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Review

Clinical Characteristics and Laboratory Findings in Coronavirus Disease 2019 (COVID-2019) Infected Cancer Patients and Chemotherapeutic Medicines against COVID-19

Nikolaos Chrysanthakopoulos[a,*]

[a]*Faculty Department of Patological Anatomy, Medical School, University of Athens, Athens, Greece*

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ABSTRACT

In December 2019 in Wuhan, China, the World Health Organization (WHO) declares that a severe pandemic of Coronavirus disease 2019 (COVID-19) was emerged and was spread rapidly resulted in dramatic global economic and health implications. The novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is responsible for a severe inflammatory reaction and clinically severe complications, although the majority of the infected individuals had mild symptoms and favorable prognosis after recovery. However, cancer patients are a high-risk group as are already susceptible to COVID-19 infection due to their underlying disease and their immunosuppression. Moreover, cancer patients are at increased risk of developing clinically severe complications in case of COVID-19 infection such as, Intensive Care Unit admission, required mechanical ventilation or even death. Another aggravating factor for oncological patients, during that pandemic crisis is the risk of postponing cancer treatment. The present review presents the clinical characteristics accompanied by the corresponding laboratory findings in COVID-19 infected cancer patients and the possible therapeutic role of some known chemo-therapeutic agents based on the recent observations of the International literature.

1. INTRODUCTION

In December 2019, a large number of pneumonia cases caused by an unknown pathogen were first reported in Wuhan, in China [1, 2]. That unknown pathogen of the pneumonia was finally identified as a novel coronavirus, known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV- 2), which is responsible for Coronavirus Disease 2019 (COVID-19) [2]. SARS-CoV-2 is a beta-coronavirus which is similar to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and the Middle East Respiratory Syndrome Coronavirus (MERS- CoV) [2]. World Health Organization (WHO) declared that COVID-19 is a public health emergency of international concern since March 2020 to date, leading to dramatic global economic and health implications as spread rapidly worldwide [3].

* *Corresponding author.*
E-mail address: nikolaos_c@hotmail.com

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SARS-CoV-1 and MERS-CoV viruses' species were identified as highly pathogenic as they are responsible for Acute Respiratory Distress Syndrome (ARDS), severe pneumonia-like symptoms and multi-organ failure. However, four different coronaviruses species cause respiratory diseases ranging from a self-limiting common cold to severe lung infection. SARS-CoV-2 mainly causes respiratory tract infections. Nevertheless, only some patients developed severe inflammatory reaction and passed away from multiple organ complications whereas the majority shows mild symptoms and have favorable prognosis after recovery [4].

COVID-19 is characterized by rapid human to-human transmission from droplet contamination [5, 6]. A recent report in hospitalized patients showed that hospital-acquired transmission was responsible for 41.3% of those admitted patients, thus involving the hospital environment as a virus spread source [7]. The rapidly developing COVID-19 disease has affected all aspects of daily life [8, 9], based on the fact that no therapeutic agent or an effective vaccine is available the only intervention to prevent COVID-19 infection is the social distancing or isolation, as the spread of infection could have a heavy impact on the National Health System [10]. Under those circumstances, the oncology community confronts incredible challenges. It has been estimated in 2020 nearly 5,000 new cases of cancer will be diagnosed per day in the United States, according to the American Cancer Society [8]. Cancer patients are regarded as a highly susceptible group in the COVID-19 pandemic to infection than healthy individuals because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments, such as chemotherapy, radiotherapy or surgery [9, 11-13]. Therefore, cancer patients might be at a higher risk of COVID-19 infection and have a poorer prognosis. Moreover, cancer patients are often recalled to the hospital for treatment and monitoring, and consequently, they are at additional risk of contamination with COVID-19.

It is obvious that during the pandemic health crisis the oncological patients are challenged on two unfavourable situations, the risk of COVID-19 disease infection and the risk of stalling cancer treatment.

2. COVID-19 INFECTION PATHOGENESIS

Several hypotheses have been proposed regards to SARS-CoV-2 infection pathogenesis. SARS-CoV-2 might pass the nasal and larynx mucosa membranes, finally through the upper respiratory tract enters the lungs and from the lungs enters the blood circulation leading to viremia [14]. SARS-CoV-2 and SARS-CoV-1 use the angiotensin-converting enzyme (ACE2) as receptor to enter the epithelial cells, which is mainly expressed in lung cells, cardiovascular cells, monocytes, macrophages, kidney and gastrointestinal system [15, 16]. Then the virus would attack the targeting organs that express ACE2. SARS-CoV-2 binds to the ACE2 receptor on the surface of Alveolar Type II Cells (AT-II). AT-II Cells play a crucial role in innate immunity as they express on their surface specific receptors for bacteria and viruses antigens, known as Toll-Like Receptors (TLRs). They also induce the production of inflammatory cytokines, chemokines and molecules that attract other immune cells such as neutrophils and macrophages in response to the invasion of pathogenic viruses and bacteria [17, 18].

ACE2 receptor may be over-expressed on some cancers including cervical, pancreatic and renal carcinomas [19]. On the contrary, ACE2 expression has been found to be significantly decreased in breast, liver and prostate cancer compared with normal adjacent tissues [20]. In COVID-19 patients, has been observed a clinical syndrome, Cytokine Release Syndrome (CRS), which is considered as a main pathogenetic mechanism that leads to the breakdown of the lungs, cardiovascular system, kidneys and liver. CRS has also been observed in other pathological conditions that activate the immune system to an extensive level, such as various infections or treatments that are able to overact the immune system leading to cause serious morbidity in patients infected with SARS-CoV and MERS-CoV [21].

In cancer patients infected with SARS-CoV-2, inhibiting of the mentioned excessive immune cell activation, cytokine and chemokine production is possibly essential, although use of corticosteroids is controversial [22, 23].

3. CLINICAL CHARACTERISTICS IN CANCER PATIENTS INFECTED WITH COVID-19

In a recent study, in Wuhan, China [24], the clinical characteristics of 28 cancer patients infected with laboratory-confirmed COVID-19 disease from three designated hospitals were analyzed and included typical symptoms such as fever, dry cough, fatigue, and dyspnoea. Dyspnoea observed much earlier from the start of COVID-19 infection in lung cancer patients as compared with the general population [10] and other cancer patients [24]. Anaemia and hypoproteinemia symptoms in cancer patients were also observed and could be attributed to their nutritional deterioration, which may unfavourably affect immunocompetence and may lead to increased risk of the susceptibility to respiratory pathogens and severe pneumonia, as those patients are at an immunosuppressive condition due to cancer and anticancer therapy [24]. In the same research was found that within 14 days, anticancer therapies were significantly associated with the appearance of severe clinical complications after COVID-19 infection which was defined as the admission to Intensive Care Unit (ICU), mechanical ventilation, or death. Lung cancer patients showed worse baseline lung function, thus they had a higher probability to develop more severe anoxia which would be progressed more rapidly in case of COVID-19 infection. That observation indicated an urgent and increased need to treat COVID-19-infected cancer patients, and especially lung cancer patients [24].

During COVID-19 progression, 53.6% of the patients

developed severe clinical complications, 21.4% were admitted to ICU, 35.7% had life-threatening complications, and 28.6% died. 70% stage IV cancer patients developed severe clinical complications, whereas 44.4% of the non-stage IV showed such complications. 83.3% of the cancer patients who received anticancer treatment within 14 days after COVID-19 diagnosis developed clinically severe complications [24]. The most common complications were ARDS (28.6%), septic shock (3.6%), and acute myocardial infarction (3.6%). 7.1% of the patients possibly developed pulmonary embolism. The cause of death consisted of the following pathological situations ARDS (62.5%), pulmonary embolism (12.5%), septic shock (12.5%), and acute myocardial infarction (12.5%) [24]. The mentioned study has some limitations. It was a retrospective study, thus did not have the reliability of the prospective ones, was non-randomized, based on a small size of sample, heterogeneity could not be avoided as the tumours types were various, some important confounders were not included in the multivariate analyses, and due to an urgent and retrospective descriptive study design, the authors only reported crude rates of complications and fatality in cancer patients with COVID-19 infection [24].

In another recent study [25] was analyzed data of 128 hospitalized haematological cancer patients in Wuhan, China. 13 of those were infected with COVID-19. Clinical information of 115 hospitalized haematological cancer patients compared with no COVID-19 infection and with 11 health care providers infected with COVID-19. COVID-19 infected haematological cancer patients had more severe disease, and a considerably higher risk of death compared with health care providers infected with COVID-19, and showed more co-infections caused by bacteria, fungi and other viruses, whereas only 3 (27.2%) health care providers with COVID-19 showed a bacterial co-infection. In addition, the same patients appeared more complications such as ARDS, acute kidney dysfunction and sepsis, whereas infected health care provider did not showed those complications [25]. It was also found that hospitalized haematological cancer patients COVID-19 infected showed a higher case fatality rate (CFR) compared with hospitalized health care providers COVID-19 infected, finding that could be attributed to their haematological cancer and/or therapy, and thus to bacterial co-infections [25].

It was expectable from patients with immune system cancers such as lymphomas and lymphoid leukaemia to have an increased risk to develop COVID-19 compared with myeloid cancer such as acute myeloid leukaemia and myelodysplastic syndrome [25], however such an association was not identified. That suggestion is in line with a higher possibility of decreased granulocyte blood levels because of the haematological disease or chemotherapy [25]. There are few data on risk of developing COVID-19 in hospitalized persons with haematological cancers. Many, if not most individuals with haematological cancers receive anticancer drugs with suppress bone marrow function or have cancers of the immune system and are at substantial risk of community- and hospital-acquired infections [26-28]. Limitations of that study were selection and recall biases, heterogeneous haematological diagnoses and disease states, confounding covariates; COVID-19 diagnosis was based initially on lung CT scan but most cases were confirmed by qRT-PCR, the control group included health care providers rather than hospitalized individuals with cancer other than haematological cancers.

In a recent nationwide analysis in China by Liang and colleagues recorded a lower rate of cancer patients (39%) infected with COVID-19 developed clinically severe complications, which were defined as the patients' admission to the ICU, invasive ventilation or death, compared with no cancer patients [8]. This finding was not in accordance with the finding of a previous research in the same country [24]. This inconsistency could be attributed to variation of the study populations and the definition of clinically severe complications. This study also showed that older age was the only risk factor for clinically severe complications, and lung cancer patients did not have a higher possibility of clinically severe complications compared with other cancer patients types (20% and 62%, respectively) [8]. Moreover, it was found that cancer patients deteriorated more rapidly than those without cancer. The limitations of this study was the small sample size with a large amount of heterogeneity, the various cancer types with different biological behaviours, possible confounders, such as smoking status, and the previous history of surgical resection in some cancer patients [8].

Kunyu Yang and colleagues, in a multi-centre research observed that fever was the most common symptom, followed by cough, fatigue, and shortness of breath. The same study reveals that invasive mechanical ventilation was applied to 21 (66%) out of 32 patients, whereas 30 (15%) out of 205 patients were referred to the ICU. Complications occurred in 126 (63%) out of 199 patients, including secondary infection and ARDS [29]. In another recent report by Jianbo Tian and colleagues was recorded that patients with cancer were more likely to receive ventilation treatment compared with patients without cancer (33% vs 23%, respectively). The same study also showed that when comparing symptoms at admission, patients with cancer were more likely to suffer from dyspnoea and expectoration than patients without cancer, but less likely to have sore throat and coryza [30].

4. LABORATORY FINDINGS IN COVID-19 INFECTED PATIENTS

Laboratory findings of hematologic examination showed anaemia in 75% of cancer patients infected with COVID-19, leucopoenia in 32.1%, and lymphopenia in 82.1% of the patients. Low levels of serum albumin were recorded in 89.3% of the patients and high levels of serum globulin were found in 39.3% of the patients. 92.9% showed normal serum levels of procalcitonin, and D-dimer was elevated in

39.3% of them. Moreover, high levels of lactate dehydrogenase (LDH) were observed in 50%, highly sensitive C-reactive protein (C-rp) levels in 82.1%, and elevated erythrocyte sedimentation rate in 57.1% of the patients. It is obvious that cancer patients infected with COVID-19 present with clinical characteristics similar to those in the general population, except for anaemia and hypoproteinemia [24].

In a multi-centre retrospective cohort study in China with 205 cancer patients infected with COVID-19 was found leucocytosis in12%, leucopoenia in 27%, neutropenia in 16%, lymphocytopenia in 50%, and thrombocytopenia in 12% of them. Elevated concentration of D-dimer was found in 129 (70%) out of 185 patients, 115 (60%) out of 192 patients had increased concentrations of C-rp, and 78 (49%) out of 160 patients had increased LDH [29]. In another recent research was observed that at the start of COVID-19 disease in haematological cancer patients infected by SARS-CoV-2 virus, they showed significantly high levels of C-rp and procalcitonin, lower levels of haemoglobin, lymphocytes and platelets, whereas had similar levels of LDH, aspartate aminotransferase (AST), alanine transaminase (ALT), bilirubin, creatinine and blood urea nitrogen (BUN), compared with those without haematological cancer. Moreover, no differences were observed regarding the levels of cytokines including interleukins IL-2, IL-4, IL-6 and IL-10, tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) among the groups examined. Some or all of those differences may be related to haematological cancers therapy rather than COVID-19 disease [25]. Jianbo Tian and colleagues in a multicentre cohort study recorded that pro-inflammatory cytokines including TNF-α, IL-6, and IL-2R were in higher levels in patients with cancer than in those without cancer, whereas infection-related biomarkers such as C-rp and procalcitonin were also higher in patients with cancer. In addition, was observed that in patients with cancer com- pared with those without cancer, they showed higher levels of neutrophils, ALT, LDH, and *high*-sensitivity cardiac troponin (hs-cTnI), whereas eosinophils, globulin, albumin, and total protein were decreased [30].

5. CHEMOTHERAPEUTIC MEDICINES AGAINST COVID-19

Several researchers and pharmaceutical corporations have focused on clinical trials investigating medicines with known activity in diseases such as autoimmune diseases, various types of cancer in an effort to discover an effective medicine for COVID-19 patients [31-38]. The trials concern COVID-19 complications and mainly the overproduction of inflammatory cytokines and chemokines, which may result in clinically severe complications observed in organs such as heart, lungs, kidneys, etc. and in some cases can lead to possible death. That pathological syndrome, known as CRS, leads to the breakdown of the lungs, cardiovascular system, kidneys and liver and has also been observed in other pathological conditions that activate the immune system to an extensive level, such as severe microbial infections and sepsis or treatments that are able to overact the immune system and is the leading cause of serious morbidity and mortality in patients infected with SARS-CoV and MERS-CoV [21].

Some of those medicines are used as chemotherapeutics agents in certain cancer types in targeted treatments and act as regulators or suppressors of the immune system or directly as inhibitors of some of the essential cytokines and chemokines implicated in the "cytokines storm".

Acalabrutinib, is a second generation Bruton's tyrosine kinase inhibitor [39, 40] and it is used for lymphomas treatment such as chronic lymphocytic leukaemia, mantle cell lymphoma, and Waldenström's macroglobulinemia [41].

Ruxolitinib, a JAK-STAT signalling pathway inhibitor, plays a crucial role in the immune response to autoimmune diseases and has been used for the treatment of myelofibrosis [42, 43], polycythemia vera (PCV), and has also been shown to improve cases of chronic graft versus host disease in patients following a bone marrow transplant. The effectiveness of ruxolitinib will be investigated in clinical trials.

Siltuximab is a chimeric monoclonal antibody, which it binds to and inhibits IL-6 [44]. IL-6 is an essential cytokine in the immune response to COVID-19 disease. Siltuximab has been used for the treatment of neoplastic diseases such as metastatic renal cell cancer, prostate cancer, and Castleman's disease, among other types of cancer [45-48].

Bevacizumab, is a monoclonal antibody binds to *Vascular Endothelial Growth Factor (*VEGF), an angiogenic factor that is implicated in the formation of new blood vessels in normal tissues and cancer, and is also implicated in the inflammatory process and increases the permeability of blood vessels and capillaries to inflammation [31]. It has been used in oncology in recent years for the treatment of cancers, such as colon, lung, kidney and ovarian cancer [32]. Bevacizumab may reduce VEGF levels that increase in hypoxia, severe inflammation and appear to be increased in the epithelium of the respiratory tract in COVID-19 infection, and may suppress pulmonary oedema in COVID-19 patients [33]. As already has stated, SARS-CoV-1 and MERS-CoV viruses' species were identified as highly pathogenic as they are responsible for ARDS. ARDS and dyspnea create hypoxia in lung tissues and other organs. Hypoxia induces VEGF expression through activation of the Prolyl hydroxylases (PHD)-hypoxia inducible factor (HIF)-1 signalling pathway, which upregulates VEGF expression through transcription activation [49]. VEGF is a potent vascular permeability factor that induces vascular leakiness in COVID-19-infected lung tissues, resulting in plasma extravasations and pulmonary oedema, which further increases tissue hypoxia [50, 51]. Moreover, VEGF significantly participates in lung inflammation [52]. VEGF and VEGFR-mediated signalling blocking by bevacizumab could improve oxygen perfusion and anti-inflammatory response and relieve clinical symptoms in patients with

severe COVID-19. Several studies support clinical evidence for the therapeutic outcomes of bevacizumab in patients with severe COVID-19. Firstly, patients with severe COVID-19 suffer from severe hypoxia and have higher VEGF levels [53]. Secondly, those patients frequently have pulmonary oedema [54, 55]. Thirdly, autopsy investigation of COVID-19 patients showed excessive extravasates in alveoli of the infected lungs and VEGF-induced vascular effects have been suggested in those patients because of the vascular disorganization and endothelial cell proliferation in the COVID-19-infected lung tissues [56, 57]. Fourthly, in COVID-19 patients exists an over reactive inflammatory response [58]. Eventually, experiments in animal models have demonstrated that anti-VEGF therapy significantly improves pulmonary oedema [59, 60]. In addition, recent studies have also demonstrated vascular dysfunction of the COVID-19-inefected tissues [61, 62].

Thalidomide is a medication used for the treatment of various types of cancer, including multiple myeloma, graft-versus-host disease, and a number of skin pathological conditions [34]. Subsequent studies have reported that thalidomide has anti-inflammatory, immunomodulatory and anti-angiogenic effects [35]. It has been used for more than 20 years for the treatment of multiple myeloma mainly and its potential effectiveness in COVID-19 patients is being investigated [35]. Thalidomide shows anti-inflammatory activity as is implicated in both innate and adaptive immune systems as it is able to down regulate the phagocytic activity of immune cells, inhibits antimicrobial mediators' release from neutrophils, and enhances the number of natural killer cells. Based on those observations it has been suggested as a potential anti-inflammatory drug for COVID-19 patients [63]. Thalidomide can also inhibit neutrophils' chemotaxis to the site of inflammation, can suppress their reactive oxygen species (ROS) generation, and can modulate their interaction with the endothelial cells at the site of inflammation [64]. Currently, the available reports for thalidomide usage in treating severe COVID-19 is not sufficient to promote this drug usage due to several reasons [65]. Thus, using this drug for treating a respiratory condition such as that encountered by COVID-19 should be further investigated before proceeding [66].

Imatinib functions as a specific inhibitor of a number of tyrosine kinase enzymes and has been used for the treatment of various types of cancer. Specifically, it is used for chronic myelogenous leukaemia (CML) and acute lymphocytic leukaemia (ALL) that are Philadelphia chromosome-positive (Ph^+), certain types of gastrointestinal stromal tumours (GIST), hyper-eosinophilic syndrome (HES), chronic eosinophilic leukemia (CEL), systemic mastocytosis, and myelodysplastic syndrome [36]. It has been previously shown that imatinib significantly inhibits SARS-CoV and MERS-CoV replication *in vitro [37]*. Imatinib has shown antiviral properties in early stages of infection with SARS-CoV and MERS-CoV, two viruses related to SARS-CoV-2 and may also reduce inflammation, endothelial permeability, and pulmonary oedema [2].

Recent medicine trials in COVID-19 patients concern those that act on the connection of immune cells with their target [31-38].Cancer cells express on their surface proteins that inhibit immune cells, specifically T-lymphocytes. Monoclonal antibody, such as nivolumab, that inhibits the binding of inhibitors to T-lymphocytes activates the immune system against cancer cells and are widely used for the treatment of lung, kidney, bladder cancer and melanoma [38]. Nivolumab is a human IgG4 monoclonal antibody that blocks programmed *cell death protein* (PD-1). It is a type of immunotherapy and acts as a checkpoint inhibitor, blocking a signal that prevents activation of T-lymphocytes from attacking the cancer [38]. In cancer and certain infection diseases nivolumab restores exhausted lymphotoxin (LT) immunity. It is possible that nivolumab-induced immunity normalization could stimulate antiviral response also during COVID-19 infection and could prevent ARDS development, which has previously been associated with low LT count concomitant with increased inflammatory cytokine production [67]. Programmed death-1 (PD-1)/programmed death ligand-1 (PDL-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)/B7 interactions play a crucial role in the inhibition of T lymphocytes. Immune checkpoint inhibitors (ICIs) such as nivolumab are able to blockade this interaction between T lymphocytes and cancer or no cancer cells [68].

Similar mechanisms may lead to depletion and deregulation of immune cells during COVID-19 infection. Those medicines that prevent this inhibition by cancer cells can, in some cases, lead to overreaction of the immune system. Consequently, their safety and effectiveness will be investigated, in combination with other cytokine inhibitors, in clinical trials. Thus, future prospective study designs with larger sample sizes are needed to further explore the clinical characteristics in COVID-19-infected cancer patients.

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