Don't blame the messenger: lessons learned for cancer mRNA vaccines during the COVID-19 pandemic

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mRNA vaccines have proven safe and effective in preventing serious illness and death during the COVID-19 pandemic. These technologies offer a novel and intriguing approach towards personalizing immune-based treatments for patients with cancer — regardless of cancer type — with the potential for immune activation beyond commonly utilized immunotherapies.

Recently, one of us received an unexpected call from a longstanding patient with an advanced gastrointestinal cancer. "Dr. Morris," she said, "I just saw a clip on [a national syndicated morning television show] about a clinical trial testing mRNA vaccines for cancers like mine. I would like more information on how I can participate." Weeks earlier, with the SARS-CoV-2 Omicron variant surging through Houston, the majority of a clinic visit with the same person was spent discussing scientific inaccuracies that had thus far led to her decision not to receive a preventive mRNA vaccine against SARS-CoV-2.

Patients want the safest and best therapies and trust us clinicians to deliver them in the face of misinformation widespread in social media. Preventive mRNA vaccines have reduced serious illness and death prior to infection with SARS-CoV-2 (REFS[1,2]). Does this technology have a role in oncology? Recent research suggests that therapeutic mRNA vaccines represent a novel and intriguing immune-based approach as a potential treatment for existing cancer. Lessons learned during the SARS-CoV-2 pandemic have provided practical insights as we seek to study and introduce these agents in clinical trials of our patients with cancer.

While cancer vaccines have been under investigation for decades, unique features of mRNA position mRNA vaccines as promising therapies. Following injection into the patient, lipophilic particles containing specified mRNA sequences of interest are taken up by antigen presenting cells, upon which mRNA transcripts are translated into the desired epitopes for immune recognition[3]. In the case of SARS-CoV-2, such constructs have been designed to target the spike protein of the virus particles, and early studies in oncology have successfully generated vaccines informed by tumour whole-exome sequencing to identify the most (bioinformatically predicted) immunogenic neoantigens — unique for each patient — as a personalized therapeutic vaccine[4]. Recognition of these engineered neoepitopes upon antigen presenting cell–helper ($CD4^+$) T cell interactions triggers activation of cellular and humoral immunity alike. In contrast to immune checkpoint blockade therapies that target PD1, PDL1 or CTLA4 and that have revolutionized oncology over the past decade via modulation of T cell-mediated antitumour immunity[5], mRNA vaccines are capable of attacking 'non-self' cancer cells via induction of T cells and B cells alike.

Understanding the fundamentals of mRNA biology may help us to dispel misconceptions regarding the safety of these vaccines as we evaluate their use as possible cancer treatments. There have been no substantiated occurrences of disruption and/or integration of mRNA into the host genome by vaccine nucleotides. Real-world experience from now hundreds of millions of people globally treated with approved mRNA vaccines against SARS-CoV-2 have substantiated the favourable safety and tolerability of this class of agents. These reassuring safety data for SARS-CoV-2 increase our confidence in the safety of therapeutic strategies for cancer as well.

While an intact, competent immune system may optimize efficacy of a vaccine, routine use of cytotoxic chemotherapy and subsequent myelosuppression presents a logistical challenge for patients undergoing cancer treatment. A recent prospective study compared immune responses with a SARS-CoV-2 mRNA vaccine between patients with solid tumours on cytotoxic, antineoplastic agents and participants without a cancer diagnosis[6]. Neutralizing antibodies against SARS-CoV-2 increased after sequential vaccine doses in patients with cancer. However, this group receiving cytotoxic chemotherapy, in contrast to the control participants, experienced less of an increase specifically in T cells following vaccine administration.

On the other hand, co-administration of CD19 or CD20 antibodies, which can deplete malignant B cell activity in the treatment of various haematological

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malignancies, may compromise mRNA vaccine-induced humoral (B cell) responses against their desired targets. In one study evaluating SARS-CoV-2 mRNA vaccination in patients with autoimmune disorders[7], treatment with the CD20 antibody rituximab blunted the humoral response (with decreased production of neutralizing antibodies against SARS-CoV-2), but not the $CD4^+$ or $CD8^+$ T cell response. The time since last administration of rituximab correlated with the neutralizing antibody response to vaccination in this setting[8]. Therefore, a longer duration between receipt of mRNA vaccines and start of treatment with agents targeting malignant B cells may increase the likelihood for vaccine efficacy. Collectively, these studies provide important insight into the effect of cancer and systemic myelosuppressive therapies on cellular and humoral immune responses to mRNA vaccines. In the future, timing of therapeutic mRNA vaccines should be informed not only by the type of preceding antineoplastic therapy but also by the temporal relationship between the treatments and vaccination.

Oncology is poised to benefit from the rapid scalability and dissemination of mRNA vaccines, as we have witnessed during the SARS-CoV-2 pandemic. With mRNA vaccines, immunological responses may be evoked regardless of the human leukocyte antigen (HLA) type for immune presentation[9]. Many clinical trials using DNA vaccines or peptide vaccines in the treatment of cancer limit the HLA types for which participants may be eligible because of the need to bind to prespecified HLA types. Implicitly, this feature introduces the potential for disparate access to emerging therapies owing to demographic differences in HLA prevalence. This facet bodes well for the development of mRNA vaccines as potential therapeutic tools in oncology that prioritize health equity and less restricted access to promising new agents.

Amid the experiential knowledge gained of mRNA vaccines over the past several years, the lessons learned between immunologists/virologists and oncologists may be bidirectional. Through the incorporation of whole-exome sequencing of resected tumours into the generation of personalized mRNA vaccines, turnaround time back to the patient has improved to under 2 months — a remarkable accomplishment for an N = 1 therapy. The pressing need to treat patients with cancer rapidly in clinical trials has driven streamlining and efficiencies in mRNA vaccine generation, which may have broader benefits. Of great global concern throughout the recent pandemic has been the emergence of the new SARS-CoV-2 variants, with others expected to follow. While mRNA vaccines have continued to prove effective thus far in providing necessary protection against serious illness and death (even against the newer variants), an understandable concern is raised regarding preservation of such immunity by currently available vaccines against evolved strains in the future. Here, as illustrated by tumour-informed therapeutic vaccines, the ability to recapitulate rapid development of updated mRNA vaccines, based upon genomic sequences of new, unfamiliar viral variants, is reassuring as we consider the long-term implications of extended prevention against an evolving and long-term SARS-CoV-2 threat.

In early 2020, the term 'COVID-19' existed peripherally on our awareness as clinicians and as citizens. Since then, multiple preventative vaccines (mRNA among others) have not only been created but have also moved expeditiously through otherwise laborious regulatory approval for rapid dissemination globally. Here, fields of industry, science, business and government have collaborated in an unprecedented manner for the welfare of the public. In doing so, millions of lives have been saved because of mRNA vaccines. Immeasurable morbidity on patients and on the burden of a health-care system has been spared. However, in 2022, cancer remains the second leading cause of overall mortality in the United States[10]. When faced with this crisis of cancer, we recognize that new treatments are warranted for development and distribution at larger scales, and the pipeline from development to approval of effective therapies in oncology remains cumbersome. Our patients with cancer deserve faster delivery of new options that improve their outcomes, and the efficient response observed with mRNA vaccines during the SARS-CoV-2 pandemic serves as a model template for future endeavors. We should be encouraged by this and must focus together on the scientific process and promise of such technologies for cancer drug development, with a goal of improving the lives of the patients sitting across the exam room from us today.

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