of the viral RNA shows negative result in contrast with the clinical findings suggesting COVID-19. In the latter case, the sensitivity of HRCT is considered higher than that of the swab to detect viral RNA.[36] HRCT is particularly useful to assess the presence and the degree of ARDS and the degree of the alveolar recruitment after postural or pulmonary ventilation. A wide use of HRCT is recommended for an early diagnosis and monitoring of lung disease, for optimizing the type and parameters of ventilation, and for highlight abdominal complications.

Doppler and Power Doppler ultrasonography have been widely used for decades to assess renal vasculature as predictor of multiorgan failure in patient with acute lung injury or in the setting of ARDS, where a massive involvement of the systemic vasculature is expected. In patients with COVID-19, renal ultrasonography is performed with the aim of integrating pulmonary vasculature evaluation performed with HRCT, or in case of impossibility to move patient into the CT suite.

Pulmonary ultrasound examination in patients with concomitant chronic obstructive pulmonary disease and/or "aged pulmonary parenchyma" has limited usefulness because it requires time and is of almost zero diagnostic value. CT is a gold standard for the evaluation of abdominal complications.

The myocardium, generally less affected than the lung due to its lower expressiveness of angiotensin-converting enzyme 2 (ACE2) receptors, is usually evaluated with ultrasound to exclude concomitant pathologies. However, in selected patients with a significant involvement of myocardium and in those with concomitant cardiovascular disease catheter angiography and or magnetic resonance imaging should be proposed.[37,38]

Overall, the wide use of diagnostic imaging is useful for a careful evaluation of the pathologies of patients with COVID-19, for identifying their early stages, for therapeutic monitoring and to get information useful to prevent some side effect of drugs.

5 | VASCULAR ACCESS IN PATIENTS WITH COVID-19

COVID-19-positive patients are at risk for respiratory complications that require either assisted ventilation or respiratory assistance through intubation or the packaging of a tracheostomy. For such serious patients is necessary to ensure a long-lasting, efficient, and safe venous access and the peripherally inserted central catheter (PICC) responds to the all the organizational and management requirements. PICC placement in patients with COVID-19 should be performed at confirmed diagnosis, in the post acute phase of the illness and after primary stabilization. The positioning of the PICC must be done by a dedicated team of experts, because the success of the system must be guaranteed quickly, and in any case within 24 hours of the request, with appropriate protection measures and respecting all the principles of sterility. For this purpose, the use of an all-inclusive kit for the installation and management of the device is suggested.

The Infusion Nursing Society (INS 2016) guidelines recommend the use of standardized and certified methods of tip location and intraprocedural tip navigation, the verification and confirmation of the correct positioning of the tip of catheter during the implant, which avoids a chest X-ray to control the position of the tip of the catheter, thus preventing further exposure of patients to infectious and/or thrombotic risk and unnecessary contagion risk for the health care personnel.

In patients with a helmet or mask for ventilation or who may need this respiratory supports in the near future, the PICC finds its full use because ventilation will always be guaranteed because the catheter insertion site is in the middle third of the arm, away from the helmet or ventilation mask, and because there is no risk of its kinking, which is possible in cases of a central venous catheter positioned on the patient's neck. Continuous ventilation is, therefore, guaranteed also for intubated patients even if it becomes necessary to reintervene on the venous access site, since PICC management would take place away from the endotracheal tube, with a low risk of contamination. Furthermore, there are no indications not to prefer the use of PICC during pronation cycles. PICC implantation in patients with COVID-19 must be carried out in compliance with the principles of sterility, with the correct vessel selection and following the INS 2016 guidelines. If a PICC type central venous catheter is not required, other types of peripheral venous catheters should be considered, such as the midline, short peripheral cannulas, and long peripheral cannulas. The management of these devices must be absolutely accurate as indicated by the INS 2016 guidelines to reduce the onset of complications which would be extremely dangerous in these patients.

6 | BIOLOGICAL CYCLE AND PATHOGENESIS

SARS-CoV-2 is a beta coronavirus which structure is composed of a single-stranded positive-sense RNA, an envelope, a nucleocapsid and membrane Spike (S) proteins.[39,40]

The entry of SARS-CoV-2 into the target cells occurs by means of the viral surface protein "S" that interact with the ACE2 membrane receptor expressed on human cells. A host serine protease TMPRSS2 splits the spikes protein S into two fragments S1 and S2, the first one responsible of the binding of SARS-CoV-2 to the ACE2 receptors and the second one of the fusions of viral and cellular membranes. ACE is a particularly abundant glycoprotein in lung tissue, where most of the transformation of angiotensin 1 into angiotensin 2 takes place. This protein is also present in brain tissue, in the vascular endothelium, in most organic liquids, in the intestinal ciliated epithelium, in the

epithelial cells of the distal nephron tubule, in the prostate, and in the renal lymph. A further function of ACE is to degrade bradykinin, a potent vasodilator peptide, to inactive metabolites. Therefore, inhibition of ACE also results in an increased activity of the local and circulating kallikrein-kinin system, which contributes to peripheral vasodilation through bradykinin and the subsequent activation of the prostaglandin system. This mechanism probably leads to a hypotensive effect of ACE inhibitors and in some adverse reactions such as coughing. Patients hospitalized for COVID-19 in the early stages of the disease are often affected by an acute and dry cough that is very reminiscent of coughing by ACE inhibitor drugs, by a marked hypotension or by more or less violent signs or symptoms of gastrointestinal damage, like abdominal cramps, nausea, and vomiting, associated or not to diarrhea. Other clinical or laboratory abnormalities may be observed in the early stages like bilateral interstitial pneumonia, anosmia, dysgeusia, pancytopenia, proteinuria, and increase in serum erythrocyte sedimentation rate, PCR, lactate dehydrogenase, creatinine phosphokinase, D-dimer, aspartate aminotransferase, alanine aminotransferase, and creatinine. After the dry cough of the acute phase, often follows a secretive cough not due to bacterial superinfection but to the activity of tachykinins that act on the NK1 and NK2 receptors that stimulate mucus secretion and bronchoconstriction, respectively.

Once the virus has overcome the first defensive barriers and penetrates the body, the innate immune system quickly intervenes with soluble cells and molecules against the aggressive agent, while the adaptive response can take days or even weeks for its full activation. The innate immune response has a rapid implementation, from 4 minutes to 4 hours for the activation of macrophages and of the alternative complement pathway and from 4 hours to 4 days to implement the production of NK cells and the release of interferon (IFN). The activation of the adaptive immunity implies the production of CD8+ specific cytotoxic T-cells and of CD4+ helper T-cells and the activation of specific B cells to produce specific antibodies. After the virus recognition by Toll-like receptor-7 (TLR -7) in endosomes, TLR -7 activation leads to the production of α-IFN, tumor necrosis factor-alpha (TNF-α), and the secretion of interleukin (IL)-12 and IL-6. In some cases, the host greatly amplifies the immune response to attack the virus, which may induce ARDS and a strong involvement of other organs. Thus, the virus is responsible for cell damage through direct and indirect mechanisms. The direct cytopathic damage is due to the viral replication in various parenchyma, mainly in the pulmonary alveoli. Histopathological analysis shows an acute alveolar damage characterized by protein exudate, fibrin deposits, thickening of septa and alveolar walls, hyperplasia of type II pneumocytes, and mononuclear inflammatory infiltrate. In clinically severe disease, even other organs (heart, liver and kidneys, and the central nervous system) are involved and patients may develop multiorgan failure (MOFS), coagulopathy clinically significant and septic shock.

The indirect damage on target organs acts through a cytotoxic effect on the endothelium with the development of systemic capillary microthrombi and consequent ischemia involving lung, brain, heart, liver, and kidney. The massive release of proinflammatory cytokines (cytokine release syndrome) including various interleukins (IL-2, GM-CSF, IL-6, IL -1, IL-8, and TNF-α) and chemokines (CXCL9, CXCL10, and CXCL1) causes an acute systemic hyperinflammation, probably associated to a secondary hemophagocytic lymphohistiocytosis due to the lack of cytolytic activity of NK or CTL cells that are unable to remove infected cells. This capillary damage may cause life threatening clinical conditions, like an acute diffuse alveolar damage, which may lead to ARDS and serious heart, brain, liver, and kidney damages, which may progress to MOFS.

In the evolution of COVID-19, in addition to the hyper monocyte-macrophage activation, the patients often experience a serious alteration of the coagulation system which, in the most severe cases, reaches a real diffuse and generalize thrombosis or a massive hemorrhage due to the consumption of fibrinogen. Interestingly, the toxic activity of the poison secreted by the glands of the viper *Bathrops jaracara*, which study allowed the discovery of ACE inhibitors, has almost superimposable clinical effects thanks to a mixture of peptides capable of potentiating the circulating effects of bradykinin.[41]

7 | SARS-CoV-2 INFECTION IN ONCOHEMATOLOGIC PATIENTS

Hematological malignancies include disorders of myeloid cells and their precursors and of cells more specifically included in the immune system like B, T, and NK lymphocytes, histiocytes, and antigen-presenting cells. These neoplasms have substantial differences from solid neoplasms. In fact, hematologic malignancies are never confined to an organ because their cells recirculate in the body through the lymphatic system and the blood and can involve organs and tissues. In addition, these transformed cells often retain some functional characteristics they had before their transformation, such as the ability to secrete cytokines and chemokines or to produce immunoglobulins.

In patients with aplasia, bone marrow hypoplasia, invasion of the bone marrow by neoplastic disease, and in those with neutropenia, SARS-CoV-2, free to replicate and spread into the body because of the reduced or absent host immune response, causes a direct strong cell damage. SARS-CoV-2 exerts this pathogenetic action in acute leukemia, leukemic lymphomas, aplastic anemia, primitive, and congenital neutropenia, all myelodysplastic syndromes with leukopenia, histiocytosis with involvement of the bone marrow and/or hematopoietic organs, paroxysmal nocturnal hemoglobinuria with bone marrow involvement, in patients treated with immunosuppressive therapy, or immunochemotherapy, in those who underwent bone marrow transplantation and in those with indolent chronic hematological diseases such as hemolytic anemia, autoimmune thrombocytopenia, and aplastic anemia.

In addition, in patients with immune system malignancies causing specific immunological deficits even in the watch and waiting phase, such as chronic lymphoid leukemia B and multiple myeloma, and in those who have recently practiced or who are taking anti-CD-20

therapies (rituximab, obinutuzumab, etc),[42-44] the reduced antibody response to the virus creates a strong predisposition to bacterial overlaps.

In oncohematologic diseases involving T lymphocytes, NK, histiocytes, and antigen-presenting cells, there is a risk of an immunological hyperactivation induced by SARS-CoV-2, with a high probability of immunopathogenic damage due to a cytokine storm.

However, for each oncohematologic pathology, it should be considered whether a specific treatment is in progress or has ended recently. In fact, purine analogs leave a lymphocyte T deficiency that may persists for months or years and rituximab causes a deficit in the B-lymphocytes and antibody production, persisting for 9 months or more. Also patients with multiple myeloma treated with immunomodulatory therapy (lenalidomide, pomalidomide, and thalidomide) and patients with chronic myeloproliferative diseases treated with ruxolitinib could have a sort of protection against the risk of activating hyperimmune responses such as a cytokine storm. In addition, the cytokine storm will occur less frequently in patients taking drugs that reduce immunological reactivity and have been proved effective in counteracting the immunopathogenic damage caused by the virus.

Similar findings can hold for Hodgkin's lymphoma that can be considered a hyperimmune syndrome since Reed-Sternberg cells can determine cytokines and chemokines activation which is used for the immunoediting that protects cancer cells from the immune system. Antiphospholipid antibody syndrome and hemolytic uremic syndromes may also fall into this phenotype of immunological hyperactivation.

For completeness of information, it is necessary to remind that cutaneous and systemic B, T, or NK cell lymphomas may promote viral invasion of human body though mucosal and skin ulcers or abrasions.[44-50] Also exposed to SARS-CoV-2 infection are the patients who have developed mucositis following radiotherapy or chemotherapy.

It is useful now to make some practical considerations on the management of oncohematological patients during SARS-CoV-19 pandemic. The real need of oncohematologic patients to access to a hospital should always be assessed by an adequate triage performed by telephone or by other online technology to verify the need of hospitalization to get started or to continue nondeferrable treatments nonpracticable at home. For patients who need to be hospitalized for transplantation or aplastizing therapy for a nonaggressive and nonlife-threatening disease, hospitalization should be postponed by 8 to 12 weeks hoping for a future strong reduction of virus circulation. In subjects awaiting allogeneic transplantation, conditioning chemotherapy should be started only after donor cell arrival and cryopreservation.

In all cases, it is advisable to practice a diagnostic swab to detect SARS-CoV-2 RNA and if signs or symptoms of influenza-like illness (ILI) have occurred, it will be necessary for their resolution and for three consecutive negative swabs. Patients with or without ILI symptomatology but with a history of documented contacts with subjects with SARS-CoV-2 infection or coming from endemic areas should be hospitalized in dedicated areas as if they were SARS-CoV-2 positive; this until the RNA test has resulted steady negative.

Oncohematologic patients with no history of contact with positive COVID-19 patients and absence of ILI symptoms who need hospitalization will have access to areas of hematology.

8 | NATURAL BODY'S DEFENSE MECHANISMS AND TREATMENT ATTEMPTS

The body's first weapons of defense against pathogens' attacks are the natural physical, chemical, and biological barriers. According to some authors, even this first line of defense can be considered as part of the nonadaptive innate immunity that, in this case, would be constituted not only of cells and mediators, but also of tissues that act as a barrier to the penetration of microbes both for their physical structuring and for specific defensive substances they produce or secrete. The epithelium of the upper and lower airways plays an important role. In fact, in addition to trapping the coarser particles through the vibrissae, the nose produces a mucus which contains in addition to water, ions, and mucins, 0.1% to 0.5% of antimicrobial proteins such as lysozyme, lactoferrin, β-defensin, IgA, and IgG. Besides, the airways contain: (a) a muco-ciliary scale with a series of cilia, which moves the mucus in the oral direction by filtering its contents; (b) surfactants and mucus capable of trapping pathogens from the inspired air; and (c) defensin-secreting cells.

In addition to these natural defense mechanisms, clinical researchers are making many attempts to identify treatments able to counteract and eliminate the SARS-CoV2 replication, its unfavorable effects on human immune system and the serious alteration of the coagulation system caused by this infection.

The current strategy to treat COVID-CoV-2 patients includes antivirals used against other viral infections, drugs active in moderating the cytokine storm and anticoagulants.

8.1 | Antiviral therapy

Several antiviral drugs have been proposed and used with preliminary results of different effectiveness:

- *the HIV-retroviral protease inhibitor lopinavir/ritonavir*, able to reduce the viral load in SARS and Middle East respiratory syndrome (MERS), and used alone or in combination to beta interferon in COVID-19[51];

- *the protease inhibitors daclatasvir and simeprevir*, acting on nonstructural viral proteins of HCV[52-57];

- *the protease inhibitors of HIV umivenovir and darunavir*, now judged untrusted by the WHO;

- *the analog of guanosine Ribavirin* that inhibits the synthesis of viral RNA, already used in HCV and in HIV infections in combination with other antivirals;

- *the inhibitor of viral genome replication remdesivir*, used in 2018 against Ebola virus, that inhibits the RNA polymerase RNA-dependent

of SARS-CoV2 and has shown a strong anti SARS-CoV-2 activity in preclinical models.[58-60] However, administered to patients with COVID-19 this drug has shown contrasting results. In a recent study by Grein et al,[61] patients with severe COVID-19 were treated remdesivir for up to 10 days and 68% of them showed a significant improvement; in addition, 57% of 30 patients under mechanical ventilation (out of the 53) were extubated.[61] This treatment, however, showed a lower efficacy in a recent study performed by Wang et al[60] on 236 patients with moderate COVID-19, randomized at a 2:1 ratio with placebo, since the time for clinical improvement and the mortality rate at day 28 did not significantly differ between these two groups. In addition, remdesivir did not significantly reduce the SARS-CoV-2 RNA loads in the upper respiratory tract.[60] Several randomized trials are in progress to evaluate the real effectiveness of remdesivir to cure patients with COVID-19.

- *the antimalarial drugs chloroquine* (CQ) *and hydroxychloroquine* (HCQ) which have been proven effective in preventing the internalization of SARS-CoV-2 in cell cultures and reported as effective in COVID-19 treatment in a small study.[62] In a retrospective observational study, COVID-19 was more severe in 811 patients receiving HCQ (600 mg twice on 1st day and then 400 mg daily for 5 days) than in 565 patients with COVID-19 treated without HCQ,[63] without a significant association between HCQ-treatment and risk of intubation, or death. In addition, the data, from 671 hospitals worldwide distributed in a multinational registry that included 96 032 subjects with SARS-CoV-2 infection, do not show satisfying results.[64] In fact, of these 96 032, 1868 patients with COVID-19 were treated with chloroquine, and 3783 in association with a macrolide, 3016 with HCQ, and 6221 in association with a macrolide, whereas the remaining 81 144 SARS-CoV-2 positive subjects were used as a control group. CQ and HCQ administered alone or association with a macrolide were independently associated both with a higher in-hospital mortality rate and with an increased risk of ventricular arrhythmia.[64] These data suggest not to treat COVID-19 with CQ or HCQ. CQ and HCQ have been used only sporadically in Italy during this SARS-CoV-2 pandemic, but the results of single centers did not show enough efficacy to suggest further investigation.

- *the neuraminidase inhibitors oseltamivir and zanamivir* used against influenza viruses; SARS-CoV-2 do not present neuraminidase or hemagglutinin and, therefore, their use appears hardly understandable.

- *the serine protease inhibitor camostat mesylate* that inhibits the host serine protease TMPRSS2 that splits the spikes protein S into two fragments S1 and 2. As mentioned above, S1 is responsible of the binding of SARS-CoV-2 to the ACE2 receptors on the surface of human cells and S2 of the fusion of viral and cellular membranes, a necessary event for virus entry into the human cells.

- *the corticosteroids*: patients with COVID-19 having serious pulmonary involvement show characteristics resembling those of ARDS and of other inflammatory lung diseases potentially sensitive to corticosteroids.[65] In addition, a reduced risk of death has been observed in patients with COVID-19 treated with methylprednisolone, especially if in ARDS.[66] However, there is some concerns about the use of corticosteroids in patients with COVID-19. First, most studies have evaluated patients with ARDS from nonviral causes so previous results cannot be automatically translated to ARDS in patients with COVID-19. In this sense, the WHO has recently expressed an opinion against the use of steroids in COVID-19 if not necessary for other reasons.[67] In addition, the literature shows conflicting data on the use of corticosteroids in SARS and in MERS, due to the significant adverse reactions[68,69] and it was also observed that patients with SARS treated with hydrocortisone show increased viremia, an unfavorable effect attenuated if low-dose steroids are used.[70]

The lack of evidence from randomized trials does not allow to conclude on the use of corticosteroids in COVID-19. However, from what it has been observed in Italy during this SARS-CoV-2 pandemic we are allowed to believe that the use of steroids is not recommended in the initial stages of COVID-19 when the disease is directly related to action of the virus, while in cases with serious lung disease and ARDS due to the cytokine storm the administration of methylprednisolone (0.5-1 mg/kg/d for 5-7 days) may be useful. Overall, only a clinical common sense can guide doctors in making a case-by-case decision, pending the results of future randomized trials to define the real usefulness of steroid therapy in COVID-19.

8.2 | Therapeutic attempts to reduce the cytokine storms

As mentioned above, COVID-19 can evolve in two phases; the first one covers the first week of infection and is characterized by an active viral replication in the host cells, while the second one, which arises only in a minor part of infected subjects, begins ~10 days after the start of viral replication when the viral load tends to decrease and host systemic inflammatory reaction arises in response to the infection. The onset of the systemic inflammatory state can be documented by a sudden worsening in clinical condition, by increased serum levels of CRP, proinflammatory cytokines IL-6, TNF-α, IL-8, and so forth, and by the development of vasculitis, hypercoagulability, or damage in various organs, more frequently lungs, myocardial liver, kidney, brain, and so forth.

It is, therefore, reasonable to treat patients with COVID-19 as soon as possible with the antiviral drugs available today and to start treatment with anti-inflammatory drugs at the onset of clinical or laboratory abnormalities testifying the beginning of the cytokine storm. Thus, anti-inflammatory therapy should start in the most suitable time, not too early in order not to hinder the trend of viral replication to decrease, but not too late to prevent the pathology induced by the inflammatory state from becoming too serious. To identify the most suitable time to start the anti-inflammatory therapy, several clinicians use the increase of some indexes of systemic inflammation (PCR, IL-6, IL-1, D-dimer, etc) and the efficiency of lung gas exchange.

The scientific community has been mobilized to treat this "cytokine storm" with therapeutic interventions like those used in chimeric

antigen receptor T cell therapy. The greatest attention has been paid to the therapeutic treatments of serious complications secondary to the cytokine storm, and to patients in the advanced stages of COVID-19 and the anti-IL-6 drug tocilizumab hitherto used. It must be noted that the tocilizumab may induce adverse reactions which may be followed by fatal outcome in elderly patients, whereas Siltuximab, a drug with the same target receptor, authorized by Food and Drug Administration and European Medicines Agency for Castleman's disease in 2014, induces less frequent and less severe adverse reactions.[7] In addition, other specific mediators of the complex biochemical cascade used against hemophagocytic lymphohistiocytosis-HLH[7,8] might be considered: (a) the antithymocyte antibodies, used alone or in combination; (b) the alemtuzumab, a monoclonal antibody, currently approved against relapsing remission, which binds to the CD52 protein selectively, with cytolytic effect on T and B cells but with a minimal effect on other immune system cells, which, however, induces bronchospasm, angioedema, and dyspnea; (c) monoclonal antibody against γ-INF; (d) Janus kinase inhibitors, such as Baricitinib or Ruxolitinib; and (e) the interleukin inhibitor, anakinra.

In addition, promising attempts are currently underway to produce monoclonal antibodies active against SARS-CoV-2, originated from COVID-19 convalescent subjects. Also promising are the data coming from studies that aim to generate humanized neutralizing monoclonal antibodies capable of effectively counteracting SARS-CoV-2 infection.

There is also evidence that alterations in the complement system play a pivotal rule in dysregulating immune mechanisms that lead to ARDS and MOFS in COVID-19. About that, the monoclonal antibody eculizumab has been proposed as a modulator of the distal complement activity. In addition, also same mTOR inhibitors, such as rapamycin and, better, everolimus have been proposed in such a therapeutic setting. Some proteasome inhibitors could be also proposed for their NFκB transcription factors which play a central role in the induction of many cytokines.

8.3 | Convalescent's plasma therapy and new therapeutic strategies to fight SARS-CoV-2

In the absence of specific effective drugs, convalescents' plasma has been used to treat or to reduce the aggressiveness of several infectious diseases in the 20th century and to successfully treat-SARS, MERS, and H1N1 infections in the first two decades of the third millennium.[71-73]

Infused intravenously with plasma from convalescent donors containing neutralizing antibodies to SARS-CoV-2, patients with severe COVID-19 have shown significant improvement in small non-randomized studies and randomized trials are now in progress.[74-77] Noteworthy, the large number of infected patients is fortunately counterbalanced by the large number of convalescent subjects, so there should be no problem of exhaustion of plasma supplies. Plasma administrations is also useful for a faster recovery of virus weakened and undernourished patients.

The extreme rapidity of spreading of the COVID-19 pandemic and the high frequency of severe or fatal forms have prompted numerous authors and pharmaceutical or technological companies to develop alternative strategies to those described so far and, in some cases, to develop innovative strategies. Some authors are attempting to identify and characterize other specific antibodies from sera of convalescent patients to evaluate their possible use as functional antibodies to COVID-19.[78,79]

In addition, a recent in vitro study has shown that human recombinant soluble ACE2 (hrsACE2), but not mouse soluble ACE2, could curtail the replication of SARS-CoV-2, resulting in a dose dependent reduced viral loads in Vero cells.[79,80] It has been also show in an in vitro model using engineered blood vessel and kidney organoids that hrsACE2 could impair virus replication, suggesting their use to prevent the virus adhesion to target cells.

8.4 | Treatment and prevention of serious alteration of the coagulation system

The abnormal activation of the coagulation cascade in patients with COVID-19, generated by various pathogenetic mechanisms, has prompted the use of low molecular weight heparin (LMWH), in prophylaxis and in critically ill patients.[67,81,82] In addition to the anticoagulant effect, useful to prevent or limit the serious thrombotic phenomena that can characterize the clinical course of COVID-19, LMWH seems to have other beneficial effects in the context of this disease (anti-inflammatory, immune-modulating, and antiviral), as previously demonstrated for other viral diseases and for sepsis.[83-85]

The results of a retrospective study suggest that in patients with COVID-19, the administration of LMWH has shown, in addition to an improvement in the hypercoagulation status, also a reduction in levels of IL-6 serum level and an anti-inflammatory activity.[86] LMWH has been used in Italian hospital wards during this SARS-VoC-2 pandemic with satisfactory clinical results.

8.5 | Attempts to develop effective vaccines

Studies aimed at developing SARS-CoV-2 vaccines are conducted in several countries with different lines of development. The attempts underway concern vaccines with inactivated or attenuated viruses, vaccines with protein subunits (mainly with the spike protein S and with the virus-like proteins vaccines based on viral vectors, vaccines based on DNA or RNA.[87] Each line of development has advantages and disadvantages, but the different lines are all pursued with diligence and effectiveness to access as soon as possible solid results.[88] Of the structural proteins of the virus, the S protein is the most promising and most tested antigen for the production of vaccine, given its exposure on the surface of the various viral strains identified so far, which makes it considered an excellent target for neutralizing antibodies produced by the host in response to the vaccine. Some of these vaccines are already being tested in humans in

randomized trials and appear to guarantee good production of neutralizing antibodies.[76] The RNA-1273 vaccine is a mRNA vaccine composed in part by the S protein genetic code embedded in lipid nanoparticles (ClinicalTrials.gov: NCT04283461)[89] currently evaluated in a clinical trial on 45 healthy individuals aged 18 to 55 years. Other mRNA-based vaccines have been developed and are currently in various stages of development.[90] INO-4800 is a DNA-based vaccine using the Spike gene that has already entered phase I clinical trials and involves intradermal inoculation by electroporation. Many other vaccines are in development with a good chance of success. It is hoped that some of the vaccines under investigation will have full success, and the results of the first clinical trials bode well. Considering that most of the world population will have to be vaccinated it is foreseeable that all vaccines that prove effective in neutralizing SARS-CoV-2 will be widely used.

9 | CONCLUSIVE REMARKS

COVID-19 is a disease known from a few months, caused by a virus recently arisen and, consequently, it is little known. It follows that there is no specific vaccine nor specific antiviral therapy. In addition, the infection is unstoppable today since a heard immunity is lacking and the virus is spreading in all countries. The disease has a benign course in most infected subjects, especially in children and young adults, while it is frequently symptomatic in adults over 50. The course of the disease is frequently severe and life-threatening in subjects with comorbidities, and in the elderly. The mortality rate for COVID-19 is different from a county to another, from 1.5% to 13%, dubious percentages because calculated on hospitalized patients in the absence of certain information on the percentage of asymptomatic cases. However, by the end of May 2020 nearly six million people had become infected, of whom nearly 400 000 have died of COVID-19 worldwide, numbers destinated to substantially increase in the following months/years. All this is strongly impressive and stresses the need for effective drugs that can block viral replication and counteract any other virus-induced pathogenetic activity. However, there are still many uncertainties and doubts about the therapeutic protocols necessary to face this pandemic, but the use of the available drugs has improved the clinical condition of many patients and limited the requirements for ICU and ventilators. No vaccine is currently available and the appropriate distance between people, the use of face masks and the frequent careful washing of the hands are the only weapons which can slow down the spread of the virus. As far as COVID-19 in patients with hemato-oncologic diseases, only a few data have been published so far, but, undoubtedly, due to the impressive spreading of SARS-CoV-2, these patients will be widely attacked by SARS-CoV-2 in the next future and already oncohematology specialists should make their patients participate in the ways to prevent the infection and they themselves should expand their knowledge of COVID-19 for an early identification of the disease in their patients.

This review article could be useful also for infectious disease specialists who for some reason have not had the opportunity to treat patients with COVID-19 and for family doctors who can in more than one opportunity visit these patients.

As often happens in situation of extreme emergency, a further contribution to the sense of uncertainty and fear of populations is given by the frequent disagreement among politicians who, instead, should decide together appropriate actions to limit the spread of the virus and ensure adequate support and treatment for citizens. Add to this, the numerous disputes between experts, politicians, and journalists worldwide shown in TV talk shows and in other media further feed the general feeling of inadequacy towards the spreading infection.

We believe, however, that we must not let ourselves be discouraged and live in the certainty that humanity will be able to effectively combat this pandemic, as in the past it has done in other catastrophic situations caused by wars, natural disasters, or terrible pandemics. This will happen again if everyone will make its contribution in the context of a joint action.

CONFLICT OF INTERESTS

All the authors of the manuscript declare they have no conflict of interests in connection with this paper.

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