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Perspectives and View Points

Fallacy of Considering Low dose Lung Radiotherapy in Treating Covid Lung

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There is a raging argument amongst Oncologist regarding offering low dose lung radiotherapy in patients with covid infection with lung symptoms. There is huge enthusiasm amongst medical fraternity and appetite to offer experimental therapies so as to contribute in managing this pandemic associated morbidity and mortality.Although the intentions are noble, offering experimental therapies like Low dose lung radiotherapy without adequate scientific scrutiny risk causing more harm than good for patients. The main argument against Low dose Lung radiotherapy is risk of long term side effects of lung radiation. Simpler alternatives like steroids which are evidence backed are available for managing immunological effects of Covid infection .The epidemiological data strongly suggests that immunolocal lung damage is not the predominant cause of lung toxicity in this infection so targeting this pathway alone is unlikely yield beneficial clinical results. Recent data on lasting lung damage including pulmonary fibrosis in patients who have recovered from covid lung also increase the concerns around Lung Radiotherapy.

Introduction

Humanity felt an existential threat before during recent times due to the Covid Pandemic. Infectious diseases which were thought to have been won by mankind have Although the mortality is 4-8% it has instilled a fear of survival in one and all. The pandemic has changed the way we live. There is concerted effort across specialities to support covid patients and explore if a new treatment modality could help reduce morbidity and mortality.

The leading cause of morbidity and mortality in Covid-19 infection is respiratory syndrome. The respiratory syndrome presents as worsening acute respiratory distress (ARDS).

The damage to pulmonary units in lungs are likely due to direct virus induced pulmonary damage. The radiological evidence on CT imaging shows diffuse lung damage manifesting in form of pneumonitis which appears to be similar to direct lung injury induced by infections including viral pneumonitis. The other clinical observation in admitted patients has been increased incidence of thrombosis. This likely causes lung damage with pulmonary emboli and infarcts. Post mortem studies on covid patients has shown micro-emboli in lungs with associated infarcts. Use of antiplatelet agents is established in hospitalised patients. Severe viremia and infections are known to be associated with hypercoagulable states. This reinforces the hypothesis that covid lung damage is probably due to direct virus effects on lungs rather than immunological mediated.

However there is another body of clinicians who think immune mechanisms are prime cause or a significant contributor to COVID-19 Pneumonia. It is possible that the complications associated with Covid ARDS could possibly have an immune mediated cytokine storm. There is some anecdotal evidence and small case series which have reported a decrease in CD3, CD4, CD8, NK cell and B-cells; rise in IL-4, IL-6 and TNF alpha; Decrease in IL -10; decrease in IFN-gamma. This indicates that there may be a component of immune mediated lung damage. Since no specific antivirals is available to treat Covid-19 infection the treatment is mainly supportive.

The current standard of care for Hospitalised/Severely ill Covid patients with lung damage includes antibiotics (to treat/prevent superimposed bacterial infections), antivirals, supportive therapy with

oxygen, antiplatelet agents or low molecular weight heparin, steroids, & Interleukin 6 inhibitor (Tocilizumab).

Antivirals act by reducing viral load and limiting pulmonary damage. Although no definitive antiviral therapy is available for Covid-19 treatment remdesivir, flavinipir and anti-retroviral (lopinavir-ritonavir) been used with improvement in morbidity and mortality. Remdesivir is recommended for hospitalized patients with severe COVID-19 [1]. Remdesivir is a novel nucleotide analogue that has activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro. Initial data supports improvement in mortality and morbidity in severe ill patients. Favipiravir is an RNA polymerase inhibitor that is used in treatment of influenza. It is available in India for treatment of mild COVID-19 and is being evaluated in clinical trials for treatment of COVID-19 in the United States. In patients with non-severe disease (including oxygen saturation >93 percent), use of favipiravir was associated with faster rates of viral clearance (median time to clearance 4) and more frequent radiographic improvement (91% by day 14) [2]. Convalescent plasma and/or hyper-immune globulin have been used for providing passive immunity with promising results [3-4]. Among the subset of patients who had severe but not life-threatening disease, the rate of clinical improvement was greater with convalescent plasma (91 versus 68 percent, HR 2.15, 95% CI 1.07-4.32) [2].

Due to initial evidence on effectiveness and utility of convalescent plasma in treatment of covid viremia there is a concerted effort to develop monoclonal antibody therapy to improve effectiveness and reduce side-effects of therapy [5]. Anti-thrombosis medications with antiplatelet agent and low molecular weight heparins to part of standard of care covid protocols for inpatients. They help prevent and treat micro-emboli in pulmonary vessels and thus prevent pulmonary infarction.

The two main strategies to address the issue of cytokine storm are systemic therapy or low dose lung radiotherapy. The common systemic therapies being trialed to target immunological/cytokine storm are IL-6 pathway inhibitors or / and steroids. Although IL6- inhibitor tocilizumab is licenced for use in severely ill however it did not show any benefit in survival or reducing morbidity in the phase 3 trial. It failed to meet both primary and secondary endpoints. Other IL6 inhibitors like sarilumab and siltuximab are under investigation for managing the cytokine induced lung damage [6]. There are few observational studies which showed decrease in pro-inflammatory markers with marginal improvement in morbidity but no improvement in mortality. Steroids help in modulating immune response and have been used earlier in mountain sickness by using similar pathway. A large randomized, open-label trial in the United Kingdom with oral or intravenous dexamethasone reduced 28-day mortality among hospitalized patients requiring oxygen therapy or ventilator support compared with usual care alone [7].

There has been an augment put forward by few investigators to use low dose Low dose radiotherapy (LDRT) to manage covid lung. LDRT has immunosuppressive features resulting from M2 macrophage phenotype activation, increase in IL-10, TGF beta, a decrease in IL-6, TNF alpha and an increase in CD3, CD4 and CD8 T cell counts may negate the harmful effects of cytokine release syndrome (CRS).There is data to support Low dose Radiation to the lungs has robust activity in managing Cytokine release syndrome .Immunologically LDRT induces IL-10 and TGF beta enhancing the immunosuppressive effect. Low dose Lung Radiotherapy also increases the T cell response (CD4 and CD8 count) which is adversely affected by steroids. However Low dose lung radiation comes with long term risks and since the disease is widely prevalent the need for caution would be immense to implement it in wider population even if the trials were positive.

The overriding argument to offer Low dose Lung radiotherapy over simpler systemic therapies in managing immunological component of lung damage is its likely effect on controlling cytokine storm while not impacting T cell activity. The host’s immune T cell response is needed in eliminating the covid virus. Steroids adversely which also impact it along with controlling cytokines. Though the argument on steroids appears scientifically robust based on lab data and cytokine and T cell level, clinical evidence indicates otherwise. The trial conclusively showed

improvement in both morbidity and mortality in hospitalised covid lung patients. IL-6 agent tocilizumab could not demonstrate efficacy in phase III COVACTA trial.

There are several strong arguments against use of Low dose lung radiotherapy in Covid patients with lung involvement .The mortality epidemiological data in Covid patient clearly establishes majority of deaths in elderly, patients with pre-existing lung disease, and hypertensives. The mortality in children and young has been very low in the current pandemic. The earlier pandemics (1918, H1N1) had predominant morbidity and mortality in younger population [8]. The studies have documented that the was a larger immune/cytokine response in these viral Pneumonias (1918 Influenza pandemic and later H1NI infections) [9-10]. This would explain the higher mortality in young adults. However in current Covid-19 Pandemic the mortality has been higher in patients with poor immunity and therefore ability to mount a good immune response. The pathophysiologic cause of lung damage is not fully understood and established, however direct virus induced pulmonary damage seems to be the predominant cause given the positive response to antivirals and doubtful benefit with immunomodulation and IL6 agents in trials so far. It’s likely that the lung damage in Covid-19 is multifactorial and combination of direct viral injury, pulmonary infarcts due to hypercoagulable state and a smaller component of immune reaction due to lung injury. Dexamethasone is a simple intervention which has shown promise in reducing mortality in hospitalised patients indicating some role of immunosuppression in hospitalised patients to manage the pneumonitis. Low dose lung radiation comes with long term risks and since the disease is widely prevalent the need for caution would be immense to implement it in wider population even if the trials were positive. Unlike other conditions where the data of radiation matures given the acute nature of this pandemic we are unlikely to have any meaningful data for implementation at population level. The studies would be more academic in nature and unlikely to benefit practice. Although combination of appropriately directed treatment with minimal intervention would be appropriate given the lack of supporting data, time for trials to establish mature data and marginal benefit with significant uncertainties Whole lung radiotherapy for Covid-19 appears to be unlikely to establish itself as treatment modality in Covid Patients.

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