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Low-Dose Radiotherapy for Late-Stage COVID-19 Pneumonia?

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Abstract

Low dose radiotherapy has been used in the pre-antibiotic era for the treatment of all kind of pneumonia, with relative success. The unimaginable daily death toll of thousands of victims dying from COVID-19 pneumonia and the marginal therapeutic value of agents tested, brings forward the re-evaluation of the position of radiotherapy in the treatment of late stage lethal COVID-induced respiratory failure. A sound biological rationale supports this idea. Immunopathology studies show that excessive inflammation and infiltration of the lung parenchyma by immune cells is the cause of death. Mice lacking IFNαβ receptors remain unaffected by the virus. Radiotherapy at doses of 50-200cG may exert an intense anti-inflammatory effect and reduce the burden of inflammatory cells infiltrating the lungs. Whether radiotherapy, in conjunction with remdesivir and/or macrolides can reduce the dramatic death rates related to COVID-19 is an open challenge, under the absence of an alternative solution.

Keywords

radiotherapy, COVID-19, low dose radiation, lung, immunopathology

Commentary

In 1905, Musser and Edsall[1] introduced radiotherapy as plausible treatment for unresolved bacterial pneumonia, based on the assumption that radiation accelerates metabolic and autolytic processes and facilitates the elimination of the exudative material. In 1913 researchers from the Rockefeller Institute introduced equine serum therapy for the treatment of lobular pneumonia, a treatment that reduced the mortality rates by 50%.[2] In 1924, Heidenhain and Fried reported on 243 pneumonia cases, providing strong evidence that radiotherapy was superior to equine serum, providing immediate improvement of patient symptomatology.[3] The introduction of penicillin, however, signaled the gradual abandonment of radiotherapy as a treatment option for pneumonia.

In 2013 Calabrese and Dhawan published a review on the history of low dose radiotherapy applied for the treatment of pneumonia.[4] Authors summarized several published studies recruiting a total of 863 patients with various types of pneumonia treated with radiotherapy, showing 83% cure rates. The unimaginable daily death toll of thousands of victims dying from COVID-19 pneumonia (https://www.worldometers.info/coronavirus/), humanity faces since January 2020, urges the development of therapeutic agents and vaccines. The already available agents are of a marginal therapeutic value, and ventilation support is the only method that rescues a fraction of patients with severe COVID-19 pneumonia. In lack of alternative solutions, radiotherapy could re-emerge as an option provided that there is, at least, a sound biological rationale to support this idea.

In patients affected by COVID-19, lung tissue cells infected by the virus become the source of a cytokine/chemokine response, inducing a massive infiltration of lung interstitium and alveoli by lymphocytes, macrophages, and polymorphonuclear cells. This immune infiltration drives the clinical development of acute respiratory failure.[5] The anti-inflammatory properties of low dose radiation may contribute to the soothing of lung inflammation to improve the respiration of patients. Calabrese et al recently reviewed and discussed on the optimal dose of radiation for inflammatory conditions, suggesting a range of doses between 20-200cG, although the evidence is in favor of the lowest dose values.[6] A postulated mechanism

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for this anti-inflammatory activity of radiation is the induction of polarization of macrophages toward an anti-inflammatory M2-phenotype, secreting TGFβ and having reduced ability to produce reactive oxygen species and TNFα.[6] Aside to a postulated anti-inflammatory effect, doses up to 200 cGy are expected to induce a substantial depopulation, mainly of lymphocytes, in the pulmonary interstitium. Lymphocytic repopulation would, however, re-occur under the continuous cytokine overproduction. A prolonged lymphocytic depopulation at a systematic level would produce a more sustainable effect. Splenic irradiation, for example, induces sustainable lymphopenia, which inevitably occurs in patients irradiated for pancreatic and gastric cancer. Although lymphopenia could permit a more intense viral replication, this is, rather, meaningless for late-stage patients with COVID-19 pneumonia, since it is not the virus that kills patients but the lung immunopathology.[5,7]

Four years before the onset of COVID-19 pandemic, Channappanavar et al. showed that injection of lethal doses of SARS-CoV to BALB/c mice results in the rapid development of pneumonia and death, in sharp contrast to mice lacking expression of IFNαβ receptors that remain unaffected by the virus.[7] The authors suggested that the suppression of the IFN-type-I pathway prevents pulmonary failure and death. Cytokine release, interstitial hyper-cellularity, and cytotoxicity are the causes of lung failure in COVID-affected patients. Depopulation of immune infiltrating cells in the lung by radiotherapy may, therefore, prove important. The beneficial effect of radiotherapy would be further substantiated if radiation also had a suppressive effect on the IFN response of lung tissue. The effect of different radiation doses on lymphocyte, macrophage, and dendritic cell secretory activity is, by and large, unclear. It is misfortunate that the impressive developments in cancer radiotherapy have not been accompanied by a similarly robust interest in radiation pathophysiology. Viral dsDNA and dsRNA induce IFN-type-I response through activation of sensors like the cGAS/STING and the MDA5/MAVS/TBK1 pathways. How these pathways respond to low dose radiation is unknown.

Remdesivir, chloroquine, and azithromycin are the main drugs under evaluation for COVID-19 patients. Remdesivir suppresses the STING pathway, reducing the production of interferons by cells and, presumably, by lung cells infected by COVID-19.[8] This could repress the chemotaxis and activation of lymphocytes and macrophages in the lung tissue. Macrolides on the other hand reduce the production of pro-inflammatory cytokines by macrophages, eventually contributing to the development of an environment reach in M2-type macrophages.[9] It is expected that such an effect will enhance the anti-inflammatory activity of low dose radiation. The clinical activity, however, of both drugs is at best marginal. Alas, the death rates from patients receiving critical care at hospitals are unacceptably high, exceeding 50% (C:/Users/Owner/Downloads/ICNARC%20COVID-19%20report%202020-04-04.pdf.pdf). A very recent phase I/II trial, by Hess et al., was posted on June 2020 during the preparation of the current letter, showing a striking improvement of the status of 9 patients receiving bilateral lung irradiation with a single fraction of 150 cGy (https://www.medrxiv.org/content/10.1101/2020.06.03.20116988v1.full.pdf). Whether radiotherapy, in conjunction with remdesivir and/or macrolides can reduce the dramatic death rates related to COVID-19 is an open challenge, under the absence of an alternative solution.

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