COVID-19 vaccination: the VOICE for patients with cancer

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To the Editor — It is becoming increasingly clear that the COVID-19 pandemic is having a considerable impact on patients with cancer. First, the scaled-down capacity to deliver cancer care, the unavoidable but non–evidence-based adjustments to oncological treatment at the start of this pandemic, lockdowns, and fear of visiting hospitals have resulted in suboptimal cancer care. Second, patients with cancer, especially those with hematological malignancies, lung cancer, and active malignancies, are at risk of a fatal outcome of COVID-19[1,2]. Third, active treatment with chemotherapy, immunotherapy, and combination therapies appears to be associated with a further increase in the risk of a fatal outcome of COVID-19[1,2]. As a result, many patients with cancer strictly adhere to self-isolation, which may lead to additional mental-health problems and further loss of quality of life.

The perspectives and needs of patients with cancer during the COVID-19 pandemic were evaluated in two surveys of the Dutch Federation of Cancer Patients Organizations (Nederlandse Federatie van Kankerpatiëntenorganisaties): one in March 2020 and another in November 2020 (refs. [3,4]). The first survey, in March, revealed that the administration of chemotherapy and immunotherapy was delayed and canceled, and patients on treatment or in the palliative setting were particularly worried by COVID-19[3]. In the second survey, in November, among 2,412 patients with cancer, 66% indicated willingness to be vaccinated against COVID-19, 37% wanted to be prioritized for vaccination, and only 6% intended to refuse vaccination[4]. A small survey ($n = 1,140$) conducted in November found a much lower willingness to be vaccinated in the general community[5].

By 1 February 2021, two vaccines against COVID-19 were approved by the US Food and Drug Administration[6], and three were approved by the European Medicines Agency. However, often patients with cancer and, in particular, those receiving systemic cancer treatment or those with an impaired immune system were excluded from the registration trials. Consequently, the efficacy and safety of these vaccines for patients with cancer are currently unknown. The oncology professional societies ASCO, AACR, ESMO, and SITC have developed strong recommendations to vaccinate patients with cancer[1,7–9]. However, they also emphasize the need for evaluation studies, as (the ongoing) registration studies will not provide robust information on efficacy and safety for these patients. It is comforting that most patients with cancers included in a prospective trial had a functional adaptive immune response during symptomatic COVID-19[10]. However, it remains unknown how active treatment with chemo- and immunotherapy affects a patient's ability to mount protective immunity against COVID-19 after vaccination.

To address this knowledge gap, we will perform the VOICE study ('vaccination against COVID in cancer'; ClinicalTrials.gov identifier, NCT04715438). VOICE is a prospective, national, multicenter, longitudinal, multi-cohort study of patients with solid malignancies undergoing active anticancer treatment.

The vaccines against COVID-19, currently being tested in phase 3 trials, induce both antibody responses and T cell responses, which most likely together confer protection against COVID-19. Insight into both responses is needed for optimal understanding of protection in this vulnerable patient group. Apart from insight into these antibody and T cell responses necessary for immediate protection, insight into the longevity of immunity is essential for understanding the duration of immunity and addressing whether revaccination or boosting would be required.

In the VOICE trial (expected to start vaccination in February 2021), the ability to mount a sufficient antibody response on day 28 after the second vaccination is the primary endpoint (protocol, Supplementary Note 1). Patients treated with chemotherapy ($n = 246$), immunotherapy ($n = 135$), and chemo-immunotherapy ($n = 246$) will be included (Fig. 1). The kinetics and strength of immune responses to one of the mRNA vaccines against COVID-19 in patients will be directly compared with that of study participants without cancer ($n = 246$). In addition to measurements of antibody responses and their longevity up to 1 year, in-depth T cell immunity against the vaccine, side effects of vaccination, and incidence and severity of COVID-19

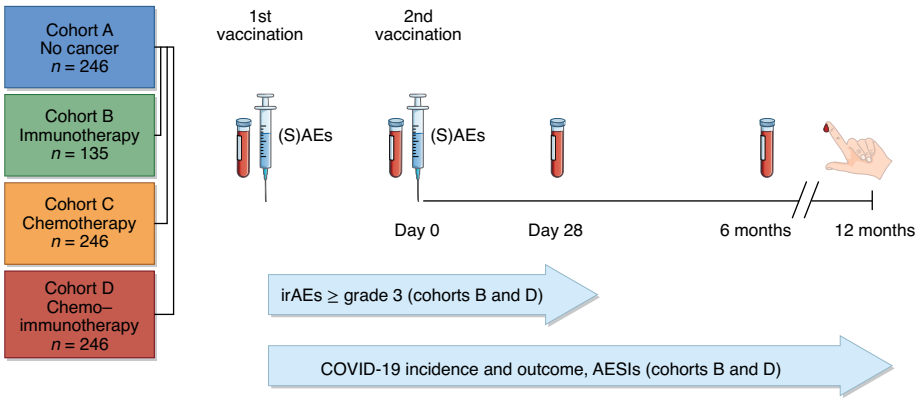

Fig. 1 | VOICE trial design. Blood samples will be collected by venipuncture and finger stick. Immune responses to the coronavirus SARS-CoV-2 will be measured as S1-reactive and neutralizing antibody responses, SARS-CoV-2-specific T cell responses, and functional and phenotypical characterization of cellular immune responses at baseline and at 28 days and 6 months after the second vaccination. SARS-CoV-2-specific antibodies and routine hematology and chemistry will be determined on the same days as those analyses and on the day of the second vaccination. Blood obtained by a finger stick will serve for measurement of the longevity of the antibody response at 12 months. The results reported will include solicited and unsolicited (serious) adverse events ((S)AEs) that occur during the 7 days after each vaccination; immune-related adverse events (irAEs) that are newly occurring at a grade of ≥3 up to 28 days after the final vaccination; and adverse events of special interest (AESIs) and incident cases of COVID-19 up to 12 months after the final vaccination.

after vaccination will be assessed. This trial will reveal whether chemotherapy, immunotherapy, or chemo-immunotherapy influences how patients respond to vaccination and could serve as a model for translational studies of other vulnerable populations or comparable cohorts vaccinated with different vaccines against COVID-19.

Understanding whether this group of patients can mount a sufficient immune response to a vaccine against COVID-19 will provide information for supporting and counseling them during this pandemic and will give them a voice. Is the antibody titer high enough to be protective against COVID-19? What is the durability of antibody titers? Do these patients mount a T cell response sufficient to support the formation of memory B cells? Are two vaccinations sufficient, or are additional doses required? Are alternative measures required?

To assure rapid dissemination of knowledge, we aim to make the results publicly available as soon as possible. Moreover, data sharing will allow comparison between VOICE results and those from other studies for rapid amplification of the knowledge gained. ❐

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Competing interests

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Additional information

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Placebo use and unblinding in COVID-19 vaccine trials: recommendations of a WHO Expert Working Group

To the Editor—The grave public-health threat posed by coronavirus disease 2019 (COVID-19) has spurred an unprecedented accelerated approach to vaccine research and deployment. Currently, hundreds of thousands of participants globally are enrolled in COVID-19 vaccine trial research, with more trials imminent or proposed[1]. As of 1 March 2021, multiple