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LETTER

Low dose radiation therapy for COVID-19 pneumonia: brief review of the evidence

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Introduction

During this COVID-19 pandemic prevention of the virus with a vaccine has not yet been successful. Treatment of those patients with the life threatening illness COVID-19 pneumonia is a priority to reduce mortality which in the world setting sits at about 5% of reported cases. Fortunately in Australia, the mortality is currently about 1% of reported cases. Most treatment options focus on existing drugs, some with positive early trial results such as the anti-inflammatory drug dexamethasone which shows a modest overall improvement in survival for non-invasive ventilated patients but a potential one third improvement in survival for patients receiving invasive mechanical ventilation (mortality 29.0% treated vs 40.7% control) [1].

This letter focuses on a novel approach to the treatment of COVID-19 pneumonia using a low dose of external beam radiation x-rays. So named "Low Dose Radiation Therapy" (LDRT). There are multiple historical cohort studies mostly dating from the 1930s that report the administration of one low dose fraction of x-rays (usually less than 0.5 Gy) to treat viral and bacterial pneumonia. Recent publications have suggested that a similar approach could be attempted in clinical trials involving pneumonia resistant COVID-19 patients as a treatment that may improve outcomes. In-fact a small clinical trial has started with 4 out of 5 patients treated with 1.5 Gy LDRT surviving [2].

This letter summarises key historical cohort data and discusses the level of evidence it provides as well as publications that point to the anti-inflammatory potential of doses of LDRT. The two most recent letters that have been published on this subject are by Kirkby and Mackenzie in Radiotherapy and Oncology [3] and Doss in Physics in Medicine & Biology [4]. There is also a very recent point/counterpoint published in medical physics on this subject [5]. While these papers provide several historical references to the cohort data they do not provide explicit detail of some of the compelling evidence provided by these historical publications.

Historical evidence

The key comprehensive review paper summarising historical cohort results was written by Calabrese et al. [6]. Note this was published in 2013, which predates the COVID-19 pandemic by seven years! They summarise results of 15 historical studies of treating non-responsive pneumonia with radiation from 1905 onward. Most reports are from 1930 to 1946. Dose levels ranged from 0.3 to 0.5 Gy. In summary, the 15 case reports outlined found 863 cases treated and 717 cases cured (17% not cured). The largest reported cohort was that of Powell [7] who reported 231 cases treated and 215 cases cured (7% not cured). As an anecdote, Powell aimed to randomise his patients but his staff would not permit this to continue as they observed relief from respiratory distress within 0.5 to 3 h after treatment.

It is important to note these studies represent data from all comer types of pneumonia in a time when advanced intensive care including the use of respirators would not have been an option. While negative pressure iron lungs were used in the 1930s to treat polio, positive pressure ventilators were not utilised until the 1960s. While control group comparisons were attempted in some studies these were not achieved. These were case reports not reflecting the randomization of subjects. Note the mortality rate for untreated pneumonia was about 30% at that time. The introduction of sulfanilamides and then penicillin in the 1940s to treat bacterial pneumonia were the main contributors to the discontinued use of LDRT. Since 1946 there have been no reports of LDRT to treat pneumonia until the current new report 74 years later in 2020 [2].

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Mechanism of action

Seriously ill COVID-19 pneumonia patients usually acquire acute respiratory distress syndrome (ARDS) and sequential organ failure. ARDS requires the use of supplemental oxygen and mechanical ventilator support, and yet despite such measures, high mortality is occurring in ventilated patients is occurring (30–40%). The main contributor to ARDS appears to be the so-called "cytokine storm". The inflammatory response is characterized by for example increased interleukin (IL)-2, IL-7 and macrophage inflammatory protein (1-α). Patients can be screened for this (e.g. decreasing platelet count). A concise and detailed explanation of mechanisms that invoke a cytokine storm is given by Mehta [8].

The basic hypothesis for LDRT action is that x-rays may induce anti-inflammatory phenotypes that could perhaps help abate the cytokine storm that is prevalent at end stage pneumonia [9]. Historical reports suggest a dose of between 0.35 and 0.5 Gy may be the optimal dose while higher doses may induce the opposite effect and may induce increased inflammation [6]. It is confounding that the first clinical trial using 1.5 Gy is high compared with other historical pneumonia treatment doses [2]. There has been the continued use of LDRT to treat a range of mild inflammatory conditions. In particular, they have been used in Germany to treat osteoarthritis. The dose for mild inflammatory conditions is usually 1 Gy per fraction with six fractions to 6 Gy total [10].

Target organs and potential risks

Caution is advised by Kefayat and Ghahhremani who recently published in the journal of Radiotherapy and Oncology [11]. They point out that Radiotherapy has been used for inhibition of low-level inflammation and not proven in the modern setting in humans to treat the cytokine storm which affects a significant amount of these patients [9].

Sufficient time window may be crirtical for effect to convert to survival. It appears there is some inference that while only a few hours may be required for patient improvement to be observed however for patient survival LDRT may need to be administered several days before the acute stage of pneumonia, an excellent discussion on the sparse evidence for optimum timing is given by Trott et al. [12].

COVID-19 has been characterized as a "disease of the sick" meaning many mortalities occur in patients with pre-existing medical health conditions such as diabetes, high blood pressure and or ischemic heart disease. Most mortality occurs in the elderly cohort because elderly patients are more likely to have pre-existing medical conditions. For example in Australia as of late July 6 out of 167 deaths have been for patients under 60 years of age and no one has died under 40 years of age. It is also likely the comorbidity status of patients would require extreme caution in trial design to avoid skewed results.

Lungs seem to be the target to induce a local systemic response. There is a frustrating lack of detail about technical delivery techniques. Dose levels are extremely low when it comes to comparison with radiotherapy regimens, These doses are approximately 100 times lower than a typical dose prescribed for a radiotherapy regimen. There are no known radiation effects to lung at less than 7 Gy and 0.5–1.5 Gy is well below this dose level [13]. Given the low therapeutic dose, a simple AP/PA treatment method with basic treatment planning may be appropriate for initial clinical trials. If these trials prove successful refining delivery using organ shielding (e.g. heart) and including or excluding nodes and some spinal cord could be assessed in clinical trial design.

Radiotherapy carries with it a 2nd cancer risk from administering the radiation. This has been calculated as follows. The stochastic excess absolute risk for a radiation-induced second primary cancer for a dose of 0.5 Gy and 1.5 Gy is calculated using Preston [14]

$$EAR\ per\ 10000\ person_{years} = \beta D e^{\theta(\text{agex}-25)}\left(\frac{age}{50}\right)^{\gamma} \quad (1)$$

with the $\beta = 10$, $\theta = -0.05$ and $\gamma = 1$. The increase in excess absolute risk is about 0.4% for 0.5 Gy and 1.2% for 1.5 Gy over a 20 year period. While the error margins for radiation-induced 2nd cancer estimates are usually large (40%). The magnitude of risk is so low particularly for an elderly patient cohort that the potential treatment benefit would far outweigh the risk in this scenario.

Treatment device options

The use of diagnostic x-ray machines or CT which typically deliver between 0.1 and 10 mGy for diagnostic scans and are not designed to deliver therapeutic doses may not be a practical option. If mobile radiotherapy machines were readily available shielding them would be the main roadblock to treating patients in-situ in A&E departments.

Transporting the patient and treating them in a radiotherapy department is the best current option. The highly skilled staff and specialised equipment seems the safest approach. A current medical linear accelerator can deliver 0.5 Gy in less than 10 s and 1.5 Gy in 30 s, however patient transfer to treatment couch and alignment would likely take about 15 min "in treatment bunker" session to complete. There could be a risk of infection to other immune-compromised

cancer patients receiving radiotherapy. Due to the current COVID-19 pandemic, most radiotherapy departments have well developed protocols for dealing with the treatment of COVID-19 patients by separation from other radiotherapy patients and infection control [15]. Hence stringent infection control measures already exist in these departments which should ameliorate this risk. There are over 11,000 medical linear accelerators worldwide used to treat about 50% of all cancer patients in developed countries [16]. While access to medical linear accelerators in developing countries is more economically challenging due to high capital cost of equipment, once installed each medical linear accelerator can treat several hundred patients per year and hence they are a relatively low-cost treatment option [16].

Concluding remarks

While dexamethasone is a convenient treatment option with similar anti-inflammatory intent to LDRT. Dexamethasone is a steroid with one contraindication being diabetes. Given the severity of symptoms in many cases, this would be an acceptable risk. LDRT involves just one visit to a radiotherapy department which is also a convenient low-risk treatment option with minimal side effects. The historical trials data should, however, be regarded as low-level evidence (level 4 cohort studies). Currently, the new clinical trial data is encouraging and there is another NIH clinical trial that has also been approved for accrual [17]. Note the mature outcomes from these two trial have not yet been reported.

Having more than one weapon in the treatment arsenal may be the best approach for the treatment of patients with life-threatening side effects from COVID-19 pneumonia. This may enable clinicians to use combined therapies or to personalise treatment based on patient comorbidities. Keeping this in mind giving LDRT as a treatment for COVID-19 pneumonia may be worth a shot!

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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