Review Article

Low-Dose Radiation Therapy for COVID-19 Pneumonia

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Abstract

The new coronavirus COVID-19 disease was declared a global public health emergency by the World Health Organization on January 2020. In the current dismal situation of the COVID-19 pandemic, effective management of patients with pneumonia and acute respiratory distress syndrome is of utmost importance. Due to the current lack of effective pharmacological concepts, this situation has caused interest in re-considering historical reports on the treatment of patients with low-dose radiation therapy for pneumonia. Although these historical reports are of low-level evidence per se, hampering recommendations for decision-making in the clinical setting, they indicate effectiveness in the dose range between 0.3 and 1 Gy, similar to more recent dose concepts in the treatment of acute and chronic inflammatory/degenerative benign diseases with, for example, a single dose per fraction of 0.5 Gy. Thus, we review the effects and mechanism and highlight the evidence for low-dose radiation that may be viable and useful in counteracting the acute inflammatory state induced by critical stage COVID-19 in the treatment of COVID-19 pneumopathy.

Keywords: *COVID-19, low-dose radiotherapy, pneumonia*

Introduction

The outbreak of the new coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]/COVID-19) has spread at a very alarming rate throughout the world, with most of the countries being medically, economically, socially, and politically unprepared to meet and respond to the pandemic threat. The clinical spectrum of COVID-19 ranges from an asymptomatic form to mild respiratory symptoms such as dry cough, fever, and moderate dyspnea, to more severe presentations, such as neurologic manifestations (e.g., cerebrovascular accident consequential to cytokine-induced changes in blood clotting; direct encephalitic effects), viral pneumonia, acute respiratory distress syndrome (ARDS), and sequential organ failure as a result of cytokine storm.[1,2] ARDS requires the use of mechanical ventilatory support and supplemental oxygen, and despite such measures, often incurs high mortality (30%–40%).[3] The patients who have required ventilator support for long duration have produced an unanticipated shortage of these devices and have imposed a significant burden on hospital systems. This situation has caused interest in re-considering the historical treatment of patients with low-dose radiation therapy for pneumonia.

Pathogenesis of COVID-19 Effects

SARS-CoV-2/COVID-19 virus belongs to the *Coronaviridae* family and is a single-stranded RNA virus that can infect both humans and animals. The entry of pathogenic COVID-19 virus in humans leads to activation of inflammatory cells, specifically CD4 lymphocytes that subsequently transform to T-helper 1 (Th1) cells. Th1 cells participate in increasing production of several pro-inflammatory cytokines and chemokines, including interleukin (IL) 1-b, IL-2, IL1RA, IL7, IL8, IL9, IL10, granulocyte colony-stimulating factor (GCSF), GMCSF, basic fibroblast growth factor 2, *interferon* c, IP10, MCP1, MIP1a, MIP1b, platelet-derived growth factor, tumor necrosis factor-alpha (TNFa), and vascular endothelial growth factor A. These mediators initiate the cascade of events that lead to an accelerated inflammatory state. The cytokines that appear to be most directly related to the severity of respiratory illness in COVID-19 are GCSF, IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1a, and TNFa. Activated inflammatory cells (Th1 cells and

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macrophages) enter the pulmonary circulation and induce a ubiquity of cytokines (i.e., "cytokine storm") that lead to rapid, wide-spread damage of the pulmonary epithelium and alveolar cells, as well as other vital organs.[1,4-7]

Pathological features of COVID-19 infection have been described recently to involve three stages: Stage one, is incubation wherein the patient is most often asymptomatic and during which time the systemic viral load may be low and thus may not be detectable; Stage two, during which the patient is symptomatic, but symptoms are not severe, although the systemic viral load has increased and the virus is detectable; and Stage three, in which symptoms become severe and the viral load is very high and detectable.[8] The immune response to COVID-19 infection can show one of two patterns. The first is a protective immune response that eliminates the virus and prevents progression to more severe stages of disease, and the second involves an impaired immune response upon entry of virus, thus leading to progressively more severe disease. This latter pattern displays extensive involvement of organs expressing the high concentration of angiotensin-converting enzyme 2, such as heart, kidneys, intestines, and lungs, with lung alveolar type II pneumocytes being the principal target site of COVID-19 virus. The damage to these tissues initiates the renin–angiotensin–aldosterone system cascade and induces pulmonary parenchymal inflammation via the activity of (pro-inflammatory) macrophages and granulocytes, which leads to ARDS.[9-11]

Comorbidities, such as diabetes, chronic renal disease, and/or chronic pulmonary disease predispose a greater risk of severe complications and mortality from respiratory viral infections such as COVID-19. The diabetic hyperglycemic environment hinders immune response, and chronic renal disease establishes a pro-inflammatory state that manifests functional defects in both innate and adaptive immunity. The lability of lung tissues in chronic pulmonary disease renders the pulmonary parenchyma precompromised and therefore at greater risk of ARDS. These comorbidities dispose patients to both increased severity of COVID-19-related multi-organ involvement and higher risk of mortality.[12-14] Given current scenario and inadequacies in treating this disease, utility and value of exploring and recognizing novel therapeutic modalities, such as low-dose radiotherapy (RT), may prove to be of benefit to critically ill patients.

Evidence on Low-Dose Irradiation for Treatment of Pneumonia

Calabrese and Dhawan published in 2013 a report on "How radiotherapy was historically used to treat pneumonia: Could it be useful today?," which may serve as a basis for current considerations.[15] This review on 15 reports covers 863 patients with severe pneumonia of different pathogeneses, including two studies of viral origin treated with low doses of kilovoltage X-rays. Good clinical responses, including a reduction of mortality, were reported, usually with a short clinical onset of 1–3 days after radiation. In addition, response rates were similar between bacterial and viral pneumonia. From a current point of view, however, these historical studies (ranging from 1905 to 1946) have to be treated with care. As compared to present standards, they are of low-level evidence, some cover low numbers of patients, and in many cases, appropriate control groups are lacking. In addition, for more than seven decades, not a single report has been published on low-dose RT for pneumonia, further hampering recommendations for decision-making based upon clinical and scientific knowledge. However, joint features of these investigations are that RT should be given early in the development of inflammation and that dose effectiveness does not vary much between 0.1 and 1 Gy. Similar protocols of radiation therapy are currently prescribed in Germany for benign painful chronic inflammatory degenerative disorders such as periarthritis of the shoulder.[16] In addition, low-dose RT has been reported to be effective in acute inflammation. In a cohort of 130 patients treated for postpartum mastitis with single doses of 0.2–0.5 Gy up to a total dose of 1–1.5 Gy, Herrmann reported on a cure rate of over 90% if given within the first 24 h of the first signs of inflammation but a decline to 50% if given at full-blown inflammation.[17]

Calabrese *et al*. published in 2019 that low-dose RT induces a highly integrated, complex, and systemic response that involves polarization of macrophages to an M-2 anti-inflammatory phenotype.[18] This anti-inflammatory phenotype mediates decreased adhesion of leukocytes and polymorphonuclear cells (PMNs) to endothelial cells, decrease in reactive oxygen species, reduction of nitric oxide (NO), decreased inducible nitric oxide synthetase (iNOS), decrease in TNF-a, and decreased tumor growth factor-alpha (TGFa). Further, and perhaps synergistically, the low-dose RT induction of the M2 phenotype invokes increased hemeoxygenase, increased anti-inflammatory cytokines – IL-10, increased tumor necrosis factor-beta (TNF-b), activation of several transcription factors, such as nuclear factor kappa beta and activating protein-1,[19-21] induction of apoptosis,[22-28] increased tumor growth factor-beta 1,[20,21] and enhancement of T-regulatory cells.[21,29,30] Low-dose RT can induce the M2 anti-inflammatory macrophage phenotype irrespective of being administered to a localized inflamed area or to the whole body.[31-33]

Calabrese *et al*. 2019 have indicated that diseases with a significant inflammatory component demonstrate reduced pathognomic features following exposure to radiation doses <1.0 Gy (i.e., that induce an anti-inflammatory phenotype (M2 polarization)). However, diseases with an infectious component such as pneumonia, gas gangrene, and sinusitis respond to radiation doses more than 1.0 Gy (i.e., that induce a pro-inflammatory phenotype [M1

Polarization]). The authors further suggested that the existence of M1 and M2 phenotypes at both the single-cell and cell population levels is not absolute but rather represents a combinatory presentation of these phenotypes. This hypothesis assumes that both pro- and anti-inflammatory phenotypes are simultaneously induced, but the final phenotypic potential (i.e., which determines the relative constitution of pro-inflammatory or anti-inflammatory phenotype) depends on the radiation dose being greater or <1.0 Gy.[18] In addition, Klug *et al*. 2013 demonstrated that M1/M2 polarization via a low dose of RT also depends on the tissue microenvironment.[34]

Based on the historical use of radiation for treating various inflammatory and infectious diseases, Calabrese *et al*. 2019 proposed a dose range from 0.2 to 2.0 Gy for optimal human therapeutic effectiveness. The authors assert that this dose range has the potential to induce polarization of both M1 and M2 macrophage phenotypes.[18] Considering the available evidence and the proposed mechanism of action of low-dose RT, a single total dose of 0.3–0.5 Gy would be beneficial for COVID-19 patients that present with and have corroborative clinical findings of cytokine storm. This dose can be administered to the chest region using both anterior and posterior fields (50% of total dose administered in each field). This targeted low dose of RT appears to be of most benefit in the acute phase of illness when cytokines surge occurs and reduces the possibility of any immediate or long-term adverse effects considerably.[18]

Dose per fraction >200 cGy exerts pro inflammatory effects, triggering common toxicities observed in radiation therapy. However, more recent work shows low doses (<100 cGy) incites anti inflammatory properties such as decreasing levels of pro inflammatory cytokines like IL 1b, or inhibiting leukocyte recruitment.[32] Therefore, it stands to reason that a low-dose RT treatment of 30–100 cGy to the lungs of a patient with COVID-19 pneumonia could reduce the inflammation and relieve the life-threatening symptoms.

The only limitation to the use of low-dose RT as a potent, nontoxic, anti-inflammatory treatment is the fear for long-term radiation-induced diseases, especially cancer. However, many of the considered "standard treatments" (nonsteroidal anti-inflammatory drugs, COX-inhibitors, steroids, etc.) also have side effects that have to be weighed against the very small risk of radiation-induced cancer. Major evidence of radiation-induced cancer comes from accidental exposures to radiation of the general population. The linear nonthreshold model developed from such accidental exposures may overestimate the risks by one order of magnitude, therefore cannot be useful for estimating the risk of cancer by the use of low dose-RT for nonmalignant diseases. The cancer-induced risks due to the RT of benign diseases based on data from epidemiological studies showed no increased risk at low dose.[17] A very important issue concerning cancer-induced risk by radiation is age. In fact, due to the expected long latency of tumor development, the risk of inducing cancer would be even lower in patients over 40 years of age. Concerning the present situation either the real risk of dying from the COVID pneumonia or the advanced age of the patients at such risk would make irrelevant such concerns.

Unlike vaccines and pharmacological treatments that are dependent on stock production and distribution from manufacturers, X-ray devices are readily available in most of the clinical settings such as urgent care, outpatient, and hospital settings. Countries with poor socioeconomic demographic profile and lack of infrastructure to avail costly trial drugs and X-ray facilities are available to serve the purpose of using low-dose RT for treatment of COVID-19 patients with ARDS.

The portable X-ray machines in hospitals can be used to deliver low-dose RT in a most hassle-free manner, such as in an isolation room and/or intensive care unit (ICU) for patients on ventilators. However, the use of diagnostic X-ray machines or CT which typically deliver between 0.1 and 10 mGy for diagnostic scans and are not designed to deliver therapeutic doses may not be a practical option. Transporting the patient and treating them in a RT department is the best current option. The highly skilled staff and specialized equipment seem the safest approach. There could be a risk of infection to other immunocompromised cancer patients receiving RT. Due to the current COVID-19 pandemic, most RT departments have well-developed protocols for dealing with the treatment of COVID-19 patients by separation from other RT patients and infection control.

Conclusion

Thus, low-dose RT can be considered for those patients who are most critical and for whom other treatments options are unsuccessful or unavailable. Low-dose RT to the whole lung should be explored under clinical trials to patients in early stages of the SARS-CoV-2 pneumonia. Low-dose RT is a cost-effective nontoxic treatment already available in most general hospitals, besides that would be used for the large number of patients that will suffer this disease and that would not receive specific anti-IL-6 treatments in ICUs in low- and middle-income countries.

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Conflicts of interest

There are no conflicts of interest.

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