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Flying by the seat of our pants: is low dose radiation therapy for COVID-19 an option?

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Historical context

The discovery of X-rays in 1895 had a dramatic impact on many aspects of society. One was the hope that it would be possible to treat some of the numerous infections and inflammatory conditions for which options were very limited. This concept grew out of anecdotal observations that prolonged exposures to X-rays for diagnostic purposes could improve certain infections (Schillinger 1932). The therapeutic value of X-rays was established for many acute and chronic conditions in the period preceding WWII. Gas gangrene, parotitis, erysipelas, acne, carbuncles, tuberculosis, mastitis, abscesses, ankylosing spondylitis, panaritium ossale, eczema, psoriasis, actinomycosis, paronychia, otitis, sinusitis, arthritis, pneumonia, and various other diseases, have been reported to respond to varying degrees (Trott 1994). Although not a panacea in infectious situations, irradiation was frequently shown to promptly relieve pain, reduce swelling and fever, shorten disease course, and constrain inflammatory foci. Further exploration of this approach was largely eclipsed around mid-20th century by the introduction of penicillin that kick-started the era of antibiotics and by the discovery of non-steroidal anti-inflammatory drugs. Additional roadblocks came from a lack of satisfactory explanations as to the mode of action, fears of late tissue damage and carcinogenesis, and uncertainties among clinicians as to what conditions and stages might respond best.

Recently, discussion of the much neglected paradigm of low dose radiation therapy (LDRT) has been revived by the proposal that it might constrain the COVID-19 viral pneumonia associated with the pandemic scourge by the SARS-CoV-2 virus (Kirkby and Mackenzie 2020). Any such use would have to be measured against the fact that the vast majority of patients get well without medical intervention (Wu and McGoogan 2020), and that a number of other anti-inflammatory and anti-viral reagents are available for testing (Arnaldez et al. 2020; FDA Reagan-Udall Foundation 2020; NIH News Releases 2020). Historically, several patient cohorts were treated with radiation for pneumonia, which have been reviewed in detail elsewhere (Calabrese and Dhawan 2013). They will not be discussed here, except to note that pneumonia is not just one disease but can be due to many causes, including viral and bacterial, each presenting with a dynamic pathology that can progress over time. Our

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goal is to provide a commentary on the most salient points that we think should feed into the overall discussion, without exhaustively reviewing the subject matter.

Treatment of infections and inflammatory conditions was established to be most effective if small or moderate radiation doses were used suggesting that radiation can be anti-inflammatory within a certain dose range (Trott and Kamprad 1999). This is very different from the dose range used in cancer radiotherapy where clinical thought processes are driven by cell killing and the highest dose protocol that normal tissue can tolerate is chosen, which is pro-inflammatory. Dose recommendations from early investigators for treatment of infections generally lay between 5% and 50% of a minimal erythematous dose for skin reactions at day 7–10 (H.E.D. Haut-Erythem-Dosis), which is in the 0.3–3 Gy range (Edling 1925). This was repeated, as needed, depending on the disease, with the aim of not taxing the normal tissues. In essence, the Arndt-Schultze Law of Biomodulation was invoked that states: minimal doses stimulate, medium doses inhibit or suppress, and large doses destroy cellular activity.

LDRT of benign diseases today

Since WWII, LDRT has been increasingly restricted to the treatment of painful degenerative joint disorders, and mostly in the elderly, especially in cases where non-steroidal anti-inflammatory drugs or corticosteroids are not an option. In most cases, these are joint osteoarthritis, periarthritis humeroscapularis, epicondylitis humeri, and plantar fasciitis with less emphasis on infections, and they are performed mainly in Germany and Eastern European countries (Trott 1994; Trott and Kamprad 1999; Seegenschmiedt et al. 2000; Micke et al. 2017; Kriz et al. 2018; Álvarez et al. 2020). In the U.S.A. and most other countries, non-cancer radiation therapy was largely aimed at causing rapid pain relief from cord compression and, until relatively recently, at arresting cancer-related bleeding. Notwithstanding spontaneous disease remission, the experience with LDRT has generally been a favorable one, even though disease diversity, the multiple endpoints with challenging scoring systems, and poor dosimetry have made convincing clinical trials extremely difficult to perform. Reliance on case series has been perhaps inevitable, making progress slow (Seegenschmiedt et al. 2004). Mechanistic insight also has been difficult to ascertain, especially considering the multiple changing pathologies and end points that may have individual dose-time relationships, and the use of wide and perhaps inappropriate dose ranges. While antiproliferative and/or autoimmune suppressive effects are likely relevant at the higher dose end of LDRT, the impressive and well documented analgesic and anti-inflammatory effects can be seen at the lower doses e.g., for osteoarthritic joints (Trott and Kamprad 1999; Micke et al. 2017; Koc et al. 2019). What is clear is that radiation dose responses are far from linear and the tendency to consider only low dose radiocarcinogenesis and high dose cancer treatment misses a range of other effects, many of which can be recreated in the laboratory with relative ease and good reproducibility. Preclinical arthritis models, for instance, confirmed the clinical narrative that LDRT reduces joint swelling, synovitis, and cartilage degradation (Steffen et al. 1982; Fischer et al. 1998).

Clutching for mechanistic straws

Several LDRT mechanisms of action have been proposed (Roedel, Frey, Manda, et al. 2012), some of which may prove to be individual aspects of a single integrated response. For one, endothelial cell activation and their ability to attract, roll and bind leukocytes appear to follow a discontinuous, biphasic dose response with lower doses reducing leukocyte adhesion. This correlates with increased shedding or decreased expression of selectins, and production of anti-inflammatory cytokines (Kern et al. 2000; Roedel et al. 2001; Roedel, Frey, Gaipl, et al. 2012; Large et al. 2015). Collectively, these might produce an inflammatory infiltrate that is functionally very different from high dose RT, and perhaps polarizes myeloid and lymphoid line-ages toward suppressive phenotypes such as M2 macrophages or Tregs. Such studies resonate with early radiobiological observations of vascular changes and activation of clotting cascades, in particular with respect to mobilization and infiltration of myeloid cells and the establishment of their functional profile (Harvey 1908). Another historical observation of Heineke in 1903 (Heinecke 1903) was the rapid extreme radiosensitivity of lymphocytes and the strong regenerative potential of the lymphoid system. This led several early investigators to consider radiation-induced death of lymphocytes in infectious lesions to be a critical step toward induction of immunity and lesion resolution. Killing lymphocytes as a mechanism may seem counter-intuitive especially considering that many COVID-19 patients present with lymphopenia of unknown causation. However, recent concepts on the role of DNA in stimulating type 1 IFN production and adaptive immune responses through pattern recognition might point at immune cell death an adjuvant angle worth reevaluation in LDRT (Deng et al. 2014; Hartlova et al. 2015). In fact, the original concept of ‘radiovaccination’ by Dean Butcher arose from abscopal responses seen in patients who had radiation therapy for acne lesions (Shohan 1916) laying the groundwork for modern concepts of how RT may induce antitumor immunity (Demaria et al. 2005).

Inflammation and infection rapidly disturb redox homeostasis through production of reactive oxygen species (ROS), a property shared with ionizing radiation. This provides a possible nexus for interaction. Such redox shifts are tightly integrated with metabolic pathway alterations and generate oxidant-anti-oxidant signaling loops that continuously monitor the redox state and feed back to restore homeostasis (Forrester et al. 2018). The importance of ROS in defense against pathogens is most dramatically seen during the respiratory/oxidative burst by macrophages and neutrophils (Baldridge and Gerard 1932; Piacenza et al. 2019). It is linked to activation of the pentose phosphate pathway that, amongst other functions, enables anti-oxidant signaling, provides reducing equivalents (i.e., NADPH) for the cell, and plays an important role in antimicrobial host defense and inflammation by fueling NADPH oxidase. Failure to restore redox homeostasis leads to unregulated release of ROS, pro-oxidant cytokines and pathology from excessive inflammation. This is particularly relevant to the multiple progressive events in lung infections, which are largely mediated by cytokines and include vascular changes that dictate the varying degrees of leucocyte infiltration into the interstitium, further feeding the inflammatory machine. Overexuberant inflammation can cause an imbalance in the transcapillary-interstitial fluid exchange system, leading to tissue fluid accumulation and edema, which can be life threatening if occurring in

the airways (Wiig 2011). LDRT has been shown to selectively impair the oxidative burst to inflammatory challenge (Schaue et al. 2002), and to dial down the nitric oxide pathway (Hildebrandt et al. 1998a, 1998b). These may contribute to its anti-inflammatory action and vascular effects. At the same time heme oxygenase-1 and other anti-oxidants are induced that are downstream of Nrf2 (Bao et al. 2016; Rodrigues-Moreira et al. 2017). Nrf2 is the master regulator of endogenous anti-oxidant, anti-stress, analgesic responses, and is also closely linked to NADPH and the pentose phosphate metabolic pathway. Nrf2 may be critical for the relief of pressure and pain associated with edema formation (Staurengo-Ferrari et al. 2018) and is probably a major player in LDRT effects, while direct functional effects of low dose radiation on the autonomous nervous systems and on nociception are probably less so (Trott et al. 2008).

Treating COVID-19 lung disease with LDRT

Although many unanswered questions regarding COVID-19 remain, there are suggestions that COVID-19 lung disease may differ from most other forms of acute respiratory distress syndrome by causing greater loss of lung perfusion, severe hypoxic vasoconstriction and hypoxemia (Gattinoni et al. 2020; Rodriguez 2020). Still, in all likelihood, macrophages and T cells direct endothelial cells, alveolar epithelial cells and fibroblasts when orchestrating the lung pathogenesis during SARS-CoV-2 infection that culminates in alveolar damage, cellular fibromyxoid exudates, pneumocyte desquamation and hyaline membrane production (Xu et al. 2020; Shi et al. 2020). Critical issues for any COVID-19 therapeutic strategy seem to be the rapid development of the disease, the exponential increases in viral load, and the raging and ever-changing immune pathology. It is worth stressing the importance of stage in disease with respect to LDRT. Early investigators noted that efficacy in irradiating various acute diseases was best if radiation was given early, suggesting that the stage impacted the outcome of LDRT (Scott 1939). For example, in 105 cases of acute lobar pneumonia treated with a 50% erythema dose, Powell (Powell 1938) noted that in the late congestive stage LDRT sometimes caused disease to spread rather than be contained. Desjardins (DesJardins 1935) also considered Roentgenotherapy ineffective if the pneumonia exudate was organized. If LDRT were to be considered for the treatment of COVID-19, early intervention would seem indicated, which would be clinically challenging.

Involvement of the immune system in the pathogenesis of COVID-19 might also seem counter-intuitive in light of the high mortality rate in those with underlying conditions and of older age, who are often considered to be ‘immune suppressed’. It seems that many factors will dictate susceptibility, including the depth of penetration of the virus in the respiratory tract, but we would suggest that many of these patients may have difficulty restoring redox balance as a result of their underlying condition, rather than lacking immune function per se, resulting in excessive pro-inflammatory cytokine cascades that drive disease pathogenesis. In support, Xu et al. have shown that T lymphocytes are hyper-activated in COVID-19, in particular cytotoxic CD8+ cells and CD4+ cells of the Th17 phenotype (Xu et al. 2020). Such T cells are major producers of pro-inflammatory cytokines and chemokines, that will feed back to orchestrate further proliferation, recruitment and infiltration in particular by myeloid cells that may exacerbate the disease. Known and feared in the field of cancer immunotherapy, cytokine release storm has also been reported in the context of COVID-19

albeit at much lower levels (Arnaldez et al. 2020). With this in mind, it is not surprising that pro-inflammatory cytokines are emerging as promising targets for therapeutic intervention, with IL-6, IL-1β, IFN-γ, TNF-α, and GM-CSF being key players. Antibodies and small molecule inhibitors targeting these cytokines and their downstream signaling pathways are being repurposed from the field of rheumatoid arthritis and other autoimmune diseases for COVID-19 treatment, with the anti-IL-6R tocilizumab (Genetech) leading the way (Arnaldez et al. 2020). One possible advantage of LDRT over these approaches would be that it acts broadly, potentially interfering with several inflammatory, pro-oxidant pathways at multiple levels, much more so than drugs targeting a single cytokine ever could (Nakatsukasa et al. 2008). However, in our opinion the chances of LDRT being effective in counteracting even a minor cytokine release storm at advanced disease stages would seem slim at best and its delivery therefore would be challenging.

Our Conclusions

Essentially, we don't know enough about the underlying mechanisms in COVID-19 viral pneumonia, nor do we know with precision the mechanisms that are invoked by LDRT that might be of clinical value. The important question is what drives COVID-19 lung disease and the fairly sudden systemic deterioration that in some cases can include injury to the heart and kidneys, stroke and shock, in addition to pneumonia. To treat that with LDRT will therefore be tricky as would be identifying those few patients most likely to benefit from radiation treatment and identifying them early enough to have the desired impact. The likelihood of finding a clinical stage of disease and treatment protocol that would restore the balance and reverse the disease is not great, especially in the absence of good data from an appropriate model. It therefore seems premature to suggest that LDRT would be superior to any of the drugs currently being tried, and until information from the drug trials is available it may be unethical. The following questions might help guide this discussion further:

1. What are the indicators that a patient with COVID-19 is likely to deteriorate: viral load, age, gender, weight, circulating leukocyte profiles, systemic inflammatory markers, procoagulant levels, environment, genetics?
2. What preexisting conditions predict susceptibility and mortality? How are these defined? How do they relate to inflammation and disease-induced redox changes? How important are cardiovascular events in susceptibility to COVID-19 and to disease outcome?
3. Does COVID-19 have distinct disease patterns in subsets of patients that might be clinically different and that might dictate treatment choice? In other words: do all patients who become critically ill and succumb to the disease, all fail in the same way? Can a single target be identified for all cases of COVID-19 that will improve outcome across the board?
4. Are there genetic features that correlate with susceptibility and mortality of COVID-19 that would indicate mechanisms of pathogenicity? How do these relate to race, MHC, and germline determinants?

5. What is the main driver for the COVID-19 lung pathology? Is this predominantly controlled by myeloid forces or T cells? How does the cytokine profile, locally and systemically change with time post-infection and disease stage? What is the incidence and composition of any cytokine storm and its role in the disease? What is the role of lymphopenia and what is the mechanism of its induction? Is lymphopenia good or bad for COVID-19 and would it be exacerbated by LDRT?

6. Defining radiation treatment parameters: In what patients should LDRT be used? When should it be started, with what dose, how often and at what volume/field size? Should there be a control arm and what should it be?

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