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.

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 compared to standard of care. 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 ≥21-day interruption in NAC. Complications related to COVID-19 included 1 patient with pneumonia and 1 patient with aphasia, both requiring hospitalization. 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
Table 1. Barriers to vaccination and potential solutions for cancer clinical trials and routine patient care.

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of vaccination of oncology patients</td>
<td>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</td>
</tr>
<tr>
<td>Vaccine hesitancy; internet vaccine disinformation and patient misinformation</td>
<td>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.</td>
</tr>
<tr>
<td>Lack of information on outcomes of vaccine education and public engagement</td>
<td>Epidemiologic study of vaccine hesitancy and effectiveness of education programs</td>
</tr>
<tr>
<td>Geographic access issues and lack of vaccine distribution equity</td>
<td>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</td>
</tr>
<tr>
<td>State mandates for vaccine distribution; need for HCO level vaccine distribution logistics</td>
<td>State and local governments cede authority to HCO committees to address patient needs within healthcare systems thereby facilitating HCO vaccination of oncology patients</td>
</tr>
<tr>
<td>Lack of information on state mandated versus county/municipal vaccine distribution outcomes</td>
<td>Epidemiologic study of vaccine distribution programs</td>
</tr>
<tr>
<td>Lack of information on vaccination status and cancer clinical trials outcomes</td>
<td>Evaluation of vaccination-associated outcomes for cancer clinical trials, including pCR and DDFS for NAC in patients with EBC, and trials-associated adverse events</td>
</tr>
</tbody>
</table>

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 Adju chemo could be studied in terms of 3- and 5-year DFS. 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.

COVID-19 Vaccination and Cancer: Education, Equity, Outcomes

Authors’ Disclosures

D.A. Potter reports grants from Quantum Leap Healthcare Collaborative and Seagen during the conduct of the study, as well as grants from Department of Defense, ImmunomedNet Therapeutics, Pfizer, Innovin, Takeda, Nektar Therapeutics, Roche, AstraZeneca, Spectrum Pharmaceuticals, Huya Bioscience International, Immuno- medics, Gilead Sciences, and National Cancer Institute of Mexico outside the submitted work. A. Thomas reports grants from Sanofi, as well as other support from Gilead Sciences, Bristol Myers Squibb, Johnson and Johnson, Pfizer, Beyond- Spring Pharmaceuticals, Lilly, and Genentech outside the submitted work. H.S. Rugo reports grants from Pfizer, Lilly, Novartis, Immunomedics, Merck, Roche, Sermonix, Polyphor, Daichi, AstraZeneca, OBI, Macrogenics, and Odonate, as well as personal fees from Puma, Mylan, and Samsung outside the submitted work.

Acknowledgments

The authors acknowledge the I-SPY 2 Clinical Trial Consortium, Quantum Leap Healthcare Collaborative (2013 to present), and the Foundation for the National Institutes of Health (2010 to 2012) and by a grant (28KS197) from the National Cancer Institute Center for Biomedical Informatics and Information Technology. The authors sincerely appreciate the ongoing support for the I-SPY 2 Trial from the Safeway Foundation, the William K. Bowes Jr. Foundation, and Give Breast Cancer the Boot. The authors thank Dr. Laura Esserman, principal investigator of the I-SPY 2 trial (UCSF), the I-SPY 2 Consortium co-investigators, as well as Smita Aseare, Laura Sit, and Xiaofan Xu for their support and guidance. The authors thank Drs. Monica Gandhi (UCSF, San Francisco, CA), Melanie Swift and John Ofiero (Mayo Clinic, Rochester, MN), Abraham Jacob (University of Minnesota, Minneapolis, MN), and John Pastor (M Health/Fairview) for helpful comments on COVID-19 vaccines and their distribution.

Received March 26, 2021; revised May 14, 2021; accepted June 3, 2021; published first June 9, 2021.

---

References

7. Olivotto IA, Gomi A, Bancej C, Brisson J, Tonita J, Kan L, et al. Inadequate access to health care. County and municipal governments need 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.

---

7. Olivotto IA, Gomi A, Bancej C, Brisson J, Tonita J, Kan L, et al. Inadequate access to health care. County and municipal governments need 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.

---

7. Olivotto IA, Gomi A, Bancej C, Brisson J, Tonita J, Kan L, et al. Inadequate access to health care. County and municipal governments need 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.

---

7. Olivotto IA, Gomi A, Bancej C, Brisson J, Tonita J, Kan L, et al. Inadequate access to health care. County and municipal governments need 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.


40. FACT Sheet: President Biden to call on all employers to provide paid time off for employees to get vaccinated after meeting goal of 200 million shots in the first 100 days. Statements and Press Releases White House Briefing Room. 2021. Available from: https://www.whitehouse.gov/briefing-room/statements-releases/2021/04/21/fact-sheet-president-biden-to-call-on-all-employers-to-provide-paid-time-off-for-employees-to-get-vaccinated-after-meeting-goal-of-200-million-shots-in-the-first-100-days/.


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

David A. Potter, Alexandra Thomas and Hope S. Rugo


Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-21-1133

This article cites 39 articles, 5 of which you can access for free at: http://clincancerres.aacrjournals.org/content/27/16/4486.full#ref-list-1

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/27/16/4486. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.