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RESEARCH ARTICLE

The Influence of Low-Dose Radiotherapy on Paraoxonase-1 and Inflammatory Biomarkers in COVID-19 Pneumonia Patients

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ABSTRACT:
The COVID-19 pandemic will be remembered for its significant health and economic impact worldwide. Severe pneumonia could often progress to acute respiratory distress syndrome (ARDS), this being a critical complication characterised by an exaggerated inflammatory response, known as cytokine-release syndrome (CRS). Amid debates regarding the efficacy of conventional treatments, low-dose Radiotherapy (LDRT) has emerged as a potential therapy due to its anti-inflammatory effects. LDRT modulates immune responses by polarizing macrophages towards an anti-inflammatory phenotype and reducing oxidative stress. While studies investigating LDRT for COVID-19 pneumonia have shown promising results, conflicting data has been published and challenges persist in patient selection and treatment timing. Biomarkers such as paraoxonase-1 activity hold promise for predicting treatment outcomes. LDRT presents an alternative approach to modulating the immune response in COVID-19 pneumonia, offering hope for improved clinical outcomes. Further research is warranted to validate its efficacy and elucidate underlying mechanisms.
This article provides summary of the radioimmunological mechanisms and the results of biomarkers research in this context.

Introduction

The COVID-19 pandemic spread globally in 2020 after the first reported case in December 2019 in Wuhan, China. This urge was marked by an increase of morbidity and mortality observed worldwide.

Across affluent nations, vaccination campaigns were successful; nonetheless, persistent infections of COVID-19 necessitated urgent plans for the medium and long-term treatment.

A substantial number of individuals developed pneumonia, leading to severe conditions such as respiratory failure or acute respiratory distress syndrome (ARDS). This life-threatening complication is the consequence of an exaggerated inflammatory response, characterized by the activation of various leukocytes (neutrophils, macrophages, and mast cells) causing the production of significant quantities of pro-inflammatory cytokines.

The course of COVID-19 infection comprises an early stage of viral replication, with a small percentage of patients progressing to severe pneumonia as a result of immunological response dysregulation, triggering a cytokine-release syndrome (CRS).

An excessive inflammatory response can lead to ARDS, causing severe respiratory failure due to the attraction and accumulation of immune cells in the lung parenchyma, resulting in acute lung tissue damage. When activated inflammatory cells enter the pulmonary circulation, they induce a cytokine storm, leading to rapid, widespread damage of the pulmonary epithelium, alveolar cells, and other vital organs. Excessive inflammation may disrupt the transcapillary–interstitial fluid exchange system, causing tissue fluid accumulation and oedema, particularly life-threatening when occurring in the airways where the gas exchange is compromised.

In severe-acute-respiratory syndrome related coronavirus (SARS-CoV-2) pneumonia, cytokine storms play a crucial role, highlighting the potential value of neutralizing key inflammatory components in CRS to lower mortality.

A notable therapeutic difficulty was providing care for patients who were not eligible for mechanical ventilation or conventional pharmacological interventions.

The initially approved medications for COVID-19 infection with pneumonia can be divided into two main groups: anti-inflammatory drugs and those that inhibit viral replication. Frequently used treatments include remdesivir and dexamethasone, along with Tocilizumab as an IL6 blocker. However, during the highest pick of health crisis, there was debate about the effectiveness of these treatments, resulting in the search for novel COVID-19 therapy options.

This is where low-dose Radiotherapy (LDRT) becomes significant. Low and high doses of radiation have different radiobiological consequences. While high doses induce pro-inflammatory cytokines, LDRT (in the range of 0.3-0.7 Gy) causes an anti-inflammatory response that affects leukocytes, macrophages, polymorphonuclear cells, and vascular endothelial cells [1, 2].

Multiple investigations have evaluated the effects of LDRT on clinical outcomes as well as inflammatory reactions in the blood. Finding predictive indicators was a shared goal in the fight against COVID-19 pandemic.

This review addresses the radioimmunological response following LDRT in critically ill patients to clarify the metabolic changes driven by SARS-CoV-2 infection.

Pathophysiology of SARS-CoV-2

The immunopathogenesis of SARS-CoV-2 involves a complex interplay of immune responses, in two phases: early stage, which involves immune protection, and severe stage, which involves inflammatory damage[3].

When SARS-CoV-2 virus particles bind to angiotensin-converting enzyme 2 (ACE2), a membrane enzyme responsible for converting angiotensin II to angiotensin, the virus is able to enter into the respiratory tract cells and cause COVID-19 infection.

The body's adaptive immune system first fights the virus during the early phase. However, if this primary defence is insufficient, the virus can propagate and harm the affected tissues, particularly in organs that have high ACE2 receptor expression such as the intestines and kidneys. Particularly in lung cells, immune effector cells stimulate an innate inflammatory pathway which, when uncontrolled activation, leads to a cytokine storm. This storm, marked by the release of numerous pro-inflammatory cytokines and chemokines, results in ARDS, multi-organ failure, especially of the cardiac, hepatic and renal systems.

Studies have shown that there are notable alterations in immunological parameters in cases of SARS-CoV-2 infection. This includes a decrease in CD8, CD4, and CD3 T cells, and an increase in proinflammatory cytokines like IL-6 and TNF-α, particularly in severe cases [4, 5]. Oxidative stress is subsequently brought on by this inflammatory response.

Other additional and frequently used biomarkers in COVID-19 include neuron-specific enolase (NSE), lactate dehydrogenase (LDH) aspartate transaminase (AST), neutrophil count, neutrophils-to-lymphocytes ratio, troponins, creatinine kinase, D-Dimer, brain natriuretic peptide (BNP), and its N-terminal prohormone (NT-proBNP) [6].

The increase in pro-inflammatory cytokines suggests that SARS-CoV-2 triggers the T helper type 1 (Th1) response[7]. The dysregulation of proinflammatory cytokines and the inactivation of T-cells contribute to ARDS, sepsis, and fatal outcomes.

Furthermore, COVID-19 patients have also shown an accumulation of hyaluronic acid (HA) in the lungs, which has been linked to severe SARS and MERS (Middle East Respiratory Syndrome Coronavirus) infections. This build-up of HA could impede the proper oxygen transfer, contributing to hypoxemia [8].

Table 1. Immune system alterations in SARS-CoV-2

Increase		Decrease
Pro-inflammatory cytokines - IL-2 - IL-6 - IL-8 - IL-10 - IL-4 - IFN-α - TNF- α	Pro-inflammatory chemokines - CCL3 - CCL4 - CCL5 - CCL2 - CXCL3 - CXCL8 - CXCL10 - CXCL9	T cells - CD8 - CD4 - CD3 Natural Killers Cytokines - IFN- γ - IL-10 - TGF- β

Abbreviations: CCL (chemokine ligand), CXCL (chemokine X-C motif ligand), IFN (interferon), IL (interleukin), TNF- α (tumor necrosis factor alpha)

Low-Dose Radiotherapy for Atypical Pneumonia

The anti-inflammatory potential of LDRT has long been recognized, making it a viable option for treating selected cases of patients with non-malignant inflammatory diseases, including infectious pneumonia [9, 10]. After the discovery of penicillin, radiation therapy progressively lost favour even if it had produced favourable clinical outcomes. A lack of broad scientific recognition and administrative support in the medical community impeded the widespread adoption of X-ray therapy as a public health pneumonia treatment.

Radioimmunology of Low-Dose Radiotherapy:

LDRT induces a highly integrated, complex, and systemic response. This response involves the polarization of macrophages to an M-2 anti-inflammatory phenotype, resulting in decreased adhesion of leukocytes and polymorphonuclear cells to endothelial cells, reduced reactive oxygen species (ROS), diminished nitric oxide (NO), lowered inducible nitric oxide synthetase (iNOS), decreased tumor necrosis factor-alpha (TNF- α), and decreased tumor growth factor-alpha (TGF- α). Furthermore, LDRT induction of the M2 phenotype invokes increased anti-inflammatory cytokines, such as interleukin-10 (IL-10), tumor necrosis factor-beta (TNF- β), activation of nuclear factor kappa beta (NFkB) and activating protein-1 (AP-1), induction of apoptosis, increased tumor growth factor-beta 1 (TGF β 1), and enhancement of T-regulatory cells . To summarize, LDRT induces down-regulation of proinflammatory cytokines and up-regulation of anti-inflammatory cytokines as well as chemokines (Table 2).

Table 2. Differences between pro-inflammatory changes and the anti-inflammatory impact induced by LDRT

Pro-inflammatory changes	**Anti-inflammatory LDRT effect**
Cell adhesion molecules expression and leukocyte-enothelial interaction (rolling, adhesion and migration to interstitial space)	Decreased adhesion of leukocytes and polymorphonuclear cells to endothelial cells
Pro-inflammatory M1 macrophages	Polarization to M2 phenotype
Oxidative stress activation	Diminished nitric oxide (NO) and iNOS, Reduced reactive oxygen species (ROS)
	Increase TNF-b
Decrease IL-10, IFN-g	Increase IL-10, TGF- β
Increase IL-6, IL-4, TNF- α, IL-1	Decrease IL-6, IL-4, TNF- α, IL-1
Decrease of NK and B-cells	Enhancement of NK activity
Decrease of CD4, CD8, CD3	Enhancement of cytotoxic activity of CD4 and CD8 (polarizing from Th1 to Th2 response)[11]
	Induction of apoptosis

Abbreviations: CD (cluster differentiation T cells), IFN (interferon), IL (interleukin), TNF (tumor necrosis factor), IFN (interferon), NK (Natural Killers)

Low-Dose Radiotherapy for Covid-19 Pneumonia

Given the urgency of the COVID-19 pandemic and the understanding of the role CRS play in the pathophysiology of the virus, LDRT was investigated as a potential therapy approach [12-15].

Identifying the few individuals who are most likely to benefit from LDRT and treating them in an early enough stage to achieve the intended impact were the challenges associated with treating patients through this approach [16, 17].

A comprehensive systematic review and meta-analysis carried out at the time when different trials were disclosing their clinical results, revealed a slight improvement in intubation-free days[18]. However, there was no significant impact on patients' overall survival. It is important to note that some publication bias may need to be considered. This bias is more noticeable when the number of studies includes a small number of patients, as tests tend to have low statistical power in such cases[19]. Additionally, the presence of substantial heterogeneity among the studies could potentially influence the test results. It is important to consider these aspects when assessing the review's conclusions.

Numerous studies have shown that whole-lung radiation (WLI) may quicken the recovery in radiographic and clinical settings at doses between 0.5 and 1.5 Gy without resulting in acute damage [20-28].

Biomarkers of Inflammation in Low-Dose Radiotherapy for Covid-19 Pneumonia

Laboratory indicators have demonstrated significant diagnostic and prognostic value in COVID-19 patients. Glycolisis and the lactate cycle are the main regulators of oxygen hemostasis and response to low oxygen levels [29]. The utilization of proteomic and metabolomic approaches to investigate the pathways linked to energy generation and aminoacid processing in SARS-CoV-2 infected patients has resulted in more attention in research.

Researchers looked at the levels of antioxidant enzymes and inflammatory markers in COVID-19 pneumonia patients receiving LDRT [30], based on the data collected from the IPACOVID trial[20]. Additionally, the relationship between these indicators and changes in lung imaging and clinical symptoms was evaluated. Comprehending the biochemical mechanisms behind the observed clinical improvements was one of the primary objectives of the WLI patient assessments. This was done in an attempt to determine potential predictors of which patients might benefit most from LDRT for COVID-19 pneumonia.

Inflammatory biomarkers after LDRT

Baseline LDH and CRP concentrations were higher in pneumonia-related fatalities than in survival rates. The multifaceted effects associated with LDRT are demonstrated by the summary already exposed in Table 2 (COVID-specific changes) in conjunction with the summary shown in Table 3.

Table 3. Modifications of inflammatory biomarker parameters after WLI with LDRT

Biomarker	24 h after LDRT	1 week after LDRT
TGFb1	Increase (p=0.0178)	
TNFa	Increase (p=0.007)	Increase (p=0.0052)
PON1	Decrease (p=0.0002)	Decrease (p=0.004)
PON1 activity		Increase (p=0.0012)
CD4+		Increase (p=0.009)
CD8+		Increase (p=0.047)
CRP	Decrease (p=0.054)	Decrease (p=0.001)
LDH		Decrease (p=0.002)

Abbreviations: CD (cluster differentiation T cells), CRP (C-reactive Protein), LDH (Lactate dehydrogenase)PON1 (Paraoxonasa), TGF (Tumor Growth factor), TNF (Tumor Necrosis Factor).

Paraoxonasa:

The paraoxonasa (PON1) is an enzyme with lactonase and esterase activities, which plays a crucial role in breaking down lipid peroxides present in lipoproteins and cells. This enzyme is primarily produced in the liver and circulates in the blood bound to high-density lipoproteins (HDL) [31]. Although PON1's enzymatic activity takes place within circulating HDL particles, it can also be transported from these particles to cell membranes [32]. PON1 protein is widely expressed in lung epithelial cells, where this transfer is especially noted. This is because PON1 is essential for reducing potential harm from exogenous compounds, and the lung epithelium is regularly exposed to oxidative stress trying to protect from exogenous chemicals [33].

Despite having greater levels of several inflammatory markers, it has been revealed that COVID-19 positive patients have considerably reduced PON1 enzyme activity compared to those who are COVID-19-negative [34]. A decreased probability of being COVID-19-positive was linked to increased PON1 activity and monocyte concentrations in the analysis done in a post-hoc retrospective study. This study highlights the significant drop in PON1 activity in COVID-19 patients, a result exclusive to this disease and suggesting a possible function for PON1 in the body's defense against the virus.

PON1 appears to have two distinct roles, depending on where it is found. In the bloodstream, it may have antiviral properties; while inside the cells, it may promote the translation and replication of viral proteins[35]. According to this, elevated oxidative stress may be the cause of the PON1 activity decline in COVID-19 patients, even if the enzyme's serum concentration remains elevated.

Remarkably, after LDRT, patients showed a significant recovery in PON1 activity, suggesting a possible therapeutic strategy to reduce oxidative stress in COVID-19. Furthermore, a significant rise in SaFI (Pulse oximetry saturation (SpO2) fraction of inspired oxygen (FiO2)) was also seen in conjunction with an increase in PON1 activity, correlating with clinical improvement (p=0.004) [30].

When comparing patients with severe COVID-19 pneumonia to those with mild and moderate disease, there are additional metabolic changes linked to the lipoprotein profile in COVID-19. These changes include higher levels of oxidised low-density lipoprotein and lower HDL overall [36, 37].

Treatment ideal timing

Timing is crucial when considering the use of LDRT for COVID-19 patients. Since the CRS can lead to worsening symptoms and clinical decline, it becomes essential to administer LDRT at the appropriate stage of the disease. However, there has no been a consensus among the studies regarding the best time to administer WLI to identify the exact moment of maximal benefit.

Some researchers warn that immunosuppression may result from using LDRT at an inappropriate time [38]. Immunosuppression could potentially weaken the body's ability to effectively clear the virus, posing a risk for prolonged illness or complications.

Conversely, glucocorticoids have the ability to cause systemic immunosuppression and they have been extensively used in the treatment of this patient group. Steroid use can also lead to consequences like increased blood sugar levels, greater requirement for insulin, and higher risk of bacterial infections or sepsis.

Radiation-induced side effects

It is speculated that the restricted application of LDRT has been influenced by worries regarding the possibility of radiation induced malignancies. Although there aren't many controlled research on the subject, a number of retrospective series have

shown that there isn't enough data to raise the worry.

Numerous well-known radiation side effects have their origins in historical whole-body low-dose irradiation events, including those observed in survivors of atomic bombs and nuclear plant accidents, among other incidents. According to recent analyses, the risk of radiation-induced cancers (RIC) increases with the dose in a nearly linear fashion [39]. However, most of these analyses were conducted on pathologies no longer treated with RT and using outdated RT techniques, making them inconsistent with modern medicine practices. Therefore, historical interpretations should be handled carefully.

It is important to take into account the size of the radiation field because smaller fields may reduce the likelihood of tumor initiation or promotion.

According to the theory of hormesis, also known as cellular adaptive response, cells exposed to very low doses of radiation may eventually become resistant to higher doses later on [40]. However, this hypothesis has been debated in light of the linear no-threshold theory. Studies have also highlighted the significance of age, with younger patients undergoing RT having a higher chance of RIC.

The high rate of RNA mutation in the SARS-CoV-2 infection is another factor to put into consideration for LDRT in COVID-19 pneumonia. The double-strand breaks induced by LDRT may cause this mutation rate to grow even more, posing a potential concern in the context of treatment [41].

Taking all this into consideration, no radiation-induced toxicity has been recorded in any of the publications that have been published using LDRT for COVID-19 pneumonia.

Conclusion

In conclusion, the exploration of low-dose radiotherapy (LDRT) as a therapeutic option for COVID-19 pneumonia has offered a new method for modulating the immune response in pa-tients with severe pneumonia. The evidence presented suggests that LDRT can influence the inflammatory milieu, characterized by a shift towards an anti-inflammatory profile, and the modulation of oxidative stress markers such as paraoxonase-1 (PON1). Initial results offer a hopeful view into the potential of LDRT to change the course of disease progression in COVID-19 pneumonia by lowering inflammation and possibly improving clinical out-comes, despite the study's inherent limitations and the need for bigger, more conclusive investigations.

The complexity of the immune response to COVID-19 is highlighted by the dual role of LDRT in downregulating harmful inflammatory responses and possibly boosting the antioxidant defense system through mechanisms involving PON1 activity. This also emphasizes the potential of radiotherapy as an additional treatment strategy.

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