

Consequences of the COVID-19 Pandemic on Cancer Clinical Trials

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ABSTRACT

The battle against cancer is formidable even in normal circumstances and the COVID-19 selectively cancer patients with an increased risk of mortality by three times higher than those without cancer but also forced us to shut down the clinical trials in cancer patients to deal with the present crisis. We discuss here the disruptions on research in cancer with its immediate and delayed consequences and offer some suggestions to modify our practices, strategies and rationalization to help succeed the cancer treatment and research after the crisis is over.

KEYWORDS

Clinical trial, Chemotherapy; Cancer; COVID-19; Research

1. INTRODUCTION

The COVID-19 pandemic has posed a significant challenge and disruption on cancer treatment and research. This is indeed a two-front war. The first fight is with cancer - a disease that claims 600,000 lives each year in the United States, despite our best minds and medicines. Data from published studies during this pandemic clearly suggests cancer was associated with an increased risk of death and/or intensive care unit admission (OR 5.4, 95% CI 1.8-16.2) [1]. In addition, cancer patients also encountered a higher risk of severe events including required admittance to the intensive care unit, ventilation support, or those that led to death [1,2]. In addition to these data, it is obvious to oncologists that those with cancer are more predisposed to get infected with the coronavirus as cytotoxic chemotherapy, immunotherapy, antibodies, protein kinase inhibitors, poly ADP ribose polymerase (PARP) inhibitors are associated with myelosuppression and

immunosuppression [2,3]. Cancer is mostly seen illness in older people and presence of other comorbidities [1,2]. Certain types of malignancies such as leukemia, lymphoma, myeloma, lung cancer (especially those receiving radical radiotherapy) and those with recent bone marrow or stem cell transplants could be at an increased risk to get infected with COVID-19. So, we as oncologists and caregivers have to take every action to safeguard the morbidity and mortality of the cancer patients as well as to minimize the exposure to our cancer team members. Social distancing means less exposure of these patients to health-care facilities. Clearly the novel coronavirus infection poses new risk, some known and some unknown.

Oncologists are accustomed to face and manage infectious complications in cancer patients but the threat and the disruptive challenges with COVID-19 are in the fact that it's a pandemic, meaning anyone around them- even asymptomatic-can give infection to them, potential

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lack of staff of care gives at home due to COVID-19 illness and finally that there is no specific treatment available yet to combat COVID-19. It is not an easy task to balance the risk–benefit ratio as the ongoing chemotherapy might enhance the risk of contracting COVID with significant potential for death, and on the other hand omission or delays in chemotherapy or other modalities in these patients might aid the progression of cancer, which may result in worsening symptoms and even death. Hence, deciding to whether to initiate treatment for a newly diagnosed cancer patient or to delay new treatment or those on treatment already, is a serious burden on the oncology community. Many governmental and professional organizations were brisk in producing guidelines, with all having one common theme that oncologists should remain vigilant and should reduce the clinic visits [4-7].

But one extremely important component of cancer treatment is clinical trials, which help us to discover, evaluate and verify the safety and efficacy of new drugs, approaches, regimens, or methods. In addition to medical insights, clinical trials also offer treatment options to patients who have an uncommon tumor type or those have stopped responding to standard therapies. Moreover, some cancer clinical trials are aimed to study prevention, new diagnostic tools or palliating the symptoms.

2. POTENTIAL CONSEQUENCES OF COVID-19 OUTBREAK ON CANCER CLINICAL TRIALS

As standard chemotherapies were halted, delayed or modified in majority of cancer patients all across the globe, similarly COVID-19 outbreak also disrupted the cancer clinical trials, leading to both immediate and delayed consequences. Regulatory agencies such as the US Food and Drug Administration, European Medicines Agency, and the UK Medicines and Healthcare products Regulatory Agency were prompt in issuing guidelines on

managing clinical trials during the COVID-19 pandemic, with emphasis on the protecting patient safety, potential flexibility in visits and tumor assessments (via protocol amendments if necessary), clearly documenting protocol deviations, and disallowing prospective protocol waivers [8,9].

3. IMMEDIATE CONSEQUENCES

Prioritizing trials testing treatments for COVID-19 and decline in recruitment of cancer trials

A steep decline reduction in recruitment to ongoing trials as well as delay in the scheduled launch of new cancer trials might be expected during COVID pandemic. To combat the COVID-19 pandemic, many academic institutions had to deploy the research staff to hospitals to help in managing the influx of COVID-19 patients. In addition to medical care, research staff was needed to support COVID-related clinical trials including drugs as well as convalescent plasma. All parties including medical staff, research team members, blood bank, staffing, regulatory started working together to conduct these trials with in a week of the pandemic. We at Northwell Health deployed almost 50% of our staff to help in fighting COVID-19 and related research and the other half to continue providing support for those on clinical trials, and continuing to offer trials to patients who do not have standard of care (SOC) options or have a potential cure [10]. However, many other institutions and hospitals challenged by COVID crisis, have suspended the clinical research for similar reasons described above. This also would result in delay in initiating new studies and planned to open due to lack of resources and focus on COVID-19.

Obviously, this change in direction of prioritization to COVID-19 research would led to delay all stages of cancer research, including review process, contracts and budgets and other procedures. Cancer research team have to make some other tough decisions in leu of

reassignment of staff and travel restrictions to flatten the curve by bringing in external teams. Thereby, all visits and related meetings for site selection, site qualification, audit, and training have been cancelled. While some sponsors decided to delay monitoring during COVID-19 crisis due to hold on enrollment, a few chose to perform remote monitoring visit, and some sponsors declined to perform remote monitoring as they could not get into EMR. During this time, remote monitoring if it's not in their policy could have changed. This implies that after the peak is over, research teams must be prepared to entertain many studies' monitors and auditors.

Potential delay in data entry into clinical trial databases

Not only study coordinators have been deployed to help enrollment onto COVID-19 studies, but some of them have been allowed to work remotely with reduced access to data either as a part of alternate rotations to decrease the risk of all staff being sick or individual's risk factors to be infected with COVID-19. In some scenarios, a sponsor requested for redacted data so that they can review, and those coordinators working from home were not able to send it. They had to call the other coordinators on site to print and redact the forms and send it to the sponsor. This has been taking a lot of coordination on the coordinators to complete this task. All these factors might result in a delay in data entry into clinical trial databases.

Potential increase in study deviations

In the start of the pandemic cancer teams had to cancel appointments of patients in the face of crisis for obvious reasons, including social distance, deployment of staff and sickness of staff or their family members. They might have contacted the sponsors to ask permission for using if we telehealth on patients instead of in-person visits, and if acceptable then figure out how to document such a visit [11]. Similarly, home blood draws or missing some collection of research labs such as pharmacokinetics associated with studies might have been issues as well.

At, Northwell Health, we were lucky to perform home blood work by using Lab-Fly. Approval by sponsor followed by plans of action were needed to deliver the investigational product (IP) to the patient's home. Amid the crisis, research team worked diligently with research pharmacist to ship the IP. All these new procedures cost extra time and new challenges, including documentation of this process, such as confirmation of patient's physical location as many relocated due to COVID-19, process of drug delivery, document of hand of custody, and confirmation of delivery. In addition, it is possible that some endpoints of studies, such as quality of life might have been missed or incomplete due to missed study visits.

Delay in restaging scans

To diminish the exposure to COVID-19 for patients and providers and staff, cancer centers needed to reduce in person visits including appointments for radiological staging of cancer patients aligned with recommendations by the Centers for Disease Control (CDC), that any clinic visits that can be postponed without risk to the patient should be postponed. These steps were essential as hospital radiology departments were stretched during the pandemic, in addition to reduce the risk of COVID-19 infection to study subjects. Therefore, we do expect to see delay on some protocol-procedures, including restaging scans and tumor assessments and biopsies. Though, the professional societies also supported recommendations by CDC and encouraged rescheduling non urgent care, including non-urgent computed tomography (CT), screening mammography, etc. but these events could add to deviations in cancer studies and could lead to variation in final assessment of efficacy such as progression-free endpoints of ongoing studies.

4. DELAYED CONSEQUENCES

The longer-term consequences of COVID-19 on cancer care and research are not unknown at present. However,

the delayed consequences of halt on cancer research due to shift towards prioritizing COVID-19 patients' care and research would result in gaps in data collection due missing visits and assessments and delayed monitoring of these data. Most importantly certain endpoints would be hard to determine as differentiating COVID-19-related deaths versus other etiologies could not be determined in every patient, unless an autopsy was performed, thereby, affecting the survival endpoint. Due to expected delay in recording clinical research forms in a timely fashion and an increase in protocol deviations during the period of COVID-19 pandemic, could result in reporting toxicities or even miss in few cases [12]. Although, we hope that majority of the deviations during the pandemic might be due to patients not coming in for their follow up visit, treatment or lab work, and in some cases treatment as patients were afraid to come even if cancer centers were open for them.

Clinical trials in cancer offers an experimental treatment for patients and also allows scientists to understand their disease, develop new drugs, test agents to target new pathways in carcinogenesis and to improve the outcome in these patients. The biggest delayed consequence of the COVID-19 pandemic would probably be on delaying the cancer drug development with its own consequences both for the cancer patients as well as for the pharmaceutical industry.

5. FINANCIAL CONSEQUENCE OF COVID-19 ON CANCER CLINICAL TRIALS

The financial impact of COVID-19 on oncology research sites is still unfolding. Sites have to bear the brunt of an ever-changing clinical landscape while tackling potential loss of revenue. In clinical research, a major portion of site revenue comes from industry sponsored trials. Payments to sites are based on enrollment, patient visits completed and timely data entry. In many sites, enrollment to studies had to be limited to ensure patient

and staff safety. Concern for safety has also led to the cancellation of many non-essential study procedures. Less recruitment and more cancellations mean less revenue sites will receive.

Lack of resources is also adding to the financial burden of sites. As more and more staff are diverted to tackle the increasing COVID-19 patient population and studies, less are available to help with recruitment, timely conduct of protocol mandated assessments and entry of data to cancer studies already open to enrollment. Delays in assessments conducted or data entry is going to lead to delay in payments received from sponsors. Also, lack of resources is leading to the cancellation of new studies. The reduction in recruitment, delays in data entry and cancellation of new studies are going to negatively impact the revenue flow of research sites for months to come.

Sites are also dealing with higher workload as available staff has to spend more time identifying, coordinating and conducting study procedures in new ways catering to the needs of each patient while ensuring their safety. Sites are also receiving increased requests for updates and remote monitoring from sponsors. These activities are often not covered in the original study budgets.

Although many of the financial consequences of this pandemic for oncology research are unavoidable, there are certain steps that can be taken to ensure site needs are met during this time. Communication with sponsors is paramount. Sponsors are an integral part of ensuring how study assessments can be done safely for patients. They might be able to assist with new ways of conducting a visit rather than cancelling it. Sites also have to be their own best advocates in ensuring sponsors cover additional requests, such as remote monitoring, that require more staff effort. It is also important to convey continued interests in being partners in future trials so that new trial opportunities are available once things go back to normal.

6. WHAT WE NEED TO DO TO OVERCOME THEM

COVID-19 pandemic has changed the way we treat cancer and perform cancer trials. Ensuring safety of cancer patients during the pandemic was our highest priority. Soon after the COVID-19 pandemic is over, it is expected that inherent complexities of cancer will challenge us further including a surge of care for patients who were delayed in initiating treatment, unable to go screening and whose restaging was delayed and now could show progression needing new plan of treatment if feasible. Training of proper use of personal protective equipment was implemented urgently to prevent the infection to staff and others. In addition, we need to carve out a long-term plan to care for our patients in anticipation of another wave of COVID-19 now or in fall. We not only need to resume the clinical research but gain acceleration urgently to move on with development of cancer drugs simultaneously with treatments for COVID-19. Above all these potential challenges, another challenge is the human factor, “the fear” by the patients and their families to return to cancer centers.

We strongly believe that risk associated with COVID-19 to our cancer patients during the pandemic has forced us to culminate a rationalization basis for cancer services, both diagnostic and therapeutic. Not only institutions were required to develop guidelines under multidisciplinary teams but many national and governmental organizations also laid out guidelines about who and how to treat. This pandemic also stretched the health systems to constraints of workforce of health care providers due to their own illness or family members but threatened to exhaust the assets, including capacity of hospital beds, ventilators, PPE, and others management and workforce constraints introduced by the financial impact of COVID-19. It is hoped that the effect this rationalization in cancer care would last long and allow us

to analyze and fix the issues of health disparity, such as access to cancer services, socioeconomic and ethnic differences.

COVID-19 pandemic a crash course of telehealth to health professional and provided a new tool to interact and manage cancer patients, a population previously reluctant to digital communication. With an extensive experience of oncology team with telehealth, it is expected that it will stay specially to manage immunocompromised patients. Telehealth also carries the potential to see second-opinions in a quick manner and could save resources at the same time. Similarly, multidisciplinary tumor boards were coordinated via digital media and successfully supplied prompt consultation to treat cancer patients, offering a new platform that should stay after the pandemic is over. Since the radiology services were stretched during the pandemic, it makes us to think outside the box and may institute central imaging review to provide a timely as well as quality data for clinical trial patients.

Pandemic also taught the research staff to identify and coordinate new ways to carry out required study assessments through telehealth, identify alternative methods to deliver IP for oral drugs, identify local laboratory centers in order carry out safety follow up. Human communication became the key to prevent the spread of the pandemic and to continue treatment on patients already enrolled onto the clinical studies. Such adaptations included increased use of technology to carry out QOLs and other tools. It allowed the research teams to learn how to collaborate with multi-institutional studies to treat COVID-19 infection, something we usually lack in cancer studies. Hence creating a hotline, group emails, spread sheets and Redcaps were one of the new tools everybody got accustomed to.

Outside the clinical trials, a demand on electronic informed consents or e-consents also occurred and may need to be assessed for further use in future. All members of cancer centers had to attend urgent lectures to learn about COVID-19 infection and its complications, both for recognition and for reporting with attributed etiology. An unseen challenge that we would face soon will be the mental health of our teams at the cancer centers and immediate steps must be taken to help all those who risked their lives to help managing the patients with COVID-19.

7. CONCLUSION

In summary, the COVID-19 pandemic has injured both the cancer care and cancer research. We not only hope but are determined to emerge from the COVID crisis and

soon return to our battle against cancer. However, we must remember the lessons learnt from the crisis and alter our practices, strategies and rationalization to help succeed the cancer treatment and research. We have to devise ways to prevent a big hit from another epidemic if COVID returns and help our patients and teams to overcome the fear with clear guidelines, policies and moral support. Resources has been diminishing at present due to shift in developing treatment for COVID-19 and we need to engage investors and other resources to revisit their priorities, not neglecting cancer. Also, it is important to convey continued interests in being partners in future trials so that new trial opportunities are available once things go back to normal.

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