

Oncology Treatment in the Era of COVID-19: We Cannot Afford to Hit the Pause Button

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The coronavirus disease 2019 (COVID-19) pandemic has far-reaching ramifications for patients undergoing cancer treatment. Oncologists and institutions have adjusted treatment practices and, in many cases, significantly curtailed clinical trial conduct. Whether these adjustments mitigate the risk of COVID-19 complications without jeopardizing treatment of the cancer is unknown. Given the expected duration of the pandemic, it is imperative that treatment of the patient's cancer remain the priority and that advances in drug development continue through appropriately designed clinical trials.

PERSPECTIVE

The scope of the COVID-19 pandemic is unprecedented in modern history. Any citation of infection/mortality statistics is immediately outdated, but COVID-19 has become the number one cause of death in the United States. It is increasingly recognized that older individuals and those with comorbidities are at higher risk for mortality, including those with active malignancies. In the United States, the median age of cancer diagnosis is 66 years (National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data) and, until the advent of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), cancer was the second leading cause of death. Cancer therapies include cytotoxic agents and/or targeted

agents and/or immune modifying agents, all of which have the potential to alter the immune response to infectious pathogens. Many hematological malignancies utilize autologous or allogeneic stem cell transplantation or cellular therapies (e.g., chimeric antigen receptor (CAR) T-cell therapy), all of which have profound impacts on the immune system.

Emerging data from China and the United States highlight the increased risk of oncology patients for morbidity and mortality from COVID-19. A report from China described the outcomes of 1,524 patients with solid tumors and noted a twofold higher risk of SARS-CoV-2 infection compared with the overall community risk.¹ These patients were more likely to require the intensive care unit or

die, compared with those without cancer (39% vs. 8%; $P = 0.0003$).¹ Furthermore, patients treated with chemotherapy within a month of COVID-19 infection experienced a fivefold risk of severe events compared with those with cancer who had not received recent treatment.¹ A report of 218 oncology patients who became infected in New York City noted a case fatality rate of 28%.²

The recognition that oncology patients are at particularly high risk for COVID-19 complications, as well as the strain that the pandemic has placed on healthcare resources, has led to rapid adjustments in the management of these patients. There has been a concerted effort to minimize patient contact to decrease the potential exposure of patients, caregivers, and healthcare providers to SARS-CoV-2 and, in some hospitals, to divert healthcare resources toward the care of patients with COVID-19. Numerous publications from societies and disease groups have made recommendations for how cancer care, including specific chemotherapy regimens, should be adjusted (or even held) during the pandemic. These recommendations are opinion-based but not evidence-based, as, at this point, it is too soon to know whether these adjustments protect patients from COVID-19 complications. For example, in a publication focused on the management of patients with multiple myeloma during the COVID-19 pandemic, it was suggested that daratumumab be administered every 4 weeks starting in cycle 3 instead of the standard every 2 weeks schedule.³ Although this practice change would result in fewer infusion center visits, there are no data that enable us to estimate the resulting impact on efficacy from a myeloma perspective, on degree of immunosuppression or on COVID-19 severity.

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Early in the pandemic, when it was predicted that the surge from the first wave would be swift, it was relatively simple to make treatment decisions, such as holding some or all of a cycle of chemotherapy or postponing stem cell transplantation if the intent was not curative. However, it is becoming evident that this approach cannot be continued indefinitely and, therefore, the risk:benefit calculation must incorporate not only the risk of potential SARS-CoV-2 infection, but also the long-term risks of making significant adjustments to standard of care chemotherapy practices. With multiple second waves now being predicted, we must learn to practice optimal oncology care, including the added risks of COVID-19.

Clinical trials are a critical component of oncology care. It is estimated that only 5–10% of all patients with cancer in the United States participate in therapeutic clinical trials.⁴ Despite the barriers that lead to this low rate of participation, clinical trials remain the cornerstone for improving oncology patient outcomes through the development of new therapies. An analysis of accrual data for national cancer treatment trials revealed a correlation between trial enrollment and 5-year cancer-specific survival rates.⁴ The conduct of clinical trials has become increasingly complicated in the era of COVID-19, significantly restricting access of clinical trials to oncology patients. Underlying factors include the desire to limit patient contact to decrease SARS-CoV-2 exposure, research personnel being required to work from home, travel bans, concern about the unknown impact of investigational therapy on severity of COVID-19, as well as healthcare resources being diverted to the management of patients with COVID-19. Industry sponsors and institutions have placed selected studies on hold and/or halted enrollment. A recent survey conducted by the American Society of Clinical Oncology (ASCO) revealed that almost 60% of respondents (from both academic and community-based programs) had halted screening and/or enrollment of clinical trials.⁵ Some institutions have encouraged investigators to remove subjects from ongoing studies. In other situations, institutions have mandated that only standard of care procedures be allowed and that study-specific procedures cease. The

ASCO survey revealed that half of respondents reported that their sites had stopped collecting research-only blood and/or tissue samples.⁵ Some institutions have halted the internal regulatory process that is necessary for new studies to open. Some sponsors have halted the internal review process that evaluates new investigator-initiated trial concepts. As a whole, these measures have led to significant changes in the clinical trial enterprise. **Table 1** provides an overview of some key clinical trial practices,

including the pre-COVID-19 era, the current COVID-19 era, as well as speculations about what the future might entail. Some of these practice changes, including the use of telehealth visits, electronic informed consents, and delivery of study medications to the home, will hopefully become permanent additions in the post-pandemic era, resulting in enhanced accrual and retention. There is opportunity to incorporate secure online consenting processes and remote monitoring (e.g., heart

Table 1 Summary of changes in oncology clinical trial conduct

| Action | Pre-COVID-19 era | Current COVID-19 era | Potential future |
|----------------------------------|--|--|--|
| Informed consent | In-person visits | Institution-dependent; some allow electronic/phone consents | In-person, secure online or phone consents |
| Clinic visit | In-person visits | Maximize telehealth visits; minimize in-person visits | Mix of in-person and telehealth visits |
| Vital signs | In-person visits | Subjects report some vital sign information during telehealth visit | Provide in-home access to temperature, blood pressure, heart rate, pulse oximetry monitoring, wearable sensors |
| Toxicity reporting | In-person visits, paper questionnaires | Telehealth visits; questionnaires may not be collected | In person-visits, online questionnaires, telehealth visits |
| Drug administration | Study drug (i.v., s.c., p.o.) administered at study center | Minimize administration of i.v./s.c. study medications; ship oral medications to patient | Utilize both local and study infusion centers; option of mailing oral medications |
| Safety labs | Study center only | May not be done or exceptions required to use local facilities | Protocols allow labs to be drawn at study center, local facilities or via home health care |
| Study-specific labs | Study center only | May not be done | Protocols allow labs to be drawn at study center, local facilities or via home health care |
| Radiology assessment | Study center only | Scans may not be done or exceptions required to use local facilities | Protocols allow scans to be performed at study center or local facilities |
| Biopsies for correlative studies | Study center only | May not be done | Protocols allow biopsies to be performed at study center or local facilities |
| Site monitoring | In-person visits | Postponed or via remote | Increased utilization of secure remote monitoring |
| COVID-19 testing | Not applicable | Inconsistent use | Protocol-specified testing for active infection, serology status, or immunization status |

COVID-19, coronavirus disease 2019.

monitor patches and wearable sensors). In addition, as recently discussed by Tan *et al.*, there is opportunity to develop a decentralized clinical trial model.⁶ It should also be noted that some institutions have opened COVID-19 clinical trials in remarkably short time periods (i.e., in a matter of weeks), which raises the question as to why most oncology trials take 3–8 months to open at academic centers.^{7,8}

Protection of human subjects is always of paramount concern; however, it is recognized that many patients participate in clinical trials because the studies represent their best therapeutic option. Furthermore, from a study perspective, failing to obtain pharmacokinetic data, perform correlative studies, electrocardiograms, or imaging or biopsies to document disease response could result in inaccurate conclusions about a novel therapy's safety profile, optimal dosing, and/or efficacy. As noted by Saini *et al.*, the long-term consequences of decreased trial accruals will affect drug development timelines and ultimately delay getting promising treatments to patients.⁹ In this country, the actions of a few (i.e., those who participate in clinical trials) affect the outcomes of the many (i.e., the general oncology population) who benefit from the approval of new drugs and therapies.

The risk that COVID-19 poses for oncology patients cannot be underestimated and it is critical that the field gather as much information as possible to guide us in making treatment decisions. To this end, there are many groups, including ASCO and the American Society of Hematology, that have created registries in order to collect data on outcomes of oncology patients infected with SARS-CoV-2. The impact of COVID-19 on the immune system, even in immunocompetent patients, is striking, and is somewhat reminiscent of the cytokine release syndrome associated with CAR T-cell therapy.¹⁰ The degree to which oncology patients have impaired immune responses varies widely depending on the specific malignancy type and therapy. It is difficult to predict what the impact of various immunotherapeutic modalities, such as CAR T-cells, immunomodulatory agents, and immune checkpoint inhibitors will have on COVID-19 severity. It

is imperative that comprehensive immune profiling studies be performed to evaluate the immune responses in these patient populations and that oncology patients be included in COVID-19 clinical trials. As COVID-19 testing (both for viral RNA and serology) become more readily available, there is an opportunity to begin rigorously assessing SARS-CoV-2 status prior to initiation of high-risk therapies. Finally, there is also significant opportunity to utilize clinical pharmacology principles and prospectively evaluate the impact of adjustments in dosing of chemotherapy during the pandemic.

It has been said that we should view the pandemic as a marathon and not a sprint, but the reality is that even marathons have a finish line. In contrast, there may not be an end in sight for COVID-19 and patients with malignancies. Even if an effective vaccine is identified, it is likely that the virus will not be eradicated, given the fraction of society who will refuse vaccination. Herd immunity may be helpful to some extent, but will not eliminate SARS-CoV-2 infections. Those patients with malignancies, particularly those with a diminished ability to mount antibody responses, will remain vulnerable to COVID-19. The mortality rate due to SARS-CoV-2 infection may be relatively straightforward to monitor. However, it will be much more difficult to estimate the numbers of lives lost or shortened due to consequences of COVID-19, such as: delays in malignancy diagnosis or presentation at more advanced stages due to lack of screening or access to primary care, reduced access to comprehensive cancer centers and clinical trials, adjustments made to standard of care chemotherapy regimens that abrogate efficacy, lack of insurance because of unemployment, and delays in drug development. The coming months to years will be incredibly challenging, but it is paramount that we continue to practice evidence-based medicine and optimize the conduct of clinical trials in order to mitigate the risk of COVID-19, thereby improving the outcomes of current and future generations of individuals diagnosed with cancer.

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CONFLICTS OF INTEREST

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