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EDITORIAL

Radiation Therapy as a Treatment for COVID-19?

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In this issue of the Red Journal, Ameri et al report the interim results of 5 patients with COVID-19 treated on a clinical trial in Teheran, Iran, with 0.5 Gy single-fraction whole lung radiation therapy.[1] The patients (aged 60-84 years) enrolled with oxygen saturation ranging from 74% to 89% and received radiation therapy at a median of 2 days after admission. One patient died, 1 patient withdrew consent 3 days after radiation therapy, and the other 3 patients were followed to discharge 5 to 7 days after radiation therapy. The patient discharged 7 days after radiation therapy still required oxygen supplementation at home. The authors report that 4 patients showed signs of clinical recovery as defined by changes in oxygen saturation and temperature within 1 day after radiation therapy. However, the average absolute improvement in oxygen saturation 1 day after radiation therapy appears to be only 3% across these 4 patients, and only 2 of the 4 patients had a baseline temperature greater than 37.7°C. This is the first published, peer-reviewed prospective study of patients with COVID-19 pneumonia treated with radiation therapy. These results should be considered in the context of contemporary outcomes for hospitalized COVID-19 patients who require oxygen support, anticipated future developments in the management of symptomatic COVID-19, and historical studies of radiation therapy for pneumonia.

COVID-19 is caused by the recently discovered SARS-CoV-2 coronavirus. Standard of care for COVID-19 is rapidly evolving and is being defined by rigorous, well-powered randomized controlled clinical trials. For example, in a randomized trial of the antiviral agent remdesivir or placebo that included 421 patients with COVID-19 receiving oxygen but no ventilation, 50% of patients recovered within 6 to 9 days with a recovery rate ratio of 1.47 (95% confidence interval [CI], 1.17-1.84) favoring the remdesivir arm.[2] In the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which is a platform trial in the United Kingdom comparing several different treatments, the preliminary results of the comparison of dexamethasone versus usual care have recently been published.[3] In 3383 patients receiving oxygen without mechanical ventilation, dexamethasone reduced deaths from 25% to 21.5% (relative risk, 0.80; 95% CI, 0.70-0.92). These clinical trials not only established dexamethasone and remdesivir as effective treatments for hospitalized COVID-19 patients requiring oxygen, but they also provide a framework for evaluating short-term outcomes of radiation therapy to the lungs as a treatment for COVID-19 pneumonia in patients with decreased oxygen saturation. Patients in the clinical trial from Tehran were treated according to national guidelines[4] but did not receive steroids or remdesivir. From the perspective of the results of the large, prospective clinical trials of remdesivir and dexamethasone, survival to discharge in 3 out of 4 evaluable patients with a mean time to discharge of 6 days[1] appears to be within the expected range for COVID-19 patients requiring oxygen in the absence of radiation therapy.

As summarized by Ameri et al, a number of ongoing prospective clinical trials are testing lung radiation therapy

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in hospitalized patients with COVID-19. If in the future well-powered, randomized trials demonstrate that the addition of lung radiation therapy improves outcome over dexamethasone and remdesivir, is it likely that radiation therapy would become part of routine treatment for hospitalized COVID-19 patients on supplemental oxygen?

It is always hazardous to predict the future of clinical care, particularly for a new infectious disease. For COVID-19, there are many ongoing clinical trials testing a wide variety of therapeutic agents and vaccines. At a recent hearing in the US Senate, the director of the National Institutes of Health, Dr Francis Collins, highlighted the potential for monoclonal antibody cocktails to have a major impact as a treatment for COVID-19: "If I had to pick one [treatment], I think the monoclonal antibody cocktails have a lot going for them. There's all kinds of reasons to think this is the kind of virus it should work for."[5]

Indeed, there is already an efficacy signal for the activity of antibodies from a randomized trial of convalescent plasma that enrolled 103 hospitalized patients with COVID-19 in Wuhan, China.[6] This trial tested whether plasma with neutralizing antibodies to SARS-CoV-2 from survivors of COVID-19 improved outcomes for patients hospitalized with COVID-19. This study was terminated early because COVID-19 infection was successfully controlled in Wuhan, and therefore the study was underpowered. However, patients randomized to receive convalescent plasma showed a trend toward decreased mortality: 15.7% versus 24% ($P = .3$). Among 55 patients with severe disease who did not require mechanical ventilation, which was defined as tachypnea (respiratory rate $\geq$30 breaths/min) or hypoxia (oxygen saturation $\leq$93% on room air or arterial partial pressure of oxygen/fraction of inspired oxygen $\leq$300), mortality was 0% in the patients randomized to convalescent plasma versus 9.1% in the control arm (P = NS). Although larger clinical trials of convalescent plasma are needed to definitively test this therapy, these results suggest that neutralizing antibodies are a promising approach for treating hypoxic patients with COVID-19.

Clinical trials are currently testing neutralizing monoclonal antibody cocktails to determine whether they can provide passive immunity to patients with symptomatic COVID-19.[7] If these clinical trials are successful, because of enhanced safety and the ability to scale up production, monoclonal antibody cocktails would likely supplant convalescent plasma as a treatment for hospitalized COVID-19 patients on supplemental oxygen. Our patients with cancer routinely receive monoclonal antibodies, such as trastuzumab, rituximab, or pembrolizumab. Several monoclonal antibodies are already approved by the Food and Drug Administration to treat infectious diseases, such as respiratory syncytial virus, anthrax, and *Clostridioides difficile*.[7] Therefore, in the future, it is conceivable that hypoxic patients with COVID-19 will be infused with highly effective neutralizing antibodies when they are admitted to the hospital. In this scenario, it is unlikely that 0.5 Gy whole lung radiation therapy, with its risks of carcinogenesis and circulatory disease,[8,9] would become a major part of the anti−COVID-19 armamentarium.

The clinical trial from Ameri et al builds on historical data in which radiation therapy was used to treat pneumonia. The initial report of using thoracic radiation therapy to treat pneumonia was published in 1905 by Musser and Edsall at the University of Pennsylvania in Philadelphia.[10] One patient with unresolved pneumonia reportedly derived benefit from 4 daily doses of x-rays. Musser and Edsall stated that "one case proves nothing, but this result is sufficiently suggestive to encourage further trial in other cases of unresolved pneumonia." Indeed, Edsall and Pemberton published a follow-up paper claiming that x-ray therapy improved the outcome of 2 additional patients with pneumonia.[11] When the devastating outbreak of H1N1 influenza occurred in 1918, causing approximately 20,000 deaths in Philadelphia, the medical system was overwhelmed and many patients with respiratory distress were not able to receive supplemental oxygen.[12] Just as some radiation oncologists today are conducting clinical trials of radiation therapy for COVID-19 pneumonia, it is interesting to speculate whether these early pioneers in Philadelphia also used x-rays to treat patients with pneumonia during the influenza pandemic. There are no reports of x-rays being used to treat patients in respiratory distress during the 1918 pandemic.

As data accumulate from clinical trials of radiation therapy for COVID-19, it will be important to not only publish the short-term outcome of survival from COVID-19 as reported here by Ameri et al, but also to follow survivors over the years ahead and report any late effects, such as lung cancer and cardiovascular events.[8,9] As we face the urgent challenge to devise novel treatments for COVID-19, we are fortunate to be able to rely on an exceptional foundation of science built up over the century since the 1918 influenza pandemic. With currently available antivirals and steroids, the likelihood of effective monoclonal antibodies for SARS-CoV-2 in the not too distant future, and the potential for effective vaccines, given the risks of late effects from whole lung irradiation,[8,9] it is unlikely that radiation therapy will be used outside of clinical trials to treat COVID-19.

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