

Commentary

A Novel Therapy for Influenza-Induced Pneumonia

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ABSTRACT

This article recommends incorporating low-dose, lung radiation therapy into the treatment strategy for patients hospitalized with pneumonia due to influenza. This proposal is based on the history of 863 patients with severe bacterial or viral pneumonia. The lives of 717 of these patients were saved by the application of one X-ray treatment to their lungs. Since many tens of thousands of people die every year from influenza, complementary treatments that are safe and effective are needed. Low-dose radiation should become a life-saving component to the overall clinical patient management for this condition.

KEYWORDS: *Flu, hormesis, inflammation, pneumonia, radiotherapy, X-rays*

INTRODUCTION

Influenza is a contagious respiratory viral illness that infects between 3% and 11% of the U. S. population each flu season, depending on the season. Most people who become sick with flu will have mild symptoms and recover in <2 weeks. Some, however, will develop flu complications (such as pneumonia) that can result in hospitalization and sometimes death. In the 2019–2020 season, the U. S. Centers for Disease Control and Prevention estimated there were between 39 and 56 million cases, 18–26 million medical visits, 410,000–740,000 hospitalizations, and 24,000–62,000 deaths. People 65 years and older are at high risk of developing serious complications from flu compared with young, healthy adults. This risk is due in part to changes in immune defenses with increasing age. Between 70% and 85% of seasonal flu-related deaths occurred in people aged 65 years and older.^[1]

BACKGROUND: CURRENT TREATMENTS FOR INFLUENZA

Antiviral drugs are used to treat flu, and prompt treatment is recommended for people who are at high risk of serious complications. Side effects vary for each medication. The most common side effects of oseltamivir are nausea and vomiting. Zanamivir can cause bronchospasm, and peramivir can cause diarrhea. Other less common side effects also have been reported.^[2] However, if the disease progresses and induces severe pneumonia or acute

respiratory distress syndrome (ARDS), then respiratory or oxygen therapy (nasal tube, face mask or mechanical ventilation [MV], fluid management, and sedation) is required in a hospital intensive care unit (ICU) until the lung inflammation subsides. Treatment of ARDS in ICUs is an important public health problem globally, with high mortality of about 40%.^[3]

Yin and Bai assessed the pharmaceutical remedies for adults with ARDS and pointed out that there is no pharmacotherapy effective enough to reduce the mortality of ARDS, which is recognized to be an inflammatory lung condition.^[4] Corticosteroid as an anti-inflammatory agent should be a perfect match for the treatment of ARDS. However, results from randomized, placebo-controlled clinical trials showed that there are no benefits from corticosteroids for the improvement of ARDS survival. Some clinical data implied that corticosteroids were able to increase oxygen level, MV-free days, and ICU-free days, which suggested that corticosteroid could play an important role during the treatment of ARDS.^[4]

TREATMENT OF PNEUMONIA WITH A LOW DOSE OF X-RAYS

X-ray therapy was employed during the first half of the 20th century to treat many diseases, including

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pneumonia. Radiologists had learned from ~30 years of prior experience which X-ray exposures were harmful and in 1925, established international recommendations for a safe occupational dose limit that precluded malignancies.^[5] They also discovered the radiation doses that were effective in remediating illnesses.

A review was carried out by Calabrese and Dhawan on the history of radiotherapy of the lungs to treat ARDS, caused by bacterial and viral pneumonia.^[6] This investigation revealed the high efficacy and low morbidity of this remedy. Their review, which examined 18 studies that treated a total of 863 cases, indicated that 717 of these patients were cured. The radiation dose used was in the range from 0.3 to 1.5 Gy (1 Gy = 1 joule/kg).^[6] Present-day concerns about the safety of this treatment dose may be addressed by comparing it with the total dose employed to cure lung cancer. Typical radiotherapy delivers a 2 Gy dose fraction to the lungs, each workday, for 6 weeks, a total of 60 Gy. The mechanism of action of this X-ray treatment was also assessed. It found that a low dose of ionizing radiation induces an anti-inflammatory phenotype that leads to a rapid reversal of clinical symptoms, facilitating disease resolution. This is a new and significant concept with widespread biomedical and therapeutic applications.^[6]

The radiation scare that the U. S. National Academy of Sciences (NAS) started in 1956, to stop atomic bomb testing, discouraged physicians from further use of radiotherapy to stimulate the healing process.^[5] The NAS Genetics Panel recommended that the risk of radiogenic mutations (and cancers) be assessed using the linear no-threshold (LNT) dose-response model instead of the safe threshold model that the early radiologists had used to establish the dose limit. A careful review of the historical record revealed that this recommendation was ideologically motivated.^[7] It ignored important biological evidence, including 60 years of human clinical data that contradicted the LNT model. It disregarded the natural protective systems and renewal processes present in all organisms. The NAS recommendation had far-reaching influence and consequences. It affected cancer risk assessment, risk communication strategies, government radiation protection regulations, community public health, and numerous medical practices in the United States and worldwide.^[7]

Within the context of cancer risk, a detailed review of the epidemiological literature by Ricci and Tharmalingam^[8] strongly dismisses potential cancer risk in the zone exposure proposed in low-dose influenza therapy. Furthermore, a recent study of breast cancer in women receiving a cumulative dose of 6 Gy to the shoulder and

followed for over two decades found no increased risk, but even a modest decrease in risk.^[9]

TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME INDUCED BY COVID-19 AND INFLUENZA

The COVID-19 pandemic with its high mortality^[10,11] has raised awareness of the enormous public health problem of treating ARDS in ICUs, pointed out earlier. A letter sent to the U. S. Food and Drug Administration went viral. It urged a short clinical trial be carried out to confirm the results of the early studies on the efficacy of one X-ray treatment to resolve pneumonia.^[12] Since then, >10 clinical trials have been initiated, starting in April 2020, to provide evidence on the efficacy of lung radiotherapy for COVID-19 induced pneumonia.^[13] They are supported by a new review with strong evidence of the anti-inflammatory efficacy and safety of a low dose of radiation.^[14]

The preliminary results and the editorial, published to date, are encouraging.^[15-17] These clinical trials are very controversial because this low-dose radiotherapy is intended to improve the performance of the patient's protection systems against disease, which challenges the accepted paradigm that a low dose of radiation increases risk of harm.

The 2013 Calabrese and Dhawan review of radiotherapy to treat pneumonia, mentioned earlier, urged a clinical research program be established in the U. S. to assess its efficacy and morbidity because pneumonia is a major cause of death.^[6] The seasonal flu infects many millions of the U. S. population every year, and about 600,000 are hospitalized with pneumonia. The validation and acceptance of low-dose lung radiotherapy for pneumonia would eliminate the need to treat about 100,000 cases of ARDS annually in ICUs, with a mortality of about 40%.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Centers for Disease Control and Prevention. 2019-2020 U.S. Flu Season: Preliminary Burden Estimates; 2020. Available from: <https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm>. [Last accessed on 2021 Jan 21].
- Centers for Disease Control and Prevention. Flu Treatment; 2020. Available from: <https://www.cdc.gov/flu/treatment/index.html>. [Last accessed on 2021 Jan 21].
- Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, *et al.* Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016;315:788-800.
- Yin J, Bai CX. Pharmacotherapy for adult patients with acute respiratory distress syndrome. *Chin Med J (Engl)* 2018;131:1138-41.
- Cuttler JM. Application of low doses of ionizing radiation in medical therapies. *Dose-Response* 2020;18(1). <https://doi.org/10.1177/1559325819895739>.
- Calabrese EJ, Dhawan G. How radiotherapy was historically used to treat pneumonia: Could it be useful today? *Yale J Biol Med* 2013;86:555-70.
- Calabrese EJ. LNTgate: The ideological history of cancer risk assessment. *Toxicol Res Appl* 2017. <https://doi.org/10.1177/2397847317694998>.
- Ricci PF, Tharmalingam S. Ionizing radiations epidemiology does not support the LNT model. *Chem-Biol Inter* 2019;301:128-40.
- Zwicker F, Kirchner C, Huber PE, Debus J, Zwicker H, Klepper R. Breast cancer occurrence after low dose radiotherapy of non-malignant disorders of the shoulder. *Sci Rep* 2019;9:5301.
- Johns Hopkins University. COVID-19 Dashboard by the CSSE. Available from: <https://coronavirus.jhu.edu/map.html>. [Last accessed on 2021 Jan 21].
- Mishra KP. Low-dose radiobiology: Opportunities for new research and technology for anticancer and anti-COVID-19 strategies. *J Radiat Cancer Res* 2020;11:73-80.
- Cuttler JM. 0.5 Gy chest X-Ray as a Potential Remedy for COVID-19 Disease. Letter to the U.S. FDA Dose-Response; 20 March, 2020. Available from: <https://journals.sagepub.com/doi/suppl/10.1177/1559325820949066>. [Last accessed on 2021 Jan 21].
- National Library of Medicine. Registry of Clinical TrialsCriteria: COVID-19, Low Dose Radiation. <https://www.clinicaltrials.gov/>. [Last accessed on 2021 Jan 21].
- Dhawan G, Kapoor R, Dhawan R, Singh R, Monga B, Giordano J, *et al.* Low dose radiation therapy as a potential life saving treatment for COVID-19-induced acute respiratory distress syndrome (ARDS). *Radiother Oncol* 2020;147:212-6.
- Hess CB, Buchwald ZS, Stokes W, Nasti TH, Switchenko JM, Weinberg BD, *et al.* Low-dose whole-lung radiation for COVID-19 pneumonia: Planned day 7 interim analysis of a registered clinical trial. *Cancer* 2020;126:5109-13. <https://doi.org/10.1002/cncr.33130>.
- Ameri A, Rahnama N, Bozorgmehr R, Mokhtari M, Farahbakhsh M, Nabavi M, *et al.* Low-dose whole-lung irradiation for COVID-19 pneumonia: short course results. *Int J Radiat Oncol Biol Phys* 2020;108:4-9. <https://doi.org/10.1016/j.ijrobp.2020.07.026>.
- Skinner HD. Mining the Past to Treat the Present, Ever Mindful of the Future: Low-Dose Radiotherapy and COVID-19 Pneumonia. *Cancer* 2020;126:5017-21. <https://doi.org/10.1002/cncr.33201>.