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COMMENTARY

A combinatorial approach of a polypharmacological adjuvant 2-deoxy-D-glucose with low dose radiation therapy to quell the cytokine storm in COVID-19 management

Amit Verma[a], Amitava Adhikary[b], Gayle Woloschak[c], Bilikere S. Dwarakanath[d], and Rao V. L. Papineni[e]

[a]PACT & Health LLC, Branford, CT, USA; [b]Department of Chemistry, Oakland University, Rochester, MI, USA; [c]Department of Radiobiology, Northwestern University's Feinberg School of Medicine, Chicago, IL, USA; [d]Department of Research and Development, Shanghai Proton and Heavy Ion Center, Shanghai, People's Republic of China; [e]Department of Surgery, University of Kansas Medical Center (Adjunct), and PACT & Health LLC, Branford, CT, USA

ABSTRACT

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a pandemic disease and is the major cause of deaths worldwide. The clinical complexities (inflammation, cytokine storm, and multi-organ dysfunction) associated with COVID-19 poses constraints to effective management of critically ill COVID-19 patients. Low dose radiation therapy (LDRT) has been evaluated as a potential therapeutic modality for COVID-19 pneumonia. However, due to heterogeneity in disease manifestation and inter-individual variations, effective planning for LDRT is limited for this large-scale event. 2-deoxy-D-glucose (2-DG) has emerged as a polypharmacological agent for COVID-19 treatment due to its effects on the glycolytic pathway, anti-inflammatory action, and interaction with viral proteins. We suggest that 2-DG will be a potential adjuvant to enhance the efficacy of LDRT in the treatment of COVID-19 pneumonia. Withal, azido analog of 2-DG, 2-azido-2-DG can produce rapid catastrophic oxidative stress and quell the cytokine storm in critically ill COVID-19 patients.

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COVID-19 is an infectious disease caused by the virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; a single-stranded RNA virus) (Tay et al. 2020). According to the World Health Organization (WHO), it is a pandemic disease that has caused more than half a million fatalities worldwide so far. Triage of COVID-19 positive patients involves an asymptomatic phase (absence of any clinical signs & symptoms), mild phase (fever, dry cough, tiredness), and a severe phase (acute pneumonia, respiratory failure, and death) (Figure 1). The severe phase is associated with acute inflammation in lungs, greater loss of lung perfusion, severe hypoxic vasoconstriction, and hypoxemia mediated by robust secretion of cytokines ('cytokine storm') and chemokines by immune cells (particularly macrophages and Th1 cells) (Ierardi et al. 2020; Shi et al. 2020; Xu et al. 2020). The primary organ targeted by SARS-CoV-2 is the lungs with varying degrees of localization in other organs like heart, kidneys, and gastrointestinal tract, having high levels of angiotensin-converting enzyme II (ACE2) receptor (Dhawan et al. 2020). The cellular receptor for SARS-CoV-2 is ACE2, which facilitates viral entry into the host cells (mainly lung alveolar type II pneumocytes) with 10–20 fold higher affinity to previously known SARS-CoV (Ciaglia et al. 2020). Patients with comorbidities, such as diabetes, chronic renal disease, cancer, immune disorders, and chronic pulmonary disease appear to be more vulnerable to SARS-CoV-2 infection, with a high mortality rate (Guan et al. 2020).

The current therapeutic management of COVID-19 is mainly supportive care (WHO Interim Guidance 2020); however anti-viral agents like remdesivir, lopinavir alone, and in combination with interferon and ribavirin have been evaluated with limited success (Barlow et al. 2020). A variety of other treatment regimens such as convalescent plasma and monoclonal antibodies have shown potential but are bogged down by logistical constraints and are still under consideration for large-scale evaluation (Barlow et al. 2020). Due to the complex pathology of the disease, an appropriate etiological model and effective treatment for COVID-19 is yet to be developed (Figure 1). Several vaccine candidates viz: DNA, RNA, and recombinant based vaccines (targeting viral Spike protein/S protein) are in their preclinical and clinical stages of development and are being evaluated for mass production (Amanat and Krammer 2020). However, no human coronavirus vaccine is approved by the FDA although hope exists that a standard coronavirus vaccine

CONTACT Rao V. L. Papineni Dr.Papineni@Connect.HKU.HK, DrPapineni@PACTandHealth.COM Department of Surgery, University of Kansas Medical Center (Adjunct), and PACT & Health LLC, Branford, CT, USA; Bilikere S. Dwarakanath DWARAKANATH@sphic.org.cn, dwarakanathdrbs@gmail.com Department of Research and Development, Shanghai Proton and Heavy Ion Center, Shanghai, People's Republic of China

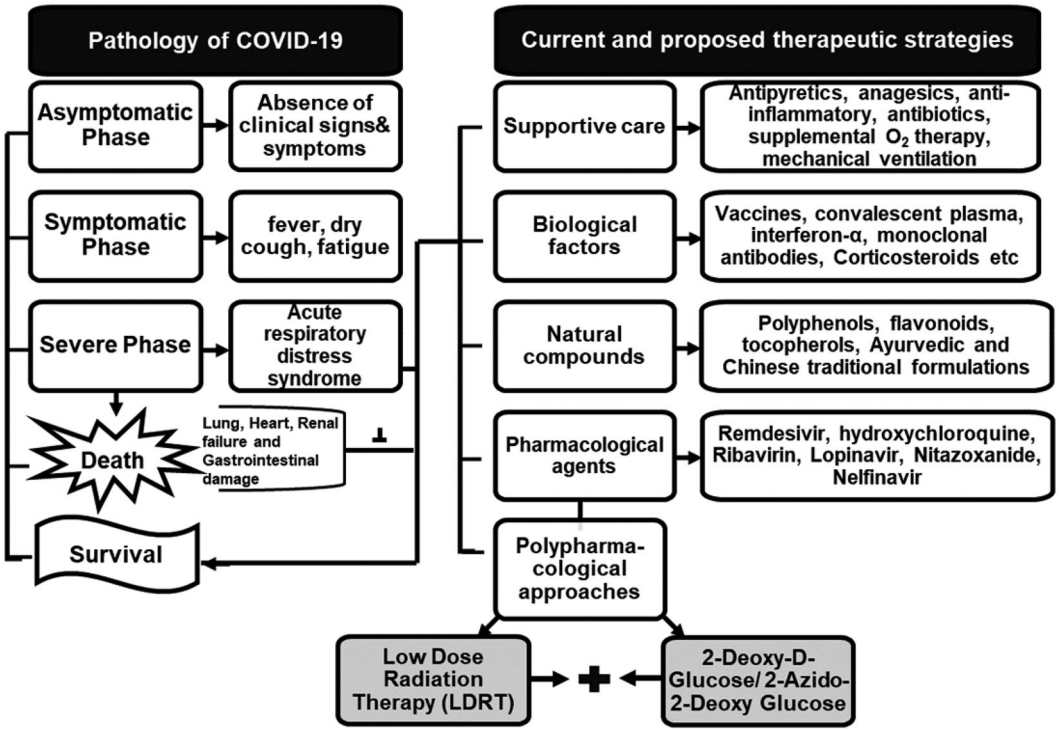

Figure 1. Progression of COVID-19 disease process and potential therapeutic approaches for the management of severe COVID-19 patients. It is expected that a combination of polypharmacological agents such 2-Deoxy-D-Glucose (2-DG)/2-Azido-2-Deoxy Glucose (Azido-2-DG) and low dose radiation therapy (LDRT) could significantly improve the treatment of COVID-19 disease.

will come into effect during the later phase of the pandemic. Since innate immune system is insufficient to generate a robust immune response against the virus, polypharmacological agents that not only attenuate viral reproduction but also modulate the host immune responses to viral infection are urgently needed.

Ionizing radiation, widely used as one of the anticancer therapeutics has been shown to elicit an immunomodulatory response, with low doses (below 2 Gy) of whole body irradiation in animal tumor models as well as focal irradiation of tumors generally causing anti-tumor immune response, while sparing the normal tissue (Sakamoto 2004; Farooque et al. 2011; Draghiciu et al. 2014; Wills et al. 2016; Yang et al. 2016; Liu et al. 2019; Torres Royo et al. 2020). Low dose radiation therapy (LDRT) activates both innate (NK cells, macrophages, and dendritic cells) and adaptive (CD4 and CD8) components of anti-tumor immunity including the reduction in immunosuppressive T-regulatory cells and the release of cytokines (IL-12, TGF-β, TNF-α, IL-10, IFN-γ, etc.) which contributes to pro-inflammatory and anti-tumor immune responses (Shan et al. 2007; Farooque et al. 2011). Pro-inflammatory immune responses induced by LDRT are implicated in antitumor effects, while anti-inflammatory immune responses are associated with the anti-bacterial/viral effects. However, a comprehensive understanding of underlying mechanisms involved in LDRT-induced anti-tumor and anti-viral immune response is still lacking. In addition to its role in cancer therapy, LDRT has been implicated in treating bacterial and viral pneumonia (Calabrese and Dhawan 2013; Li 2020; Schaue and McBride 2020). The studies have also shown that LDRT is effective in reducing the pathology if administered at an early stage of the disease (Schaue and McBride 2020). Progression and severity of COVID-19 has been linked to immunological disturbances as evidenced by decrease in CD4+ and CD8+ as well as NK cells and the cytokine storm coupled with a fall in IFNγ secretion by these cells in moderate and severely affected patients (Chen et al. 2020). Since LDRT can reduce the cytokine storm due to its ability to induce anti-inflammatory responses, and also increase the immune responses due to its pro-inflammatory effects LDRT of the SARS-CoV-2 infected lungs has been suggested as a promising therapeutic regimen for COVID-19 pneumonia. However, time of LDRT appears to be crucial as it may affect differentially the moderate vs severe disease conditions. Accordingly, several protocols utilizing LDRT for COVID-19 treatment are being investigated or proposed with encouraging preliminary results (Rödel et al. 2020; Wilson et al. 2020).

In addition to the immunomodulatory effects of the virus described above, viral infection also results in the metabolic reprogramming of the host cells by way of enhanced glycolysis that facilitates the viral replication and progress of infection (Thaker et al. 2019). Thus, inhibitors of glycolysis have been suggested as potential therapeutic agents for treating viral infections (Lampidis Foundation 2020). We present here our perspective on the historical and current status of LDRT as a potential treatment modality for COVID-19 and propose a combinatorial approach for using adjuvants like 2-deoxy-D-glucose (2-DG) for enhancing the therapeutic efficacy of LDRT against COVID-19.

Ionizing radiation at high doses is widely used as an anti-tumor therapeutic due to its ability to induce multiple forms of cell death (mitotic, interphase, autophagic, etc.) primarily linked to the induction of DNA damage (mainly double-

strand breaks). Ionizing radiation also causes immunomodulatory effects, particularly at low doses (Farooque et al. 2011) suggesting its limited poly-pharmacological potential. In the early 20th century LDRT doses (<2 Gy) was successfully used to treat pneumonia by irradiating the lung using X-rays (Calabrese and Dhawan 2013). The underlying mechanism while poorly understood, involves modulation of the inflammatory properties of leukocytes, macrophages, fibroblasts, and endothelial cells, as well as the secretion of cytokines/chemokines and growth factors (Dhawan et al. 2020). Macrophage polarization to anti-inflammatory M2 phenotype, reduction in the adhesion of leukocytes to endothelial cells and reactive oxygen species (ROS) as well as increased anti-inflammatory cytokines like interleukin-10 (IL-10) and tumor necrosis factor-beta (TNF-β) linked to the activation of several transcription factors, such as nuclear factor kappa beta (NFκB), Nrf-2 and activating protein-1 (AP-1) have been observed (Dhawan et al. 2020; Lara et al. 2020). LDRT also induces apoptosis in certain cell types, increased transforming growth factor-beta 1 (TGF-β1), and enhancement of immunosuppressive T-regulatory cells (Dhawan et al. 2020; Lara et al. 2020). Due to its anti-inflammatory properties, LDRT has been reevaluated for treating COVID-19 pneumonia with encouraging results in a small pilot clinical trial (Hess et al. 2020). Interestingly, a single fraction of 1.5 Gy ionizing radiation improved the clinical status, encephalopathy, and radiographic infiltrates without acute toxicity or worsening of the cytokine storm (Hess et al. 2020). However, the success of LDRT for COVID-19 pneumonia is critically influenced by the timing of irradiation following infection as improper timing can aggravate the disease by causing deleterious pro-inflammatory responses (Tharmalingam et al. 2020; Montero et al. 2020; Kirsch et al. 2020), besides damage to other normal cells linked to genomic instability (Elbakrawy et al. 2019). Therefore, there is a need to develop an approach that has the potential to selectively enhance the death of virus-infected cells, while sparing the uninfected normal (lung and other tissues) cells thus preventing systemic infection and multi-organ dysfunction in critically ill COVID-19 patients.

Metabolic reprogramming and enhanced glucose usage by aerobic glycolysis is an important hallmark of cancer cells referred to as the Warburg effect (Warburg 1930). Targeting of the glycolytic pathway by 2-DG has been well established for its radio- and chemo-sensitizing effects in vitro and in vivo, including its cancer-preventive potential when administered as a dietary component (Dwarakanath and Jain 2009; Dwarakanath et al. 2009; Singh et al. 2015, 2019). Phase-I, II and III clinical trials in glioblastoma have shown that a combination of hypofractionated radiation with orally administered 2-DG is well tolerated with minimal acute and late toxicity and improved quality of life with a modest survival benefit (Mohanti et al. 1996; Singh et al. 2005; Dwarakanath et al. 2009). Most importantly radiosensitization of tumors and tumor cells by 2-DG is accompanied by sparing the normal cells (Swamy et al. 2005) and tissues as has been noted in clinical trials (Farooque et al. 2009; Prasanna et al. 2009; Venkataramanaa et al. 2013). The multiple mechanisms underlying this sensitization by 2-DG have been elucidated, which include depletion of energy, disturbed redox balance and altered N-linked glycosylation leading to the unfolded protein response (UPR), inhibition of DNA repair, impaired cell cycle regulation, altered calcium influx, and apoptosis (Dwarakanath 2009). It is pertinent to note that the radiosensitization of tumors in mice by 2-DG is partly attributed to the immune stimulatory effects by a combination of 2-DG and radiation involving the restoration of $CD4^+$ and $CD8^+$ ratio, shift from Th2 to Th1, reduced IL-17 (Th17), improved antigen presentation (MHC II and CD80/86), enhanced NK cells, macrophage repolarization as well as functional stimulation (phagocytic activity) and decrease in immune suppressive network (Farooque et al. 2014, 2016). Besides immune stimulation, 2-DG with radiation generates anti-inflammatory responses (Gupta et al. 2017; Papineni et al. 2018; Verma et al. 2019) and mitigates bacterial infection (Papineni et al. 2017). These studies have also shown that 2-DG alone could enhance antigen presenting ability (MHC II and CD86) and functionality of macrophages (phagocytosis) and reduce TNFα, while enhancing IFNγ (Farooque et al. 2014, 2016).

Viral infection (both DNA and RNA viruses) causes a metabolic shift from oxidative phosphorylation to aerobic glycolysis in the host cells, which facilitates viral replication (Thaker et al. 2019). The progress of COVID-19 pathogenicity linked to SARS-CoV-2 replication is also facilitated by enhanced aerobic glycolysis (Cavounidis and Mann 2020). Further, LDRT increases aerobic glycolysis resulting in increased radiation resistance in normal human cells linked to increased expression of glucose transporters, glycolytic genes, and hypoxia-inducible factor1α (HIF1α) (Lall et al. 2014). Thus it appears that the increased aerobic glycolysis due to SARS-CoV-2 infection and LDRT might even favor the SARS-CoV-2 replication and reduce the therapeutic gain. In fact, several studies have demonstrated induction of viruses with radiation exposure, although this has not yet been shown for Coronaviruses (Libertin et al. 1994; Mehta et al. 2018). Studies have nevertheless demonstrated the antiviral effects of 2-DG (Passalacqua et al. 2019), which is attributed to the direct interaction of 2-DG with the virus (preventing viral entry into host cells) and compromising the high energy demand by glycolysis inhibition. Recent *in silico* studies suggest that the structure of 2-DG fits into protease 3CLpro as well as NSP15 endoribonuclease, leading to the inhibition of SARS-CoV-2 receptors binding to the host cells, which requires validation (Balkrishna et al. 2020). Moreover, 2-DG has also been shown to exert anti-inflammatory effects (Choi et al. 2020). Preliminary in vitro studies have shown the potential of 2-DG in reducing the viral load in host cells (Bojkova et al. 2020). Based on these polypharmacological effects of 2-DG (glycolysis inhibition, anti-inflammatory action, and interaction with viral proteins), 2-DG has been suggested as a therapeutic for the management of COVID-19 patients (Lampidis Foundation 2020). Further, the ability of 2-DG in restoring CD/CD8 ratio, enhancing NK cells and IFNγ levels coupled with improved antigen presenting ability of macrophages reported by us

earlier (Farooque et al. 2014, 2016) suggest that 2-DG may also improve the immune status compromised by COVID-19 (Chen et al. 2020). However, the dose of 2-DG required and daily administration needed may cause concern regarding non-target effects in the form of CNS disturbances and cardio-respiratory disturbances (Landau and Lubs 1959; Vijayaraghavan et al. 2006), although protection of normal brain tissue has been reported during hypofractionated radiotherapy combined with 2-DG (Prasanna et al. 2009; Venkataramanaa et al. 2013). Therefore, we suggest that an optimum dose of 2-DG administered soon after the infection will be a potential adjuvant to enhance the efficacy of LDRT in the treatment of COVID19 pneumonia.

Since the administration of LDRT (with or without 2-DG) can be only accomplished at oncology centers with radiotherapy facilities (sparse and generally located at urban centers), it imposes a limitation on the number of patients who can be treated, particularly at places far away from these facilities as the infection continues to expand across the globe. We recently demonstrated the potential of the azido analog of 2-DG, 2-azido-2-DG in facilely generating the radiation-produced electron-mediated formation of oxidizing neutral pi-type aminyl radicals from the azido moiety (Papineni and Adhikary 2020). Such potent oxidative radicals (Hawkins and Davies 2001; Mudgal et al. 2017) will augment the generation of rapid catastrophic oxidative stress that can synergize with other well-known effects of 2-DG on the metabolism and UPR, impeding the viral replication and death of infected host cells as well as quelling the cytokine storm. From this perspective, the polypharmacological 2-azido-2-DG will be highly useful as it can be easily administered everywhere (similar to 2-DG) (including dispensing across the counter) if it is found to be more effective than 2-DG alone and hopefully as effective as the combination of 2-DG and LDRT. Carefully planned pre-clinical studies in animal models comparing the efficacy of 2-DG, LDRT, LDRT plus 2-DG, and 2-azido-2-DG are warranted that can lead to the design of clinical protocols using this polypharmacological approach based on 2-DG or its novel derivatives either as a mono-therapeutic agent or as an adjuvant to LDRT.

Perspective

Critical evaluations are warranted before LDRT is considered as a potential treatment approach for COVID-19 patients. Further, due to heterogeneity in disease manifestation and inter-individual variations, effective planning for LDRT is limited for this large scale event. The perspective is to use 2-DG (readily available, cost-effective, and can be administered easily) as an adjuvant with LDRT to treat COVID-19 patients in moderate or severe phases including patients with other comorbidities. Due to its polypharmacological effects on the virally-infected lung cells mainly comprising inhibition of glycolysis (thus the energy status), modulation of inflammatory responses (cytokine storm) and alterations in glycosylation of viral proteins, 2-DG will be an effective adjuvant to LDRT to inhibit viral replication and preventing lung damage (Figure 1). 2-DG in combination with LDRT (Papineni 2020) may also protect other virus sensitive tissues and organs leading to the reduction in mortality and morbidity. However, systematic studies related to the optimization of dose and time of administration and evaluation of associated toxicities are warranted.

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Disclosure statement

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper. The views expressed in this paper represent collective opinions of the authors and are not necessarily those of their professional affiliations.

Notes on contributors

Amit Verma Ph.D, PACT & Health LLC, Connecticut, USA.

Amitava Adhikary Ph.D, Department of Chemistry, Oakland University, Michigan, USA.

Gayle Woloschak Ph.D, Department of Radiobiology, Northwestern University's Feinberg School of Medicine, Chicago, USA.

Dwarakanath S Bilikere Ph.D, Department of Research and Development, Shanghai Proton and Heavy Ion Center, Shanghai, People's Republic of China.

Rao V. L. Papineni Ph.D, Department of Surgery, University of Kansas Medical Center, and PACT & Health LLC, Connecticut, USA.

ORCID

Amitava Adhikary http://orcid.org/0000-0001-9024-9579
Gayle Woloschak http://orcid.org/0000-0001-9209-8954
Bilikere S. Dwarakanath http://orcid.org/0000-0001-6988-2601
Rao V. L. Papineni http://orcid.org/0000-0002-1263-4292

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