The Impact of Chemotherapy and Immunotherapy on the Efficacy of COVID-19 Vaccination

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The presenter has no financial interests to disclose.
Overview

• Introduction
• Study design
• Results
• Discussion
• Conclusion
Introduction

• 986,000 people have died in the USA from SARS-CoV-2 viral infection (COVID-19) since JAN2020 with 6.2 million deaths worldwide

• Patients with cancer have a higher risk of dying from COVID-19 than patients without cancer

• Both the National Comprehensive Cancer Network and American Society of Clinical Oncology have advised vaccination against SARS-CoV-2 for patients undergoing cancer-targeted therapies

• It is estimated that COVID-19 vaccinations have prevented over 100,000 deaths in the US
Introduction

• COVID-19 vaccine serum titers have been measured in specific subtypes of cancer (CLL), however data on vaccine effectiveness is wanting in landscapes:
  • General oncology clinic, multiple modality chemotherapy, solid malignancies
  • Titer level correlate to degree of protection
  • Degree of protection against variants and other coronavirus strains
Objectives

• Primary
  • Evaluate COVID-19 vaccine titer levels in patients vaccinated while receiving chemotherapy and immunotherapy
  • Correlate titer levels with degree of serum neutralization

• Secondary
  • Determine if vaccine response differs depending on:
    • B-cell malignancies
    • Degree of protection against variants
    • Degree of protection against other strains of coronavirus
    • Characterize COVID-19 breakthrough infections and potential vulnerable population
Study Design

• Prospective observational study assessing titer response to COVID-19 vaccination in patients 18 and older receiving chemotherapy or immunotherapy
  • Excluded: Bone marrow transplants, primary immunodeficiency, acute myeloid leukemia

• Vaccination against SARS-CoV-2 via two doses of mRNA-1273 (Moderna), two doses of BNT162b2 (Pfizer), or single dose of Ad26.COV2 (Janssen)

• Serum obtained at 1, 3, and 6 months after COVID-19 Vaccination

• Measured anti-SARS-CoV-2 antibodies from the initial Wuhan strain for:
  • Spike trimer, Spike S1 subunit, Spike receptor binding domain (RBD), and the Nucleocapsid protein
  • Ratio of patient titers: negative control >1.3 indicative of titer presence
  • Antibody titers to SARS-CoV-2 spike protein variants: B.1.1.7 (α), B.1.351 (β) and P.1 (γ)
Study Design-Antibody Assessment

- 11 proteins and a negative control are assessed in a single well per sample

- Mean fluorescent intensity (MFI) values from standards were utilized to generate a standard curve

- A negative control which was established based on 160 healthy PCR negative and 69 PCR positive SARS-CoV-2 samples was run with each kit

- The ratio of subjects antibody level compared to the negative control was calculated (Ratio = MFI of the sample / MFI of the low control)
  - Ratio > 1.3 = Ig is present
  - Ratio between 1 – 1.3 = indeterminate result
  - Ratio of < 1 corresponds = Ig that is absent for that given protein
Study Design

• Serum Neutralization Assay correlates performed using 10 serum samples from “low” titers, 10 from “intermediate” titers and 20 from “high” titer

• 20% neutralization indicated a protective titer level from infection
  • Defined based on screening of 160 healthy (negative for SARS-CoV2) samples and correlated to a 50% plaque reduction in virus culture samples
Demographics

• 120 total patients enrolled in first half of this study (not including booster data)
  • 28 dropped out

• 92 patients assessed: 57% Female, 43% male

• Age range 23-84, median 64

• 24% from patients with B-cell malignancies

• 48.9% Stage IV cancer
Vaccines Obtained

- Pfizer: 82.9%
- Moderna: 16.1%
- Janssen: 0.9%
Malignancies

- Marginal Zone Lymphoma, 2%
- Prostate, 1%
- Esophageal, 1%
- MDS, 1%
- CLL, 2%
- Melanoma, 2%
- Liposarcoma, 1%
- CUP, 1%
- Ovarian, 2%
- Bladder, 2%
- Thymoma, 1%
Vaccine Side Effect Profile

- Fever, 1%
- Fatigue, 6%
- Backache, 1%
- Chills, 1%
- Nausea, 1%
- Myalgia, 7%
- Headache,
Detectable Titer Response at 1 Month

Percent COVID-19 Vaccine Titers >1.3 at 1 Month

- Anti-Spike: 71.0%
- Anti-S1 IgG Titers: 66.7%
- Anti RBD: 68.1%
1 Month Titer Response in Multiple Myeloma

Covid Vaccine Titers >1.3 at 1 Month

<table>
<thead>
<tr>
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<th>All comers</th>
<th>MM</th>
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</thead>
<tbody>
<tr>
<td>Anti-Spike</td>
<td>71.0</td>
<td>.9</td>
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<tr>
<td>Anti-S1 IgG Titers</td>
<td>66.7</td>
<td>40.0</td>
</tr>
<tr>
<td>Anti RBD</td>
<td>68.1</td>
<td>30.0</td>
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</table>
B-Cell Malignancies

- Anti-spike, anti-S1 and anti-RBD titers decayed from 1-6 months for non-B cell malignancies (P<0.001)

- Statistically significant difference in titer levels at 1 and 3 months between B and non-B cell malignancies, but not at 6 months

- No significant decay amongst titers in patients with B cell malignancies
  - Too low at start
Chemotherapy vs. Immunotherapy

• No significant response difference at 1, 3, and 6 months between chemotherapy (less B-cell malignancies) and immunotherapy

• Equivalent decay over time
Stage IV Malignancies

• Statistically significant higher titer response for Spike trimer, S1 and RBD at 1 month, not 3 or 6 months (P<0.0001)

• Equivalent rate of titer decay between Stage IV and all others

• 50% of patients with stage IV malignancies on non-cytotoxic chemotherapies at 1 month after vaccination
  • Molecularly targeted therapies or single agent chemo
Response Rates for Moderna vs. Pfizer

• Higher titer response to Spike, S1 and RBD for Moderna vs. Pfizer at 1 month (P<0.001)

• No significance difference in titer levels at 3 and 6 months after vaccination
Anti-RBD Correlating to Variant Protection

- >500 U/ml manufacturer cutoff for high-titer
- Higher titer of RBD portended greater protection against:
  - B.1.351 (β) > B.1.1.7 (α) > P.1 (γ)
- Even at high anti-RBD titer, limited protection against gamma variant
Anti-RBD IgG vs. Neutralization of Coronavirus Strains

- Increasing anti-RBD IgG levels showed no significant improvement in protection against common coronavirus strains.
Nominal Logistical Fit Analysis

- Determined threshold of anti-RBD IgG of 7.43 and above correlates to consistently >20% neutralization

<table>
<thead>
<tr>
<th>X</th>
<th>Prob</th>
<th>1-Specificity</th>
<th>Sensitivity</th>
<th>Sens-(1-Spec)</th>
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Multivariate Correlation for Titer Levels to Serum Neutralization for Variants

<table>
<thead>
<tr>
<th></th>
<th>SARS-CoV-2 N</th>
<th>SARS-CoV-2 Spike (Trimer)</th>
<th>SARS-CoV-2 S1</th>
<th>SARS-CoV-2 RBD</th>
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</thead>
<tbody>
<tr>
<td>SARS-CoV-2 N</td>
<td>1</td>
<td>0.3283</td>
<td>0.2644</td>
<td>0.2716</td>
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<td>SARS-CoV-2 Spike (Trimer)</td>
<td>0.3283</td>
<td>1</td>
<td>0.8621</td>
<td>0.8503</td>
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<tr>
<td>SARS-CoV-2 S1</td>
<td>0.2644</td>
<td>0.8621</td>
<td>1</td>
<td>0.97</td>
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<tr>
<td>SARS-CoV-2 RBD</td>
<td>0.2716</td>
<td>0.8503</td>
<td>0.97</td>
<td>1</td>
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<tr>
<td>SARS-CoV-2 Spike UK (B.1.1.7)</td>
<td>0.1887</td>
<td>0.6438</td>
<td>0.8243</td>
<td>0.819</td>
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<tr>
<td>SARS-CoV-2 Spike SA (B.1.351)</td>
<td>0.1211</td>
<td>0.5577</td>
<td>0.7534</td>
<td>0.6947</td>
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<td>SARS-CoV-2 Spike Brazil (P.1)</td>
<td>0.2142</td>
<td>0.6065</td>
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<td>0.7323</td>
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<td>CoV-OC43</td>
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<td>0.1204</td>
<td>0.062</td>
<td>-0.0507</td>
<td>-0.0612</td>
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</tbody>
</table>
37.7% of all patients exhibited adequate titer response at month 1
Neutralization Correlating to Detectable RBD Titers at 1 Month

Percent Adequate Neutralization & Titer Level at 1 Month

- Multiple Myeloma: 10% RBD Neutralization, 30% Titer
- Colorectal: 45.5% RBD Neutralization, 81.8% Titer
- Breast: 47.1% RBD Neutralization, 64.7% Titer
RBD Titer Correlation to Neutralization

Adequate Titer and Neutralization

RBD Titer All Malignancies

- 1 Month: 37.7%
- 3 Month: 27.6%
- 6 Month: 11.8%

RBD Titer $>7.49$
Titer $>1.3$
# Break Through Infections

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
<th>Vaccine</th>
<th>Time of Infection after vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Myeloma</td>
<td>Daratumumab, dexamethasone</td>
<td>Pfizer</td>
<td>4 months</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>Daratumumab, bortezomib, dexamethasone</td>
<td>Pfizer</td>
<td>5 months</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>Daratumumab</td>
<td>Pfizer</td>
<td>5 months*</td>
</tr>
<tr>
<td>Primary Myelofibrosis</td>
<td>Ruxolitinib</td>
<td>Moderna</td>
<td>6 months</td>
</tr>
<tr>
<td>Waldenstrom Macroglobulinemia</td>
<td>Ibrutinib</td>
<td>Moderna</td>
<td>6 months*</td>
</tr>
</tbody>
</table>

*Patient died from COVID-19
### Other Notable Non-Responders

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Detectable Titers at 1 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL</td>
<td>Ibrutinib</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Breast</td>
<td>ddAC+T</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Ewing Sarcoma</td>
<td>Irinotecan+ Temodar</td>
<td>1</td>
<td>0</td>
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</table>
Conclusion

• Vaccination against SARS-CoV-2 appears safe in patients with active malignancies undergoing cancer-targeted therapies

• Titers levels decay over six months but do not decay in patients with B-cell malignancies (due to limited response)

• Blunted response to vaccination were observed in patients receiving:
  • B cell malignancy therapies (notably Multiple Myeloma)
  • Breast cancer receiving: doxorubicin, cyclophosphamide and paclitaxel
Conclusion

• Vaccination with COVID-19 vaccines do not appear to provide protection against common coronavirus strains in this population

• Adequate titers do no correlate to adequate neutralization
  • 37.7% of patients able to adequately neutralize at 1 month
  • 11.8% adequate neutralization by month 6

• Breakthrough infections observed in hematologic malignancies:
  • Multiple myeloma, Waldenstrom macroglobulinemia, primary myelofibrosis
  • Two patients died from COVID-19 between 5-6 months after vaccination
Research Team

Dr. Chung-Ting Kou, Manuel Caballero, Dr. Tom Gibbons, Dr. Jason Okulicz, Dr. James Aden, Patricia Blas, Peggy Smith, Dr. Joshua Fenderson
Questions