Low Dose Radiation Therapy and Convalescent Plasma: How a Hybrid Method May Maximize Benefits for COVID-19 Patients

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ABSTRACT

Physicians and scientists around the world are aggressively attempting to develop effective treatment strategies. The treatment goal is to reduce the fatality rate in 15% to 20% of individuals infected with SARS-CoV-2 who develop severe inflammatory conditions that can lead to pneumonia, and acute respiratory distress syndrome. These conditions are major causes of death in these patients. Convalescent plasma (CP) collected from patients recovered from the novel corona virus disease (COVID-19) has been considered as an effective treatment method for COVID-19. Moreover, low-dose radiation therapy (LDRT) for COVID-19 pneumonia was historically used to treat pneumonia during the first half of the 20th century. The concept of LDRT for COVID-19 pneumonia was first introduced in March 2020. Later scientists from Canada, Spain, United States, Germany and France also confirmed the potential efficacy of LDRT for treatment of COVID-19 pneumonia. The rationale behind introducing LDRT as an effective treatment method for pneumonia in COVID-19 patients is not only due to its anti-inflammatory effect, but also in optimization of the activity of the immune system. Moreover, LDRT, unlike other treatment methods such as antiviral drugs, does not have the key disadvantage of exerting a significant selective pressure on the SARS-CoV-2 virus and hence does not lead to evolution of the virus through mutations. Given these considerations, we believe that a hybrid treatment including both CP and LDRT can trigger synergistic responses that will help healthcare providers in mitigating today's COVID-19 pandemic.

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Keywords

Low Dose Radiation; Radiotherapy; COVID-19; Convalescent Plasma; Anti-Inflammatory Responses; Immune System; Selective Pressure; Mutations

Introduction

COVID-2019 disease is caused by a novel coronavirus known as SARS-CoV-2, and its pandemic was identified as an international public health crisis by the World Health Organization (WHO) [1, 2]. SARS-CoV-2 has four main structural proteins; namely spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, as well as several accessory proteins [1]. The S glycoprotein is surface-exposed and mediates entry into host cells through binding to its receptor called ACE2. The S protein

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is the main target for neutralizing antibodies upon infection and the focus of vaccine design [1]. The COVID-19-related clinical symptoms appear after an incubation phase of about 5-6 days. The time period from the beginning of the COVID-19 symptoms to death vary from 6-41 days, with a median of 14 days [3]. The clinical manifestations of SARS-CoV-2 infection have similarities with SARS-CoV as its most common symptoms include fever, dry cough, dyspnea, chest pain, fatigue, myalgia and bilateral pneumonia [1, 3, 4]. The severe pneumonia related to coronaviruses is usually characterized by rapid viral replication, extensive lung infiltration with inflammatory cells, elevated production of inflammatory mediators contributing to acute lung injury (ALI), and acute respiratory distress syndrome (ARDS), which may lead to death in some severe cases. Similar to MERS-CoV and SARS-CoV, there is still no specific antiviral treatment for COVID-19. Isolation and supportive care, including oxygen therapy, fluid management, and antibiotics treatment for secondary bacterial infections are recommended [5]. Although a wide range of therapeutic agents are being investigated, the mortality rates might increase [6]. As a new suggested treatment approach, convalescent plasma (CP) transfusion is receiving attention as a feasible way to treat patients. In addition, the US Food and Drug Administration (FDA) is supporting a national expanded treatment protocol to provide CP to COVID-19 patients across the country [7]. Besides CP, a wide array of research projects have been conducted on the impact of exposure to low doses of ionizing radiation (LDR) in the treatment of severe pneumonia in COVID-19 patients. While the suggested radiation doses range from 100 mGy to 1Gy, anti-inflammatory effects of LDR and optimization of the immune system are the bases of these treatments. We believe that possible synergistic interactions of CP and LDR on the COVID-19 pathogenesis can justify an attempt to investigate the combinational effects of CP and LDR as a more effective treatment method.

Convalescent plasma can interfere with viral dissemination

It has been hypothesized that SARS-CoV-2 might pass through mucous membranes, especially nasal and larynx mucosa, with the virus subsequently entering the lungs through the respiratory tract. The virus may enter the peripheral blood from the lungs, causing blood viremia. Following this, the virus could attack target organs that express ACE2, including lungs, heart, kidneys, and gastrointestinal tract [8]. SARS-CoV-2 detected in fecal samples has revealed that the virus enters the blood from the lungs and then travels via blood to the intestines [9, 10]. The expression and distribution of ACE2 in the human body may indicate potential infection routes of SARS-CoV-2. High ACE2 expression was identified in type II alveolar cells (AT2) of lung, esophagus upper and stratified epithelial cells, absorptive enterocytes from ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [11]. COVID-19 also invades the central nervous system (CNS) to induce neurological abnormalities. SARS-CoV-2 may initially invade peripheral nerves and enter the CNS via the synaptic route [12]. Expression of ACE2 was reported in the CNS, which provides a route for SARS-CoV-2 entering into the brain [13]. A certain population of peripheral leukocytes are also infected by SARS-CoV-2 as they express ACE2 on their cell surface [14]. These findings indicate that ACE2-expressing tissues and cells should be considered as potential targets of SARS-CoV-2 infection [11]. Convalescent plasma originating from patients who have previously recovered from viral infection contain neutralizing antibodies against SARS-CoV-2. Once transfused into the patient, the antibodies from the CP are thought to neutralize the virus and limit its transmission. Accordingly, the protective antibody binds to the virus and prevents its attachment

to ACE2-expressing tissues and cells. The results from an exploratory meta-analysis of 32 studies showed evidence of reduced mortality after receiving various doses of CP in patients with severe acute respiratory infections of viral etiology [15]. The data collected by Chinese scientists show that human CP is a potential therapeutic option to decrease the severity and/or duration of the illness caused by COVID-19 [16].

CP collected from patients who have recovered from COVID-19 has been introduced as an effective treatment method against it. Given this consideration, in some countries, people who have fully recovered from COVID-19 for greater than 2 weeks are encouraged to donate their plasma to help saving lives. In three recent case studies, 19 COVID-19 patients were treated with CP from donors who had recovered from COVID-19 [17-19]. The results of these studies showed that CP improves clinical and laboratory symptoms, reduces viral loads, thus allowing discharge of patients. The results of these studies are summarized in Table 1. CP is a passive immune therapy approach historically used in anti-inflammatory therapy of patients infected with various microorganisms, including bacteria, fungi, and viruses [20]. For viral infection therapy, CP is used for the treatment of Ebola, influenza, MERS and SARS-CoV coronaviruses [21]. In CP therapy, the collected plasma from survived patients is enriched with immunization factors, including immunoglobulins and high concentrations of antibodies to enhance its therapeutic effects through mechanisms, including neutralization of virus infectivity, enhancing recovery of the immune system, and inducing immediate or durable immunity.

Discussion

Low dose radiation can modulate inflammatory responses

Low dose radiation therapy (LDRT) was historically used to treat pneumonia during the first half of the 20th century [22]. The anti-inflammatory effects of LDRT are well known. Given this consideration, Ghadimi-Moghadam et al. suggested that LDRT (at radiation doses of 0.10, 0.18 or 0.25 Gy) to the lungs may reduce inflammation in pneumonia caused by SARS-CoV-2 [23]. If the innate immune is effectively activated during infection of the respiratory system, SARS-CoV-2 would efficiently be eliminated. Therefore, it would not enter the blood. In this situation, the infected patient does not show clinical signs nor exhibits symptoms of COVID-19. However, when the immune responses fail, the virus will enter the blood and cause tissue damage in ACE2-expressing tissues and cells. Overall, the viral replication, SARS-CoV-2-mediated apoptosis and pyroptosis, host inflammatory responses, and cytokine storm may contribute to the COVID-19 pathogenesis. Low dose radiation can trigger beneficial effects for alleviation of COVID-19 through anti-inflammatory responses and optimization of the activity of the immune system. Excess release of pro-inflammatory cytokines such as IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, and chemokines CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 from the immune effector cells causes hyperinflammation, which eventually leads to ARDS [1].

It has long been known that LDR can induce anti-inflammatory responses. Historically, LDRT was used for the treatment of infectious diseases, such as pneumonia and pertussis. The concept of using LDRT for COVID-19 pneumonia (Figure 1) was first introduced by a group of Iranian and American scientists in March 2020 [23]. Later Canadian [24], Spanish [25], American [26], German [27] and more recently French [28] scientists also confirmed the potential efficacy of LDRT for COVID-19 pneumonia. These studies focused on anti-inflammatory and immunomodulatory effects of LDRT and suggested that doses ranging from 100 mGy to 1000 mGy could be beneficial for treatment of severe pneumonia in COVID-19

Table 1: Summary of CP studies.

Authors	Case's characteristic	Volume of transfusion	Serum neutralizing antibody titers	Serum viral load	Endpoints	Time from admission to CP transfusion	Main results	Ref
Duan et al.	10 cases (6 males and 4 females), median age 52.5 years, with severe symptoms (Fever, cough and shortness of breath)	200 mL	Before transfusion: 1; 160, 1:320 and 1:640 After transfusion: 1:640	Before transfusion: 34.64 to 38.19 After transfusion: Negative	Safety of transfusion Improvement of clinical symptoms and laboratory parameters	Median time: 16.5 days	All clinical symptoms including especially fever, cough, and shortness of breath and chest pain are improved. Patients weaned from Mechanical ventilation and nasal cannula. Pulmonary lesions on chest CT examinations are reduced. Laboratory parameters including C-reactive protein, lymphocyte, alanine aminotransferase, aspartate aminotransferase, total bilirubin and oxyhemoglobin saturation are improved.	[17]
Shen et al.	5 cases (3 males and 2 females), median age 60 years, with severe symptoms (Fever, cough and shortness of breath)	400 mL	Before transfusion: 40 to 60 After transfusion: 40 to 480 (1-7 days after transfusion)	Before transfusion: 22 to 35.9 After transfusion: Negative (12 days)	Improvement of clinical symptoms and laboratory parameters	Median time: 20 days	All clinical symptoms and laboratory parameters including body temperatures, functions of respiratory, coagulation, hepatic, cardiovascular, central nervous system, and kidney, partial pressure of arterial oxygen to the percentage of inspired oxygen, C-reactive protein, Procalcitonin, Mechanical ventilation and IL-6 are improved	[16]
Zhang et al.	4 cases (2 males and 2 females), median age 62 years, with severe symptoms (Fever, nausea, pharyngalgia, cough and shortness of breath)	200–2400 mL (1–8 infusions)	Before transfusion: Not reported After transfusion: Not reported	Before transfusion: 85 × 105 copies/Ml After transfusion: 180 copies/mL	Improvement of clinical symptoms and laboratory parameters Discharge	Mean time: 15.5 days	Some clinical symptoms such as load or antibodies IgM and IgG are improved and all patients discharged	[18]

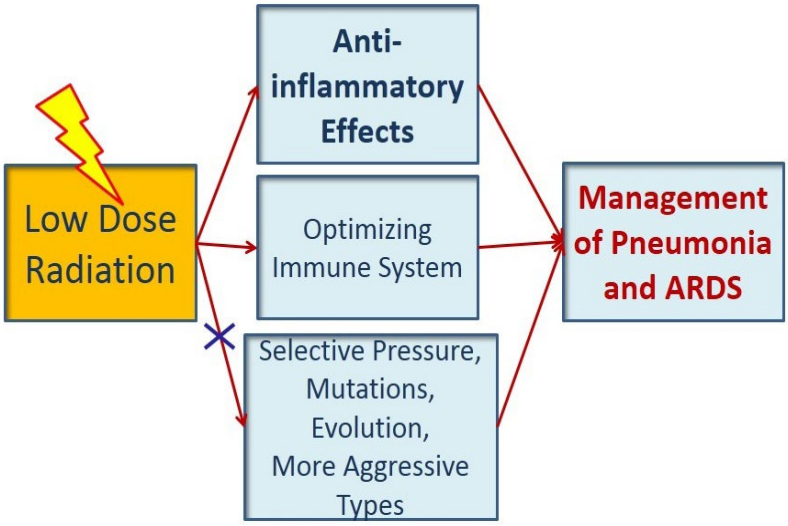

Figure 1: Possible mechanisms involved in the utilization of LDRT for the management of ARDS in COVID-19 patients.

patients.

Moreover, a wide array of global studies have been conducted to investigate the impact of LDR on the immune system, involving different levels of radiation exposure. Several studies indicated that LDR can enhance the immune system response. A review by Hekim et al., indicated that radiation-induced immunity could be obtained by altered expression of several genes involved in the immune-system signaling pathways [29]. The authors showed that LDR increases interferon-γ production, activates natural killer cells, stimulates antigen processing and antigen presentation to T- cells, and activates natural killer T-cells (NKT), γδ T cells, and αβ CD8+ T-cells. In addition, LDR has been shown to demonstrate significant effects on the secretion of pro-inflammatory cytokines, such as IL-8 and G-CSF.

In less than a month, the report by Ghadimi-Moghadam et al. [23] received attention not only for introducing LDRT as a treatment technique for pneumonia in COVID-19 patients but also for noting the key disadvantages of other treatment methods such as antiviral drugs. Rodel et al. [27] recently stated "SARS-COV-2 is an RNA virus with an expected moderate to high mutation rate similar to other SARS RNA viruses and usually higher than the corresponding rate of the human host cells [30]. In addition, as discussed in a recent manuscript [23], any antiviral drug treatment against SARS-CoV-2 would probably result in a more intense selective pressure on the virus". Moreover Dilucca et al. highlighted the importance of LDRT and address the potential problems associated with the widespread use of different antiviral drugs "In addition, an interesting potential idea for the treatment of pneumonia-related to SARS-CoV-2 and other similar viruses is a low dose of ionizing radiation (LDIR). SARS-COV-2 is an RNA virus with an expected mutation rate similar to other RNA viruses, as discussed above. This mutation rate is usually much higher than the corresponding one of any human host. Therefore, as discussed in a recent paper [23], any antiviral drug against SARS-CoV-2 would exert an intense selective pressure on the virus. This may result in highly adaptive and treatment-resistant virus types with enhanced pathogenicity". It is worth noting that currently, there is no effective antiviral therapy available for SARS-CoV-2 infection, which mostly leads to

life threatening inflammatory responses and acute lung injuries. [31].

In this work, we propose combination therapy involving both CP and LDR. We hypothesize that the immunomodulatory and anti-inflammatory effects of radiation and plasma will synergistically impact COVID-19 patients. This combination therapy could activate both radiation and plasma pathways, and possibly new immune-system related pathways for better management of COVID-19. To conduct this therapeutic strategy, the following scenarios could be studied:

1. Low dose irradiation of chest area of CP donors prior to donation (not recommended due to ethical issues).

2. Low dose irradiation of COVID-19 patients' lungs few hours before CP transfusion.

3. Low dose irradiation of COVID-19 patients a few hours after CP transfusion.

In the first strategy, after irradiation of the chest area of CP donors, the provided plasma is used for treatment. However, due to ethical considerations, healthy donors should not be exposed even to low levels of radiation. The second option seems practical, since COVID-19 patients are irradiated prior to or following CP transfusion. Additional options that could potentially maximize the synergistic effects or provide guidance for additional treatment are CP transfusion, followed by LDRT, and then a subsequent CP transfusion as well as LDRT, followed by CP transfusion, and then followed by a subsequent LDRT administration.

Conclusion

CP has emerged as a potential antiviral and immunomodulatory therapy option for COVID-19. Recently, the immunomodulatory and inflamma-modulatory effects of LDR in COVID-19 have also been proposed. CP and LDR have significant potential to therapeutically impact COVID-19 through a positive synergistic interaction. We believe that this hybrid treatment framework has the potential to help healthcare providers in mitigating the adverse health effects of COVID-19.

Conflict of Interest

None

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