



Low dose lung radiotherapy for COVID-19 pneumonia. The rationale for a cost-effective anti-inflammatory treatment

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ARTICLE INFO

Article history:

Received 7 April 2020

Revised 11 April 2020

Accepted 13 April 2020

Available online 25 April 2020

Keywords:

COVID-19 pneumonia

Low dose radiotherapy

Lung

ABSTRACT

The COVID-19 pandemic is affecting people worldwide. Most of the patients suffered of a respiratory disease that will progress to an acute respiratory distress syndrome (ARDS). SARS-CoV-2 pneumonia severely ill patients, develop a systemic inflammatory response with a Cytokine Release Syndrome (CRS), that is characterized by a sudden increase in several pro-inflammatory cytokines, mainly IL-1, IL-6 and TNF- α by activated macrophages (M1 phenotype). Blocking IL-6 with tocilizumab and using respirator equipment seems to be a very important issue in this (SARS-CoV-2) pneumonia, but not all patients are referred to such treatments.

Low dose radiotherapy (0.5 Gy), is an evidence-based anti-inflammatory treatment, that could modify the immune landscape in the lung affected of SARS-CoV-2 pneumonia, through macrophages polarization to alternatively activated Macrophages (M2 phenotype). Radiation-induced cancer risk could be assumed due to the very low dose used, the advanced age of the patients and the life-threatening condition of SARS-Cov2 pneumonia.

LDRT is a cost-effective non-toxic treatment already available in most general hospitals. This fact allows that it 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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1. Introduction

The COVID-19 pandemic is affecting people worldwide. By April 11th 102.774 patients have died of this disease. Most of the patients suffered of a respiratory disease that will progress to an acute respiratory distress syndrome (ARDS). The affected lung presents alveolar edema, proteinaceous exudates, and reactive pneumocyte hyperplasia, accompanied by monocytes and lymphocytes alveolar inflammatory infiltration. The so-called SARS-CoV-2 pneumonia, is associated with high mortality specially for those included in high risk categories: advanced age, underlying comorbidities (hypertension, diabetes, cardiovascular disease) and high levels of inflammatory Dimer D/Ferritin [1].

1.1. Macrophages in the immune basis for SARS-CoV2 pneumonia

SARS-CoV-2 pneumonia severely ill patients, develop a systemic inflammatory response with a Cytokine Release Syndrome (CRS),

that is characterized by a sudden increase in several pro-inflammatory cytokines, mainly IL-1, IL-6 and TNF- α [2]. This CRS was also observed in other viral infections (SARS-Cov and MERS-Cov pneumonia) [3] and is one of the major adverse-effects after immune system-related diseases therapy (Chimeric Antigen Receptor T-Cell Immunotherapy, CAR-T cell therapy) [4].

The COVID-19 activates both innate and adaptive immune system. Macrophages seems to be an important component of this CRS syndrome, related to its phagocytic activity through the danger-associated molecular patterns (DAMPs) activated by Toll-Like Receptors (TLR). COVID-19 activated TLRs makes possible the liberation of cytokines by macrophages (IL-1/IL-6/TNF- α) and subsequent activation of inflammasome [5].

This classically activated, “proinflammatory” M1 subset is activated by infectious microorganisms (lipopolysaccharides) and cytokines (interferon- γ). As already discussed, M1 macrophages participate in the initiation and development of inflammatory events, through the liberation of inflammatory cytokines such as IL-1 β , IL-6, and TNF- α . Continued, non-controlled activation of M1 macrophages can cause tissue damage [6].

The alternatively activated, “anti-inflammatory” M2 macrophages, are primed in response to Th2-related cytokines such as

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IL-4 and IL-10, and they express high levels of anti-inflammatory cytokines. At present time, available evidence suggests that M1/M2 imbalances, favoring M1 phenotype, is in the pathogenesis of rheumatoid arthritis [7] and possibly in the SARS-CoV-2 IL-6 related pneumonia [2,3].

Although Inflammation changes try to restore the homeostasis after COVID-19 infection, can cause deleterious effects in uncontrolled. Cytokines release in response to virus, by immune, endothelial cells and fibroblasts are crucial in the progression of pulmonary fibrosis [8].

Interleukin-6 (IL-6) is produced by TLR stimulated macrophages in the early stages of inflammation and plays a central role in promoting acute inflammation. IL-6 promotes the expansion and activation of T cell /B cell populations. IL-6, is activated by IL-1 β and tumor necrosis factor (TNF- α) [9].

Cytokine storms play an important role in severe cases of (SARS-CoV-2) pneumonia, so neutralizing key inflammatory factors in Cytokine Release Syndrome (CRS) will be of great value in reducing mortality of this disease [2].

1.2. The treatment of SARS-CoV-2 pneumonia

Blocking IL-6 seems to be a very important issue in this (SARS-CoV-2) pneumonia [2]. Tocilizumab is a monoclonal antibody against human IL-6 receptor. Although is worldwide approved for the treatment of rheumatoid arthritis [10], tocilizumab is also effective in the treatment of severe CRS patients caused by CAR-T (Chimeric Antigen Receptor T-Cell Immunotherapy) therapy [11]. As CRS occurred in severe patients with SARS-CoV-2 and all of them showed high levels of IL-6, tocilizumab is used in Covid19 patients at the present time [2].

Steroids are also a used treatment in SARS-CoV-2 CRS, but there are several concerns about toxicity in patients already affected by comorbidities or advanced age, that precludes its use in a relevant number of cases [2].

Unfortunately, restrictive criteria for the use of tocilizumab and referral to Intensive Care Units (ICUs) during this COVID-19 pandemic, is the daily practice in most hospitals worldwide, due to the shortage of breath assisted equipment and access to tocilizumab treatment. New approaches should be considered for the treatment of this SARS-CoV-2 pneumonia.

1.3. Low-Dose radiotherapy in the treatment of SARS-Cov-2 pneumonia

Among those demonstrated effective anti-inflammatory treatments, radiotherapy has been widely used since the early 20th century. Patients who are progressing to or unfit for common anti-inflammatory treatments, low-dose radiotherapy (LD-RT)) emerges as a evidence-based beneficial alternative. In fact, LD-RT reduces the existing inflammation in musculoskeletal diseases when used at very low doses (0.5 Gy/fraction) [12].

Ionizing radiation is able to reduce inflammation through various mechanisms including the induction of apoptosis in immune cells, the secretion of anti-inflammatory factors, and a reduced function of macrophages [13]. Concerning the use of low-dose radiotherapy in SARS-CoV-2 IL-6-related pneumonia, the role of radiotherapy in the modification of monocyte-macrophage axis would be very relevant.

Recent studies indicate that LDRT polarizes macrophages towards a M2-like phenotype in a rheumatoid arthritis model. In this study, LDRT at a single dose of 0.5 Gy influenced M1/M2 balance towards M2 "anti-inflammatory" phenotype when Fibroblast-like synoviocytes and bone marrow-derived macrophages were co-cultured in a experimental model of RA. Therefore LDRT could have a relevant role in those situations that hyperinflammation resem-

bles RA, through reduction of IL-1 and TNF-alfa target cells producing IL-6. Therefore, localized very low dose radiotherapy, would modify the inflammatory environment in the lung of SARS-CoV-2 IL-6 related pneumonia patients [14].

Radiotherapy for pneumonia has been used since the 30s of the last century with promising results [15] including and specially in interstitial viral pneumonia. Openheimer [16] treated 56 patients with life-threatening progressive interstitial pneumonia at doses of 0,5 Gy. Patients treated in the first 14 days responds successfully to the therapy but after 14 days responses were around 50%. Experimental LDRT treatment for influenza virus in animals models demonstrated the efficacy of such treatment in almost half of the experimental cases [17].

LDRT is available worldwide, as is administered in standard LINACS. One single-fraction at very low doses, the whole lung volume, would make possible to treat large number of patients in a dedicated LINAC. This initiative would result in cost-efficient and non-toxic treatment for the large number of patients that will suffer this disease, and that would not receive specific anti-IL-6 treatments in ICUs.

1.4. The fear of radiation induced cancer (RIC) after LDRT

The only limitation to the use of low dose radiotherapy as a potent, non-toxic, anti-inflammatory treatment is the fear for long term radiation induced diseases, specially cancer. However, many of the considered "standard treatments" (NSAIDs, COX-inhibitors, steroids, etc) also have side effects that has to be weighted against the very small risk of RIC.

Major evidence of radiation induced cancer, comes from accidental exposures to radiation of general population. The linear non-threshold (LNT) 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 LDRT 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 [18].

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 [12]. Concerning the present situation either the real risk of dying from the SARS-CoV-2 IL-6 pneumonia and the advanced age of the patients at such risk, would make irrelevant such concerns.

2. Conclusion

Low doses radiotherapy to the whole lung should be explored under clinical trials [19] to patients in early stages of the SARS-CoV-2 IL-6 pneumonia, especially those with unfavourable risk factors as advanced age, comorbidities and hyperinflammation markers of elevated Ferritin and Dimer D. LDRT is a cost-effective non-toxic 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.

Authors contribution

- 1) Pedro C Lara, developed the idea, write the paper and critically discussed the final format.
- 2) David Macias-Verde, contributed to the idea, write the paper and critically discussed the final format.
- 3) Javier Burgos-Burgos, contributed to the idea, write the paper and critically discussed the final format.

Funding source

Hospital Universitario San Roque/Universidad Fernando Pessoa Grant 19-001.

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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