Review Article

Low Dose Radiation Therapy for Covid-19: Benefit or Threat?

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ABSTRACT

The new coronavirus outbreak emerged at the end of 2019 worldwide in a very short period of time. The number of victims of this virus until 2020/11/17 has been 1323143. The consequences of these viruses in humans are common cold or mild illness in the upper respiratory region. In more severe cases can causes severe interstitial pneumonia and acute respiratory distress syndrome (ARDS) and Middle East respiratory syndrome (MERS) and, severe acute respiratory syndrome (SARS). So far various drugs have been prescribed and used for the treatment. However, their efficiency and their side effects for treatment of pneumonia of COVID19 are unknown and should be more investigated. Low-dose radiation (LDR) (30 to 100 cGray(Gy)) has been used historically since the early 1930s with hopeful results for pneumonia treatment and was a common treatment solution for viral pneumonia until the 1940s.

As some recent studies have raised the use of LDRT for COVID19 treatment, we sought to review previous evidence oftherapeutic role of LDRT in the inflammatory diseases as well as recent recommendations about consider LDRT as the treatment method for COVID19.

Based on the available evidence and the background of studies, it seems that choosing a dose 0.3-0.5 Gy in severe cases of the disease, as well as using radiation for the whole body instead of the lungs, can optimize the immune system, and optimizing the immune system will help improve COVID-19.

KEYWORDS: Coronavirus, LDRT, X-ray, Radiotherapy

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INTRODUCTION

The new coronavirus outbreaks emerged at the end of 2019 to the entire world in a very short time. The number of victims of this virus until 2020/11/17 has been 1323143[1]. The Coronavirus (CoV) is a single-stranded, RNA viruses that can infect animals and humans[2] and, like other RNA viruses are mutating[3]. At first, the new virus was named 2019-nCoV[4], subsequently, the International Committee on Taxonomy of Viruses (ICTV) applied the term SARS-CoV-2 for the virus and COVID-19 for the disease[4].

The consequences of these viruses can be in humans, common cold or mild illness in the upper respiratory region. In more severe cases can cause severe interstitial pneumonia and acute respiratory distress syndrome (ARDS) and the middle east respiratory syndrome (MERS) and, severe acute respiratory syndrome (SARS) [5,6]. In acute cases, the virus cannot be controlled effectively by the immune system and can spread more widely, this lead to activate macrophages and granulocytes and release pro-inflammatory cytokines and lung tissue damage[2]. Proinflammation and secretion of cytokines, including IL-6, occur in COVID-19 (7). To control inflammation leading to ARDS and respiratory failure, several promising medicines that directly or indirectly play an anti-inflammatory and inhibitory role in IL-6 have been investigated[7-9].

The WHO has confirmed that currently there isn't any safe and effective drug [10] but only supportive drugs[11]. So far, various drugs have been prescribed and used for treatment. New research shows that antiviral drugs that inhibit neuraminidase (Oseltamivir, Peramivir Zanamivir, Ganciclovir, Aciclovir, Ribavirin) are ineffective against COVID19[12]. There is some evidence about the effectiveness of the (Remdesivir, Lopinavir, Ritonavir, Lopinavir/ Ritonavir Combined with interferon-β, plasma therapy, and monoclonal antibodies for COVID19. However, their efficiency and their side effects for the treatment of pneumonia of COVID19 are unknown and should be more investigated[12].

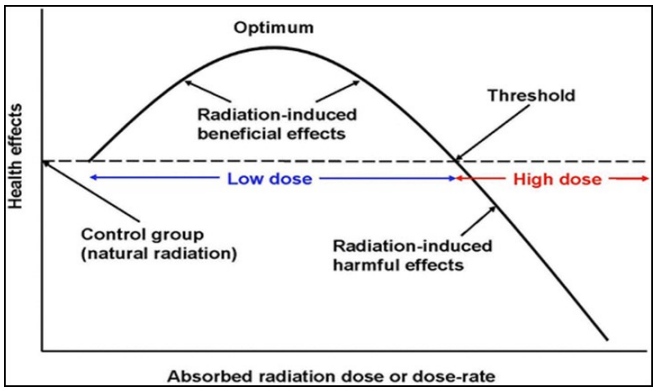
Besides, it may not be necessary to take medicine at the early stages of the disease and may weaken the immune system and cause viral replication. The use of drugs in an advanced stage of the disease is still debatable[13]. Improper use of the drug may also lead to rapid adaptation to resistance[14]. The provision of medicine and treatment economically has put a lot of pressure on the treatment system of all countries. Therefore, it is necessary to find an effective treatment method that is both economically viable and reliable.

At the beginning of the discovery of X-rays, its diagnostic application was more considered, but later doctors noticed significantly changes in the patient's medical condition by radiation, and it is considered as a therapeutic applications[15].

Low-dose radiation (LDR) (30 to 100 centiGray(cGy)) has been used historically since the early 1930s with hopeful results for pneumonia treatment and was a common treatment solution for viral pneumonia up to the 1940s [16-18]. The low dose of radiation (LDR) is a

dose that creates multiple collisions and sufficient reactive oxygen species (ROS) to actuate the immune system and cause visible health advantages. High-dose radiation(HDR) is a dose that suppresses and damages the immune system, causing immediate or latent damage (Figure I)[15].

FIGURE I: DEFINITION OF A LOW DOSE AND A HIGH DOSE OF RADIATION[15]



HDR Vs LDR

There is strong evidence, in contrast, high-dose radiation that produces inflammatory cytokines into immune and endothelial cells[19] low-dose radiation, Induces anti-inflammatory effects through a various mechanism such as inducing apoptosis in immune cells, secreting anti-inflammatory factorsand reducing macrophage function, and preventing cytokine storms[13,20,21] and reduction of inflammatory cytokines such as IL-6[22]. Low-dose radiation therapy's (LDRT) anti-inflammatory effect reaches its maximum 48 hours after irradiation and disappears after 72 hours[22-25].

There are also studies showing that LDRT can improve the immune response in animals [26]. Animal models show LDRT can halve the acute phase of pneumonia[18].Over the past decade, the modulation of many immunological procedures by LDRT has been studied in vitro and in vivo. The most effective modulation of these processes occurs at doses of 0.3-0.7 Gy. [23]. LDRT (0.5 Gy per fraction) also reduces inflammation in musculoskeletal disorders [27].

Mechanism of action of LDRT

A review of a study on the therapeutic effects of LDRT on bacterial pneumonia (lobular and bronchopneumonia), sulfanilamide non-responsive, interstitial, and atypical pneumonia, especially when irradiation was performed on days 6-14, clinical symptoms started, answered appropriately and lead to rapidly relieving symptoms, increased recovery, and reduced mortality[16].

Various environmental factors polarize macrophages into two separate phenotypes: a pro-oxidative/pro-inflammatory M1 phenotype and an anti-inflammatory M2 phenotype [28]. Calabrese considers the polarization of macrophages to an anti-inflammatory or M2 phenotype a possible the process by which radiation therapy(RT) decreases inflammation and simplifies recovery[29].

LDR, on the other hand, can increase the toxicity of Natural Killer cells (NK cells) and differentiate mature dendritic cells (mDCs) and M1 macrophages and activate T helper type 1 (Th1) and B cells, which improve the immune system and LDR regulates the negative effects of the immune response by converting immature DCs to mDCs and inducing M2F macrophagesdifferentiation and stimulating Regulatory T cells(Treg) retention/expansion[30].

A study on rats showed that LDRT regulates immune responses that exhibit immune hormone features. Multiple molecular functions and cellular components are involved in the clinical efficacy of LDRT[31].

Past studies also show that LDRT regulates the number of lymphocytes, control bacterial infections, and can regulate excessively inflammatory responses, exactly what COVID-19 patients need [32].

Use of LDRT in the treatment of Covid-19

Recently, a team of American and Iranian researchers proposed the use of LDRT to treat COVID-19. Kirkby and Mackenzie also said that pneumonia treatment with X-rays is not a new issue in the 20th century and treat the lungs affected by pneumonia caused by COVID-19 with low linear energy transfer(LET)and dose fewer than 100cGy radiation has been shown to reduce inflammation and relieve life-threatening symptoms[33].

Several medical institutions have begun radiation therapy for COVID-19 and several LDR tests to the lungs were being performed in the United States for people with COVID-19 pneumonia. And there are several similar cases internationally[34].

The countries undergoing these tests are the United States, Spain, Italy, Iran, France, Belgium, and India [35].

A clinical study is performing on COVID19 patients in Spain, with a dose of 0.5Gy to lung at a single fraction of 1 Gy in 2 separate fractions 48–72 h after the first. Judgment is based on measuring the PaFio2 ratio [the ratio of the partial pressure of oxygen, PaO2 and the percentage of oxygen supplied, FiO2) 48-72 hours after irradiation, comparing radiographs, molecular adhesion, anti-inflammatory cytokines, and oxidative stress mediators. The results of this study have not yet been published [19].

It is important to note that in recent reports, in 20% - 30% of patients, blood clotting has been reported [36-38]. Which oxidative can reduce or block blood clotting [39]. So instead of irradiating the lungs, the whole body should be irradiated[40].

Concerns about the consequences

Despite all evidence that supports the anti-inflammatory effects of LDRT, but some scientist raised concerns about the suppression of immune response against infectious agents due to the anti-

inflammatory effects of LDRT in the treatment of COVID-19. And also Since there is some evidence about the possibility of the spread and transcription of viruses due to the use of radiation therapy[41-44], they have suggested that the whole body be irradiated at the right time instead of only lung radiation[45].

In response to these concerns, Carles agrees with the need for preclinical and clinical examination of this procedure and the importance of the timegiving this dose. However, he believes that the risks posed by this study are very small and the induction of secondary diseases for doses less than 600cGy is negligible[46]. Evidence suggests that the threshold dose that induces secondary cancer is higher than 1.1 Gy[15].

Some scientists believe that LDR can induce anti-cancer effects and inhibit tumor growth and metastasis. They even believe DNA repair ability and T-cell reactive ability, in people who live in a high level of natural radiation(HNR) area are increased[47]. Since computed tomography (CT) dose is 5cGy and the recommended dose for treatment is 6 to 20 CT, the risk of secondary complications is very small [13].

The safety of this method has been investigated by various studies, which show the risk of radiation effects with low doses is very small [48-51]. Despite all the previous studies on the treatment of non-malignant diseases [52] and the induction of anti-inflammatory effects in animals by LDRT[31], it is not possible to determine the correct time of irradiation and the start and end time of treatment in COVID-19. Therefore, the need for preclinical studies is undeniable.There are also problems such as the workload pressure on radiotherapy devices and the problem of isolating cancer patients from COVID-19 patients[33].

CONCLUSION

LDRT is an affordable non-toxic treatment that is available in most public hospitals. So It can be used for a large number of patients who do not receive specific anti-IL-6 treatments at the intensive care units (ICU) in low and middle income countries. Based on the available evidence and the background of studies, it seems that choosing a dose 0.3-0.5 Gy in severe cases of the disease, as well as using radiation for the whole body instead of the lungs, can optimize the immune system, and optimizing the immune system will help improve COVID-19.

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AUTHOR CONTRIBUTIONS

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