Six-Month Efficacy and Toxicity Profile of BNT162b2 Vaccine in Cancer Patients with Solid Tumors

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ABSTRACT
We had previously reported short-term efficacy, immunogenicity, and safety of the BNT162b2 vaccine among cancer patients with solid tumors. We aimed to evaluate these outcomes at six months postvaccination. The study cohort comprised patients who were on treatment during vaccination and throughout six months postvaccination. Serologic tests were performed after second vaccination and six months afterward. An age-matched cohort of healthcare workers served as controls. Documentation of COVID-19 infection, blood tests, and imaging studies during the study period was reviewed. Participants included 154 patients and 135 controls. Six months postvaccination, 122 (79%) patients were seropositive compared with 114 (84%) controls ($P = 0.32$). Serology titer dramatically decreased in a similar manner in both cohorts. No COVID-19 cases were documented in controls, and one case occurred in patient cohort. All previously reported adverse effects resolved. Taken together, the pattern of immunogenicity, efficacy, and safety of BNT162b2 in patients with cancer with solid tumors at six months postvaccination resembles that of the general population.

SIGNIFICANCE: Evidence regarding efficacy and safety of COVID-19 vaccines in patients with cancer indicate a favorable short-term profile. Immunomodulation due to anticancer treatments may affect immunity and immunogenicity of patients with cancer to the BNT162b2 vaccine over time. Our study sheds light on these long-term outcomes and portrays a trend that resembles the general population.

INTRODUCTION
The COVID-19 pandemic, with more than 4 million deaths worldwide as of July 2021, has led to a global effort to develop SARS-CoV-2 vaccines (1–3). High efficacy of the mRNA-based BNT162b2 vaccine against SARS-CoV-2 has been demonstrated in both a large clinical trial and real-life data in the general population (1, 4). However, patients with cancer were underrepresented in these prospective...
Six-Month BNT162b2 Vaccine Outcomes in Solid Tumor Patients

Participants

The original study cohort (13) consisted of 232 patients with solid tumors. This study included 154 patients with solid tumors who were receiving active intravenous treatments at the Rambam Health Care Campus (RHCC) Oncology Center (Haifa, Israel) and a cohort of 135 age-matched health care workers from RHCC who served as controls. From the entire patient cohort (n = 154), 88 patients were enrolled in the initial study (January 2021) and 64 patients who met inclusion criteria were added at the later time point (for whom all data are available except for serology status shortly after vaccination). Reasons for dropout from the initial study cohort are elaborated in Fig. 1. The patient group comprised 84 (55%) men and 70 (45%) women (median age, 66 years; range, 32–87); the control group comprised 75 (56%) women and 60 (44%) men (median age, 63 years; range, 50–87). The patients were tested 166 ± 29 days after second vaccination dose (187 days from the first dose). Patient characteristics are reported in Table 1. The majority of patients (84%, n = 129) had metastatic disease. The most common cancers were gastrointestinal (36%, n = 56), lung (23%, n = 36), breast (17%, n = 26), and genitourinary (11%, n = 18). Treatment protocols consisted of chemotherapy (62%), biological agents (36%), and immunotherapy (30%), and some patients received more than one treatment class. In patients with cancer with active intravenous treatment, 79% (n = 122) of the patients had positive serologic test results, compared with 84% (n = 114) in the control group (P = 0.32). Analysis by age, sex, or disease stage yielded no significant differences within the patient cohort, as depicted in Table 2. Within the patient group, chemotherapy treatment was associated with seronegative serologic status compared with other treatment modalities.

RESULTS

Participants

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(27% vs. 10%; OR = 0.31; P = 0.02), as previously reported (13). OR was adjusted as described above. Among the seropositive individuals, there was female predominance in the control cohort (93% vs. 75% in the patient group, OR = 0.21, positive individuals, there was female predominance in both cohorts depicted a drastic decline over time (February 2021–August 2021) in serology titer but remained above threshold value. For patients with known serologic status of COVID-19 in either cohort throughout the study period. There were no documented cases of COVID-19 infection two weeks after vaccination or neutropenia in other cycles. Treatment delay was renewed within a week in all patients. This delay was a single treatment delay episode in the timeline of these patients.

**DISCUSSION**

Several studies have indicated the short-term efficacy and safety of the COVID-19 vaccines in the general population as well as unique groups such as patients with cancer. However, the long-term outcomes of the vaccines remain to be elucidated. Evidence is mounting regarding extended efficacy at three to six months postvaccination in healthy individuals such as health care workers (14, 15), yet there are no reports regarding these outcomes in patients with cancer. We have previously prospectively determined the immunogenicity, efficacy, and safety of the BNT162b2 vaccine in a cohort of patients with solid cancers who were receiving systemic intravenous antineoplastic treatments and demonstrated favorable profile following the second vaccination. Despite these corresponding rates of immunogenicity and efficacy comparable to those of healthy controls, patients with cancer demonstrated a gradual slower immunogenicity compared with the general population, manifested by significantly seronegative rates after the first vaccination that have risen to comparable rates following the second vaccination. Seroconversion rates after the second vaccination that resembled the general population were reported in other studies (8, 9). In our former study, we documented an increase in liver transaminases in 10% of the patients, and regional lymphadenopathy (cervical or axillary) was noted in 5% of CT or PET scans (performed as routine cancer care). These adverse reactions were resolved during the study period in all patients. Delay of anticancer treatment two weeks after vaccination occurred in nine (6%) patients, all of them under chemotherapy treatment. Treatment delay was due to neutropenia (n = 7), mild thrombocytopenia (n = 1), and neutropenia with herpes labials (n = 1). All neutropenic patients had gradual decline before vaccination or neutropenia in other cycles. Treatment was renewed within a week in all patients. This delay was a single treatment delay episode in the timeline of these patients.

**Systemic Reactions and Treatment Delays**

As reported previously (13), elevation of liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase) was documented in 10% of the patients up to six weeks after the first vaccine dose. Newly documented regional lymphadenopathy (cervical or axillary) was noted in 5% of CT or PET scans (performed as routine cancer care). These adverse reactions were resolved during the study period in all patients. Delay of anticancer treatment two weeks after vaccination occurred in nine (6%) patients, all of them under chemotherapy treatment. Treatment delay was due to neutropenia (n = 7), mild thrombocytopenia (n = 1), and neutropenia with herpes labials (n = 1). All neutropenic patients had gradual decline before vaccination or neutropenia in other cycles. Treatment was renewed within a week in all patients. This delay was a single treatment delay episode in the timeline of these patients.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>154 (100)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>67 (32–87)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>70 (45)</td>
</tr>
<tr>
<td>Male</td>
<td>84 (55)</td>
</tr>
<tr>
<td>Type of cancer</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>56 (36)</td>
</tr>
<tr>
<td>Lung</td>
<td>36 (23)</td>
</tr>
<tr>
<td>Breast</td>
<td>26 (17)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>25 (16)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>129 (84)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96 (62)</td>
</tr>
<tr>
<td>Biological agent</td>
<td>55 (36)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>47 (30)</td>
</tr>
</tbody>
</table>

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the patients disappeared on later imaging studies. It is notable that former evidence regarding immunocompromised patients with hematologic malignancies or organ transplants depicted a differential pattern, manifested by an initial lower seroconversion rate shortly postvaccination (8, 18–21). Note that geographic variant differences might affect the efficacy of COVID-19 vaccination. In Israel, the most common variant was Alpha until June 2021 (70%–90%), when the Delta variant became predominant (>90%; ref. 22).

There are several limitations to our study. First, this study cohort was comprised of patients who were on active anti-cancer treatment at the time of the two doses of vaccination and throughout the study period (six months). Patients who either had completed their treatment or are currently without systemic treatment or who had been diagnosed/commenced their treatment after vaccination were excluded from the study. We were therefore able to analyze only a part of the initial study cohort (subtracting the ones who concluded treatment) and added individuals who met inclusion criteria and who were not included at the initial time of vaccination. Nevertheless, due to uncertainty of the extended efficacy of the vaccine in the general population and recent reports on rising infection rates among vaccinated individuals, adherence to health care risk reduction recommendations is cardinal.

**METHODS**

**Participants and Design**

The study population was comprised of patients with solid tumors receiving intravenous treatment administered at the infusional ambulatory unit of the oncology center within the RHCC, Haifa, Israel. As previously described (13), this is a prospective follow-up report of the primary study. Initially, following mass vaccination of high-risk populations that was launched in Israel on December 20, 2020, patients with cancer without prior COVID-19 documented infection, who were vaccinated (first and second dose),...
were enrolled during their routine visit to the oncology center. Primary study time points were after the first vaccination and approximately 14 days after the second dose. Participants were followed for six months. The study flowchart is depicted in Fig. 1. The current study population consisted of patients who were on active intravenous anticancer treatment at the time of the two doses of vaccination and throughout the entire study period. To expand the study cohort, patients who met inclusion criteria and were not part of the original cohort (i.e., were on active intravenous anticancer treatment at the time of vaccination and throughout the six-month period afterward) were enrolled into the current phase of the study between July 14, 2021, and August 1, 2021, during their routine treatment visit to the oncology center. Patients who either had completed their treatment or are currently without systemic treatment or who had been diagnosed/commenced their treatment after vaccination were excluded from the study. The control group consisted of healthy health care workers who were tested for serology at the same time points. Once the accrual of patients into this study was completed and cohort profile was established, an age-matched cohort was randomly cropped (computer generated) from the large general workers' cohort, to match the same age range of the patients and to avoid selection bias. All participants consented to the study and signed an informed consent form. The study protocol was approved by the Institutional Ethics Committee of RHCC (RMB 0209–20). The study was conducted in accordance with the Declaration of Helsinki. Electronic health records of RHCC were accessed by the study investigators to review patients’ clinical characteristics as well as laboratory tests (complete blood count, liver enzymes, creatinine) and imaging assays (PET and CT scan) performed as part of routine cancer care (January 15, 2021–August 1, 2021), during their routine treatment visit to the oncology center. Patients who either had completed their treatment or are currently without systemic treatment or who had been diagnosed/commenced their treatment after vaccination were excluded from the study. The control group consisted of healthy health care workers who were tested for serology at the same time points. Once the accrual of patients into this study was completed and cohort profile was established, an age-matched cohort was randomly cropped (computer generated) from the large general workers' cohort, to match the same age range of the patients and to avoid selection bias. All participants consented to the study and signed an informed consent form. The study protocol was approved by the Institutional Ethics Committee of RHCC (RMB 0209–20). The study was conducted in accordance with the Declaration of Helsinki. Electronic health records of RHCC were accessed by the study investigators to review patients’ clinical characteristics as well as laboratory tests (complete blood count, liver enzymes, creatinine) and imaging assays (PET and CT scan) performed as part of routine cancer care (January 15, 2021–August 1, 2021) as well as documented COVID-19 infection (by RT-PCR assay) throughout the study period.

**SARS-CoV-2 Serology**

Serum samples were analyzed at all measurement times for the detection of anti–SARS-CoV-2 antibodies. For IgG expression, we used SARS-CoV-2 anti-spike (S) S1/S2 IgG assay (Liaison; DiaSorin) to detect S1/S2 IgG antibodies. Cutoff values for positive serologic findings were 15 arbitrary U/mL, as established previously (23). All serologic tests were conducted at the RHCC Virology Diagnostic laboratory.

**Statistical Analysis**

Negative and positive serologic samples among patients with cancer and controls were compared using the \( \chi^2 \) test or Fisher exact test for categorical variables and a two-tailed unpaired \( t \) test or Mann–Whitney test for continuous variables. Adjusted ORs were calculated using multivariate logistic regression with a stepwise model-reduction procedure, including the covariates of age, gender, type of treatment, disease stage, laboratory tests, and imaging assays. Statistical analysis was conducted using R, version 4.1.0 (R Foundation for Statistical Computing). The significance threshold was set at \( P < 0.05 \) for the two-sided unpaired tests.

**Data Availability Statement**

The data generated in this study are available within the article.

**Authors’ Disclosures**

A. Peer reports other support from MSD, BMS, Pfizer, Janssen, Eisai, Bayer, Astellas, Ferring, and other support from AstraZeneca outside the submitted work. No disclosures were reported by the other authors.

**Authors’ Contributions**

I. Waldhorn: Conceptualization, data curation, formal analysis, methodology, writing–original draft, writing–review and editing. 
R. Holland: Data curation, validation. T. Goshen-Lago: Conceptualization, data curation, validation, methodology.

**Acknowledgments**

This study was partially supported by the Israel Cancer Research Fund (ICRF) 16-1276-CRCDA. Serologic testing of the control cohort was supported by the Ministry of Health, Israel.

**Figure 2.** Alluvial diagram of seroconversion rate. Schematic representation of seroconversion and seropersistence in patients with cancer six months postvaccination.
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Received August 8, 2021; revised August 25, 2021; accepted August 31, 2021; published first September 2, 2021.

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Cancer Discov 2021;11:2430-2435. Published OnlineFirst September 2, 2021.

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