Low-dose Whole-lung Irradiation for COVID-19 Pneumonia: Short Course Results

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Short Report

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Abstract

Objectives: The COVID-19 outbreak is affecting people worldwide. Most of the infected patients suffering from respiratory involvement that may progress to acute respiratory distress syndrome. This pilot study aimed to evaluate the clinical efficacy of low-dose whole-lung radiotherapy in patients with COVID-19 pneumonia.

Methods: In this clinical trial, done in Iran, we enrolled patients with COVID-19 who were older than 60 years and hospitalized to receive supplementary oxygen for their documented pneumonia. Participants were treated with whole-lung irradiation in a single fraction of 0.5 Gy plus national protocol for the management of COVID-19. Vital signs (including blood oxygenation and body temperature) and laboratory findings (IL-6 and CRP) were recorded before and after irradiation.

Results: Between 21 May 2020 and 24 June 2020, five patients received whole-lung irradiation. They followed for 5-7 days to evaluate response to treatment and toxicities. The clinical and paraclinical findings of four patients (except for patient #4 that get worst and died on day 3) improved on the first day of irradiation. Patient #3 opted-out the trial on the third day of irradiation. The mean time to discharge was 6 days for the other three patients. No acute radiation-induced toxicity was recorded.

Conclusion: With a response rate of 80%, whole-lung irradiation in a single fraction of 0.5 Gy had encouraging results in oxygen-dependent patients with COVID-19 pneumonia.

Background

Since the end of 2019, the novel coronavirus disease (COVID-19) has been a major health issue all over the world. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has led to more than five hundred thousand deaths until July 2020 with an estimated crude mortality rate of 3-4% [1-3]. Four phases are proposed for the pathogenesis of SARS-CoV-2, including suppression of interferon type 1 (IFN-1) production, blockage of IFN-1 signaling, massive inflammatory response (so-called cytokine storm), and immune exhaustion [4]. The lethality of COVID-19 mainly pertains to the cytokine storm-induced thrombotic dysregulation and multi-organ failure [5]. During the cytokine storm, monocytes and macrophages mainly recruit, which may explain elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) [5]. Suppression of cytokine storm can potentially reduce the morbidity and mortality of COVID-19 [6]. Experimental studies have demonstrated the anti-inflammatory effect of low dose radiotherapy (LD-RT) by modulating the function of a variety of inflammatory cells, including endothelial cells, polymorphonuclear leukocytes, and macrophages [7-12]. Being such, LD-RT is considered as an opportunity to block the deadly cytokine storm and save the patients' lives. Herein we report the outcomes of the first 5 patients with COVID-19 pneumonia who were treated with low-dose whole-lung irradiation at Imam Hossein Educational Hospital, Tehran, Iran.

Patients And Methods

Ethical consideration

Before commencing the study, ethical clearance was obtained from the Ethical Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (Ethical code: IR.SBMU.RETECH.REC.1399.073). Prior to assigning the patients to radiotherapy, written informed consent was obtained.

Trial design and participants

This pilot clinical trial was conducted at Imam Hossein Educational Hospital to examine the safety and efficacy of single-fraction low-dose whole-lung irradiation in patients with COVID-19 pneumonia (Clinical Trial Registration Number NCT04390412). Individuals more than 60 years old who had clinical manifestations of COVID-19 with a positive polymerase chain reaction (PCR) of the nasopharyngeal swab, antibody test, or radiographic pneumonic consolidations that required oxygen supplementation (with $SpO_2 \leq 93\%$ and/or $PaO_2/FiO_2 \leq 300$ mmHg) were enrolled. For patients who had stable vital signs, we used SpO_2 to estimate PaO_2 [13]. The exclusion criteria were patients with hemodynamic instability or requiring mechanical ventilation, with a history of malignancy or heart failure, with contraindication for radiotherapy, with septic shock or end-organ failure, and with severe acute respiratory distress syndrome (with $PaO_2/FiO_2 \leq 100$ mmHg). The primary objectives were alteration in blood oxygenation (in terms of O2 saturation) and the number of hospital/ICU stay days. The secondary objectives were changes in laboratory results [including C-reactive peptide (CRP) and IL-6]. Clinical recovery was defined as the first day a subject was discharged or weaned from supplemental oxygen. A total of five of 40 eligible patients who approached were signed the consent and entered the study between May 2020 and June 2020. This clinical trial was approved by the Institutional Review Board.

Radiotherapy and follow-up

The treatment protocol was low-dose whole-lung irradiation in conjunction with the standard national guideline for the management of COVID-19 [14]. All participants allocated to receive single-fraction 0.5 Gy to the whole lungs. Radiation therapy planning was done on patients' diagnostic CT scans with patients in a supine position using a multislice spiral CT scanner without intravenous contrast. Planning target volume (PTV) covered both lungs in all patients with sufficient margins to account for the intrafraction movements (5–10 mm in our unit). All patients were planned with AP/PA photon fields with a three-dimensional conformal technique using the ISOgray treatment planning system. Vital signs, consciousness, performance status, blood oxygenation, CRP, and IL-6 were assessed at baseline and then daily following the irradiation. To assess core body temperature, we used tympanic membrane thermometry.

Results

From 21 May 2020 to 24 June 2020, forty patients with COVID-19 pneumonia were asked to participate in the trial and five of them (four males and one female) signed the consent form and received low-dose whole-lung irradiation at the Clinical Oncology department of Imam Hossein Hospital. All participants but one (patient #3) were positive for PCR of the nasopharyngeal swab. Patient #3 was admitted for her loss of consciousness, typical findings of COVID-19 pneumonia in chest CT scan, and elevated CRP level. The baseline characteristics of participants are summarized in **Table 1**. The patients were between 60 and 84 years old (mean: 71.8 years). All patients had comorbidities, including hypertension in three patients, past ischemic heart disease in two patients, and heart failure in one patient. At the time of admission, the median Karnofsky Performance Score (KPS) and Glasgow Coma Scale (GCS) were 60 (range 50-80) and 15 (range 10-15), respectively. LD-RT was delivered one to three days after admission day (median 2 days).

Table 1 Patients' demographics and clinical characteristics

Characteristics	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Gender	Male	Male	Female	Male	Male
Age	60	69	82	84	64
Comorbidity	Heart failure	HTN, IHD	IHD	HTN	HTN
KPS at admission	80	80	60	50	60
GCS at admission	15	15	10	15	15
Presenting symptom(s)	Shortness of breath	Fever & cough	depressed level of consciousness	Fever & cough	Shortness of breath & Cough
Vital signs at admission					
Pulse rate (per minute)	75	88	90	82	90
Respiratory rate (per minute)	12	16	20	12	15
Systolic blood pressure (mmHg)	110	130	110	140	120
Temperature (°C)	37.5	38.1	37.6	37	39
O_2 saturation (%)	87	86	75	89	74
P/F ratio	192	126.7	160	101.4	110
Between onset of symptoms and RT	1 day	3 days	3 days	2 days	2 days
Diagnosis of COVID-19	Clinical findings & PCR	Clinical findings & PCR	Clinical & imaging findings	Clinical findings & PCR	Clinical & imaging finding & PCR
O_2 supplementation	Facial mask	Nasal cannula	Facial mask with reservoir bag	Facial mask	Facial mask with reservoir bag
Length of stay at hospital after RT	7 days	5 days	3 days	3 days	6 days
Outcome	Discharged	Discharged	opted out of trial	Expired	Discharged

GCS, Glasgow coma scale; HTN, hypertension; IHD, ischemic heart disease; KPS, Karnofsky performance scale; PCR, Polymerase chain reaction; P/F ratio, PaO_2/FiO_2; RT; radiation therapy.

Four patients (80%) clinically recovered for their O_2 saturation and body temperature within one day. Of these, one patient (patient #3) chose to opt-out of the trial on the third day of irradiation. The mean time to discharge was 6 days for three patients (patient #1, #2, and #5). Patient #4 started to deteriorate with his O_2 saturation and body temperature from the first day of irradiation and died on the third day of irradiation. The laboratory findings (IL-6 and CRP) were in line with the clinical findings. Regarding IL-6, although the fluctuation pattern was documented in patient #1, the overall trendline was as per clinical findings. **Figure 1** demonstrates the change in clinical and laboratory findings following irradiation. During the observation, no acute skin, cardiac, pulmonary, or gastric toxicities were detected.

Discussion

This pilot trial had several important findings. First, for oxygen-dependent patients with COVID-19 pneumonia, whole-lung irradiation had a response rate of 80% in terms of clinical and paraclinical findings. Second, considering the patient opted-out the trial, the clinical recovery of patients receiving LD-RT was 75%. Third, our results showed that LD-RT starts to demonstrate its efficacy from the first day of irradiation. Fourth, CRP changes were consistent with the clinical findings, however, IL-6 showed a fluctuation pattern in one patient but followed the patient's clinical condition. This may be due to the short-term release of IL-6 upon irradiation [15]. Fifth, despite the clinical efficacy no acute toxicity was reported with LD-RT.

To the best of our knowledge, there are three other ongoing clinical trials applying LD-RT in patients with COVID-19 pneumonia. The summary of these trials is presented in **Table 2**.

Table 2 Overview of clinical trials evaluating the efficacy of low-dose whole-lung irradiation in patients with COVID-19 pneumonia

Clinical trial	RESCUE 1-19	COLOR-19	Present trial	VENTED
NCT number	NCT04366791	NCT04377477	NCT04390412	NCT04427566
Start date	April 29, 2020	May 6, 2020	May 15, 2020	June 11, 2020
Country of origin	United States	Italy	Iran	United States
Current status	Preliminary results are published in a non-peer reviewed journal	Recruiting patients	Pilot study (published)	Recruiting patients
Participants				
Gender	Male/Female	Male/Female	Male/Female	Male/Female
Age (years)	≥ 18	≥ 50	> 60	≥ 18
Clinical presentation	Receiving O_2 with NIV	Receiving O_2 with NIV	Receiving O_2 with NIV	Receiving O_2 with MV
Number of participants	5	30	5 (for pilot study)	24
Treatment plan	Single-fraction whole-lung irradiation	Single-fraction whole-lung irradiation	Single-fraction whole-lung irradiation + national guideline	Single-fraction whole-lung irradiation
Radiation dose (Gy)	1.5	0.7 (on average)	0.5 (+ an additional 0.5 if needed)	0.8
Primary Objectives	- Safety - Clinical recovery	- Length of hospital stay - No. of ICU admission	- Change in blood oxygenation - Length of hospital/ICU stay	Mortality rate after 30 days of ICU-based MV initiation

ICU, intensive care unit; MV, Mechanical ventilation; NIV, non-invasive ventilation.

To the best of our knowledge, the only available results are from RESCUE 1-19 trial that was recently published in a non-peer-reviewed journal [8]. The study detail is summarized in **Table 2**. In this pilot study, five patients with COVID-19 pneumonia received whole-lung irradiation with a single-fraction of 1.5 Gy. Four of the patients recovered rapidly and weaned from supplemental oxygen at a mean time of 1.5 days. In all patients, no acute toxicity was reported.

Similar findings were reached by our trial in terms of response rate and safety. However, we obtained these results with lower radiation doses. This finding supports the hypothesis that radiation doses as low as 0.5 Gy can modify the immune reaction of COVID-19 pneumonia by activation of macrophages with M2 phenotype [9]. We also included the national protocol for the management of COVID-19 in the treatment plan that may affect the results. We went beyond the RESCUE 1-19 trial by examining the body temperature, IL-6, and CRP of patients following irradiation.

Conclusion

Notwithstanding the small sample size, the interim results of the RESCUE 1-19 trial and ours demonstrate that LD-RT may be a successful treatment to save patients with severe COVID-19 pneumonia. Longer follow-up with more patients is needed to confirm this notion. Given the encouraging results of this pilot trial, the Ethical Committee of Shahid Beheshti University of Medical Sciences allowed continuing the trial using 1.0 Gy whole-lune irradiation.

Declarations

Conflicts of interest: The authors have no relevant relationships to disclose.
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Clinical trial registration number: NCT04390412
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References

[1] Our World in Data. (2020, June 28, 2020). Mortality risk of COVID-19, . Available: https://ourworldindata.org/coronavirus

[2] A. Shankar et al., "Cancer care delivery challenges amidst coronavirus disease–19 (COVID-19) outbreak: specific precautions for cancer patients and cancer care providers to prevent spread," Asian Pacific Journal of Cancer Prevention, vol. 21, no. 3, pp. 569-573, 2020.

[3] World Health Organization. (2020, June 28, 2020). Coronavirus disease 2019 (COVID-19) situation report – 46, . Available: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04adf_4

[4] F. Taghizadeh-Hesary and H. Akbari, "The powerful immune system against powerful COVID-19: A hypothesis," Medical Hypotheses, p. 109762, 2020.

[5] M. Soy, G. Keser, P. Atagündüz, F. Tabak, I. Atagündüz, and S. Kayhan, "Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment," Clinical Rheumatology, p. 1, 2020.

[6] P. Horby et al., "Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report," medRxiv, 2020.

[7] M. Arenas et al., "Anti-inflammatory effects of low-dose radiotherapy," Strahlentherapie und Onkologie, vol. 188, no. 11, pp. 975-981, 2012.

[8] C. B. Hess et al., "Low-Dose Whole-Lung Radiation for COVID-19 Pneumonia: Planned Day-7 Interim Analysis of a Registered Clinical Trial," medRxiv, 2020.

[9] P. C. Lara, J. Burgos, and D. Macias, "Low dose lung radiotherapy for COVID-19 pneumonia. The rationale for a cost-effective anti-inflammatory treatment," Clinical and Translational Radiation Oncology, 2020.

[10] A. Kefayat and F. Ghahremani, "Low dose radiation therapy for COVID-19 pneumonia: a double-edged sword," Radiotherapy and Oncology, 2020.

[11] C. Kirkby and M. Mackenzie, "Is low dose radiation therapy a potential treatment for COVID-19 pneumonia?," Radiotherapy and Oncology, 2020.

[12] E. V. POWELL, "Roentgen therapy of lobar pneumonia," Journal of the American Medical Association, vol. 110, no. 1, pp. 19-22, 1938.

[13] S. M. Gadrey et al., "Imputation of partial pressures of arterial oxygen using oximetry and its impact on sepsis diagnosis," Physiological Measurement, vol. 40, no. 11, p. 115008, 2019.

[14] Ministry of Health. (July 1, 2020). 19 □□□□□ □□□□□□□ □□ □□□□□ □□ □□□□□ □□□□□□□ □□ □□□□□□□□□□ □□□□□ □□□□□□□□□□. Available: http://treatment.sbmu.ac.ir/uploads/2-2-zip_saratan.zip

[15] V. De Sanctis et al., "Cytokines, fatigue, and cutaneous erythema in early stage breast cancer patients receiving adjuvant radiation therapy," BioMed research international, vol. 2014, 2014.

Figures

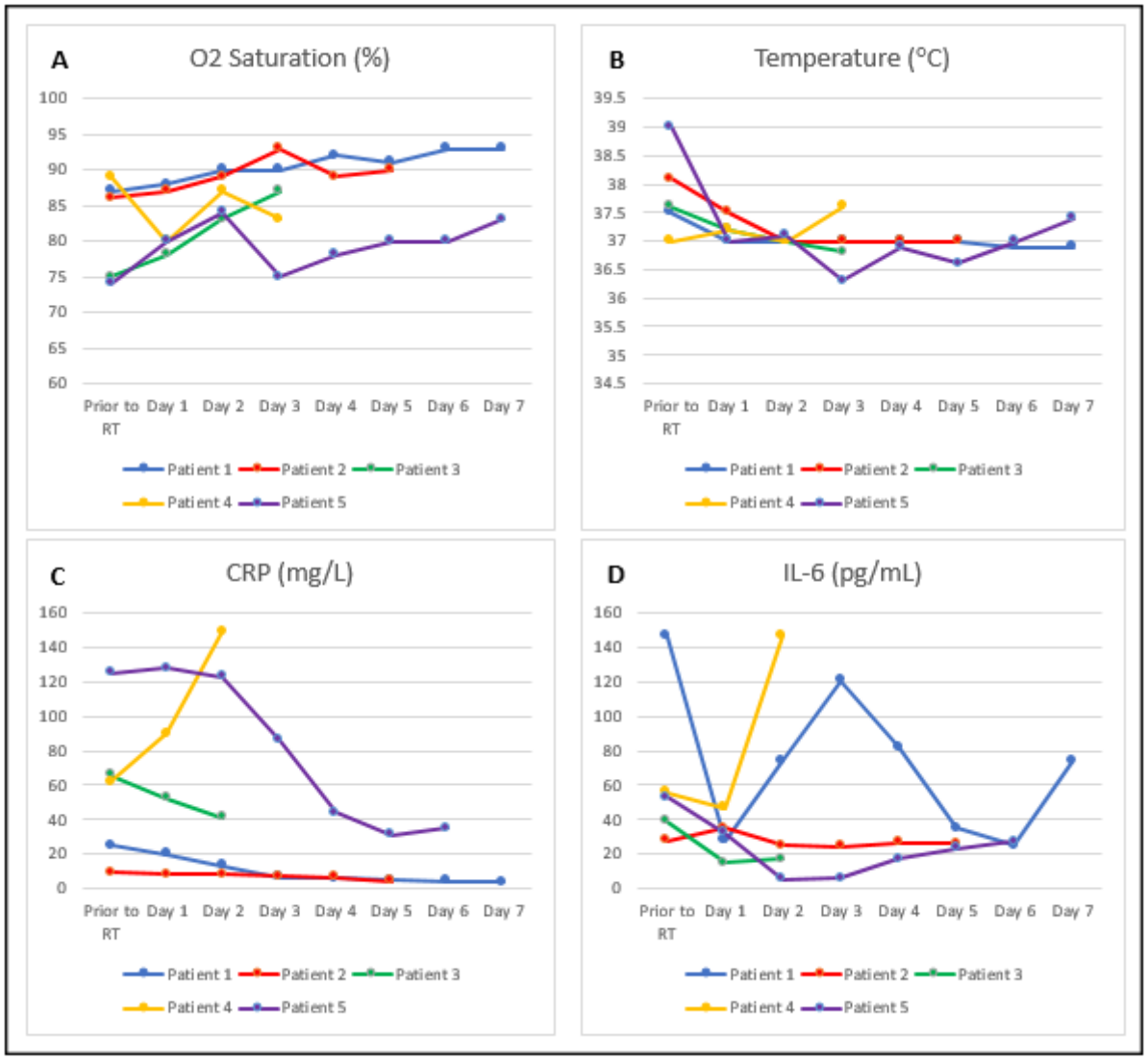

Figure 1

Evolution in time of (A) O2 saturation, (B) body temperature, (C) c-reactive peptide, and (D) IL-6 in patients with COVID-19 pneumonia following single-fraction whole-lung irradiation.