Early results of COVID-19 pneumonia cases treated with Ultra-Low doses of Radiotherapy (ULTRA-COVID study)

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Case Report

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Abstract

Introduction:

Since the outbreak of COVID-19 pandemic, healthcare system has focused its effort to find a treatment to avoid the fatal outcome of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Benefits and risks of systemic treatments are unclear. Radiotherapy could play a role in reducing the inflammatory response in the lungs and relieve life-threatening symptoms

Methods:

We designed a prospective study of Ultra-Low-Doses of Therapy with Radiation Applied to COVID-19 (ULTRA-COVID) for patients that are no candidates for invasive mechanical ventilation and show no improvement with medical therapy. (ClinicalTrials.gov Identifier: NCT04394182)

Results:

We present the preliminary results of two patients diagnosed with COVID-19 pneumonia treated with ULTRA-COVID. Significant clinical response is accompanied by lower radiological one, both have happened, achieving hospital discharge after 1 radiotherapy session over a period of 8 and 14 days, respectively.

Conclusion:

Preliminary clinical and radiological results suggest a potential benefit of treating COVID-19 pneumonia with ultra-LDRT.

Introduction

The onslaught of coronavirus disease 2019 (COVID-19) has challenged the healthcare's infrastructures worldwide. In this evolving situation with unanswered questions about proper clinical management and therapeutic approach, the healthcare system has struggled with a raise of critically ill patients (1).

Although most part of COVID-19 patients will be asymptomatic, complications such as severe pneumonia, respiratory failure, or acute respiratory distress syndrome (ARDS) can occur, leading to fatal consequences. Most of the time, these cases require of intensive care unit (ICU) admission and invasive mechanical ventilator (IMV) (2).

In these critically ill patients, the host response against the virus appears to be mediated by a 'cytokine storm or release syndrome (CRS)', leading to a macrophage-mediated inflammatory mechanism (inflammatory M1-phenotype) (3) and ARDS, in the form of a bilateral pneumonitis. In terms to prevent progression to the critical state, it has also been proposed that the CRS can be safely treated by a single course of ultra-low-dose of radiotherapy (Ultra-LDRT) < 1 Gy (2,4) which could potentially alleviate symptoms of respiratory distress quickly, helping to reduce mortality without significant long-term sequelae (5).

As Confucius said: "Study the past if you would define the future", indeed the past may hold the key. The use of a single ultra-LDRT to treat pneumonia was reported in the early 1900s in 15 studies, involving 863 patients. It showed 80-85% rates of inflammatory relief success, and a mortality decrease from 30% to 10% (6). Besides, the use of RT in non-malignant inflammatory conditions (7) and its anti-inflammatory properties such as decreasing levels of pro-inflammatory cells including cytokines and macrophages (polarizing them toward an anti-inflammatory M2- like phenotype) have been considered in our study (8-10).

Therefore, we hypothesized that Ultra-LDRT applied to COVID-19 patients (ULTRA-COVID) could play a role in reducing the lungs inflammatory response, counteracting the CRS, reducing the risk of requiring IMV and relieve life-threatening symptoms (4).

Given the need to rapidly communicate information on the global clinical effort against COVID-19 we would like to share this report that describes the eligible criteria, clinical course, treatment and evolution of our first two COVID-19 cases treated with ultra-LDRT.

Methods

After approval by an Ethics Committee, a prospective study was designed and initiated at La Milagrosa Hospital (Madrid, Spain) to treat COVID-19 patients with Ultra-LDRT. The main purpose of the study was to analyze the efficacy of LDRT, as an anti-inflammatory intention, in patients with SARS-Cov-2 pneumonia with a poor response to medical treatment and would otherwise have no other treatment except IMV, to which they were no candidates. Given the extremely unusual situation and poor prognosis of the disease if left untreated the study has been designed without a control arm, to evaluate security and efficiency of the treatment.

We reviewed the medical records of these patients to evaluate biographical data and medical history. Based on that, Charlson Comorbidity Index (CCI) (>or< 6 score) (11) was calculated for each patient. Previously to the treatment, diagnosis of COVID-19 was proven by polymerase-chain-reaction (PCR), as well as blood gas analysis was performed to calculate the PaO₂ / FiO₂ (>or< 300 mmHg). We measured the oxygen saturation status (>or< 93%) and the ventilatory support with oxygen therapy (from less to more: Nasal Cannula-NC-; Ventimask -VMK- and VMK with reservoir). Blood analysis was obtained to assess inflammatory and immunological parameters, such as lymphocytes, IL-6, D-dimer, ferritin, LDH, C Reactive Protein (CRP) and fibrinogen (12,13).

All patients underwent a baseline thoracic computed tomography (CT) scan, in which we assessed the radiological involvement through the Total Severity Score (TSS) (14). This score values ranged from 0 to 20 according to the sum of the percentage of involvement of each 5 lung lobes, which were scored from 0 to 4 points. The same senior thoracic radiologist also estimated the lung involvement qualitatively (subjectively) as mild (TSS 0-5), moderate (TSS 6-15), or severe (TSS >15). A worsening of TSS during the hospital stay or score at admission > 5 was considered as inclusion criteria.

Additionally, Eastern Cooperative Oncology Group (ECOG) (15) (Status ≤ 3), life expectancy (> 1 month) at hospital admission for COVID-19 and previous thoracic RT (relative-criteria) or chemotherapy history, was assessed.

All the patients were provided and signed a written informed consent.

Treatment protocol:

Ultra-LDRT was administered for 6-MV photon beams by a Tomotherapy Hi-Art Accuray® under institutional safety procedures.

The simulation images were acquired by megavoltage CT (MVCT) in the Tomotherapy®. Immobilization was done in supine position with thorax board with arms support. Three radiopaque-marks were placed on the patient skin. The contouring was made in Pinnacle® station and dosimetry in Tomotherapy Hi-Art Planning Station®. The planning target volume (PTV) was defined as both whole lungs extended 1cm isotropically. No dose constraints were applied to surrounding organs. Regarding the target coverage, the 90% of PTV should receive 100% of the prescription dose and the maximum hotspots dose should be <110%.

Verification imaging was carried out using a MVCT limited to the central third of the thorax, to correct for any error. Total single dose administered was 0.8 Gy in a 3-minutes session.

Response evaluation:

The radiological response, assessed by TSS change, was evaluated from a thoracic CT scan 7 days and 4 weeks after the treatment. Radiological improvement was defined as mild (TSS decrease <3 points), moderate (TSS decrease 3-5 points), or high (TSS decrease >5 points) from the baseline CT.

The clinical response was evaluated by pulse-oximetry, blood gas analysis and labs at days 2, 5, 7, and at 4 weeks after Ultra-LDRT. Two months later, oxygen status and pulse-oximetry were evaluated again. SatO₂>93%, descent of oxygen therapy support, PaO₂ / FiO₂ > 300 mmHg and the achievement of normal range value in one or more of the inflammatory and immunological parameters, was considered as clinical improvement.

Toxicity was assessed according to the NIH Common Terminology Criteria for Adverse Events (CTCAE v5.0) scale (16).

Cases report

After establishing our protocol, 4 patients with COVID-19 pneumonia were candidates for LDRT. One refused to participate and another died before receiving the treatment. The other two participants met the study criteria and are discussed below.

Patients' clinical characteristics are summarized in Table 1.

Patient 1

An 80-year-old-man presented to the emergency department with a 3-day history of dyspnea, cough and chest pain. He showed 70% O₂-Sat and tachypnea. Pulmonary auscultation revealed crackles predominantly in bilateral lower two-thirds. During hospitalization his evolution was torpid with a 87% O₂-Sat needing of increased ventilatory support (50% reservoir, 15L of flow). The baseline CT showed bilateral pneumonia and extensive bilateral ground-glass opacities corresponding to an acute inflammatory stage. (*Figure 1.A*)

Patient 2

A 65-years-old-woman debuted with dry cough. A week after, she reported to the emergency department with persistent cough, fever, asthenia and dysgeusia, hence she was admitted. During hospitalization, radiological study showed pneumomediastinum, making her not a candidate to IMV. After 5 weeks of admission and several desaturation episodes her respiratory status evolved until support with VMK 40%. The CT scan ruled out the possibility of Pulmonary Embolism and showed a moderate pneumonia, bronchiectasis, and subpleural bands suggesting an advanced inflammation phase (*Figure 1.D*).

The medical therapy administrated to both patients consisted of lopinavir/ritonavir, hydroxychloroquine, azithromycin, piperazillin/tazobactam, prophylactic doses of low- molecular-weight-heparins (LMWHs), corticosteroids (methyprednisolone 250mg x 3 boluses) and Tocilizumab (single dose). Despite this pharmacotherapy, prone position and the oxygen support, the respiratory status and high inflammatory parameters of both patients kept worsening. At this point, their enrollment in the ULTRA-COVID study was decided and a single ultra-LDRT was administered on April 23rd, 2020.

Results

Clinical Status

Respiratory status improved rapidly in both patients. Patient 1 showed an improvement on his O2- Sat and PaFiO2 (>300) two days after the treatment. Supplemental oxygen with 2L NC was discontinued at day five and he was discharged on day eight after ULTRA-COVID with 95% O2- Sat values while he was breathing ambient air, keeping this breath status 1 and 2 months later.

Patient 2 showed a slower recovery, achieving less need of oxygen support at 2, 5 and 7 days after the treatment, intermittently requiring 2L NC 1 month after and, finally, two months later no longer need of it. PaFiO2 passed 300mmHg at day 5. She was discharged 14 days after ultra- LDRT.

Subjectively, both patients reported improvement of symptoms such as less asthenia and dyspnea. After 48h the inflammatory parameters showed a decrease, however they fluctuated or stabilized on subsequent controls. Above all, we highlight the decrease in IL-6 (CRS). The viral status results by PCR 1 month after were positive in patient 1 and negative in patient 2. Immune state showed immunity measured as positive IgG by rapid test.

No significant or acute adverse events were observed, even after two months of follow-up period.

Radiological status

ULTRA-COVID intervention showed an improvement on the TSS score in both patients after the first scan, with a higher improvement on patient 1 (*Table 2*). The first CT-scan on patient 1 showed fibrotic subpleural bands and bronchial and vascular retraction was also present (*Figure 1.B*). The second scan-at 4 weeks showed fewer consolidation areas, although moderate lung involvement persisted. (*Figure 1.C*)

Patient 2 first scan showed the resolution of the pneumomediastinum, fibrosis and loss of volume were present, most accused during the monthly control, as well as fewer consolidation areas. Globally, we observed an improvement from moderate to mild-moderate pattern. (*Figure 1.E and 1.F*).

Discussion

Experimental therapies have been used since the outbreak of the COVID-19 pandemic and expert societies guided to enroll patients in clinical studies when possible, as no standard treatment exists so far. Although other drugs have been tested, the only potential supportive treatment for COVID- 19 appears to be an IL-6 inhibitor, tocilizumab (17).

RT is a cost-effective non-toxic treatment available in most hospitals (18). The radiobiological basis is not well known, but literature available suggests that the ultra-LDRT would modulate the overreacted immune-landscape (8-10). The design of clinical trials to investigate RT effectiveness in COVID-19 scenario has been justified by the RT community and ongoing trials such as the one in Atlanta (RESCUE1-19), Italy (COLOR-19), 2 in Spain (IPACOVID and LOWRAD-Cov19), Iran (NCT04390412), Ohio (VENTED), New Delhi (NCT04394793) and Massachusetts (NCT04393948) exist (19). Despite these ongoing trials, the patient recruitment is still challenging.

With ULTRA-COVID study we wanted to analyze the anti-inflammatory effect of ultra-LDRT and its potential use to mitigate this pandemic. We discuss the potential activity of ultra-LDRT by presenting clinical recovery of two patients with SARS-Cov-2 pneumonia with a poor response to standard medical therapy and would otherwise have no other treatment than IMV, for which they were not candidates. To our knowledge, these are the first results of using a single 0.8 Gy of helicoidal-RT for COVID-19 pneumonia treatment, with a follow-up of 2 months, and adding lung CT scan and immunity status assess.

We agree that the timing of the irradiation in relation to disease progression is likely to influence treatment outcomes. However, it is still unclear the best timing for ultra-LDRT administration. It appears that is imperative to distinguish between the dominant viral phase versus the host inflammatory-cytokines-mediated response. Literature supports that at chronic stages of disease low-dose irradiation might not be as efficient as in the early progressive stage (20). In fact, in our study, the faster recovery and the greater radiological improvement in patient 1 who presented with an early stage of the disease, as opposed to patient 2, whose disease stage was advanced, suggests that the earlier we apply the ultra-LDRT in the acute inflammation host phase, the better the global response.

We defend that ultra-LDRT target is the cytokine storm and the treatment key is anticipating the need of ICU and IMV, because not all critical cases are candidates for it (19,20). Between 7 to 12 days from the onset of the symptoms appears to be the most effective moment to apply LDRT (3).

The use of RT could stop the progression to an advance stage of the disease; and this could help curb down the death rates, now 3.4% on average, and higher among elder and ICU patients (21). The optimal dose of RT is unknown with evidence supporting 0.5-1Gy (2,4,5). The average prescription doses of the ongoing trials are 0.5 and 0.7 Gy in a single dose and; optionally, an additional 0.5 Gy fraction 48h later. We decided to escalate dose and apply 0.8 Gy in a single session given the unawareness about the virus' response and because this is the minimum effective dose of the technique used (helicoidal Tomotherapy).

We believe that the strengths of our study are that we have been rigorous in our inclusion criteria. In addition, patients have been followed by CT scan and, although significant clinical response is accompanied by lower radiological one, both have happened. Finally, we have performed viral and immunity status control by PCR and rapid antibodies tests, respectively.

Although LDRT may increase the effectiveness of anti-viral immune responses, it does not decrease the viability of virus directly (20). It could be the reason why the PCR of patient 1 was positive 4 weeks later.

The main general concern about the RT use in non-neoplastic disease is its carcinogenesis risk. Evidence available supports this risk is quite scarce when low-doses are used (0.1-4/1000- $<1/10000$) (22-24). Given this, the old age of patients and the life-threatening condition they face, we believe it could be assumed. Nevertheless, a bigger study sample and a longer follow-up period is necessary to ratify this.

Our results should be understood as preliminary and more definitive results are expected from this prospective study as well as from other ongoing clinical trials. A bigger study will need to face the possible bias, such as the lack of study recruitment due to a decrease in COVID-19 cases when the trial started.

We also consider the possible lead time bias as a factor in our study, due to the difference disease phase in which patients were included. Another survival factor that could interfere with our results is the drug response, above all, tocilizumab.

Despite these limitations, the preliminary results on our first two patients suggest a good response to RT and encourage us to continue.

Researchers at Emory University have also shared the preliminary results of day-7 analysis of their phase I/II trial (RESCUE1-19). Five patients were treated with a single dose of 1.5Gy. They have also supported that LDRT appears to be safe without any acute toxicities noted and have shown early promise of efficacy. (27)

This report highlights the importance of identifying those patients and could benefit from LDRT in order to decrease the worsening of the disease, especially in those patients who cannot benefit from IMV.

Further studies could demonstrate the effectiveness of LDRT, considering it as an alternative co-treatment with pharmacotherapy (or even exclusive). This could be of a great importance in countries without or limited access to expensive drugs or ICUs where it can, even become a standard of care in SARS-CoV-2 management. Additionally, we support that it could have an impact on other possible viral pneumonia epidemics in which CRS has been observed (28).

Conclusion

Preliminary clinical and radiological results suggest a potential benefit of treating SARS-Cov-2 pneumonia with ultra-LDRT during the acute inflammatory phase with a positive impact on the disease's evolution.

Declarations

Ethic statements:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Approved by the HM Hospitales Group Ethics Committee (CEIm) on April 21st. CEIm code 20.4.1597-GHM

Consent statement:

Patients signed consent was obtained after verbal information on the procedure, objective and secondary effects of the treatment.

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Code availability:

Not applicable

Competing Interests:

The authors declare no competing interests

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Tables

Table 1. Patients Characteristics		
Variables	Patient 1	Patient 2
Gender	Male	Female
Ethnic	South-American	Caucasian
Age	80	65
Smoking History	No	No
Medical History	Hypertension Right lower limb amputation due to myxofibrosarcoma on remission.	Asthma Lumbar stenosis Uterine polypectomy
CCI	2	2
Previous thoracic RT	No	No
Chemotherapy History	No	No
Onset symptoms Date	12.04.2020	12.03.2020
Admitted Hospital Date	15.04.2020	19.03.2020
Onset Symptoms	Dyspnea, cough, mild fever and chest pain	Dry cough, fever, asthenia and dysgeusia
ECOG at admission	3	2
T (°C)	37,5°	38,5°
BP (mmHg)	153/80	120/70
Heart Rate (bpm)	92	100
Oxygen Saturation	70%	87%
Cardiac auscultation	Rhythm without murmurs	Tachycardia heart rhythm without murmurs
Pulmonary auscultation	Crackles predominantly in bilateral lower 2/3	Decrease in vesicular murmur. Crackles predominantly bibasal and left
CCI= Charlson Comorbidity Index; ECOG= Eastern Cooperative Oncology Group; T=Temperature; °C= degrees Celsius; BP=Blood Pressure; mmHg= millimeters of mercury; bpm=beats per minute		

Table 2. Results										
	Patient 1					Patient 2				
	Pre-RT (Baseline)	Day2	Day5	Day7	Month1	Pre-RT (Baseline)	Day2	Day5	Day7	Month1
Blood Test										
D-Dimer(mg/dl)	4.11	1.7	1.13	0.80	0.27	1	0.44	0.42	0.41	0.30
IL-6(pg/ml)	112.2	67.1	40.1	39.8	7.76	46	20	12.1	6.2	4.19
Hb(g/dl)	15.8	15.0	15.6	15.9	15.0	12	10.7	9.9	9.9	12.9
CRP(mg/dl)	0.4	0.10	0.00	0.10	0.14	1	0.10	0.30	0.10	0.02
Ferritin (ng/ml)	747	685	721	775	367	916	647	545	469	185
Lymphocytes (cel/ul and %)	760 (8%)	750 (14%)	760 (14.4%)	670 (13.7%)	1509 (30%)	740 (27.5%)	1310 (30.5%)	760 (22.6%)	1100 (24.6%)	700 (6.6%)
LDH(UL/l)	457	350	341	346	396	727	567	607	523	672
Fibrinogen(mg/dl)	598	443	458	395	325	492.00	516	419	557	260
Radiological assessment (CT scan)										
CT TSS	16			11	9	10			9	7
RUL TSS	4			3	3	1			1	1
RML TSS	3			2	2	1			1	1
RLL TSS	3			2	2	3			2	2
LUL TSS	3			2	1	2			2	1
LLL TSS	3			2	1	3			3	2
CT subjective	Severe			Moderate	Moderate	Moderate			Moderate	Mild- Moderate
Oxygen Status										
Support	VMK 40% (10L)	NC 2L	Part time NC	None	None	VMK40% (10L)	VMK 35% (8L)	VMK 30% (6L)	Part time NC 2L	Patient demand (NC 2L)
O2-Sat	90%	94%	94%	95%	95-97%	91%	92%	92%	94%	97%
PaFiO2	272	327				268	270	330		
COVID-19 status										
PCR	+			+	-	+			+	-
Rapid Test					IgG+					IgG+
<i>RT=Radiotherapy; Normal range values: IL-6 (Interleukin-6) <7 pg/ml; D-Dimer <0.5 mg/l; Hb (Hemoglobin) males 14-18 and females 12-16; CRP (C Reactive Protein) < 0.500 mg/dl; Ferritin: males 22-322 ng/ml and females 10-291 ng/ml; LDH (Lactate dehydrogenase) 208-378 U/L; Fibrinogen 200-400 mg/dl; Lymphocytes 45%. CT= Computed Tomography; RUL =Right upper lobe; RML(Right middle lobe); RLL (Right lower lobe); LUL(Left upper lobe); LLL(Left lower lobe). TSS=Total Severity Score. 1=0-25%; 2=26-50%; 3=51-75%; 4= 76-100%; VMK= Venturi Mask (Ventimask); NC= Nasal Cannula; O2-Sat=Oxygen Saturation; PCR=Polymerase-Chain-Reaction; Ig= immunoglobulin.</i>										

Figures

Figure 1

CT scan evaluation