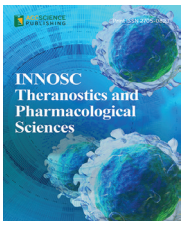
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REVIEW ARTICLE

Impact of COVID-19 Pandemic on Cancer Patients with Pulmonary Fibrosis on Chemosurveillance

Kiran R. Dudhat*

Department of Pharmaceutics, School of Pharmacy, RK University, Kasturbadham, Rajkot, Gujarat, India

***Corresponding Author:** Kiran Rameshbhai Dudhat, *Email:* kichupatel@gmail.com

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Abstract:

COVID-19 infection and multiplication can be regulated with the aid of vaccines, immunosurveillance, and antiviral medications, such interferon and nucleoside analogs. The main concern with COVID-19 infection is the proliferation of the virus. However, there is no medication to treat pulmonary fibrosis, a life-threatening condition, once it has manifested. To treat critically ill patients with cancer and pulmonary fibrosis, it is imperative to develop cell differentiation agent (CDA) formulations that can kill cancer stem cells. Chemosurveillance for cancer patients no longer functions as intended. As a result, people with cancer are more likely to experience severe symptoms of pulmonary fibrosis. The harm to chemosurveillance caused by cancer treatments that focus on cell death, such as cytotoxic drugs, radiation, and immunotherapy, may gravely accelerate the development of fatal pulmonary fibrosis. To prevent the development of fatal pulmonary fibrosis symptoms, cancer patients should be advised against contracting COVID-19, but, if they do, targeted therapy should be their first choice. The purpose of this study was to highlight the significance of chemosurveillance in determining when fatal pulmonary fibrosis manifests after COVID-19 infection in cancer patients and to conceptualize CDA formulations that can be used to treat both pulmonary fibrosis and cancer. COVID-19 infection causes biological and immunological reactions that are similar to those of a wound, leading to the production of prostaglandins and tumor necrosis factor, which cause respiratory illness symptoms, such as fever and cough, and cachexia symptoms, respectively. This results in the breakdown of chemosurveillance, a natural defense mechanism that ensures optimal wound healing, thus further promoting the development of cancer and pulmonary fibrosis.

Keywords: Cancer, COVID-19, Cell differentiation agent formulations, Chemosurveillance, Pulmonary fibrosis, Wound healing

1. Introduction

In December 2019, the COVID-19 pandemic began in China and swiftly spread to other nations, resulting in 6.34 million confirmed deaths and 571 million confirmed cases worldwide as of August 2022 [1,2]. Most individuals suffered either directly from infection or indirectly as a result of restrictions on public gatherings. The COVID-19 infection may result in deadly pulmonary fibrosis and severe acute respiratory syndrome [3]. The development of vaccinations significantly slowed the spread of the pandemic. However, the rapid development of viral variations has led to the COVID-19 pandemic's incessant spread in successive waves [2].

Immunosurveillance, vaccinations and antiviral medications such as interferon and nucleoside analogues can all slow the growth of COVID-19. Lung fibrosis, as the primary cause of death from COVID-19 infection, is not yet treatable with medication. If pulmonary fibrosis can be successfully treated, COVID-19 might not

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impose as much socially disruptive restrictions on patients [4,5]. Our goals were to investigate the causes of pulmonary fibrosis and conceptualize the cell differentiation agent (CDA) formulations that can be used as efficient treatments for the disease.

The repair of lung damage brought on by COVID-19 infection is crucial to restoring lung function. However, the healing process is not going as it should be as evident in the formation of pulmonary fibrosis [6,7]. Another outcome of improper wound healing is the development of cancer [8]. COVID-19 infection must, therefore, have a significant impact on cancer, and vice versa. Chemosurveillance is a built-in process that controls how well wounds heal [8-10]. A careful investigation of how COVID-19 infection affects cancer patients is conducted.

A reported risk factor for the emergence of severe events was receiving cancer therapy within 14 days of receiving a COVID-19 diagnosis [11]. Septic shock, acute myocardial infarction, and acute respiratory distress syndrome are a few of the reported serious complications in the study group. Millions of people worldwide are affected by the deadly illness of cancer. Patients with cancer must attend medical institutions more frequently than individuals with other diseases because of the nature of the disease and its treatment [12]. Multidisciplinary teams must be fully involved in the treatment of cancer patients at all stages of the disease, from diagnosis to survivorship or end-of-life care. Patients need numerous hospital visits over the course of the disease for evaluation by various clinicians, as well as numerous imaging or laboratory tests for diagnosis, staging, or monitoring the effects of treatment, in addition to various types of surgeries and interventions [13].

Patients with cancer require assistance from a wide range of professionals in addition to medical professionals, including social workers, psychologists, educators, and other support services. Patients who have been diagnosed with cancer require ongoing care and support both during and after treatment [14]. Because any unjustified divergence from the well-established standards may result in fragmented and subpar care and a worse patient outcome, these services should be operating in harmony and a timely manner with strong commitment and compliance from the patients [15-17]. The COVID-19 global pandemic had a wide-ranging impact on health care services, interfering with the flow of patients to medical facilities as usual, taxing, and overwhelming the system's resources, and forcing the adoption of additional protective measures and social segregation with increased telehealth and remote treatments use.

2. Viewpoints and conversations

The concept of chemotherapy surveillance was introduced as a built-in protection against cancer. Later, it was altered as a natural system to guarantee optimal wound healing as the main goal of preventing the development of diseases as a result of improper wound healing. Cancer, dementia, and tissue fibrosis are some of the illnesses linked to poor wound healing [18,19]. The idea behind chemosurveillance was inspired by the discovery that while cancer patients frequently displayed deficiencies of these metabolites due to excessive urinary excretion, healthy individuals were able to maintain a steady level of metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs) [20]. DIs are compounds that can remove telomerase from aberrant methylation enzymes (MEs), while DHIs are ME inhibitors [21].

Methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolases (SAHH) are the building blocks of MEs. Since the hypomethylation of nucleic acids is a crucial mechanism for achieving terminal differentiation, the connection of telomerase with MEs renders MEs to be highly persistent and active [22]. Normal stem cells, also known as progenitor stem cells (PSCs), produce telomerase, which causes MEs to become aberrant cancer cells (CCs). The cells responsible for wound healing are the PSCs, which require DIs and DHIs to promote terminal differentiation for effective wound healing [23]. CDA is the moniker given to the concoction of DIs and DHIs. CDAs are metabolites that aid in wound healing and are actively involved in chemo-surveillance. Depending on the extent of cancer, patients have varying degrees of CDA insufficiency [24].

Low molecular weight metabolites include DIs and DHIs. Major DIs include acidic peptides and organic acids. Uroerythrin and pregnenolone

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have been identified as important DHIs, while arachidonic acid (AA) and its metabolites have been identified as organic acids of major DIs [21,22]. In general, MT and SAHH inhibitors are considered excellent DHIs [25]. The function of acidic peptides as surveillance DI is still a mystery. Acidic peptides, uroerythrin, and other products of erythrocyte breakdown make up a significant portion of CDAs [26]. Organs that are actively involved in steroid metabolism, such as the adrenal gland, liver, and reproductive system organs, provide pregnenolone and steroid metabolites.

Evidently, proper wound healing depends on the preservation of a constant amount of CDAs [27]. Since injuries tend to heal naturally without the need for effort, research on chemosurveillance and wound healing has received little attention [28]. For good reasons, the natural world includes chemosurveillance to prevent fatal conditions such as cancer, lung fibrosis, and Alzheimer's disease. Cancer is the leading cause of death in most countries, and pulmonary fibrosis is the primary cause of death from COVID-19 infection; meanwhile, Alzheimer's disease remains incurable [29]. If medical establishments continue to downplay the significance of wound healing and chemosurveillance, these diseases remain incurable [30-32].

3. Impact of COVID-19 pandemic on cancer patients

The lung damage brought on by COVID-19 infection triggers wound repair processes that result in the production of prostaglandins (PGs) and tumor necrosis factor (TNF) [33]. PGs help wounds heal faster by increasing the levels of CDA. TNF; however, hinders wound healing by lowering CDA levels. TNF is also known as cachectin due to the cachexia symptoms it causes. The increased excretion of low molecular weight metabolites as a result of TNF's capacity to cause vascular hyperpermeability is a sign of cachexia [16,34]. The breakdown of chemosurveillance is caused by the excretion of low molecular weight metabolites, including active CDAs. Pulmonary fibrosis results from a lack of adequate CDAs to trigger terminal differentiation of PSCs [35].

The failure of chemosurveillance to induce terminal differentiation of PSCs is another reason for the development of cancer [36]. The renowned German scientist Virchow first proposed the idea of cancer as a non-healing wound in the 19th century [37]. MacCarthy-Morrogh and Martin observed the link between cancer and wound healing [38]. The most crucial information on this subject is related to abnormal MEs to prevent differentiation [39]. The mechanism of wound healing; the hypomethylation of nucleic acids as the most important mechanism to achieve terminal differentiation of PSCs, cancer stem cells (CSCs), and CCs; the evolution of CSCs from PSCs as a result of chemosurveillance breakdown; and the DIs and DHIs as wound healing metabolites and active players in chemosurveillance are all discussed [40,41]. For a cancer symptom to manifest, the chemosurveillance functioning must be severely impaired. Therefore, cancer patients are particularly susceptible to developing life-threatening pulmonary fibrosis symptoms when infected with COVID-19. To prevent infection, immunization is indicated [42]. If patients become infected, a transition of treatment from cell-killing treatments, such as cytotoxic drugs, radiation, or immunotherapy, to targeted treatments, like growth factor inhibitors or signal transduction blockers, is encouraged [43]. The loss of chemosurveillance brought on by cell killing can exacerbate COVID-19 infection by causing harm similar to that brought on by viral infection. Targeted therapy drugs are excellent DIs or DHIs that can stop the progression of fatal pulmonary fibrosis.

Compared to the general population, some cancer patients have higher infection risks due to their immunosuppressed state, which can be brought on by the illness itself or treatment. Immune response may put cancer patients at risk for severe infection-related side effects, which could delay treatment and necessitate hospital stay. These could be harmful to the prognosis of such patients. When compared to patients without cancer, cancer patients have a roughly 3.5-fold higher chance of dying, needing mechanical ventilation, being admitted to the intensive care unit, and developing severe infections. Due to their immunosuppressed state from having cancer and receiving anticancer therapies such as chemotherapy or surgery, cancer patients are more vulnerable to serious COVID-19 complications. Studies have found that the risk of severe events was higher in patients who had

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experienced surgery or chemotherapy within 30 days before presenting with COVID-19 than in patients who had not. In addition, it has been discovered that having a history of cancer increased the chance of serious complications and was associated with poor COVID-19 outcomes [42,43]. Compared to patients with other cancer types, patients with lung cancer did not show a greater likelihood of developing serious complications. When lung cancer patients receive immune checkpoint inhibitor therapy, medical professionals must be aware of the side effects that may occur with the medication (such as severe myocarditis and pneumonitis) as they may have a negative impact on patients' prognosis.

4. Conceptualization of CDA formulations to fight against COVID-19 and cancer

Since pulmonary fibrosis accounts for a significant portion of COVID-19 fatalities, this symptom causes the most concern. The accumulation of PSCs that are unable to undergo terminal differentiation due to chemosurveillance failure is what leads to pulmonary fibrosis. This scenario is rather reminiscent of myelodysplastic syndrome (MDS), which is brought on by an accumulation of CSCs that cannot differentiate further [44-46]. By silencing the ten-eleven translocation 1 (TET-1) enzyme with a single hit, PSCs can be converted into CSCs [47]. The problems in MDS and pulmonary fibrosis are identical. The only remedy is to stimulate the terminal differentiation of diseased cells, which transforms them into functioning cells and is a crucial component for wound healing [48-50]. The induction of terminal differentiation is, therefore, the most effective treatment for pulmonary fibrosis and MDS. Drug resistance and anti-apoptosis mechanisms guard PSCs and CSCs [48].

Radiation is likewise ineffectual and toxic substances are unable to reach these cells. They are partnered with metabolites that promote wound healing in their natural mission to heal wounds. Metabolites that promote wound healing can easily enter these cells and induce terminal differentiation. Hence, they are the best medication option for treating pulmonary fibrosis and MDS [37,44]. China Food and Drug Administration (FDA) has approved the use of CDA-2, a preparation of wound healing metabolites purified from recently collected urine, for the treatment of cancer and MDS [51,52]. If pulmonary fibrosis could be successfully treated, the virulence of COVID-19 can be subdued to that of an influenza virus.

Following the peak in COVID-19 infection in February 2020 across several cities in China, there was a decline in cases, indicating that preventive measures such as closing all public transportation and entertainment centers and prohibiting large public gatherings were effective in preventing hundreds of thousands of cases of infection. Since it is unlikely that the decline occurred due to a decrease in number of susceptible individuals, relaxing control measures could result in resurgence. The reductions in case incidence were correlated with the suspension of intracity public transportation, closure of entertainment venues, and outlawing of public meetings. The COVID-19 epidemic in China appeared to have slowed down and kept in check during the peak of infection due to its national emergency response.

In addition to the travel ban in Wuhan, as part of the national emergency response, suspected and confirmed cases were isolated, public transportation by bus and subway was suspended, schools and entertainment venues were closed, public gatherings were banned, health checks on migrants were performed, travelling within and outside of cities was prohibited, and information on COVID-19 was widely distributed. These control measures may be instructive to other countries across the globe. During the first week of the outbreak, fewer cases were reported in areas that immediately suspended intracity public transportation, closed their amusement parks, and/or restricted public gatherings. This study did not offer any evidence that the intercity travel restriction reduced the number of COVID-19 cases.

5. Conclusion

For almost 3 years, the COVID-19 pandemic has wreaked havoc across the world, killing 6.34 million people. The primary factor in fatalities is the onset of lung fibrosis brought on by chemo-surveillance failure, which also leads to the development of cancer. Cancer patients are susceptible to developing fatal pulmonary fibrosis when infected with COVID-19. Therefore, vaccination against COVID-19 infection is indicated for cancer

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patients. The failure of chemosurveillance is a result of cancer treatments that focus on cell death, such as cytotoxic drugs, radiotherapy, and immunotherapy. To prevent the development of pulmonary fibrosis following COVID-19 infection, cancer patients are recommended to switch their medications to targeted therapies entailing DIs or DHIs that promote wound healing.

To end the threat posed by the COVID-19 pandemic, new treatments for pulmonary fibrosis must be developed. COVID-19 symptoms are varied from minor upper respiratory tract symptoms to serious acute respiratory distress syndrome. The main risk factors for serious COVID-19 are similar to those for idiopathic pulmonary fibrosis, including aging and having comorbid conditions such as diabetes and hypertension. Moreover, due to their immunosuppressed state brought due to their disease and anticancer therapies such as chemotherapy, cancer patients are more vulnerable to serious COVID-19 complications.

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Conflict of interest

The author declares no conflicts of interests.

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