

Integrative Cancer Therapies: Learning From COVID-19

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Integrative therapies have been associated with the coronavirus pandemic since shortly after it began. Traditional Chinese medicine was used with COVID-19 (coronavirus disease-19) patients at the start of the pandemic and featured in the Chinese National Plan.¹ In this journal, Yan et al² discussed the use of traditional Chinese medicine therapies with cancer patients afflicted with COVID-19. They suggested the use of Tai Chi and Qi Gong as indoor exercise during times when the public is restricted to home to help strengthen the constitution. They also raised an alarm about therapies like massage and acupuncture that involve close contact with patients, and suggest they be rigidly considered or forbidden for cancer patients in endemic areas, with stronger personal protection provisions for both patients and therapists.

Their caution was prescient. Since COVID-19 is now widespread throughout the globe, integrative and conventional medical practices alike have restricted or eliminated “high-touch” therapies that involve close personal contact, ranging from dentistry to surgery, not to mention massage and acupuncture. We hear reports of integrative therapy departments in cancer-focused hospitals being shut down, with widespread halts to ongoing research. For health professionals in “high-touch” occupations practicing in areas with high COVID-19 presence, the economic devastation is palpable, with closed private clinics, and layoffs in hospitals.³ This is raising serious concerns of how COVID-19 may shape the future of integrative cancer therapies.

Cancer patients are reported to have severe outcomes in COVID-19.⁴ Medical practices are already instituting ways to reduce personal contact through, for example, expanded telehealth visits. How will medical administrators view some of the staples of integrative cancer therapies in the next few years? Reiki, yoga classes, meditation classes, acupuncture, art therapy, and similar interventions may be considered hazardous to immunocompromised cancer patients, and thus medically contraindicated. Furthermore, the cost to health care systems from the COVID-19 pandemic is astounding. Recent projections show a cost to the US health care system of \$654 billion if 80% of the US population is infected with COVID-19 or \$405.8 billion in direct costs if only 50% of the population is infected.⁵ The

loss of revenue from delayed or cancelled elective procedures compounds the hospitals’ financial plight. Will administrators be eager to restart programs that rely on in-person services for high-risk patients?

We are especially concerned about a possible imminent contraction or restructuring of in-person hospital-based integrative care for cancer patients. Integrative cancer care may need to rely more on services that can be delivered by telehealth in the future, such as consultations with integrative physicians and remotely delivered mindfulness or exercise therapies.⁶ In-person yoga and meditation classes, acupuncture, and other in-person therapies may eventually reappear in smaller private consultation settings that cancer patients may access on their own well after the end of treatment, as their risk levels decrease.

But, to the extent that integrative care for cancer patients does reemerge in the conventional care setting, there are areas for which telehealth may be quite effective. Not only has COVID-19 suddenly converted us to a reliance on telehealth that is likely to persist in the future, it has also highlighted the use of some integrative therapies commonly used by cancer patients that have previously been thought to be too controversial for conventional clinics, but that might bear further research attention. Specifically, high-dose intravenous vitamin C has come to the attention of the conventional medical community as a potential COVID-19 therapy. In the remainder of this editorial, we will discuss both proposed areas in which telehealth may be particularly effective for integrative care, and the potential emergence of the “alternative” intravenous therapies.

Telehealth: a Focus on Biology

One of the lessons of COVID-19 is that we must pay attention to the underlying health of patients. Comorbidities, among them diabetes, hypertension, cardiovascular or

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cerebrovascular disease, and chronic obstructive pulmonary disease as well as cancer are widely known to increase the severity of COVID-19. The growing understanding of the biology of COVID-19 reminds us of the importance of understanding the biology of cancer, especially from an integrative treatment approach. And indeed, some of the biology driving COVID-19 overlaps with processes driving cancer: inflammation, effects of reactive oxygen species, immunity, and even deficiencies in vitamin D.⁷

Overlapping comorbidities and biology both have significant effects on cancer and COVID-19 outcomes. Diabetes, for instance, influences the course of both COVID-19 and cancer, increasing both mortality and morbidity.⁸ Diabetic patients in a large clinical trial in metastatic colorectal cancer, for instance, had an overall median survival of 22.7 months, while nondiabetics survived 27.1 months ($P < .001$).⁹ Markers of systemic inflammatory response, interleukin-6 (IL-6) and C-reactive protein (CRP), both were related to overall survival in metastatic colorectal cancer.¹⁰ And adequate vitamin D levels predicted a 13% reduction in cancer mortality (risk ratio = 0.87, $P = .05$) in a meta-analysis of randomized trials.¹¹

The overall influence of comorbidities and dysfunctional biology on cancer outcomes is crystallized in the measurement of performance status. Performance status is commonly assessed in oncology trials and clinical treatment, and widely known to be associated with treatment response, tolerance, and survival. For instance, 3 meta-analyses of randomized trials of chemotherapy in colorectal cancer patients found that performance status predicted mortality,¹²⁻¹⁴ in addition to treatment side effects.¹² Performance status integrates multiple aspects of a patient's health. Improvement of performance status will contribute to both improved daily well-being and better response to conventional treatment, 2 major goals of integrative cancer therapy. Comprehensive integrative treatment approaches that aim at multiple targets are ideally suited to improvement of performance status and can, we believe, form the foundation of interventions that can be delivered by integrative physicians and other practitioners using telehealth platforms.

Such multitargeted interventions have been described in the literature,¹⁵⁻¹⁸ and one experimental study of such a system published in this journal even included remote delivery of lifestyle counseling using Facetime.¹⁷ While in-person counseling has significant advantages, the safety and potential economy of telehealth consultations with integrative physicians, dietitians, and specialists in psychosocial oncology may allow for very relevant interventions, particularly for patients in treatment. Referrals to in-person therapies can be made for lower-risk patients, perhaps at locations outside the treating hospital if necessary. Webinar-style presentations can also offer patients helpful information.

Lifestyle interventions to lower inflammation and inflammatory cytokines can be examined as an example of one

facet of a multi-targeted integrative program. Lifestyle interventions that can be delivered by telehealth include nutrition and supplement counseling, exercise direction, and psychosocial oncology interventions.⁶ A dietary intervention that routinely brings about changes in multiple cytokines and overall inflammation is weight loss. In breast cancer survivors, positive correlations were observed of body mass index and body fat with CRP, IL-6, IL-8, and tumor necrosis factor- α (TNF- α).¹⁹ Plant-based diets in other populations were correlated with reduced IL-6, CRP, and sICAM (soluble intercellular adhesion molecule), though not TNF- α .²⁰ Healthful diets may affect recurrence or survival, so such changes are of clinical relevance. A review of randomized trials in breast cancer found that low-fat diets were associated with better survival, and a diet rich in phytoestrogens with reduced risk of recurrence.²¹ Furthermore, a recently published 19-year follow-up of the Women's Health Initiative trial found that among participants who suffered from breast cancer, those who followed the low-fat diet had a reduced incidence of breast cancer-related death.²²

Other lifestyle changes to reduce inflammation and inflammatory cytokines that can be directed or imparted by telehealth include supplements, exercise, and mind-body medicine. According to a meta-analysis, fish oil supplements reduce IL-6 in surgical patients, and CRP in chemotherapy patients.²³ Randomized trials also showed maintenance of CRP in treatment-naïve breast cancer patients versus un-supplemented controls, and improvement in CRP as well as survival in fish oil-supplemented hematological malignancy patients.^{24,25} A trial of walking and resistance exercise in chemotherapy patients observed a shift to an anti-inflammatory cytokine profile, related to reductions in interferon- γ .²⁶ Finally, a randomized trial of mindfulness-based stress reduction reduced IL-6 as well as cortisol in the experimental group.²⁷

Intravenous Therapies in COVID-19 and Cancer

Integrative oncology practitioners may not be aware of the increasing interest of intravenous vitamin C in treatment of patients with sepsis.²⁸ Sepsis causes notable vitamin C deficiencies, and the intravenous administration of elevated doses helps overcome the rampant oxidative stress and inflammation observed in hospitalized septic patients. Multiple trials have demonstrated safety, and 2 recent studies suggest promising results on mortality. High-dose intravenous vitamin C has also been used in acute respiratory distress syndrome, and promising data in this setting suggest that it may be effective in COVID-19.²⁹ Three clinical trials of intravenous vitamin C in hospitalized patients with severe COVID-19 are listed in clinicaltrials.gov as of early May 2020 (NCT04357782, NCT04344184, NCT03680274).

Many of us are used to seeing intravenous vitamin C treated as a scandalously alternative cancer treatment, and its emergence in the intensive care units of hospitals with the goal of treating oxidative stress and inflammation is both surprising and heartening. Along with the previously published beneficial effects of parenteral fish oil emulsions in cancer patients,³⁰ these vitamin C trials raise the question of the potentials of other unconventional intravenous treatments in cancer patients.

Injectable administration of traditional herbal formulas has been routine in Chinese medicine for years, shown by multiple meta-analyses,³¹ as has the use of injectable *Viscum album* in Europe.³² As is the case with intravenous vitamin C in cancer,³³ the benefits of these alternative therapies are still somewhat in question due to inferior quality of clinical trial design. However, the apparent safety shown in scientific studies, together with the increased awareness of potential benefits of vitamin C in a completely conventional hospital setting, raises the profile of injectable herbal therapies.

Three other intravenous therapies based on phytochemicals are coming into use in North America and elsewhere, and we propose to briefly examine the reasons for the interest in these therapies. They are intravenous curcumin, quercetin, and resveratrol. It is important to note that these therapies, as well as intravenous vitamin C, should only be given in facilities equipped with appropriate emergency supplies, including respiratory support for patients, because of the infrequent but real potential for anaphylactic reactions. Chemotherapy drugs can cause also anaphylactic shock, so oncology units are among the facilities that routinely contain such emergency supplies.

Interest in intravenous administration of these 3 phytochemicals came about because of their poor oral bioavailability and the need for higher blood levels of these compounds for effective treatment. Although curcumin has been used in numerous clinical studies that show some promise in treatment of cancer, its poor oral availability, and the need to take very large oral doses, is well known.³⁴ Interestingly, a 2016 publication reported a case of adenoid cystic carcinoma (ACC) of the salivary gland treated with intravenous curcumin alongside imatinib.³⁵ ACC is a generally chemoresistant tumor, and the patient in question had metastatic disease that did not respond to cisplatin and etoposide. Imatinib, a monoclonal antibody therapy for tumors expressing c-kit, was not found to be typically effective in ACC tumors. However, the patient's tumor expressed nuclear factor κ B (NF- κ B) as well as c-kit, and the patient's physicians thus chose to treat with imatinib and intravenous curcumin (an inhibitor of NF- κ B).³⁵ At 24 months after starting treatment, a near complete response to the combination was observed, with no adverse reactions. The authors report that their clinical experience with more than 3000 prior curcumin infusions also suggests safety.

A phase I study of an intravenous liposomal curcumin formulation, specifically designed to overcome bioavailability

concerns, reported safe dosing up to 300 mg/m² in 32 patients.³⁶ In this study, 1 patient with metastatic prostate cancer had a temporary decrease in prostate-specific antigen from 644 to 355 ng/mL, stable disease on scans, a reduction of lactate dehydrogenase to normal range, and improved performance status. A patient with metastatic colorectal cancer had a temporary decline in carcinoembryonic antigen from 18 542 to 6441 μ g/mL from the intravenous curcumin alone.

While these are promising results, further clinical trials are clearly called for. Animal studies of human xenograft tumors, however, also provide some interesting perspectives on possible lines of investigation. Curcumin retarded growth of MCF-7 and MDA-MB-231 breast cancer xenografts in mice³⁷; a curcumin preparation with increased bioavailability inhibited esophageal squamous cell cancer xenografts in mice³⁸; and a turmeric extract, including turmerones to promote curcumin uptake, inhibited colon tumor xenografts, and retarded chemotherapy-related immunosuppression in mice.³⁹ Previous reviews of curcumin have indicated it may improve the activities of various chemotherapy drugs; recent studies highlight effects with 5-FU (fluorouracil) in gastric cancer cells,⁴⁰ paclitaxel in breast cancer cells,⁴¹ and cisplatin in lung cancer cells.⁴²

A phase I clinical trial of intravenous quercetin found that a safe dose could be given weekly or in 3-week intervals, although some studies have raised questions about how long intravenous quercetin remains in the body.^{43,44} An aim of the phase I study was to determine whether quercetin could reduce tyrosine kinase activation; tyrosine kinase inhibitors are an important class of anticancer drugs. Such inhibition was observed in lymphocytes for up to 16 hours following dosing. A patient with metastatic hepatocellular carcinoma treated at the lowest dose level used in the trial had a sustained fall in serum α -feto protein tumor marker and alkaline phosphatase. A metastatic ovarian cancer patient was treated with quercetin while receiving carboplatin after previous treatment with other chemotherapy regimens. This patient's CA125 fell from 290 to 45 units/mL after 6 months of treatment. Intravenous quercetin was also given with a stabilizing agent once daily for 10 days at a dose of 0.5 g at the start of medical tuberculosis treatment, and showed no adverse effects while hastening symptomatic recovery and radiological resolution of lung damage.⁴⁵ These studies suggest safety and potential efficacy that could be explored in further trials.

Studies of quercetin administered to human tumor xenografts in mice have observed, for instance, inhibition of implanted prostate cancer growth and sensitization to docetaxel, along with reduction of Ki67 expression beyond that observed with docetaxel treatment⁴⁶; reduction of cancer stem cells and expression of the signaling protein Notch-1 in colon cancer xenografts during radiation treatment⁴⁷; and inhibition of the growth of lung cancer xenografts.⁴⁸ Quercetin has other potentials for combination with medical cancer treatments.⁴⁹ It increased the effectiveness of doxorubicin and etoposide in lymphoid leukemia cell lines, and the

effectiveness of doxorubicin in myeloid leukemia lines,⁵⁰ and improved the activity of cisplatin in nasopharyngeal cancer cells.⁵¹

Intravenous administration of resveratrol at a very low dose (0.2 mg) was compared with an oral dose of 25 mg (also a low dose) in a human trial. The intravenous dose raised blood levels quickly although the resveratrol was then absorbed by tissues and metabolized (some metabolites of resveratrol may be active compounds). Levels in the blood declined quickly after the first 6 hours and more slowly thereafter.⁵² Trials of intravenous doses of resveratrol that might be more clinically relevant, and that are being used in clinics, are not available. Safety concerns have not arisen in animal studies. Resveratrol was noted to inhibit lung metastasis in a breast cancer xenograft in mice,⁵³ and to increase the antitumor effects of radiation and cisplatin on head and neck cancer xenografts.⁵⁴ It also reduced glycolysis, liver metastasis, and tumor growth in ovarian cancer xenografts.⁵⁵ A recent review of resveratrol found more than 30 laboratory studies indicating chemoprotective effects or synergistic effects of resveratrol with cancer chemotherapy.⁵⁶

It is also notable that all 3 phytochemicals affect multiple molecular targets in their mechanisms of action. Curcumin and resveratrol were both noted to affect multiple hallmarks of cancer in a comprehensive review.¹⁵ Some of the targets that these agents affect are also targets of conventional drug treatment, such as the androgen receptor (curcumin, resveratrol, quercetin),⁵⁷⁻⁵⁹ Her-2 (curcumin, quercetin),^{60,61} KRAS (quercetin),⁶² and vascular endothelial growth factor (curcumin, resveratrol, quercetin).^{57,61} While targets such as androgen receptor, Her-2, KRAS, and vascular endothelial growth factor can be managed by conventional treatment, these phytochemicals also each affect a number of other important molecular targets in cancer that are not directly affected by conventional drugs, but may nevertheless be relevant for cancer control. For example, curcumin is well known as an inhibitor of NF- κ B, and also inhibits hypoxia-inducible factor 1 α (HIF-1 α), activator protein-1, epidermal growth factor receptor, and matrix metalloproteinases 2 and 9.⁵⁷ Resveratrol also inhibits NF- κ B, phosphatidylinositol 3-kinase, sirtuins, telomerase, and mitogen-activated protein kinase.⁵⁶ Quercetin inhibits Janus kinase-signal transducer and activator of transcription, PI3K, protein kinase B (Akt), p53, and cyclooxygenase-2.⁶¹ Each of these also modulates many other molecular targets, suggesting the potential for systemic effects.

Learning From COVID-19

The coronavirus pandemic will change the world in many ways, and is likely to bring a significant rethinking of many aspects of medical practice. The use of telehealth may eventually overcome barriers many patients face in accessing

different aspects of integrative cancer therapies, such as travel to treatment centers for exercise or meditation classes at times when they are fatigued from their treatment or disease. Telehealth can make consultations with integrative practitioners more accessible to a geographically scattered population—an important fact, since there are as yet relatively few integratively trained health professionals. COVID-19 may make us reconsider general approaches to treatment that emphasize patients' biology and performance status, and may open the door for research on new integrative therapeutics. But substantial research needs to go into the practicality and efficacy of all of these. We hope to see such research begin to flourish again as the coronavirus crisis passes.

Declaration of Conflicting Interests

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Keith I. Block is the owner and medical director of the Block Center for Integrative Cancer Treatment, Skokie, IL, USA.

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