A Neoadjuvant Chemotherapy Trial for Early Breast Cancer is Impacted by COVID-19: Addressing Vaccination and Cancer Trials Through Education, Equity, and Outcomes

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ABSTRACT

While COVID-19 vaccine distribution has addressed vulnerabilities related to age and comorbidities, there is a need to ensure vaccination of patients with cancer receiving experimental and routine treatment, where interruption of treatment by infection is likely to result in inferior outcomes. Among patients with cancer, those undergoing neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (Adj chemo) for early breast cancer (EBC) are at particularly high risk for inferior outcomes, in part, because optimal timing of chemotherapy is essential for promoting distant disease-free survival. COVID-19 data from the ongoing multicenter I-SPY 2 trial of NAC for EBC provides a window into the magnitude of the problem of treatment interruption, not only for the trial itself but also for routine Adj chemo. In the I-SPY 2 trial, 4.5% of patients had disruption of therapy by COVID-19, prior to wide vaccine availability, suggesting that nationally up to 5,700 patients with EBC were at risk for adverse outcomes from COVID-19 infection in 2020. To address this problem, vaccine education and public engagement are essential to overcome hesitancy, while equity of distribution is needed to address access. To accomplish these goals, healthcare organizations (HCO) need to not only call out disinformation but also engage the public with vaccine education and find common ground for vaccine acceptance, while partnering with state/local governments to improve efficiency of vaccine distribution. These approaches are important to improve trial access and to reduce susceptibility to COVID-19, as the pandemic could continue to impact access to clinical trials and routine cancer treatment.

Introduction

Patients with cancer are more vulnerable to adverse outcomes from COVID-19, indicated by meta-analyses (1, 2), and hospitalized patients with cancer with COVID-19 infection are at higher risk of mortality (3). In terms of the initial impact of COVID-19 on breast cancer diagnosis and treatment, reduction of mammography rates occurred early on in the pandemic (4, 5). Fear of infection and temporary closure of mammography facilities were contributing factors. Mammography in combination with adjuvant therapy is tied to reduction in mortality from breast cancer (6), and the full impact of reduction of mammography rates at the beginning of the pandemic is unknown at this time. There are correlations between delay in diagnosis and tumor size (7–9), risk of nodal metastases (7, 10), and death (11), suggesting that COVID-19–related delays in diagnosis may result in adverse outcomes. Once a diagnosis is made, as many as 45% of patients with early breast cancer (EBC; depending on age and tumor biology) may be recommended to receive neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (Adj chemo) and the benefits are related to maintaining dose and schedule (12–16). NAC is generally recommended for the treatment of high-risk EBC (17), and this approach continues to be appropriate during the pandemic (18). Delay or interruption of NAC or Adj chemo by COVID-19 infection could result in adverse outcomes including development of drug resistance and cancer progression. This Perspective addresses the impact of the pandemic on NAC and the impact of vaccine hesitancy and vaccine deployment barriers on cancer clinical trials and routine care. We propose the role of the oncologist as a primary vaccine educator and support the concept of partnerships between state/local governments and healthcare organizations (HCO; ref. 19) to address these problems (**Table 1**).

Impact of COVID-19 on the I-SPY 2 NAC trial for EBC

The on-going I-SPY 2 NAC trial for high-risk EBC provides a measure of the impact of COVID-19 infection on NAC/Adj chemo trials. The I-SPY 2 clinical trial is a multicenter phase II platform trial of NAC and seeks to improve outcomes by studying new drugs for the treatment of high-risk breast cancer (20–23). Patients participating in the trial receive 20 weeks of NAC followed by definitive surgery. The I-SPY 2 trial has continued to operate thorough the pandemic and has collected data on the impact of COVID-19 cases on study conduct. Patients who test positive for the virus while on study treatment must stop therapy; between February 1, 2020 and February 2, 2021, 6 patients of 157 enrolled (3.8%) were diagnosed with COVID-19 infection during active treatment and consequently had early discontinuation of study NAC. Of the 6 patients who discontinued investigational therapy on the I-SPY 2 trial due to COVID-19, 2 resumed NAC off trial with minimal or no interruption. Four of the 6 patients had a ≥21-day interruption in NAC. Complications related to COVID-19 included 1 patient with pneumonia and 1 patient with aphasia, both requiring hospitalizations. Another of these 4 patients received outpatient bamlanivimab. Adjuvant chemotherapy for most of these patients remains to be determined or reported. An additional patient developed COVID-19

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Translational Relevance

The COVID-19 pandemic has affected cancer clinical trials, but there is limited information about its impact. During the pandemic, from February 2020 to January 2021, 4.5% of patients treated on the neoadjuvant I-SPY 2 trial for high-risk early breast cancer experienced interruption of treatment due to COVID-19 infection, providing information on the pandemic's impact on clinical trials. While COVID-19 vaccination is expected to reduce attrition from trials, vaccine hesitancy and poor vaccine access in underserved communities are significant barriers to inclusive cancer clinical trials. On the basis of a recent poll, 28% of patients identifying as White said they would decline vaccination, whereas patients identifying as being of color may have less access to vaccination, related to health equity issues. Vaccine education is needed to build trust when facts are insufficient. Improved vaccine distribution is also needed. Both are essential for inclusive trials and require partnership between government and healthcare organizations.

infection after treatment, in the 30-day post-surgery follow-up period. Altogether, 7 active trial patients were affected of 157 enrolled (4.5%), with impact affecting NAC or the perioperative period. Notably, most of the trial patients affected by COVID-19 were young (median age 48.5; range, 27–70; ref. 22).

Nationally, it is estimated that there will be 281,550 patients diagnosed with invasive breast cancer in 2021 (24) and about 45% will be recommended to have either NAC or Adj chemo based on having high-risk estrogen receptor–positive/HER2-negative (25, 26), HER2-positive (26), or triple-negative subtypes (26). Therefore, an estimated 127,000 women were at risk in 2020 for interruption or delay of NAC or Adj chemo due to COVID-19. If the proportion of patients with EBC impacted by COVID-19 infection is 4.5%, as estimated by the I-SPY 2 trial, up to 5,700 patients with EBC may have had interruption of NAC or Adj chemo during the initial 12 months of the pandemic.

Vaccine hesitancy and its estimated impact on NAC trials and routine care for EBC

While vaccination is a standard recommendation for patients participating in cancer clinical trials (27), vaccine hesitancy resulting in COVID-19 infection of patients with EBC is an important issue. In a large international study of vaccine acceptance conducted from October to December of 2020, vaccine refusal was estimated to be 34% in the United States (28). In a subsequent Monmouth University poll (March 8, 2021), vaccine reluctance had decreased, but nonetheless, 24% (95% confidence interval $\pm$ 3.5%) of those polled ($n = 802$; national sample of respondents 18 or older of whom 51% were female) were unwilling to receive COVID-19 vaccination and 21% preferred to wait and see how the vaccine is tolerated (29). Notably, 28% of those self-identifying as White were unwilling to be vaccinated compared with 14% of those identifying as of color (29). As of the end of March 2021, a similar 25% refusal rate was observed by polling (NPR/Marist polls), the data being from a poll of 1,309 U.S. adults conducted between March 22 and March 25 (margin of error: 3.4 percentage points; ref. 30). These persistent polling results of vaccine hesitancy present a significant barrier to vaccination of patients with EBC and may affect the inclusiveness and conduct of clinical trials. There is a significant disparity on vaccination rates between "blue" and "red" states where the I-SPY 2 trial is open (New York 80,379 per 100,000 vs. Alabama 52,847 per 100,000; April 30, 2021; ref. 31). If 24% of the U.S. population remains unvaccinated and there is a 4.5% attrition rate due to COVID-19, it is possible that up to 1,400 women undergoing NAC/Adj chemo could have their therapy interrupted due to COVID-19 in 2021. In addition, symptoms suspicious for COVID-19, particularly in unvaccinated patients, also create barriers for timely care and efficient enrollment in clinical trials.

Overcoming disinformation through education: different roles for states and HCOs

Vaccine hesitancy is related, in part, to disinformation and misinformation. Disinformation is the intentional dissemination of factually incorrect information to alter public opinion. Disinformation has been directed toward COVID-19 vaccines, building on a preexisting

Table 1. Barriers to vaccination and potential solutions for cancer clinical trials and routine patient care.

Barrier	Solutions
Lack of vaccination of oncology patients	**Facilitate vaccination in HCO oncology clinics or advise patients of state/local vaccination centers, as part of intake for all trials and routine cancer care**
Vaccine hesitancy; internet vaccine disinformation and patient misinformation	**The oncologist as first-line educator. Vaccine must be available in the oncology clinic. State and HCO-driven education, community outreach, peer-to-peer counseling, experiential videos, and other media interviewing diverse vaccinated individuals, teaching by primary care clinicians, lay persons, and clergy. Build common ground when facts alone are insufficient.**
Lack of information on outcomes of vaccine education and public engagement	Epidemiologic study of vaccine hesitancy and effectiveness of education programs
Geographic access issues and lack of vaccine distribution equity	**State and local governments improve vaccine distribution for underserved ZIP codes; provide Internet, phone, and in-person access for scheduling of vaccine appointments in accessible locations; and provide transportation to vaccination sites**
State mandates for vaccine distribution; need for HCO level vaccine distribution logistics	**State and local governments cede authority to HCO committees to address patient needs within healthcare systems thereby facilitating HCO vaccination of oncology patients**
Lack of information on state mandated versus county/municipal vaccine distribution outcomes	Epidemiologic study of vaccine distribution programs
Lack of information on vaccination status and cancer clinical trials outcomes	Evaluation of vaccination-associated outcomes for cancer clinical trials, including pCR and DDFS for NAC in patients with EBC, and trials-associated adverse events

Note: Bolded solutions are recommendations that could be rapidly implemented.
Abbreviation: DDFS, distant disease-free survival.

antivaccination movement (32). At times, prominent leaders may express opinions in the media about COVID-19 and vaccination that contradict scientific guidance of the NIH, CDC, or FDA, thereby entering the space of patient safety without the required credentials (32). Misinformation is what the public may be left with, as a result of disinformation (33). To protect the public from vaccine misinformation, our government agencies and HCOs need to be engaged and consistently call out disinformation about vaccination, describing and disabling it by providing current and factual information that allows members of the public to make educated decisions.

Government agencies, particularly state and local agencies, and HCOs can counter fact-free opinion with education, but when facts alone are not enough, establishing common ground takes even more effort and involves community engagement (34). While many states perform an outstanding job generating print media and video material to promote vaccination, HCOs have a boots-on-the-ground advantage in the communities they serve, through their clinics and opportunities for personal outreach. By partnering with the state and local governments, HCOs can take the case for vaccination directly to the patients they serve by providing leadership in the form of local public forums and focus groups, media interviews, distribution of informational pamphlets in the HCO clinics, peer-to-peer counseling, and by having vaccination patient advocate programs. People are more likely to be vaccinated when peers talk to them about vaccination in ways that are culturally sensitive and in their first language. By finding common ground through greater engagement of the public, HCOs may be able to accomplish a greater depth of vaccine acceptance. Furthermore, epidemiologic study of the efficacy of HCOs' outreach could enable allocation of resources to the most effective methods of overcoming vaccine hesitancy.

In terms of EBC care, the most effective advocates of vaccination may be the oncologists themselves. Oncologists need to be primary educators and address COVID-19 vaccination on the first visit for our patients with EBC regardless of treatment plan. For patients with EBC, education should also include instruction that the vaccination be contralateral to the breast cancer, to avoid ipsilateral lymphadenopathy that could confound MRI or PET imaging (35, 36). Finally, more broadly, the deep trust that many patients with cancer have in their oncologist may make this a space where they are more willing to consider a recommendation for a vaccine.

Vaccine distribution and health equity

While COVID-19 vaccination is expected to reduce attrition from clinical trials, a bottleneck exists within HCOs to vaccinate these patients, because of the logistics of vaccine distribution, and health equity issues that affect cancer clinical trials and routine cancer care alike. Lack of patient trust in vaccination and lack of vaccine access in underserved communities may be barriers requiring teaching of expected risks and benefits as well as outreach. Health equity issues may be related to ZIP code, with geographic healthcare deserts resulting in inequitable vaccine distribution, although federal and state efforts are being made to address this problem. While "most lives saved" (MLS) approaches for vaccine distribution may have some merit, they may fail to adequately help underserved minority groups, which suffer from increased risk of COVID-19 hospitalization (37). Health equity issues leading to "long COVID" may also lead to underenrollment of patients with EBC to trials in areas with low vaccine acceptance and in underserved minority communities where vaccine access may be limited.

While structural barriers to vaccine distribution have been previously thought to be primarily vaccine access and supply chain issues (38), major barriers for efficient vaccine distribution include need for cold chain protection of Pfizer BioNTech and Moderna vaccine, need for −80°C freezers, need for optimized use plans for multiuse vials, and the need to be able to provide vaccine in HCO clinics, including oncology clinics. To this end, the Mayo Clinic system has developed an exemplary HCO vaccine distribution strategy (39) with the establishment of a COVID-19 Vaccine Allocation and Distribution Workgroup to provide an organizational structure for vaccine distribution addressing health equity and logistics in three states. The Mayo strategy includes branches of program governance, pharmacy supply chain distribution, vaccine site logistics, patient education including media development, data management in the electronic health record (EHR), subject matter experts, as well as plans to address hesitancy and disparity through community engagement (39).

Vaccine incentives versus mandates

While COVID-19 vaccination is important for safety in cancer clinical trials during the pandemic, mandates for vaccination may be difficult to enforce and could deprive patients from trials participation in situations where risk of COVID-19 infection may be low, but the subject is adamantly opposed to vaccination. For phase I cancer trials, a case has been made for vaccine mandates, because risk is substantially heightened by lack of vaccination (40). While government incentives for vaccination such as employer tax credits (41) or a "Green Pass" to allow access to public events and venues (42) may help, these approaches have limitations. Whether incentives can be adapted to individual clinical trials is controversial and dependent on regulatory approval. Arguments against incentives is that they may be intrusive, worsen rather than overcome disparities, and take advantage of differences in economic distress between social groups (43). Bioethicist Dr. Nancy Jecker provides an enabling insight that it is patronizing to treat less affluent and disenfranchised individuals as if they might be "children." (43) Arguments for incentives include that they could help patients achieve access by providing financial support, help members of the public feel respected and enabled, and speed vaccination as we race against variants (43). For the hesitant, novel and creative efforts to build common ground remain to be developed and are very worthy of method development and efficacy testing (34).

Measurement of vaccination outcomes for EBC trials

It is unknown whether delay or interruptions of NAC can be overcome by resumption of NAC, and the use of pathologic complete response (pCR) rates and 3- and 5-year DDFS may be informative (44). Similarly, the impact of COVID-19–related delay in diagnosis and treatment as well as delays of Adj chemo could be studied in terms of 3- and 5-year DDFS. The impact of COVID-19 infection will be important to track for EBC clinical trials not only because of treatment interruption, but also because there could be modulation of innate (45) and adaptive immunity (46, 47) impacting outcomes of EBC NAC trials, including those that test immune-oncology interventions. Also of interest will be the impact of COVID-19 on event-free survival (EFS) outcomes of neoadjuvant endocrine therapy trials, if endocrine therapy is interrupted by COVID-19 infection (48).

Recommendations

The outcomes of clinical trials and routine care are at risk due to COVID-19 and both stand to gain from a partnership approach between states and HCOs to facilitate vaccine distribution with patient education and equity, while measuring outcomes. When an unvaccinated patient signs consent for a trial, oncologists need to be able to

address this problem that day and administer a first or definitive dose of vaccine in clinic while recording that in the EHR. Recently, the COVID-19 and Cancer Clinical Trials working group has provided a COVID-19 operational guidance for patients with cancer participating in oncology clinical trials (27). This guidance recommends that an authorized vaccine be considered as a concomitant medication, be entered in the EHR once given, and given to all patients with cancer, including those participating in all phases of clinical trials (27). We add to this that vaccine should be made available in the oncology clinic. To accomplish these goals, we recommend that states cede authority to HCOs for vaccine administration while assisting infrastructure for distribution. HCOs can take up much of vaccine education, meeting the public where they live. States can partner with HCOs by providing cold storage and multidose vials, while providing statewide education materials. Mobilizing use of the HCO EHR may help mitigate vaccine waste. State and local governments can also help bridge the gap between state distribution and individual patient needs, by reaching patients in ZIP code locations that have historically suffered from inadequate access to health care. County and municipal governments may assist with access by Internet, phone, or in-person means for appointment scheduling and provide transportation to actualize appointments. Division of labor between state/local government and HCOs needs to be well organized. Effective partnership between state/local governments and HCOs can provide education, equity, and measurement of outcomes that meet the broader needs of society while focusing on the individual.

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