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Authors: Wilson, George D., Mehta, Minesh P., Welsh, James S., Chakravarti, Arnab, Rogers, C. Leland, et al.

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REVIEW

Investigating Low-Dose Thoracic Radiation as a Treatment for COVID-19 Patients to Prevent Respiratory Failure

George D. Wilson,[a,1] Minesh P. Mehta,[b] James S. Welsh,[c] Arnab Chakravarti,[d] C. Leland Rogers[e] and James Fontanesi[a]

[a] *Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan;* [b] *Miami Cancer Institute, Baptist Health South Florida, Miami, Florida;* [c] *Loyola University Chicago, Stritch School of Medicine, Department of Radiation Oncology, Maywood, Illinois;* [d] *Department of Radiation Oncology, Ohio State University, Columbus, Ohio; and* [e] *Barrow Neurological Institute, Phoenix, Arizona*

THE COVID-19 PROBLEM

Coronavirus disease 2019 (COVID-19) is the name given to the newly emerged respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The pandemic continues to spread worldwide with over 3 million people infected and more than 208,000 deaths, numbers that are escalating on a daily basis. Mortality ranges from 1–6%, but these are very crude estimates, since the denominator is usually substantially underestimated due to inadequate testing, and the numerator is often defined differently in different nations. Most patients with COVID-19 exhibit mild-to-moderate symptoms, but approximately 15% progress to a severe ''pneumonic'' state and approximately 5% eventually develop cardiopulmonary dysregulation that has been likened to a form of acute respiratory distress syndrome (ARDS). However, there is now a growing understanding that it comprises a very different and unique clinical category, which may include septic shock, multiple micro-thromboemboli, and/or multiple organ failure (*1, 2*). The mainstay of treatment consists of a three-pronged approach, including symptomatic and supportive management such as oxygen therapy, with or without mechanical ventilation, investigational antiviral therapies such as Remdesivir, convalescent plasma (passive antibody transfer), etc., and investigational measures to counter the cytokine storm which is the presumed underlying mechanism of cardiopulmonary failure. Some estimates suggest that 50% or more of all ventilated patients die, and unless extubation is rapidly achieved, this number approaches or even exceeds 80%.

Several antiviral drugs, including the adenosine analogue chain terminating agent remdesivir, are actively undergoing testing; however, to date none have been approved for COVID-19. Additionally, over two dozen vaccines, mesenchymal stem cell infusion therapy, as well as convalescent plasma therapy approaches are in development. Hydroxychloroquine and azithromycin have been extensively promoted with little prospective data, in addition to a number of other empiric therapies. Approaches that directly target the virus (such as microRNA-based therapies) or block viral entry (since the binding receptor is well known and can easily be targeted) are under active investigation. However, it is not the viral infection that is the cause of death, but rather the cytokine storm unleashed by the immune system in response to the pathogen (*3*). Thus, treatments that address the immunopathology of the cytokine storm are becoming a major focus in terms of improving the survival of patients who are rapidly hurtling toward a ''pneumonic'', respiratory-failure state (*4*).

THE IMMUNE RESPONSE IN COVID-19 PATIENTS

SARS-CoV-2 infection can activate both innate and adaptive immune responses. The virus enters the cell through the angiotensin-converting enzyme-2 (ACE2) receptor (*5*). Early published studies described the presence of ACE2 receptors predominantly in the heart, kidneys and testes, and at a lower level in a wide variety of other tissues, particularly the colon and lung (*6*). In the lung, ACE2 receptor-expressing cells are mainly alveolar type-1 or type-2 pneumocytes and vascular endothelial cells but also lung epithelial stem/progenitor cells (*7*). After binding the ACE2 receptor, the virus fuses to the membrane, is endocytosed and releases viral RNA by uncoating itself. These viral RNAs, as pathogen-associated molecular patterns (PAMPs), are detected by the pattern recognition receptors (PRRs) which are usually toll-like receptors (TLR) 3, TLR7, TLR8 and TLR9. These receptors sense viral RNA and DNA in the endosome (*8*). TLR activation triggers downstream cascades, leading to the production of type I interferons (IFN-α/β) and a series of pro-inflammatory cytokines

[1] Address for correspondence: William Beaumont Hospital, 3811 W. Thirteen Mile Rd., 105-RI, Royal Oak, Michigan 48073; email: george.wilson@beaumont.edu.

including TNF-α, IL-6 and IL-12. This results in the formation of $CD8^+$ specific cytotoxic T cells which, through the $CD4^+$ helper T cells leads to the formation of antigen-specific B cells and antibody production. In patients with mild disease the adaptive immune response controls the infection and leads to recovery.

However, patients with severe COVID-19 infections may not be able to mount an adequate immune response, and lymphopenia is a common clinical feature with drastically reduced $CD4^+$ T cells, $CD8^+$ T cells, B cells and natural killer (NK) cells (*9*). These impaired adaptive immune responses may lead to harmful tissue damage seen both locally in the lung and systemically. More commonly, however, patients with severe COVID-19 exhibit a cytokine storm (*10*) characterized by substantially elevated serum levels of pro-inflammatory cytokines including IL-6 and IL-1β, as well as IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1α and TNF-α (*4*). High levels of pro-inflammatory cytokines may lead to shock and tissue damage in the heart, liver and kidney, as well as respiratory failure or multiple organ failure. These cytokines mediate extensive pulmonary pathology, leading to massive infiltration of neutrophils and macrophages, diffuse alveolar damage with the formation of hyaline membranes and a diffuse thickening of the alveolar wall. Respiratory failure is the leading cause of mortality in these patients.

The study of COVID19 is a rapidly developing field where much of the literature appears as epubs and may not have undergone extensive peer review. This limitation of the current literature requires critical consideration. However, this is balanced against the need to share new knowledge that may add to the collective experience and help move forward treatments for this disease. Analysis of inflammation-related indicators and disease severity was performed in a group of mild, severe or critical patients, and the findings showed that inflammation was closely related to severity of COVID-19, and that IL-6, TNF-α and IL-8 might be promising therapeutic targets (*11*). Indeed, IL-6 is emerging as a strong predictor of respiratory failure in hospitalized symptomatic COVID-18 patients (*12*) and as playing a key role in the cytokine storm. It is emerging as a promising therapeutic target with preliminary evidence that blockade of its receptor using tocilizumab leads to recovery in severe COVID-19 patients (*13*). These developing human data on the importance of IL-6 are supported by extensive animal data on the effects of low-dose radiation on a variety of animal diseases, including collagen-induced arthritis (CIA), experimental encephalomyelitis (EAE), and systemic lupus erythematosus, which were summarized in an extensive review (*14*). A unifying theme in these rodent models of human disease was that IL-6 levels were constitutively upregulated in the majority of the diseases and were significantly inhibited by low-dose radiation (*15–18*).

CYTOKINE RELEASE SYNDROME OR "CYTOKINE STORM"

Cytokines running amok and causing severe morbidity and even mortality hit the headlines at about the same time as major improvements in immunotherapeutic approaches were being made in the last decade. Whereas immune checkpoint inhibition and T-cell-engaging therapies [e.g., bispecific T-cell engaging single-chain antibody constructs and chimeric antigen receptor (CAR) T cells] have shown remarkable efficacy, increasing awareness of the cytokine release syndrome (CRS), with potential mortality has been garnered. CRS is a severe inflammatory response, triggered by several infectious agents (including possibly bacterial pneumonias, as we will review later), as well as some therapeutic agents. The phrase ''cytokine release syndrome'' was first coined in the early 1990s, when the anti-T-cell antibody muromonab-CD3 (OKT3) was introduced as an immunosuppressive treatment for solid organ transplantation (*19*). Subsequently, several additional therapeutic agents, mostly immunomodulatory in nature, were shown to be possibly associated with this phenomenon. More directly relevant to the COVID-19 phenomenon, cytokine storm due to massive T-cell stimulation is also a proposed mechanism of severe viral syndromes that can occur with influenza (*20*). Much of what we know today clinically about CRS comes from the experience with CAR T-cell therapeutics and the use of blinatumomab for B-cell precursor ALL, where relatively high rates of this phenomenon have been observed, including almost universal occurrence when CD 19-targeted CAR T-cell therapies are used (*21*).

THE ROLE OF LOW-DOSE RADIATION IN TREATING INFLAMMATORY AND DEGENERATIVE DISEASES

The anti-inflammatory effects of low-dose radiotherapy (LD-RT) have been known for decades (*22–25*). However, LD-RT in benign conditions is often only used as a last resort because of the possibility of delayed toxicities observed with much higher doses of radiotherapy, but presumptively also ascribed to LD-RT. In Germany, LD-RT is used extensively, whereas the use of radiotherapy for these conditions remains infrequent in other countries (*26–28*). The explanations for the limited use of radiotherapy for treating benign diseases include the potential for radiation carcinogenesis and a lack of controlled studies investigating this application. However, the evidence of cancer risk comes from disparate sources using outdated radiotherapy techniques or data from Hiroshima and Nagasaki where radiation exposure was evenly distributed throughout the body. In a review of radiotherapy for benign disease, it was concluded that the risks of cancer after radiotherapy for benign disease for currently advised protocols are low, especially in older patients (*29*). The doses proposed in the

TABLE 1
Human Inflammatory Diseases/Conditions Successfully Treated with Radiotherapy

Ailment	No. of subjects	Successful treatment (%)	No. of studies
Arthritis	>5,000	~85	Cumulative
Bronchial asthma	>4,000	75–80	57
Carbuncles	187	60–90	5
Cervical adenitis	893	75–90	11
Deafness	15,000	>95%; performed prior to age 15	Cumulative
Furuncles	420	75–95	5
Gas gangrene	365	Mortality decreased from 40 to 10%	13
Otitis media/mastoides	564	~90	16
Pertussis	~2,400	~80	22
Pneumonia	863	80–85	18
Sinus infection	4,492	75–90	16
Tendonitis/bursitis	3,333	70–90	31
Total	37,517		

Note. Adapted from Calabrese and Dhawan (*31*).

COVID-19 trial discussed below are lower than those commonly used for benign diseases.

Germany has been the main proponent of radiotherapy for benign disease, with over 37,000 patients treated annually (*26–28*). Two-thirds of these patients are treated for inflammatory or degenerative osteoarticular diseases, degenerative joint disorders or the prevention of heterotopic ossification. In 2002, the German Working Group on Radiotherapy of Benign Diseases published a consensus on possible indications and guidelines for treatment (*27*). The consensus was that low doses should be administered for acute and chronic inflammatory diseases and painful acute and chronic degenerative joint disease (*27*). The mechanism of low-dose radiation in these inflammatory diseases is finely regulated by sequential leukocyte-endothelial cell interactions and by the action of inflammatory mediator and adhesion molecules secreted by a variety of peripheral blood cells including leukocytes, neutrophils and macrophages (*25*).

The use of radiation to treat inflammatory diseases was recently reviewed by Calabrese *et al* (*30*). In this comprehensive review, they summarized the data from over 37,000 patients with 13 different ailments. Despite the ailments differing from each other extensively in terms of etiology, symptomatology and conventional therapy, all 13 ailments were resolved using radiotherapy, with response rates of 70–90%. This impressive and consistent success of radiotherapy was achieved at a relatively narrow dose range of between 30 roentgen (r) and 150 r (0.3–1.5 Gy).

The only commonality of these ailments was that inflammation was a central feature of each, and that radiotherapy counteracted the inflammatory process, affording protection and enabling tissue repair. Therefore, the authors concluded that it was not unreasonable to deduce that radiotherapy at the right dose can act as a potent anti-inflammatory agent (*30*). The caveat to the Calabrese *et al.* review is that most of the studies were carried out in the early part of the last century when technology was more primitive and dosing was based on the skin erythema (i.e., skin reddening) dose (SED), which was used as an upper bound exposure point of reference, and in the estimation and selection of most doses for all end points. The SED estimate could be affected by X-ray filtration techniques and multiple patient characteristics, such as age, gender, degree of skin pigmentation and vascularization, among others, and thus carries a significant degree of uncertainty and inaccuracy. However, the more recent German consensus study using modern technology and contemporary data recommends single doses of 0.5–1.0 Gy, total doses of 3.0–6.0 Gy and two or three fractions per week with orthovoltage or megavoltage techniques for inflammatory diseases (*27*).

THE EXPERIENCE OF RADIATION TREATMENT OF PNEUMONIA

Of particular interest to the current respiratory manifestations of COVID-19 is that X-ray therapy was used to treat pneumonia during the first half of the 20th century, prior to and concurrent with the advent of antibiotics. While the principal therapeutic option for the treatment of pneumonia prior to 1939 was serum therapy, this was expensive, time consuming, and not useful to patients with allergic reactions to horse sera. The use of serum therapy was eliminated after the introduction of sulfonamides in 1939. Just prior to this, radiotherapy was emerging as an alternative as a result of its notable successes in the treatment of a wide range of inflammatory and infectious diseases, outlined in the previous section.

The efficacy of X-ray treatment in reducing mortality was similar to serum therapy as well as to sulfonamide treatment during the same time period. The data from 18 studies with over 800 cases of bacterial and atypical pneumonia were reviewed by Calabrese and Dhawan (*31*). The conclusion was that patients were effectively treated with low-dose X rays, leading to disease resolution, based on clinical symptoms, objective disease biomarkers and mortality incidence (Table 1). Their review includes a pertinent quote

from the early studies of Heidenhain and Fried, which reveals the rapidity of the response to LD-RT: ''A patient with a high fever, severe dyspnea, and cyanosis is irradiated. A few hours later, often within a period of six hours, he states that he can breathe more easily, and he takes some nourishment. After twelve to twenty-four hours the fever abates, in most cases by crisis, breathing is no longer painful, and dyspnea decreases or disappears entirely. In most of the cases reacting favorably a normal condition is re-established in twenty-four to forty-eight hours.''

This rapid effect was achieved with a single dose. However, the selection of a dose to treat pneumonia patients was problematic, and was guided to a significant extent by publications in the clinical literature concerning carbuncles. As mentioned previously, dose selection was typically based on the framework of the skin erythema dose (SED) concept. During the 1920s and 1930s, the SED varied in the carbuncle literature by author and assessing the dose delivered was problematic. One of the last reports of radiation treatment of pneumonia was a 1942 United States Medical Bulletin by Correll and Cowan (*32*), who reported on a series of 155 cases of atypical pneumonia, which had a typical abrupt onset characterized by chills, a sharp rise in temperature, sore throat and a non-productive cough, with the pneumonia confined to one or both lower lobes. In 23 of these patients, X-ray therapy alone was used, and within 4 days, 96% of patients responded; the febrile period, total number of sick days and the number of days to improvement seen on chest X ray was halved in these patients compared to those not receiving X-ray therapy. In 9 patients, who had failed to respond to all available treatments for 30 days or more, X-ray therapy was used and 7/9 cleared their pneumonic processes within 4 days. Radiation therapy was administered immediately after a positive X-ray diagnosis at a dose of 112 roentgen (r) to the involved lobe, and was repeated at 24 h if necessary. It was found that two treatments were usually necessary, but never more. This highlights the rapid effect of low-dose radiation on the acute phase of respiratory diseases characterized by inflammation.

Nevertheless, it is appropriate to maintain perspective on these old studies, given that the conversion from r to cGy is not 1:1 and the fact that the r was measured in air proximal to the patient in the published series of Chamberlain (*33*), Oppenheimer (*34*) and others. Additionally, Oppenheimer (*34*) specifically cautioned against the use of higher doses: ''For the treatment of virus pneumonia. . .. An average dose of 50 r (measured in air) through portals covering the involved parts of the lungs usually 20 by 20 cm was used. This technique was adopted after treatment with 100 r or more at early stages had induced severe systemic reactions with chills, convulsions, and cold sweats in 3 instances. . ..'' Although it remains uncertain, from his description of chills, convulsions and cold sweats, it appears that higher doses in Oppenheimer's experience might have provoked, rather than prevented, a cytokine release syndrome. Of course, a rational explanation for chills, convulsions and cold sweats in a patient with an infection such as pneumonia is the infectious process itself, and therefore, not too much can be deciphered regarding the correct dose from these older studies.

It is likely that in the 1930s and 40s these patients, treated with nominal exposures of 0.1–0.2 SED, received only 35–70 r at midplane, and these translate to doses well under 100 cGy using modern radiotherapy delivery systems and current dosimetric calculation algorithms.

LOW-DOSE RADIATION AND THE INFLAMMATORY RESPONSE

The relationship between radiation and the inflammatory response is dichotomous and dependent on dose. While high-dose radiation initiates a DNA damage response that regulates DNA repair, cell cycle and cell death, and induces inflammation through various transcription factors, including nuclear factor kappa B (NF-κB) leading to expression of cytokines such as IL-6, IL-1β and TNF-α, low-dose treatment results in activation of anti-inflammatory molecules such as TGF-β_1 and IL-10 (*24, 25*).

Low-dose radiation modulates the function of a variety of inflammatory cells, including endothelial cells, polymorphonuclear leukocytes, and macrophages. Various hypotheses have been offered to explain the mechanisms of low-dose radiation, such as a decreased adhesion of leukocytes to endothelial cells (*35, 36*), induction of apoptosis in the cells that comprise the inflammatory infiltrate (*37, 38*), decreased expression of adhesion molecules (*39*), decreased inducible nitric oxide synthetase (iNOS) that results in a decrease in nitric oxide and reactive oxygen species (ROS) (*40*), increased activation of NF-κB (*41*), and increased expression of anti-inflammatory cytokines (IL-10, TGF-β1) (*24, 25*), among other potential mechanisms.

The inflammatory response is a tightly regulated process in which endothelial cells play a key role. This is particularly relevant in the lung where endothelial cells make up 30% of the total lung. An early event in the inflammatory tissue response is characterized by local vasodilatation, increased blood flow and microvascular permeability, resulting in erythema and edema. Furthermore, pro-inflammatory mediators mainly produced by macrophages and dendritic cells at the site of the damaged tissue stimulate the adherence of leukocytes from the peripheral blood to the vascular endothelial cells and mediate their transendothelial migration. This is followed by accumulation of a variety of immunocompetent cells such as lymphocytes (B and T), granulocytes (neutrophils, eosinophils and basophils), and monocytes/macrophages which perform functions such as phagocytosis, cytotoxicity, antigen presentation, cytokine secretion, release of ROS, and expression of iNOS that result in the production of nitric oxide (*24, 25*). It has been reported that low-dose irradiation of endothelial cells resulted in an elevated

expression of TGF-β1, which has been shown to play a major role in decreasing leukocyte adhesion and ameliorating the inflammatory response (*42*).

Activation of macrophages is an important step in inflammation because, once activated, macrophages produce nitric oxide and pro-inflammatory cytokines responsible for pain, erythema and edema. An important effect of low-dose radiation is that it appears to alter the phenotype of the more radioresistant alveolar macrophages with a change in their polarization from an M1 pro-inflammatory phenotype to an anti-inflammatory or M2 phenotype (*43–45*). This phenotype results in decreases in nitric oxide levels, iNOS and ROS, with increases in heme oxygenase, suppression of TNF-α and IL-1β and TGF-β. Importantly, low-dose radiation does not affect the phagocytic function or viability of these cells, since alveolar macrophages play pivotal roles in the clearance of dying and damaged cells.

THE POTENTIAL ROLE OF LOW-DOSE RADIATION IN COVID-19 PATIENTS

The major cause of death in COVID-19 patients is cardiopulmonary dysfunction, mimicking an ARDS-like syndrome. Increased capillary permeability is a hallmark of this ARDS-like picture, involving similar mechanisms of endothelial-leukocyte interaction with release of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6. Damage to the capillary endothelium results in impairment of fluid removal from the alveolar space, causing accumulation of protein-rich fluid inside the alveoli. This results in diffuse alveolar damage (*46*). Neutrophils are recruited to the lungs by cytokines, become activated and release toxic mediators, such as ROS and proteases (*47*). Inflammation due to neutrophil activation is important in the pathogenesis of ARDS. Macrophages are also essential for the process of the inflammatory response in ARDS. Notably, macrophages play a dual pro-inflammatory and anti-inflammatory role based on the microenvironment in different pathological stages (*48*). In the acute phase of ARDS, resident alveolar macrophages, which typically express the M2 phenotype, shift into M1 phenotype and release various potent pro-inflammatory mediators.

In the context of low-dose radiation, reduction of endothelial-leukocyte interaction, removal of radiosensitive neutrophils and activated T cells (*49*), and change in the polarization of macrophages, could be important components of the response to treatment (Fig. 1). It is unclear which of these mechanisms will play the most important role; however, the description of the time-scale of response of pneumonia patients to LD-RT suggests that apoptosis of cytokine-producing infiltrating cells must be a substantial component, since symptoms started to improve within hours.

For COVID-19 patients who progress to severe disease where there is no established treatment and death is a significant possibility, LD-RT would appear to be a relatively safe strategy that could be widely implemented, once evidence of efficacy is produced; this can be readily achieved with a small, pragmatic and expeditious clinical trial, with an extremely rapid clinical signal of benefit.

THE THERAPEUTIC WINDOW FOR RADIATION TREATMENT OF COVID-19 PATIENTS

Studies from China (*50*) have shown that the median time from illness onset (i.e., before admission) to discharge was 22 days (IQR 18–25), whereas the median time to death was 18.5 days (15.0–22.0). Of 191 patients, 32 required invasive mechanical ventilation, of whom 31 (97%) died. The median time from illness onset to invasive mechanical ventilation was 14.5 days (12.0–19.0). This time-scale presents two opportunities to intervene with LD-RT. The first population would represent high-risk patients prior to invasive ventilation. This population could be identified by emerging biomarkers such as ferritin, IL-6 and TGF-α levels as well as other molecules under investigation. These patients would be in the early stages of their acute respiratory inflammation and represent an ''early intervention'' treatment group. The second population would be patients in the early stages of invasive ventilation where the ARDS-like condition may be reversible, since it appears from the current U.S. experience that the overall mortality for mechanically ventilated patients is approximately 50%, but approaches 80% for those intubated for 5 days or more. These patients could be enrolled immediately upon intubation (or within the first 48–72 h) and would constitute the ''late intervention'' group.

LD-RT PreVent TRIAL

A group of over 20 investigators, representing more than 15 clinical sites, convened on multiple occasions by videoconferencing to develop the ''PreVent'' trial concept, and reviewed all available literature on the topic, and also other developing clinical trials proposing the use of low-dose radiotherapy for this indication. The group has rapidly expanded to include those with expertise in pulmonary/critical medicine, biostatistics, medical physics, as well as pertinent radiation radiobiology experts.

Although some institutions are considering trials on intubated patients, the PreVent committee's overall consensus was that this might be a ''bridge too far'', in that the anti-inflammatory effects of low-dose single-fraction radiotherapy might be simply inadequate to change the natural course of progression of this disease by the time patients require mechanical ventilation.

Therefore, the basic design of the proposed ''PreVent Trial'' is to select patients with COVID-19 pneumonia who are experiencing moderate-to-severe pneumonia but have not yet progressed to the need for ventilation. Based on the experience of front-line pulmonologists and intensivists on our team, we believe that this targets a population where the

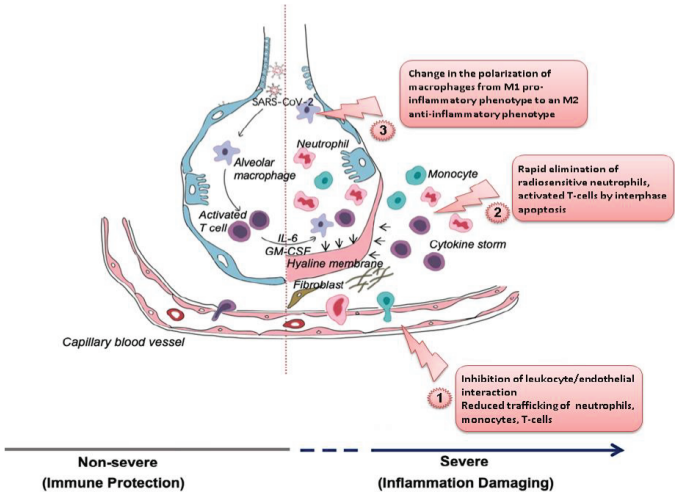

FIG. 1. Potential role of LD-RT to combat the cytokine storm in severe pneumonia associated with COVID-19 pulmonary damage. Three potential mechanisms of low-dose radiation are highlighted, acting on different components of the respiratory syndrome. (Published and modified, with permission, from Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020; 27:1451–4.)

cytokine storm has been initiated but has not yet peaked. The respiratory status of these patients has started declining to a point where hospitalization is indicated and supportive respiratory measures have been initiated, but patients are not yet being mechanically ventilated. We surmised that this point reflects the emergence of the cytokine storm that has not yet induced multi-organ failure, a condition that would likely not be ameliorated by low-dose radiotherapy. For definitional purposes, multiple variables governing respiration and SpO2 would allow patients to be enrolled, as long as they are at least 60 years of age and the respiratory parameters yield a ratio of partial pressure of arterial O_2 to fraction of inspired air of less than 320. This would enrich enrollment of patients with a higher likelihood of the occurrence of a clinically significant event, thereby lowering the total n required for the trial.

Patients would be stratified as ''high'' or ''low'' risk, based on two separate categories, resulting in four stratification cells. The two stratification variables selected include a validated algorithm consisting of seven biomarkers from the Wuhan/Guangdong experience, reflective of acute mortality in this population, and the Charlson Comorbidity Index, which was highly prognostic in the 5,000+ patient Northwell Health Care System, New York City experience.

Approximately 60 patients would be randomized, 2:1 to standard of care with or without radiotherapy. The cohort of approximately 40 patients randomized to radiotherapy would be further randomized to receive a single, ultra-low radiation dose (35 cGy or 100 cGy). The protocol recommends the use of the simplest of techniques (no simulation, AP/PA beam arrangement, no blocks, no heterogeneity corrections, mid-plane point dose prescription) with full PPE and decontamination measures in place.

The response of these patients in the first 15 days would allow selection of the most effective radiation dose, using a pre-defined algorithm based on any observed differences in grade 4 or higher toxicities, clinically meaningful event rate, facility resource utilization, or differences in AUC alteration in IL-6, a biomarker of the intensity of the cytokine storm. An additional cohort of approximately 47 patients would then be enrolled into the more-effective dose arm, allowing a total of 51 patients in this so-called ''therapeutic arm'', for a total study enrollment of 87 patients.

The control and treated groups would be compared for improvement in a composite primary end point of mortality, rate of intubation and mechanical ventilation, and rate of prolonged hospitalization. The total event rate for this composite end point would be compared between the control and the ''effective radiotherapy dose'' arms. We expect that 40–80% of patients in the control arm will have an event. We consider a 33% reduction in events to be a clinically meaningful improvement. Calculations consider a 5% dropout rate. Considering 36 control and 51 treated patients, a one-sided log rank test achieves 80% power to detect a 33% reduction in events from 0.4 in controls to 0.2668 in treated patients considering an alpha = 0.1. This would be considered sufficient for a signal-searching phase 2 randomized trial.

Additional secondary goals would be to determine whether the post-recovery lung function is superior in the irradiated patients, whether we could identify blood and radiologic markers that could permit selection of patients most likely to benefit from a such a strategy, and whether the velocity of biomarker change varies between groups. Exploratory analysis would be used to evaluate the total episodic cost of care between the two cohorts, as well as to explore, in a multivariate model, the impact of various host and treatment characteristics, such as race, gender, viral strain, etc. The future goal would be to test the most effective pharmacologic agent, identified from ongoing clinical trials, alone versus in combination with X-ray therapy, in a phase 3 randomized trial.

CONCLUSION

We face a pandemic that has not been seen before in our lifetime. In the U.S., over 56,000 individuals have succumbed to this disease. While the more traditional influenzas may occasionally have more yearly deaths, we do have established vaccines for influenza. Vaccines for coronavirus are at a very preliminary developmental phase.

We suspect that there have been more individuals who have had asymptomatic exposure than are being reported as ''COVID'' positive cases and in that situation the number of symptomatic cases can be expected to continue to grow, although hopefully at a slower pace. Until we have an active

useful vaccine this will be reality, and several health policy leaders have cautioned about a second wave in the fall.

Sadly, there is a cohort of individuals who are at higher risk for developing respiratory compromised COVID infections. Currently, many of these individuals (i.e., those aged >65, and those with pre-existing health conditions such as diabetes or heart disease, as well as immunocompromised patients) will end up on ventilator support. Additionally, the mortality rates of those on prolonged ventilation are reported be as high as 88%. It is believed that the underlying mechanism of this is uncontrolled inflammation induced by the cytokine storm.

In this setting, the development of approaches to counter the cytokine storm is a meaningful clinical research direction. From a pharmaceutical perspective, IL-6 antagonism represents one such direction. Another is the application of low-dose whole-lung irradiation, which has a long forgotten and well-established history of use for pneumonias in the pre-antibiotic era, with overall success rates of approximately 80% and minimal reported side effects. The extremely low doses have yielded IL-6 inhibition in preclinical rodent models, as well as other immunomodulatory effects, but are too low to have any meaningful direct anti-viral effects.

This approach is not a cure; rather, it must be placed in the quiver of medical arrows that we can use to target and defeat this ravaging virus that is so adept at moving from one person to another.

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