



Original Research Article

Low dose anti-inflammatory radiotherapy for the treatment of pneumonia by covid-19: A proposal for a multi-centric prospective trial



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ABSTRACT

Background: COVID-19 is a highly contagious viral infection with high morbidity that is draining health resources. The biggest complication is pneumonia, which has a serious inflammatory component, with no standardized treatment. Low-dose radiation therapy (LD-RT) is non-invasive and has anti-inflammatory effects that can interfere with the inflammatory cascade, thus reducing the severity of associated cytokine release and might be useful in the treatment of respiratory complications caused by COVID-19.

Study design and methods: This multicentric prospective clinical trial seeks to evaluate the efficacy of bilateral lung LD-RT therapy as a treatment for interstitial pneumonia in patients with COVID-19 for improving respiratory function.

This prospective study will have 2 phases: I) an exploratory phase enrolling 10 patients, which will assess the feasibility and efficacy of low-dose lung irradiation, evaluated according to an increase in the PaO₂/FiO₂ ratio of at least 20% at 48–72 h with respect to the pre-irradiation value. If a minimum efficiency of 30% of the patients is not achieved, the study will not be continued. II) Non-randomized comparative phase in two groups: a control group, which will only receive pharmacological treatment, and an experimental arm with pharmacological treatment and LD-RT. It will include 96 patients, the allocation will be 1: 2, that is, 32 in the control arm and 64 in the experimental arm. The primary end-point will be the efficacy of LD-RT in patients with COVID-19 pneumonia according to an improvement in PaO₂/FiO₂. Secondary objectives will include the safety of bilateral lung LD-RT, an improvement in the radiology image, overall mortality rates at 15 and 30 days after irradiation and characterizing anti-inflammatory mechanisms of LD-RT by measuring the level of expression of adhesion molecules, anti-inflammatory cytokines and oxidative stress mediators.

Trial registration: ClinicalTrials.gov NCT-04380818 <https://clinicaltrials.gov/ct2/show/NCT04380818?term=RADIOTHERAPY&cond=COVID&draw=2&rank=4>.

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1. Background

COVID-19 is a viral disease originated by a single-stranded RNA virus of the *Coronaviridae* family and is characterized by being highly contagious, having a non-negligible morbidity rate and

being a drain on health resources, which is causing a blockage of almost the entire world health system. Most of the patients developed pneumonia with a serious inflammatory component, the so-called cytokine release syndrome or cytokine storm syndrome (CSS), which in some cases can lead to acute respiratory distress syndrome (ARDS) and death from respiratory failure. According to Chinese experience, 81% of the clinical cases were mild in nature with an overall fatality rate of 2.3%, while a small subgroup of 5% suffered respiratory failure, septic shock, and multiple organ

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failure leading to death in half of these cases, suggesting that it is within this group that the opportunity to save lives exists if appropriate measures are taken [1]. Clinical observations suggest that when the immune response is unable to effectively control the virus, as in older people with a weakened immune system, the virus spreads more efficiently, causing lung tissue damage, which activates macrophages and granulocytes and leads to the massive release of pro-inflammatory cytokines responsible of associated ARDS [2].

There appear to be two distinct but overlapping pathological subsets, the first triggered by the virus itself and the second, by the host response. In the first stage patients will benefit from drug therapy directed against the virus and use of anti-inflammatory therapy might not be necessary and might even lead to viral replication although its usefulness in advanced stages might be questionable. In the second stage of established lung disease, viral multiplication and localized inflammation in the lung is the norm. During this stage, patients develop viral pneumonia, with a cough, fever, and possibly hypoxia, producing chest radiograph images or computed tomography with bilateral infiltrates or ground glass opacities. Blood tests reveal an increase in lymphopenia along with transaminitis. Markers of systemic inflammation might be somewhat elevated. It is at this stage that the majority of COVID-19 patients would need to be hospitalized for close observation and treatment. If hypoxia occurs, patients are likely to progress to requiring mechanical ventilation, and in that situation, the use of anti-inflammatory therapies, such as corticosteroids, might be helpful and might be used judiciously. A minority of patients with COVID-19 will progress to the third and most severe stage of the disease, which manifests as a syndrome of extra-pulmonary systemic hyper-inflammation. A CSS occurs, involving a considerable release of pro-inflammatory cytokines: interleukin (IL) -2, IL-6, IL-7, IL-12, the stimulatory factor of granulocyte colonies, macrophage inflammatory protein 1- α , TNF- α , ferritin, and D-dimer are significantly elevated in those patients with a more severe disease [3]. To date, there has been no a standardized treatment for such a hyper-inflammatory state. The only treatment options are those aimed at the side effects caused by the virus, such as inflammation and pulmonary ARDS. Suppression of the pro-inflammatory members of the IL-1 and IL-6 family has been shown to have a therapeutic effect in many inflammatory diseases, including viral infections [3,4]. Corticosteroids are used because of their known ability to modulate a variety of involved cytokines and apparently being effective in reducing immune-pathological damage. Other treatments that have shown to be effective are the use of cytokine inhibitors, such as the monoclonal anti-human interleukin (IL)-6 receptor antibody, tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist) [4,5]. The lack of a highly effective specific treatment together with the possible failure in the supply of commonly used drugs because of the great demand, makes it necessary to investigate new anti-inflammatory therapies.

LD-RT has an anti-inflammatory effect, which might be useful in the treatment of respiratory complications of COVID-19. The anti-inflammatory efficacy of LD-RT has been proven in clinical studies and there have been several experimental models, both *in vitro* and *in vivo*. The radiobiological mechanisms that support this claim are becoming increasingly known. Unlike high-dose radiation therapy, which induces the production of pro-inflammatory cytokines in immune and endothelial cells, LD-RT (0.5–1.5 Gy) acts on cells involved in the inflammatory response, producing anti-inflammatory effects. These effects include the inhibition of interactions between leukocytes and endothelial cells, a decrease in the production of endothelial adhesion molecules, a decrease in the mediators of inflammation and a lower expression of pro-inflammatory cytokines. As well as promoting the induction of macrophage and polymorphonuclear apoptosis low-dose

irradiation also lowers the levels of NO, iNOS, L and E selectins, ROS, TNF- α or IL-beta 1 secretion together with an increase in production and expression of anti-inflammatory cytokines, such as anti-inflammatory cytokine TGF- β 1 and of apoptosis mediators such as NF- κ B. This anti-inflammatory effect of LD-RT was greatest at 48 h after irradiation and was lost after 72 h [6–10]. All of these changes result in a local anti-inflammatory environment that would explain the clinical effects of LD-RT by reducing inflammation and alleviating threatening-life symptoms and could be an option to consider for the symptomatic relief of COVID-19 associated pneumonia [11–13]. This type of treatment is non-invasive and therefore, *a priori*, and can be used for all types of patients. With this objective, we designed a pragmatic clinical protocol to evaluate the efficacy of low-dose lung irradiation as an adjunctive treatment in interstitial pneumonia in patients with COVID-19.

2. Methods

2.1. Study hypothesis

Bilateral low-dose lung irradiation with a low dose of 0.5 Gy in a single fraction or 1 Gy in 2 separate fractions 48–72 h after the first depending on the response might interfere with the inflammatory cascade and reduce the severity of cytokine release, improve patient oxygenation, and decrease the risk of fatal evolution and death in patients with symptomatic COVID-19 pneumonia.

2.2. Protocol design

Adult patients with COVID-19 with at least moderate to severe pneumonia that warranted hospitalization will be considered for this protocol. We propose to include those patients with moderate to severe dyspnoea, respiratory frequency ≥ 30 /min, oxygen saturation with supplemental O₂ supply (SpO₂) < 92%, PaO₂/FiO₂ ratio or PaFiO₂ ratio [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO₂) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO₂)] < 300 mmHg. Where cases are impossible to determine, PaFiO₂, SaO₂/FiO₂ or SaFiO₂ (percentage of oxyhaemoglobin saturation in capillary arterial blood) < 315 mmHg will be used instead. We will also consider presence of lung infiltrates > 50% within 24 to 48 h or patients with laboratory abnormalities such as C-reactive protein (CRP) > 100 mg/L, D-dimer > 1500 ng/ml, IL-6 > 40 IU or suspected cytokine release syndrome, all consistent with a more severe disease.

This prospective, multicentre study was conceived in 2 phases: an exploratory phase, which will include 10 patients, in order to assess the feasibility and efficacy of bilateral lung LD-RT, bearing in mind that if there is no improvement in PaFiO₂/ SaFiO₂ in at least 30% of patients the study will not be continued, and a second comparative phase in two groups, a control group, which will only receive pharmacological treatment, and an experimental one receiving pulmonary LD-RT. This second phase will include 96 patients, the allocation will be 1: 2, that is, 32 in the control arm and 64 in the experimental arm. This number has been calculated by accepting an alpha risk of 0.05 and a beta risk of a 0.2 in a two-sided test, to find as statistically significant a proportional difference, expected to be of 0.2 in the control group and 0.5 in the experimental group, with a drop-out rate of 10%.

2.3. Objectives

The primary end-point will be to evaluate the efficacy of low-dose pulmonary irradiation as an adjunctive treatment in interstitial pneumonia in patients with COVID-19 by improving the PaFiO₂ by 20% measured 48–72 h after treatment with respect to baseline pre-irradiation measurement. The secondary objectives

include assessing the safety of bilateral pulmonary LD-RT, evaluating the improvement of the radiological image, overall mortality rates at 15 and 30 days after irradiation and characterizing anti-inflammatory mechanisms of LD-RT by measuring level of expression of adhesion molecules, anti-inflammatory cytokines and oxidative stress mediators

2.4. Patient selection

All patients with moderate to severe COVID-19 pneumonia will be evaluated by a multidisciplinary board (including different specialties such as Internal Medicine, Pneumology, Infectious Diseases, Geriatrics, Intensive Care and Radiation Oncology) to determine the benefit of their inclusion in the study.

Inclusion criteria (Table 1) are: patients over 18 years old with moderate to severe COVID-19 pneumonia as previously described, with <8 days of symptom onset and currently receiving standard medication for COVID-19 at appropriate doses (which would include, among others, hydroxychloroquine (or chloroquine), azithromycin, antivirals, corticosteroids, or anti-IL-6 (tocilizumab)) and patients who are not candidates for admission to the Intensive Care Unit (ICU) due to age, concomitant diseases or general condition. All patients must read and sign an informed consent document prior to inclusion. Those patients not meeting inclusion criteria, those with white cell count below 1000/ml in analytical determination within 24 h prior to inclusion, pregnant or those unable to understand purpose of the study will not be enrolled.

2.5. Treatment procedure

Fig. 1 gives the study flowchart. CT Simulation will be carried out on all patients using a simple and repositionable immobilization device (pillow and leg wedge) exclusive to COVID-19 patients. The volume of both lungs will be determined as CTV, which will be increased by 5 mm in all directions, except the superior-inferior which will be 10 mm. Planning will aim to achieve a homogeneous distribution in the area to be treated that meets ICRU criteria of between 95% and 107% of the prescribed dose of 0.5 Gy in single fraction or 1 Gy in two fractions 48–72 h apart ($D_{95\%} \geq 95\%$ prescribed dose and $D_{max} \leq 107\%$ prescribed dose). The heart will be considered an organ at risk and the dose will be established, although given the ultra-low doses this is not necessary for critical organs beyond the ALARA principle (As Low As Reasonably Achievable <https://www.cdc.gov/nceh/radiation/alara.html>). All patients will receive a single dose of 0.5 Gy and in the case of non-efficacy and at the discretion of the researcher another 0.5 Gy dose will be repeated 48–72 h later. The patient will be followed up in the hospital unit, measuring the PaFiO₂/ SaFiO₂ and taking clinical data at 6, 24, 48 and 72 h and on days + 4 and + 7, and a control chest CT will also be carried out on days + 7 and + 30. Blood determination of lymphocytes and mediators of inflammation (CRP, D-dimer, ferritin and LDH) will be determined on days + 1, +4 and + 7 and later depending on the evolution of the condition (Table 2). Treatment-related acute adverse events will be assessed according to CTCAE v5.0.

For the preparation and administration of the irradiation, all necessary measures will be followed to guarantee the safety of patients and staff regarding the risk of SARS-CoV-2 transmission, following the regulations and instructions of each centre. On the day of treatment, two technicians with the appropriate personal protective equipment (PPE) will place the patient according to the protocol of the Radiation Oncology Department in order to carry out the planned radiotherapy CT. The radiation oncologist will verify the correct positioning (using a planar or tomographic image) and the treatment will be carried out from the CT console. Subsequently, the lungs will be delimited, a radiation oncologist

Table 1

Inclusion and exclusion criteria of patients with COVID-19 pneumonia.

Inclusion Criteria	≥18 years old Moderate or severe pneumonia Not candidate for Intensive Care Unit (ICU) <8 days of symptom on-set Standard Medication Hydroxychloroquine or chloroquine Azithromycin Antivirals Corticosteroids Anti-IL-6 (tocilizumab) Signed Informed Consent
Exclusion Criteria	Pregnancy White cell count below 1000/ml Unable to understand the study Decline to participate in the study

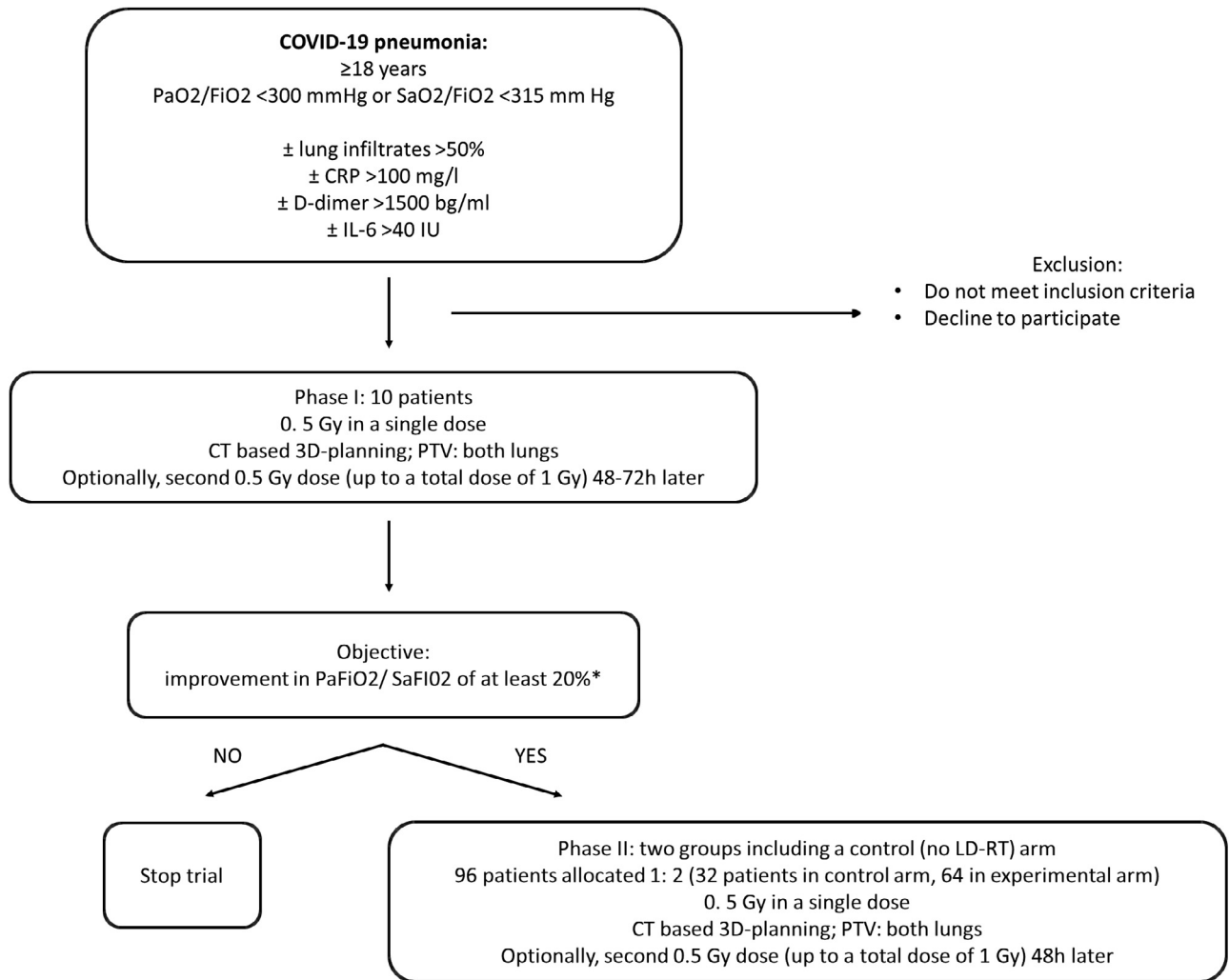
will define the PTV and the dosimetry plan will be carried out. Meanwhile, two radiotherapists wearing PPE will place the patient in the linear accelerator (linac) couch. At the end of the treatment, patients will be removed from the unit by radiotherapists, again equipped with the appropriate PPE, and will be returned to their room. The treatment will be carried out on the same linac to a time schedule in order to avoid the risk of contagion to other patients. After the completion of the treatment, the treatment room and linac will be decontaminated according to the established protocol.

2.6. Statistical analysis

Through descriptive statistics, the normality of the distributions will be determined and the test will be chosen for comparisons between groups. The prospective nature of these comparisons will be taken into account. For the probability of mortality and toxicity calculations the Kaplan-Meier method will be used. In comparisons between two groups, we will use the Mann-Whitney *U* test for non-parametric data and the Student's *t*-test for parametric data. Comparisons among multiple groups will be made by the Kruskal-Wallis test or by ANOVA. The diagnostic accuracy of the analysed parameters will be studied using ROC curves. Multivariate analyses will include the PLDSA and the VIP, calculated using the MetaboAnalyst program. In the case of multiple comparisons, the results will be interpreted according to a previously designated False Discovery Rate value. For the analysis of results, software programs such as SPSS, GraphPad Prism 6.0, MIX 2.0, “R” (<https://cran.r-project.org/>) and the Ingenuity Pathway Analysis (IPA) will be used. For more complex statistics, which mainly include the integration of metabolic and biochemical data, existing analysis and specific “R” packages will be required.

2.7. Ethical aspects

No financial compensation is foreseen for volunteer participants, there will be no healthy volunteers and all subjects included must present the SARS-CoV-2 infection. This project will be carried out in accordance with national and international guidelines, the basic principles of protection of human rights and dignity as stated in the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and according to the regulations in force. The treatment, communication and transfer of the personal data of the study subjects will be processed and notified as necessary for the purposes of the study and in accordance with Regulation (EU) 2016/679 of the European Parliament and the Council of April 27, 2016 Data Protection (RGPD). The results of this study will be published regardless of whether they are positive, negative or inconclusive. The study has been approved by the Institution Research Board of each centre and is registered in ClinicalTrials.gov, NCT-04380818.



* Observed in at least 30% of treated patients

CRP: C-reactive protein; IL: interleukin; CT: computed tomography; PTV: planning tumor volume; LD-RT: low-dose radiation therapy

Fig. 1. Study flowchart.

Table 2
Chronogram and monitoring plan.

Procedures	Selection	Day 0	6 h	12 h	Day 1	Day 2	Day 4	Day 7	Day 30
Inclusion Criteria	X								
Informed Consent signature	X								
Medication	X							X	X
PAFiO ₂ /SAFiO ₂	X	X	X	X	X	X	X	X	X
Chest CT	X							X	X
Blood determinations	X		X		X	X	X	X	
Blood samples	X		X		X			X	
Irradiation		X				X*			
Adverse effects			X		X	X	X	X	X

*When needed.

2.8. Status of the study

Phase I of the study is currently ongoing and patients are being recruited.

3. Discussion

Radiotherapy has been used for more than a century in the treatment of pneumonia, especially interstitial and atypical. In a

review by Calabrese et al., LD-RT to the lungs has demonstrated good response rates and resolution of symptoms. The authors reviewed 15 studies covering 863 cases of bacterial pneumonia (lobular and bronchopneumonia), interstitial, and atypical pneumonia that were effectively treated with low-dose X-rays, improving symptoms, increasing cure rates, and reducing mortality. The mechanism by which X-ray treatment acts on pneumonia involves the induction of an anti-inflammatory phenotype that leads to a rapid reversal of clinical symptoms, facilitating resolution of the disease. Treatment was most effective when irradiation was administered 6 to 14 days after the clinical onset of the disease. After 14 days, the successful response rate decreased by approximately 50%. The authors' conclusion is that LD-RT offers excellent potential as a treatment for interstitial pneumonia, especially when used during the early stages of the disease [14]. The group of Calabrese et al. reviewed the results published for >37,000 patients treated in the first half of the 20th century with LD-RT (between 0.3 and 1.5 Gy total) for different benign diseases characterized by inducing inflammatory states, including both degenerative and infectious disorders. The authors justify that the success of LD-RT is directly related to the hyper-inflammatory state and to the anti-inflammatory effect of radiation at low doses. The authors conclude that a total dose in the range of 0.3–1 Gy probably induces the expression of an anti-inflammatory phenotype that can reduce inflammation and pain and promote tissue recovery in most subjects, although it should not be surprising that a percentage of patients did not respond equally well [15].

Recently, in a 2020 publication, Dhawan et al. propose a total dose of 0.3–0.5 Gy in the thoracic region for patients with COVID-19 in the acute phase of the disease, when cytokines increase, and for those who present a moderate or severe clinical situation ("cytokine storm"). According to those authors, the theoretical basis that would justify the use of LD-RT in patients with COVID-19 rests on the fact that inflammation mediators triggered by COVID-19 initiate the cascade that leads to a hyper-inflammatory state, the so-called "cytokine storm", ultimately responsible for the rapid and extensive damage to the lungs and other organs. The well-known anti-inflammatory phenotype induced by LD-RT is expected to decrease the intensity and severity of COVID-19 pneumonia [12].

As with any other clinical protocol, both strengths and weaknesses can be found when considering the use of LD-RT for COVID-19 pneumonia. We are fully aware that the use of LD-RT does not replace any of the treatments currently in use and that it should not be recommended for all COVID-19 patients, but it could be considered for those patients in a more critical condition and when other treatment options have failed, are not indicated or it is not possible to access them quickly and easily. An additional advantage of this treatment would be that, unlike vaccines and pharmacological treatments that depend on the stock, radiotherapy devices are always available for the treatment of patients without being subject to fluctuations according to higher demand. But on the other side, one of the aspects that has sometimes prevented researchers from using LD-RT for the treatment of benign diseases has been the risk of late complications, especially the development of secondary cancers. Studies into the safety of LD-RT for the treatment of benign non-tumour pathology have all concluded that the risk of presenting complications attributable to irradiation is extremely low at the doses suggested in the present study [16–19].

In conclusion, there is a broad metabolic and immunological basis that would justify the use of LD-RT in COVID-19 patients, mainly in the most advanced stages of the disease when it could be effective by acting as a powerful anti-inflammatory agent against the cascade of pro-inflammatory cytokines, and together

with its low acute and late toxicity profile, it is an option that could be considered for patients with COVID-19 pneumonia.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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