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

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Running title: Six Month BNT162b2 Vaccine outcomes in Solid Tumor Patients

Key Words: BNT162b2 Vaccine, cancer patients, immunogenicity, COVID-19

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Abstract:
We had previously reported short-term efficacy, immunogenicity and safety of BNT162b2 vaccine among cancer patients with solid tumors. We aimed to evaluate these outcomes at 6-months post-vaccination. Study cohort comprised of patients who were on treatment during vaccination and throughout 6-months post-vaccination. Serological tests were performed after second vaccination and 6-months afterwards. An age-matched cohort of healthcare workers served as controls. Documentation of COVID-19 infection, blood tests and imaging studies during study period was reviewed.

Participants included 154 patients and 135 controls. Six-months post-vaccination, 122 (79%) of patients were seropositive compared with 114 (84%) of controls (p = 0.32). Serology titer dramatically decreased similarly 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 cancer patients with solid tumors at 6 months post-vaccination resemble that of the general population.

Statement of significance: Evidence regarding efficacy and safety of COVID-19 vaccines in cancer patients indicate favorable short-term profile. Immunomodulation due to anti-cancer treatments may affect immunity and immunogenicity of cancer patients to 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 over 4 million deaths as of July 2021, has led to a global effort to develop severe acute respiratory syndrome coronavirus 2 (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, cancer patients were underrepresented in these prospective clinical trials. Furthermore, patients who received systemic cytotoxic therapy or immune modifying agents prior to screening were excluded, reflecting the need to study the effect of SARS-CoV-2 vaccination on cancer patients. Cancer patients represent a unique population that was initially considered as a high-risk group to present higher morbidity and mortality rates due to COVID-19 infections. Nevertheless, it had been shown throughout the pandemic that this population is heterogeneous and subsequently clinical outcomes and manifestations differ across types of malignancies and treatments, while patients with hematological malignancies and lung cancer experienced excessively high mortality (5). Moreover, it was reported that COVID-19 pandemic had a great impact on the delivery of cancer care, decreasing patients’ visits and delaying treatments which encouraged their early vaccination in mass immunization operations (6). Recent follow-up studies on SARS-CoV-2 vaccine efficacy in cancer patients have demonstrated 80-95% seroconversion rates following the second vaccination (7–9). Toxicity profile was similar to the general population. Efficacy of BNT162b2 vaccine after six months in the general population was high in preventing COVID-19 infections, despite gradual decline over time (10). Antibodies elicited by the vaccines persisted through 6 months after the second dose with a steady decay rate over time (11,12). There is a paucity of data regarding the late term efficacy in cancer patients. In our previous work (13), we indicated
that patients with solid tumors who are on active anti-cancer treatments display short-term efficacy, immunogenicity and safety of the BNT162b2 vaccine similar to that found in age-matched vaccinated healthcare workers who served as controls. The current study prospectively evaluated these outcomes at six months post vaccination.

**Results:**

**Participants**

The original study cohort (13) consisted of 232 patients with solid tumors. The current study included 154 patients with solid tumors who were receiving active intravenous treatments at the RHCC oncology center 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 (1/2021) and 64 patients who met inclusion criteria were added at the later time point (for whom all data is available except for serology status shortly after vaccination). Reasons for drop-out from the initial study cohort are elaborated in Figure 1. The patient group comprised of 84 (55%) men and 70 (45%) women (median age, 66 years; range, 32-87); the control group comprised of 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 cancer patients with active intravenous treatment, 79% (n=122) of the patients had positive serologic test results,
compared to 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 to other treatment modalities (27% vs 10%, OR- 0.31, P=0.02), as previously reported (13). Odds ratio 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, p-0.004). There was no significant difference in the median absolute serology titer between the seropositive individuals within the two cohorts (patients versus controls). Furthermore, both cohorts depicted a drastic decline overtime (2/2021-8/2021) in serology titer though remained above threshold value. For patients with known serologic status shortly after second vaccination dose (initial cohort) - 15% of the seropositive patient became seronegative after six months, comparable to the control group (Supplementary Table S1). All seronegative patients at the former short-term time point (2/2021) remained negative in both groups throughout the study period (Figure 2).

Review of the electronic medical records noted that only one case of COVID-19 infection was documented after the second dose in the patient cohort (severe illness required hospitalization). Otherwise, there were no documented cases of COVID-19 in either cohort throughout the study period. To note every PCR for COVID19 (positive or negative) is strictly documented routinely in the EMR countrywide. 

Systemic Reactions and Treatment Delays

As previously reported (13), elevation of liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and γ-glutamyltransferase) was documented in 10% of the patients up to 6 weeks after the first vaccine dose. Newly
documented regional lymphadenopathy (cervical or axillary) was noted in 5% of computed tomography or positron emission tomography scans (performed as routine cancer care). These adverse reactions were resolved during the study period in all patients. Delay of anticancer treatment 2 weeks after vaccination occurred in 9 (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.
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 cancer patients. However, the long-term outcomes of the vaccines remain to be elucidated. Evidence is mounting regarding extended efficacy at 3-6 months post vaccination in healthy individuals as healthcare workers (14,15), yet there are no reports regarding these outcomes in cancer patients. 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 anti-neoplastic treatments and demonstrated favorable profile following the second vaccination. Despite these corresponding rates of immunogenicity and efficacy comparable to that of healthy controls, cancer patients demonstrated a gradual slower immunogenicity compared with the general population, manifested by significantly seronegative rate after the first vaccination that has 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 depicted in 5% of CT or PET scans which had not been documented in prior exams. This is in concordance with subsequent studies indicating similar rates of regional adenopathy in routine imaging studies (16,17).

Our current study represents a longitudinal follow-up of cancer patients with solid tumors who had been on active intravenous treatment at time of vaccination, remained on treatment throughout the 6-month study period and at current time point of evaluation.
There were no differences in the pattern of immunogenicity, efficacy and safety between patient and control cohorts. Both groups demonstrated a similar pattern of decline in antibody titer at 6-month post second vaccination, though the vast majority of patients remained seropositive. Among the seronegative individuals, there were female predominance in both cohorts that was more pronounced in the control group. The subgroup of patients who received chemotherapy throughout the study period was in positive correlation to negative serology status. In our longitudinal follow-up the observed phenomenon of elevated liver enzymes appeared transient and normalized in all affected patients. Moreover, lymphadenopathy that was observed shortly after vaccination in 5% of the patients disappeared on later imaging studies. It is notable that former evidence regarding immunocompromised patients with hematological patients or organ transplanted depicted a differential pattern, manifested by initial lower seroconversion rate shortly post vaccination(8,18–21). To note, 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 Delta variant became predominant (>90%) (22).

There are several limitations to our study. Firstly, 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 (subtracted the ones who concluded treatment) and added individuals who met inclusion criteria and who were not included in the initial time of vaccination. Nevertheless, the trends demonstrated
in the large cohort were also significant in the smaller longitudinal cohort, affirming the implication of the results. Secondly, there is still an ongoing debate as for the correlation of positive serology and effective immunity, or negative serology to lack of immunity. Since there were no documented cases of COVID-19 also in the seronegative individuals, clear correlation of serology status to effective immunity cannot be determined.

In conclusion, our study indicates that the pattern of immunogenicity and efficacy of the BNT162b2 vaccine in patients with solid tumors on active intravenous anti-cancer treatment 6-months post vaccination resemble the pattern of the general population. Former subtle differences which were evident between the two cohorts shortly after vaccination disappeared throughout time. Nonetheless, 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 healthcare risk reduction recommendations is cardinal.

**Methods:**

*Participants and Design*

Study population was comprised of patients with solid tumors receiving intravenous treatment administered at the infusional ambulatory unit of the oncology center within the Rambam Health Care Campus, 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 from December 20th 2021, 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 following the
second dose. Participants were followed for 6 months. Study flowchart is described in Figure 1. Current study population consisted of patients who were on active intravenous anti-cancer 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 anti-cancer treatment at the time of vaccination and throughout the 6-month period afterwards) 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. Control group consisted of healthy healthcare workers who were tested for serology at the same time points. Once the accrual of patients into the current 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 the study and signed an informed consent form. Study protocol was approved by the Institutional Ethics Committee of Rambam Health Care Campus (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 (1/15/2021-8/1/2021) as well as documented COVID-19 infection (by RT-PCR assay) throughout the study period.
SARS-CoV2 serology

Serum samples were analyzed at all measurement times for the detection of anti–SARS-CoV2 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 units per milliliter, as previously established (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 χ2 test or Fisher exact test for categorical variables and a 2-tailed unpaired t test or Mann-Whitney test for continuous variables. Adjusted odds ratios 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 < .05 for the 2-sided unpaired tests.

Data Availability Statement

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


### Tables

<table>
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<tr>
<th>Characteristic</th>
<th>No. (%)</th>
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<tr>
<td><strong>Total</strong></td>
<td>154 (100)</td>
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<td>Age, median (range), y</td>
<td>67 (32-87)</td>
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</table>

**Sex**

- Female: 70 (45)
- Male: 84 (55)

**Type of cancer**

- Gastrointestinal: 56 (36)
- Lung: 36 (23)
- Breast: 26 (17)
- Genitourinary: 18 (12)
- Head and neck: 5 (3)
- Gynecologic: 5 (3)
- Neurologic: 3 (2)
- Melanoma: 2 (1)
- Sarcoma: 2 (1)
- Unknown primary: 1 (1)

**Stage**

- Local: 25 (16)
- Metastatic: 129 (84)

**Treatment**

- Chemotherapy: 96 (62)
- Biological agent: 55 (36)
- Immunotherapy: 47 (30)

Table 1 – Patient characteristics
Table 2 - Patient characteristics 6-months post-vaccination

![Table image]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
<th>Controls</th>
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<tr>
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<td>Seropositive</td>
<td>Seronegative</td>
</tr>
<tr>
<td>Total</td>
<td>122 (79)</td>
<td>32 (21)</td>
</tr>
<tr>
<td>Median day from 2nd vaccine dose</td>
<td>176</td>
<td>171</td>
</tr>
<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Female</td>
<td>53 (43)</td>
<td>17 (53)</td>
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<tr>
<td>Male</td>
<td>69 (57)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>66 (32-86)</td>
<td>69 (32-87)</td>
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<tr>
<td>Type of cancer</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal</td>
<td>45 (37)</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Lung</td>
<td>29 (24)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Breast</td>
<td>19 (16)</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>16 (13)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>4 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>4 (3)</td>
<td>1 (3)</td>
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<tr>
<td>Neurologic</td>
<td>2 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Melanoma</td>
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<td>0 (0)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>1 (1)</td>
<td>0 (0)</td>
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<tr>
<td>Stage</td>
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</tr>
<tr>
<td>Local</td>
<td>18 (15)</td>
<td>7 (22)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>104 (85)</td>
<td>25 (78)</td>
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<tr>
<td>Treatment</td>
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<tr>
<td>Chemotherapy</td>
<td>70 (57)</td>
<td>26 (81)</td>
</tr>
<tr>
<td>Biological agent</td>
<td>44 (36)</td>
<td>11 (34)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>41 (34)</td>
<td>6 (19)</td>
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Figure Legends

Figure 1 – Study flow chart of patient cohort

Figure 2 – Alluvial diagram of seroconversion rate – schematic representation of seroconversion and seropersistence in cancer patients six months post-vaccination.
Figure 1

232 Patients tested after vaccination

144 Excluded
- No active IV treatment (n=72)
- No IV treatment during recruitment period (n=34)
- Declined to participate (n=20)
- Died (n=17)
- Covid infected (n=1)

66 Patients newly recruited

88 Patients 6 months post vaccination

154 Patients
Figure 2

- Seropositive: Seropersisted 85%
- Seroconverted 15%
- Seronegative

Vaccination to 6 Months
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