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Review Article

Ongoing Trials of Low Dose Radiation Therapy for Covid-19 Pneumonia: Studying the Past to Define the Future?

Angel Montero[1]*, Manel Algara[2], Meritxell Arenas[3]

[1]Department of Radiation Oncology, University Hospital HM Sanchinarro, Madrid, Spain; [2]Department of Radiation Oncology, Hospital del Mar, Autonomous University of Barcelona, Tarragona, Spain; [3]Department of Radiation Oncology, University Hospital Sant Joan de Reus, Rovira i Virgili University, Tarragona, Spain

ABSTRACT

The current COVID-19 pandemic, caused by the infection by the SARS-CoV-2 virus, is a disease with great contagiousness, a non-negligible morbidity rate and a very important consumption of health resources, which is leading to a blockade of practically the entire world health system. The main complication is pneumonia, which has an important inflammatory component and for which there is still no definitive treatment. The absence of a standardized treatment coupled with the possible failure in the supply of drugs due to the great existing demand makes it necessary to investigate new anti-inflammatory therapeutics. The anti-inflammatory efficacy of Low-Dose Radio Therapy (LD-RT) has been confirmed in several experimental models, both in vitro and in vivo, as well as in different clinical studies. The radiobiological mechanisms that confirm this claim are becoming increasingly well known. Unlike high-dose radiotherapy that induces the production of pro-inflammatory cytokines in immune and endothelial cells, low doses of radiotherapy (0.5-1.5 Gy) act on the cells that participate in the inflammatory response, producing anti-inflammatory effects. At this time, there are different clinical studies underway that seek to demonstrate the usefulness of LD-RT against COVID19 pneumonia and open the possibility of offering an effective and widely affordable therapeutic alternative for this infection. Perhaps, as Confucius wrote, it is necessary to “study the past if you would define the future”

Keywords: Low-dose radiation therapy; COVID-19 pneumonia

INTRODUCTION

SARS-CoV-2 is an RNA virus that can cause severe lower respiratory tract infection with non-negligible morbidity and mortality rates and which is causing a blockage of almost the entire world health system. Most of the patients developed pneumoniawith a serious inflammatory component, the so-called cytokine release syndrome or Cytokine Storm Syndrome (CSS), which in some cases, especially in the elderly patients with low respiratory function, can lead to Acute Respiratory Distress Syndrome (ARDS) and death from respiratory failure [1]. To date, there has not been a standardized treatment for COVID-19. The only treatment options are those aimed at the side effects caused by the virus, such as inflammation and pulmonary SARS. 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 [2,3]. Corticosteroids are used because of their known ability to modulate a variety of involved cytokines and apparently being effective in reducing immune-pathological damage. The RECOVERY Collaborative Group recently published results of a randomized phase III trial in 6425 patients hospitalized with Covid-19 comparing dexamethasone for up to 10 days against usual care alone. The use of dexamethasone reduced mortality among those who were receiving either invasive mechanical ventilation or oxygen alone, reinforcing utility of corticosteroids for COVID-19 patients. [4]. Another treatment that has been shown to be effective is the monoclonal anti-human interleukin (IL) -6 receptor antibody, tocilizumab, used in the treatment of rheumatoid arthritis. Similarly, remdesivir has been shown to accelerate the recovery of hospitalized patients with COVID-19 pneumonia [5]. Other drugs such as Janus Kinase-Inhibitor and Type I Interferon seem promising, although they still require clinical studies to confirm their efficacy and usefulness [6].

Correspondence to: Angel Montero, Department of Radiation Oncology, University Hospital HM Sanchinarro, Madrid, Spain, E-mail: angel.monteroluis@gmail.com

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Nevertheless, 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 necessary to investigate new anti-inflammatory therapies. The idea of using radiation therapy to treat respiratory disorders is not new. There is evidence, since the beginning of radiotherapy in the late nineteenth and first half of the twentieth century, of its use and efficacy. Calabrese et al. had already published different reviews collecting the results observed with radiotherapy for the treatment of pertussis [7], of bronchial asthma [8] or pneumonia [9]. Several publications have analyzed, studied, and raised the theoretical bases of the usefulness of radiotherapy in COVID-19, while trying to respond to the fears and prejudices, often baseless, traditionally associated with the use of any radiation therapy. The interest in the possibility of using radiotherapy, a low-cost and easily accessible treatment without the stock restrictions that can be seen with certain drugs, has transcended the purely scientific researchto be considered in the mainstream media. Thus, James Conca recently pointed out in Forbes magazine: “As we try lots of possible solutions to rein in the coronavirus SARS-CoV-2, we need to use every tool we have, and low-dose radiation therapy may be an important one. It would be unethical not to investigate this approach as thousands are still dying every day from this pandemic and a vaccine is a long ways off ”.

We intend to review in this article ongoing studies that address the role of Low-Dose Radiation Therapy (LD-RT) for COVID-19 pneumonia. At the time of writing this review, there are 14 studies registered on the Clinicaltrials.gov platform that seek to study the usefulness of LD-RT as a symptomatic treatment for COVID-19.

RATIONAL AND JUSTIFICATION FOR THE USE OF LOW-DOSE RADIOTHERAPY FOR COVID-19 PNEUMONIA

The entry of the virus SARS-CoV-2 into epithelial / endothelial cells, through binding to ACE2 (and CD147), induces apoptotic and necrotic pathways that result in lung damage, release of numerous cytokines, recruitment of large numbers of immune cells within the lungs and induction of a hyperinflammatory state that appears to be the key triggering mechanism for the most severe forms of infection. Released cytokines play a determining role in the pathophysiology of COVID-19: while some are beneficial (type I interferon, interleukin-7), others appear harmful (interleukin-1, -6 and TNF-) particularly in the context of the so-called "cytokine storm" [10]. On the other hand, macrophages play a prominent role in the physiopathogenesis of the inflammatory response of the lung to infections. The lung harbors two distinct populations of macrophages, Alveolar Macrophages (AM) and Interstitial Macrophages (IM). MIs are located in the interstitium, together with dendritic cells and lymphocytes. Recently, the existence of a population of macrophages associated with the respiratory and nervous tracts (NAM) that are different from other subsets of macrophages resident in the lungs has also been described. and they express immunoregulatory genes. NAMs proliferated after viral lung infections, such as influenza, and in their absence, the inflammatory response increases, leading to excessive production of inflammatory cytokines and immune infiltration of immune cells. NAMs function to maintain immune and tissue homeostasis and regulate infection-induced inflammation through the secretion of immunosuppressive factors such as IL-10. The absence of NAM during a viral infection is characterized by the excess presence of pro-inflammatory cytokines and chemokines such as IL-6, CCL2, CCL3, and CCL5 [11,12].

Regarding its clinical and symptomatic presentation, there appear to be 3 different phenotypes for COVID-19: 1) "Mild" (benign infection: 80%) in patients with minor and nonspecific symptoms that will not progress to a more serious disease; 2) “Moderate” (overt pneumonia with or without hypoxia and localized inflammation: 15%) in patients requiring hospitalization; and 3) “Severe” (systemic hyperinflammation and SDRS: 5%) in patients requiring ICU management with a risk of fatal outcome (1-2%). Despite multiple attempts, no treatment has yet proven to be effective for the definitive cure of SARS-CooV-2. [2,3,13]

Radiotherapy has been used for more than a century in the treatment of pneumonia, especially interstitial and atypical and could be useful in the treatment of respiratory complications of COVID-19 because of its anti-inflammatory properties. The anti-inflammatory efficacy of LD-RT has been proven in several experimental models, both in vitro and in vivo and the radiobiological mechanisms that support this claim are becoming increasingly known. Unlike high-dose radiotherapy, that induces the production of pro-inflammatory cytokines in immune and endothelial cells, low doses of radiotherapy (0.5-1.5 Gy) act on cells that participate in the inflammatory response, producing effects anti-inflammatories. These effects include the inhibition of interactions between leukocytes and endothelial cells, a decrease in the production of adhesion molecules to the endothelium, a decrease in inflammatory mediators and a lower expression of pro-inflammatory cytokines, in addition to favoring the induction of macrophage and polymorphonuclear apoptosis. LD-RT also produces a decrease in the levels of NO (Nitric Oxide) synthetase (iNOS), L and E selectins, Reactive Oxygen Species (ROS), TNF-a or IL secretion -beta 1, along with an increase in the production and expression of anti-inflammatory cytokines, such as the transforming growth factor of anti-inflammatory cytokine 1 (TGF-1) and of apoptosis mediators such as the nuclear factor kappa-beta (NF-B). LD-RT also induces a complex systemic response that involves the polarization of macrophages to an anti-inflammatory M-2 phenotype (versus the pro-inflammatory M-1 (pro-inflammatory phenotype induced, for example, in the presence of infections). All these changes result in a local anti-inflammatory environment that would explain the clinical effects of LD-RT [14-17].

According to available evidence and the proposed mechanism of action of low-dose radiotherapy, a single total dose of 0.5-1.5 Gy is likely to be beneficial for patients with COVID- 19 presenting clinical symptoms consistent with the “cytokine storm”. These radiation doses are very low (<1% of the doses used for cancer radiotherapy) and do not exceed the tolerance doses of critical organs in the irradiated volume, such as the heart, thyroid, the stomach or kidneys [18-20].

CLINICAL TRIALS OF RADIOTHERAPY FOR COVID-19 PNEUMONIA

Since last March 11, 2020, when the World Health Organization declared the new SARS-CoV-2 infection a pandemic, 14 clinical trial protocols have been registered on the clinicaltrials.gov platform using radiotherapy as a treatment for pneumonia due to COVID-19 (Table 1). Not surprisingly, most of the trials come from countries strongly affected by the pandemic such as the USA (5 trials), Spain (4 trials), or Italy, Iran, India, Switzerland, or Mexico (1 trial each).

Table 1: Suggested Training Modules for establishing a CAGT training curriculum within your team or organization.

NCT Number	Location	Status	Intended enrollment	Inclusion criteria	Radiotherapy total dose (number of fractions)	Primary outcomes
NCT04366791 RESCUE 1-19 (Preprint published results [22])	USA	Recruiting	10	≥ 18 years-old, confirmed diagnosis of COVID-19, Severe acute respiratory syndrome or pneumonia Visible consolidations/ground glass opacities on chest x-ray or computed tomography, endotracheal intubation a on ventilator support for no longer than 5 (five) calendar days prior to the schedule date of delivery of low-dose radiation therapy.	WLRT 1.5 Gy (1	Rate of extubation up to 28 days after radiation therapy
NCT04377477 COLOR-19	Italy	Recruiting	30	≥ 50 years Brescia Covid Respiratory Severity Scale (BCRSS) score 2-3 Interstitial pneumonia on chest X-ray and/or chest CT At least 3 of: PCR>5 times maximum normal limit of the normal value Ferritin>500 ng/ml; LDH>2 times maximum limit; D-dimer>3 times maximum limit AST>2 times maximum limit; Total lymphocytes count <1000/ml	WLRT 0.7 Gy (1)	Length of hospital stay Number of ICU admissions
NCT04380818 IPACOVID (Published protocol [23])	Spain	Recruiting	100	≥ 18 years-old, confirmed diagnosis of COVID-19, moderate to severe COVID-19 pneumonia<8 days of symptom onset, PAFIO2<300 mmHg or SaFI02<315 mmHg, patients not candidates for admission to the Intensive Care Unit due to age, concomitant diseases or general condition.	WLRT 0.5 (1) Gy (1 ± 1)	Efficacy of low-dose pulmonary irradiation assessed by change in PAFI O2 (SaFIO2) by 20% on day 2 after interventional radiotherapy
NCT04390412 (Published results [21])	Iran	Not recruiting	5	≥ 60 years-old, proven COVID-19 and presence of pulmonary involvement with less than 3 days since the onset of ARDS	WLRT 0.5 (1) Gy (1 ± 1)	Change from baseline blood oxygenation at 28 days Length of Hospital stay after treatment Number of ICU stay days after treatment
NCT04393948	USA	Recruiting	48	≥ 40 years-old, proven diagnosis of SARS-CoV-2 infection ≤ 3 days before enrollment or ≤ 14 days before enrollment with progressive disease Current hospitalization for ≤ 14 days with SARS-CoV-2 infection at the time of enrollment Use of supplemental oxygen or oxygen saturation ≤ 94% on room air	Randomized phase III single lung irradiation (1 Gy) vs. bilateral lung irradiation (1 Gy)	Feasibility and safety of treating hospitalized patients with SARS-CoV-2 pneumonia with single or bilateral whole lung irradiation Proportion with clinical improvement on day 4 after irradiation

NCT04394182 ULTRA-COVID	Spain	Recruiting	15	≥ 18 years-old, confirmed diagnosis of COVID-19,	WLRT 0.8 Gy (1)	Oxygen Saturation (Sat02; Pulse oximeter measurement) at Day 2 Improvement criteria is considered as a Sat02 with/without oxygen therapy >93% (Pulse oximeter measurement)
NCT04394793	India	Recruiting	10	≥ 18 years-old, confirmed diagnosis of COVID-19 and National Early Warning Score (NEWS) score ≥ 5. ≥	WLRT 0.7 Gy (1)	Symptomatic improvement by National Early warning score (NEWS) at day 3, 7 and 14 after treatment Length of hospital stay Number of ICU admissions or deaths
NCT04414293	Spain	Not yet recruiting	41	≥ 6 5 years-old, with COVID-19 positive not subsidiary of ICU with severe disease defined by unilateral or bilateral pulmonary infiltrates in chest X-ray or chest-CT and acute respiratory failure expressed by PaO2/FIO2<300 and lymphopenia ≤ 800 lymphocytes/ml and ≤ 8 days from the onset of symptoms.	WLRT 1 Gy (1)	Blood oxygen saturation level at 48 hours] Radiological improvement 48 hours after treatment.
NCT04420390 LOWRAD-Cov19	Spain	Recruiting	41	≥ 60 years-old, proven COVID-19 pneumonitis with thoracic imaging study (chest X-ray, chest CT or PET-CT), compatible with lung involvement.	WLRT 1 Gy (1)	Radiological response at 3 and 7 days after low dose radiation
NCT04427566 Vented	USA	Recruiting	24	≥ 18 years-old, confirmed diagnosis of COVID-19; CT findings typical of COVID-19 pneumonia within 5 days of enrollment and receiving ICU-based mechanical ventilation+life expectancy ≥ 24 hours+hypoxemia (Pa/FIO2 ratio<300 or pO2/FiO2<315)	WLRT 0.8 (1.6) Gy (1 ± 1)	Mortality rate 30 days after the ICU-based mechanical ventilation initiation
NCT04433949 RESCUE1-19	USA	Recruiting	52	≥ 18 years-old, confirmed diagnosis of COVID-19, clinical signs of severe acute respiratory syndrome or pneumonia (dyspnea, cough, fever), visible consolidations/ground glass opacities on chest imaging, requiring supplemental oxygen	Randomized Phase III of Best Supportive Care ± WLRT in hospitalized patients 1.5 Gy (1)	Time to clinical recovery based on reducing the need of supplementary oxygenation in COVID 19 patients on day 14
NCT04466683 Prevent	USA	Not yet recruiting	100	≥ 50 years-old, confirmed diagnosis of SARS-CoV-2 pneumonia Currently hospitalized with symptomatic fever, cough and/ or dyspnea for<9 days	Randomized phase III WLRT 0.35 Gy (1) vs. 1 Gy (1)	Rate of grade 4 toxicity Rate of mechanical ventilation Rate of hospital stay greater than 10 days Crude all-cause mortality rate
NCT04493294	Switzerland	Not yet recruiting	500	≥ 65 years-old, proven COVID-19 pneumonitis who may or may not require oxygen	WLRT 0.5 Gy (1)	Mortality rate
NCT04534790	Mexico	Recruiting.	30	>18 years-old, laboratory confirmation of SARS-CoV-2 infection and Acute Respiratory Distress Syndrome in any degree with a hospital treatment requirement.	WLRT 1Gy (1)	Improvement of oxygen saturation

WLRT: Whole Lung Radiation Therapy

Even though they are similar, some differences can be seen between the different studies. The number of patients expected to be included varies between the 5 patients in the Iranian study and the 500 expected in the Swiss study. Most are prospective trials and only 3 are randomized studies. The RESCUE1-19 study from Emory University will compare pulmonary radiotherapy versus supportive treatment (NCT04433949); the Brigham and Women's Hospital study will compare bilateral versus single lung irradiation (NCT04393948) and the Ohio State University Comprehensive Cancer Center study seeks to compare two different lung radiation therapy doses (NCT04466683).

Six studies limit the consideration of LD-RT treatment to patients 50 years of age or older, while the other 8 studies allow for younger individuals. The inclusion criteria require the presence of confirmed COVID-19 disease together with radiologically evident pneumonia and severe symptoms of ARSD in 8 of them.

Most studies include the administration of a single fraction of radiotherapy to both lungs (with the exception already mentioned of the randomized study in Ohio) with doses that vary between 0.5 and 1.5 Gy. Three studies contemplate the possibility of administering a second identical fraction if there is no adequate response after the first in a time interval that varies between 48 and 240 hours after the first fraction.

Despite the similarities between all clinical trials, differences in the primary endpoints can be seen. The improvement in oxygen saturation rates is the main objective of many of them, although some studies evaluate, jointly or independently of the improvement in oxygenation, other aspects such as the length of hospital stay, the need for admission in ICU, radiological improvement or associated crude mortality rates. Whether these differences in the proposed objectives will offer a clear picture of the role of LD-RT in COVID-19 pneumonia or will contribute to creating greater confusion is something difficult to determine in this global pandemic scenario in which there is no specific treatment definite.

To date, 2 studies have already published results observed using LD-RT in patients with SARS-CoV-2 pneumonia. Ameri et al. have presented the results of the Iranian study (NCT04390412) on 5 patients who received a single dose of 0.5 Gy to both lungs. In 4 of the 5 patients, an improvement in clinical parameters (blood oxygenation and body temperature) and paraclinical parameters (IL-6 and CRP levels) was observed on the first day after treatment. No patient received other specific treatment for COVID-19 infection.

One patient died after 3 days, one patient chose to drop out of the study after 3 days, and another 3 patients were discharged. No complications related to LD-RT were observed [21,22]. Preliminary results of the Emory University Hospital RESCUE 1-19 trial have been published in a non-peer reviewed journal by Hess et al. Five patients diagnosed with COVID-19 pneumonia received a single 1.5 Gy fraction over both lungs. Four of the five patients experienced a clinical recovery, 3 of them within the first 24 hours after irradiation and could be discharged after a median admission of 12 days. No patient received treatment with drugs directed against COVID-19 in the days before or after lung LD-RT. The authors found no acute toxicity attributable to treatment [23].

CONCLUSION

The world is facing a new and practically unknown in all its behavior situation, facing an infection against which there is still no cure, in which there are many therapeutic alternatives that have been proposed without being found, and waiting for an effective vaccine to control the infection, a definitive treatment. When the panorama begins to clear up, and treatments accepted as "standards" and used profusely in the belief of their efficacy do not confirm the hopes placed in them, perhaps it is time to consider an old, modest treatment (because of its cheapness and not being subjected to market fluctuations), apparently unsexy but unfortunately rich in unfounded prejudices, such as low-dose pulmonary radiotherapy and recognizing that it may have an effective, effective and efficient role against SARS-CoV-2 pneumonia. Lung LD-RT is a very cost-effective, non-toxic treatment that is already available in most general hospitals. This fact would allow its use in large number of patients who will suffer from this disease, and who would not receive specific anti-COVID19 treatments, especially in low and middle-income countries. The preliminary results already known, as well as those expected from the ongoing studies, may allow confirming in a short time the statement from Isaac Asimov: “It is only afterwards that a new idea seems reasonable. To begin with, it usually seems unreasonable"

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