Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Personal View: Low-Dose Lung Radiotherapy Should be Evaluated as a Treatment for Severe COVID-19 Lung Disease

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As of July 2020, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 600 000 deaths globally [1]. Infection by SARS-CoV-2 causes the clinical syndrome COVID-19, which varies widely in severity from asymptomatic to severe pneumonia and life-threatening acute respiratory distress syndrome (ARDS). The population-wide case–fatality ratio is estimated at 2.3% [2]; 20 times higher than seasonal influenza. The case–fatality ratio rises sharply with age (14.8% > 80 years) and pre-existing comorbidities. The highest mortality rates are seen in patients with severe pneumonia and ARDS, which account for 14% of cases [2]. Hospitalisation rates are estimated at 4.6 per 100 000 and correlate with age and comorbidities [3]. The COVID-19 pandemic is putting severe strain on health and social care and causing unprecedented social and economic disruption.

Severe disease is characterised by hypoxia and a requirement for oxygen or ventilatory support [4]. Ward-based management includes oxygen, antibiotics for superimposed bacterial infections, proning, non-invasive ventilation and management of thromboembolic risks and complications [4]. In cases of ARDS, intensive care unit admission may be required, where specialised management involves intubation, low tidal volume and prone ventilation [4].

Treatment options for COVID-19 remain limited. The RECOVERY trial (UK) reported that dexamethasone reduced 28-day mortality in patients requiring ventilatory support (relative risk 0.65) or oxygenation (relative risk 0.80), but not in patients not requiring respiratory support (relative risk 1.22) [5]. Of note, this study awaits peer-reviewed publication and baseline mortality was higher than in other trials.

Antiviral therapies are under intense investigation. Preliminary results from one study indicated that remdesivir reduced the time to recovery from severe COVID-19, but no impact on mortality has yet been shown [6]. Recent unpublished data from the RECOVERY trial indicated no benefit from lopinavir/ritonavir in hospitalised patients [7]. Ongoing trials are evaluating convalescent plasma [8] and there is interest in hyperimmune globulin and the development of monoclonal antibodies to neutralise SARS-CoV-2.

Despite this progress, many patients do not respond to treatment and morbidity and mortality remain high, providing a strong argument to consider innovative therapies and test them appropriately. This concept is recognised within the Helsinki declaration, which states:

> where proven … therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new … therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering [9].

COVID-19 lung disease exhibits an acute, hyper-inflammatory state, the severity of which correlates with morbidity and mortality [10]. The characteristic lung

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pathology and associated systemic deterioration are consistent with ARDS and cytokine release syndrome, respectively. The immunopathology of COVID-19 lung disease is reviewed elsewhere [11], but the key features include florid alveolar infiltration by neutrophils, macrophages and lymphocytes plus markedly increased proinflammatory cytokines, including interleukin-6 (IL-6), IL-1β, tumour necrosis factor and interferon gamma (IFNγ). Nerve and airway associated macrophages (NAMs) may play a role in regulating infection-induced inflammation via pro- (IFNγ/IL-6) and anti-inflammatory (IL-10) cytokines [12].

The early efficacy data for dexamethasone support the concept of hyper-inflammation as a critical pathological process, and the pulmonary focus of this immune response indicates that a lung-specific immunosuppressive intervention may have therapeutic value. Numerous case series from the early 20th century document the successful use of low-dose radiotherapy (LDRT) to the lungs to treat pneumonia of various aetiologies [13]. That LDRT acts primarily by curbing inflammation is supported by multiple pre-clinical and clinical studies that illustrate efficacy in a broad range of inflammatory (non-malignant) pathologies [14,15]. The severity and global impact of the current pandemic and the paucity of effective drug treatments have prompted renewed interest in the use of LDRT to treat COVID-19-related pneumonitis [16,17].

Evidence for Efficacy of Low-Dose Radiotherapy in Pneumonitis and Acute Inflammatory Diseases

Calabrese and Dhawan [13] reviewed 15 studies comprising about 860 individuals with severe pneumonia who were treated with LDRT. Viral and bacterial pneumonias were included, and comparisons with historical controls were made in most studies. Radiation doses below 100 cGy per session were generally delivered, with absorbed lung doses as low as 20 cGy if superficial absorption of low beam energies is considered. These studies independently reported LDRT to be associated with reduced mortality and shorter recovery times [13]. These reports lack dosimetric rigor, fail to meet current clinical trials standards and were probably subject to publication bias. Nonetheless, there is clear consensus that thoracic irradiation did not adversely affect outcomes, and reductions in mortality were consistently reported [13]. Reduced usage of LDRT coincided with the introduction of effective antimicrobial therapy and heightened awareness of radiation-induced malignancies. The development of effective alternative therapies has also seen the use of radiotherapy for other non-malignant conditions fall sharply. Reports by the UK Royal College of Radiologists on the use of radiation for non-malignant disease reveal highly varied practice and recognise the difficulties in estimating carcinogenic risk [18]. This paradigm therefore sits outside the ‘comfort zone’ of UK-trained radiation oncologists.

By contrast, LDRT remains widely used in Germany for the management of non-malignant diseases [19,20], with about 50 000 patients treated per annum [21]. Data relating to the use of LDRT for degenerative joint disease, for example, are insufficient to determine dose, scheduling and patient selection in the context of COVID-19 pneumonitis [22]; thus, clinicians are rightly calling for more relevant pre-clinical data.

In response, Meziani and colleagues [23] initiated laboratory experiments, using intratracheal lipopolysaccharide to induce pneumonitis in a mouse model. Their early data (not yet peer-reviewed) show that LDRT (0.5–1 Gy) increased the immunosuppressive profiles of human lung macrophages *in vitro* and murine NAMs *ex vivo*, and reduced lung inflammation in mice with lipopolysaccharide-induced pneumonitis [23]. The proposed mechanism is induction of anti-inflammatory IL-10 and suppression of proinflammatory IL-6 and IFNγ (Figure 1) [24,25]. These early findings, and the established roles of these factors in

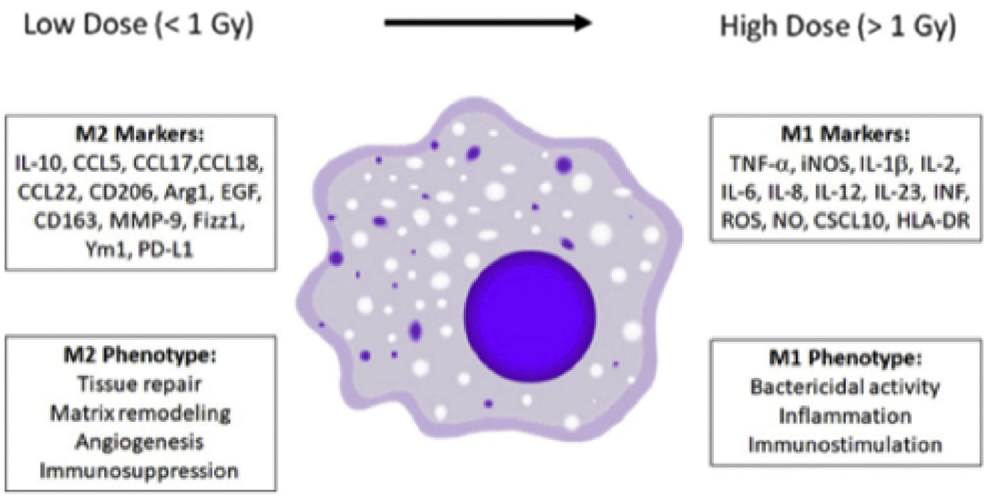

Fig 1. Effects of radiation dose on macrophage polarisation (adapted from [24,25]).

cytokine release syndrome and ARDS, support further investigation of LDRT in COVID-19 patients with acute pneumonitis.

Very early interim data from a US pilot trial in which older, comorbid patients with severe COVID-19 lung disease received LDRT (1.5 Gy) at standard dose rate are reassuring, with no acute deteriorations or measurable early toxicity [26]. Although the study is too small to provide an efficacy signal, the observation that four of the five patients exhibited clinical improvement within 1–3 days provides further evidence of safety [26].

Risks

Alongside the biological rationale for testing LDRT in COVID-19 patients exist valid and well-articulated concerns [27]. The pre-clinical data are inconsistent and largely extrapolated from other models of inflammation. Potential risks to the patient include acute toxicity, lymphopenia and immunosuppression, viral activation or mutation, and secondary malignancy. Exposure of radiotherapy staff and facilities to infection is another significant hazard [28]. Full discussion of these important issues is not possible within this article, but some key points are summarised here:

(i) Although extensive clinical experience provides reassurance that radiation doses below 1 Gy are extremely unlikely to induce clinically significant acute toxicity, the integral dose delivered to the irradiated volume could cause lymphocytopenia. In patients with COVID-19, lymphopenia has been correlated with disease severity and mortality [29]. Owing to pulmonary infiltration by proinflammatory lymphocytes, the local anti-inflammatory effects of LDRT within the lungs will probably be more significant than effects on circulating immune cells [11]. Similarly, alveolar macrophages (antiviral response contributors), are generally mobilised from the circulation and should be minimally affected by thoracic LDRT, particularly if delivered at standard high dose rates [12]. Lymphocyte subset analyses in clinical trials may help to mitigate concerns and inform patient selection by enabling a better understanding of the impact of LDRT on the systemic immune response.

(ii) Radiotherapy techniques such as volumetric modulated arc therapy often deliver significant doses to organs located outside the target volume, and integral diffused lung doses of 0.15–0.5 Gy are frequently recorded [30]. Despite this, the shift from three-dimensional techniques to volumetric modulated arc therapy has not been associated with detectable increases in acute or late lung toxicity [31].

(iii) LDRT to infected lungs is expected to induce RNA damage and, theoretically, may induce viral mutations. However, as discussed by Rödel *et al.* [32], anti-viral drug treatments would generate more intensive selective pressure on the SARS-CoV-2 virus than radiation doses of 1 Gy or less. Anxiety that viral infectivity might be exacerbated by LDRT is countered by evidence that radiation doses of 1 Gy have not been shown to induce viral reactivation [33].

(iv) Kirsch and colleagues [28] have cited concerns about late-occurring toxicities, specifically secondary lung cancers and cardiovascular disease. Their mortality estimations and approximation of overall lifetime risk of LDRT-induced cancer are based on models developed to define dose limits for occupational radiation exposure. These reflect the recommendations of the International Commission for Radiological Protection and are not necessarily accurate in the context of individual medical exposures. Nonetheless, long-term outcomes must be measured in phase II and III trials.

(v) Radiotherapy teams advocating for the study of LDRT in COVID-19 propose a safe procedural approach consistent with modern trial methodologies and ethics. Key components such as ethical approvals, patient age $\geq$50 years, informed consent, continuous monitoring of patient outcomes and clearly defined stopping rules for unexpected toxicities are included in the clinical protocols currently accruing [34]. Staff safety is a high priority and is achieved by strict adherence to the use of personal protective equipment and protocols to maintain 'clean' treatment facilities, including 'end-of-day' treatment on designated linear accelerators.

Conclusion

We have outlined historical and contemporary evidence for a potential role of LDRT in managing the acute inflammatory response associated with severe COVID-19 infection. In the absence of definitive, effective treatments for these patients, we believe that the potential benefits of LDRT outweigh the theoretical risks, and thus support its evaluation in carefully designed clinical trials.

Conflict of interest

C. Peedell reports personal fees from Elekta, personal fees from Boston Scientific, personal fees from AstraZeneca, outside the submitted work. R. Simcock reports grants and personal fees from Novartis, personal fees from Exact Sciences, outside the submitted work. E. Deutsch reports grants and personal fees from Roche Genentech, grants from Servier, grants from AstraZeneca, grants and personal fees from Merck Serono, grants from BMS, grants from MS, outside the submitted work.

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