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COVID-19 Rapid Communication

Low dose radiation therapy as a potential life saving treatment for COVID-19-induced acute respiratory distress syndrome (ARDS) ☆

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ABSTRACT

The new coronavirus COVID-19 disease caused by SARS-CoV-2 was declared a global public health emergency by WHO on Jan 30, 2020. Despite massive efforts from various governmental, health and medical organizations, the disease continues to spread globally with increasing fatality rates. Several experimental drugs have been approved by FDA with unknown efficacy and potential adverse effects. The exponentially spreading pandemic of COVID-19 deserves prime public health attention to evaluate yet unexplored arenas of management. We opine that one of these treatment options is low dose radiation therapy for severe and most critical cases. There is evidence in literature that low dose radiation induces an anti-inflammatory phenotype that can potentially afford therapeutic benefit against COVID-19-related complications that are associated with significant morbidity and mortality. Herein, we review the effects and putative mechanisms of low dose radiation that may be viable, useful and of value in counter-acting the acute inflammatory state induced by critical stage COVID-19.

The recent outbreak of the new corona virus (SARS-CoV-2/COVID-19) has spread throughout the globe at an alarming rate, with many countries being scientifically, medically, economically, socially, and/or 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 (SOF) as result of cytokine storm [1,2]. ARDS requires the use of supplemental oxygen and mechanical ventilatory support, and yet despite such measures, often incurs high mortality (30–40%) [3]. The number of patients who have required mechanical ventilation for extended periods of time produced an unanticipated shortage of these devices and imposed a significant – and often near catastrophic burden on hospital systems. In this review, we provide evidence that radiotherapy has been successfully used to treat a number of inflammatory/infectious conditions including bacterial/viral pneumonia in the 20th century, and we opine that based upon its proposed mechanism of action, this may represent a viable treatment option to reduce the cytokine storm-induced ubiquitous inflammatory effects that occurs in the majority of critically ill COVID-19 patients.

Abbreviations: IL, interleukin; FGF, fibroblast growth factors; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon γ; IP, induced protein; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; PDGF, platelet derived growth factor; RANTES, regulated on activation and normally T-cell expressed; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor..

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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 animals and humans. 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: IL1-β, IL-2, IL1RA, IL7, IL8, IL9, IL10, GCSF, GMCSF, basic FGF2, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. These mediators initiate the cascade of the accelerated inflammatory state. The cytokines that appear to be most directly related to severity of respiratory illness in COVID-19 are: GCSF, IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα. Activated inflammatory cells (Th1 cells and 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].

Recently, the pathological features of COVID-19 infection have been described to involve three stages: Stage one, is incubation wherein the patient is most often asymptomatic, and during which time the systemic viral titer 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 generally can assume one of two patterns. The first entails an endogenous, protective immune response that eliminates the virus and prevents progression to more severe stages of disease; and the second which involves an impaired immune response upon entry of virus, thereby leading to progressively more severe disease. This latter pattern displays extensive involvement of organs expressing high concentration of angiotensin-converting enzyme 2 (ACE2), 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–angioten sin–aldosterone system (RAAS) cascade and induces pulmonary parenchymal inflammation via the activity of (pro-inflammatory) macrophages and granulocytes, which leads to ARDS [9–11].

Effects of hyperinflammatory state in COVID-19

The "cytokine storm" induced by activated lymphocytes creates a systemic platform for the rapidly deteriorating presentations characteristic of critical COVID-19 illness. This hyper-inflammatory host–response poses significant challenges for medical management, as efforts are being made to employ experimental drugs (e.g., cytokine inhibitors and/or interleukin antagonists) that may effectively modulate immune system responses. Individuals with comorbidities, such as diabetes, chronic renal disease, and/or chronic pulmonary disease are at greater risk of severe complications and mortality from respiratory viral infections such as COVID-19. The diabetic hyperglycemic environment hinders immune responsivity, 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 pre-compromised 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 limitations and inadequacies in treating this disease, we posit the utility and value of exploring and recognizing novel therapeutic modalities, such as low dose radiotherapy (RT), which may prove to be of benefit to critically ill patients.

Historical perspectives on the use of low dose radiation in pneumonia and bronchial asthma

A 2013 review of low dose RT by Calabrese and Dhawan illustrated the use of this approach to treat pneumonia during the 20th century [15]. The authors reported that approximately 700 patients of bacterial (lobar and bronchopneumonia), interstitial, sulfanilamide resistant, and atypical pneumonia were effectively treated by low doses of RT. As well, their discussion addresses studies with induced bacterial and viral pneumonia in four experimental animal models (i.e., mice, guinea pigs, cats and dogs), the results of which supported the clinical findings. The X-ray therapy successfully reduced the mortality from approximately 30 percent to 5–10 percent, and clinical outcomes were further improved when these treatment effects were compared to cases treated with serum therapy or sulfonamides. The positive therapeutic results occurred quickly (within 0.5–3 h) and were often (if not mostly) evident after a single X-ray treatment. The symptoms (especially respiratory distress) were rapidly relieved following administration of the X-ray dose. This X-ray therapy was equivalently effective against viral pneumonia, as well. These findings were consistently reported by numerous clinicians in diverse medical settings, with patients of highly variable health status, disease history, and age differences. As well, reports have noted successful treatment of bronchial asthma with X-rays in approximately 6000 cases [16]. The outcomes of several dozen studies indicated that approximately 4200 cases displayed remarkably rapid and marked reduction of pulmonary symptoms, with fifty percent of these patients presenting complete resolution of clinical signs and symptoms. While essentially all historical human studies were case reports, it should be noted that six studies incorporated comparison control groups that were unique to each study. For example, the types of controls ranged from the selection of alternative subjects into treatment and control groups, the use of historical community control groups and similar national data, as well as contemporary subjects with pneumonia in the same hospital served as controls. The control group data in these respective studies tended to be generally consistent with the national normal at that time of about 30% mortality rates. While these studies are not at the level of contemporary methodological study designed standards, the multiple findings were highly consistent, supported by responses in multiple animal models and supported with contemporary mechanistic findings.

Putative mechanism of low dose radiation therapy

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 [17]. This anti-inflammatory phenotype mediates decreased adhesion of leukocytes and polymorphonuclear cells (PMNs) to endothelial cells, decrease in reactive oxygen species (ROS), reduction of nitric oxide (NO), decreased inducible nitric oxide synthetase (iNOS), decrease in tumor necrosis factor-alpha (TNF-α), and decreased tumor growth factor-alpha (TGFα). Further, and perhaps synergistically, the low-dose RT induction of the M2 phenotype invokes increased heme oxygenase, increased anti-inflammatory cytokines – interleukin-10 (IL-10), increased tumor necrosis factor-beta (TNF-β), activation of several transcription factors, such as nuclear factor kappa beta (NFkB) and activating protein-1 (AP-1) [18–20], induction of apoptosis [21–27], increased tumor growth factor – beta 1 (TGFβ1) [19,20], and

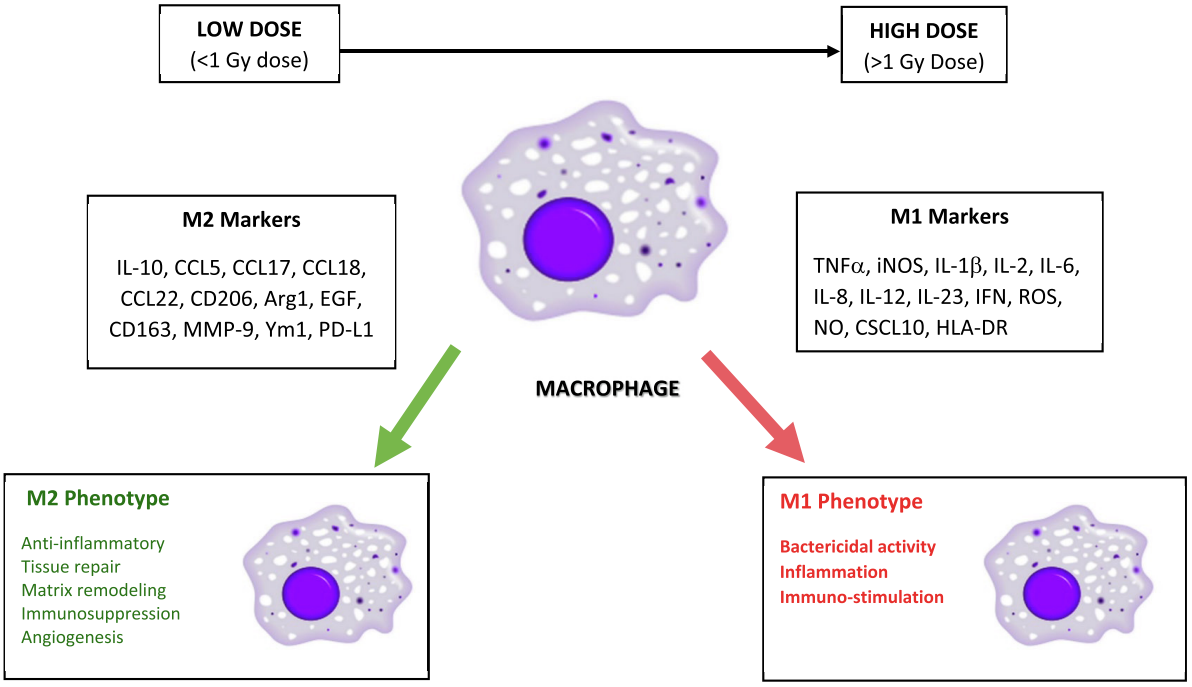

Fig. 1. Radiation dose and macrophage polarization (adapted from: Genard et al. [35], Calabrese et al. [37], Pinto et al. [38]).

enhancement of T-regulatory cells [20,28,29]. 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 [30–32].

This putative mechanism of action is well-supported by the induction of anti-inflammatory phenotypes using low doses of ionizing radiation in a variety of *in vivo* models (e.g., Lewis Rats, BALB/C mice, murine air pouch models with Tuck mice, DBA mice, human tumor necrosis factor 2 transgenic mice, NMRI mice, C57 BC/6 mice) and *in vitro* models (e.g., adult human peripheral mononuclear cells, human umbilical vein endothelial cells, activated murine macrophages-RAW 264.7 cells, mouse resistant peritoneal macrophages, murine endothelioma cell line mlEnd and the hybrid endothelial cell line EA-hy.926) [33].

In a recently published study, Abd El-Fatah et al. 2020, evaluated effects of low dose gamma radiation on systemic inflammatory disease (i.e., experimentally-induced arthritis) in rats, in which the inflammatory environment affected joints, kidney, liver, and the hematological system. The study demonstrated that low dose RT induced a clinically protective hormetic immune response. Arthritis was induced by injecting Complete Freund's Adjuvant (CFA), resulting in marked increases in systemic lymphocytes, (both CD4 and CD8). Additionally, CFA-injected rats showed elevated liver enzymes and creatinine levels. These rats were exposed to low dose gamma radiation (0.25 Gy/week × 4). Treatment with low dose RT produced significant reduction (p-value <0.01) in total leucocyte counts by 44.4 %, serum creatinine by 26.3% and serum liver enzymes by approximately 30% (Alanine aminotransferase ALT 31.4% and Aspartate aminotransferase AST 34.6%) back towards normal values. These results elucidate positive effects of low dose RT in reducing systemic inflammation, and it was suggested that such therapeutics could be used in patient populations that present with multi-system pro-inflammatory states, such as that incurred in chronic kidney disease [34].

Using various murine models and human cell lines, Genard et al. 2017 elaborated upon the possible molecular mechanisms that lead to the polarization of macrophages (inflammatory vs anti-inflammatory). Their results demonstrated a triphasic dose response curve wherein low dose RT (<1 Gy) and high dose RT (>10 Gy) induced M2 polarization (i.e., anti-inflammatory phenotype), while moderate dose of RT (1–10 Gy) induced M1 polarization (i.e., pro-inflammatory) phenotype [35].

Calabrese et al. 2019 have indicated that diseases with a significant inflammatory component demonstrate reduced pathognomic features following exposure to radiation doses less than 1.0 Gy (i.e., that induce an anti-inflammatory phenotype (M2 polarization)). However, diseases with an infectious component, such as pneumonia, gas gangrene, sinusitis etc. respond to radiation doses more than 1.0 Gy (i.e., that induce a pro-inflammatory phenotype (M1 Polarization)) (Fig. 1) [17].

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 upon the radiation dose being greater or less than 1.0 Gy [17].

In addition, Klug et al. 2013 demonstrated that M1/M2 polarization via low dose of RT also depends upon the tissue microenvironment [36].

Recommended radiation dosing for COVID-19 patients in ARDS

Based on the historical use of radiation to treat 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 [15–17,33,39–45]. The authors assert that this dose range has the potential to induce polarization of both M1 and M2 macrophage phenotypes [17].

Considering the available evidence and the proposed mechanism of action of low dose RT, the authors recommend that 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 acute phase of illness when cytokines surge occurs and reduces the possibility of any immediate or long-term adverse effects considerably [17].

Other potential benefits of using low dose RT for treatment of COVID-19 patients with ARDS:

- The portability and ready availability of X-ray machines in hospitals allows researchers to deliver low dose RT in most hassle-free manner, such as in an isolation room and/or Intensive Care Unit for patients on ventilators, compared to high dose radiation therapy which needs to be done in a formal setting.
- In addition, 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. In fact, areas/countries with poor socioeconomic demographic profile and lack of infrastructure to avail costly trial drugs, X-ray facilities are available to serve the purpose. Additional benefits of this treatment modality include exemption from any shortages in supply, minimal immediate or long-term side effects.

To be sure, this remains speculative and it is imperative that the hormetic characteristics of the response to low dose RT be used to guide any experimental and/or clinical intervention. To such ends, and based upon extant empirical findings, we advocate and urge the critical importance of administering a single dose of 0.3–0.5 Gy to patients experiencing pneumonia, ARDS with Cytokine storm, so as to attempt rapid amelioration of the systemic inflammatory cascade, while avoiding unacceptable or adverse long-term effects of RT. Certainly, we do not endorse the use of RT for all COVID-19 patients; but we do offer its consideration for those patients who are most critical, and for whom other treatments options are unsuccessful or unavailable.

Ethics committee approval

This manuscript is a review article and thus did not need an Ethics Committee Approval.

Conflicts of interest

None.

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