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# Immunogenicity of COVID-19 vaccine among multiple myeloma patients post autologous stem cell transplant

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## Abstract

**Introduction:** The safety and efficacy of mRNA vaccines against SARS-CoV-2 have proven widely among all age groups but not well studied among cancer patients who received Autologous Stem Cell Transplant (ASCT). Multiple Myeloma (MM), a clonal plasma cell disease shown to have poor vaccine response by weakening host immunity due to the disease and anti-MM therapy. The effect of Autologous Stem Cell Transplant (ASCT), which is the standard of care for fit MM patients on vaccine response has not been well studied and we investigated the seroconversion rate among MM patients who received at least one vaccination post ASCT to elucidate optimal timing and number of vaccines post ASCT.

**Methods:** We retrospectively analyzed the seroconversion rate among sixty-four (64) MM patients at our institution who underwent ASCT and subsequently received at least one dose of either available mRNA vaccine (Pfizer or Moderna) by measuring antibody titers against SARS-CoV-2 spike glycoprotein.

**Results:** We categorized the patients into complete responders with titers levels more than 250 U/ml and partial respond-ers/non-responders with titers levels less than 250 U/ml. 25/64 (39.1%) had received at least 3 vaccines prior to titer assessment. Of those, 18/25 (72%) were complete responders compared to 7/25 (18%) partial/non-responders, p=0.02. 53.1% of subjects in the entire cohort were complete responders. Among them, more patients received at least 3 vaccines post ASCT 76.5% vs 23.5%, p=0.03. Factors that adversely impacted antibody response were higher age (>65), p=0.02, daratumumab containing mainte-nance, p=0.04 and Ig G Iso type, p=0.03. A total of three patients developed symptomatic Covid infections, all of which were in the non-responders/partial responders' group; none of them required hospitalization.

**Conclusion:** Our results suggested administration of at least 3 mRNA Covid vaccines post ASCT leads to significantly improved antibody titers and periodic checking of antibody titers to identify patients with suboptimal response to explore additional strate-gies for adequate protection.

## Introduction

As of August 2022, more than a million people have died from Covid-19 in the United States (US) with higher deaths noted among elderly and immune suppressed [1,2]. The rapid development and implementation of mRNA vaccines for Covid-19 (BNT162b2 from Pfizer/Bio N Tech and mRNA-1273 from Moderna) resulted in a significant lowering of disease severity, hospitalizations, and mortality [3]. Even though the vaccines were initially made first available to elderly and immune suppressed, their efficacy in these populations was uncertain as they were excluded in most of the vaccine trials [3,4]. Recent studies revealed sub-optimal vaccine responses among hematological cancer patients with poor seroconversion rates, which was attributed to the weak immune system from disease and treatment [5,6].

Multiple Myeloma (MM) is a hematologic cancer characterized by proliferation of abnormal plasma cells and weakened host immunity causing substandard vaccine responses [7]. High dose chemotherapy followed by Autologous Stem Cell Transplant (ASCT) is the standard of care for newly diagnosed eligible patients and leads to prolonged immune suppression. In addition Immuno Modulatory Drugs (IMIDs), Proteasome Inhibitors (PIs), and monoclonal antibodies are most commonly used drugs in MM patients at various treatment phases, including during maintenance therapy post ASCT. These regimens further add to post ASCT immunosuppression. For example, MM patients on daratumumab are shown to have poor vaccine response rates in pre-vious studies [8,9]. Covid-19 vaccine response after high dose chemotherapy followed by ASCT has not been well studied to date and there is little guidance how many vaccines are required post ASCT. In the light of this complex disease and therapy related immune consequences, we investigated the seroconversion rates among MM patients who received at least one vaccination post ASCT.

## Materials and methods

In this retrospective study, we studied a total of 64 patients, who underwent ASCT for MM and subsequently received at least one dose of either available mRNA vaccine (Pfizer or Moderna) at the University Of Arkansas Medical Center (UAMS). Antibody titers against SARS-CoV-2 spike glycoprotein were checked at various timelines post vaccination. Testing was performed using Roche Elecsys Anti SARS CoV-2 reagent assay from Roche diagnostics. We categorized the patients into two groups: complete responders with titers levels more than 250 U/ml and partial responders/non-responders with titers levels less than 250 U/ml. Co-variates used were age, sex, race, MM isotypes, vaccine count, time from last transplant to first dose of vaccine and maintenance therapy post ASCT. Welch's t-test and Wilcoxon rank-sum test were used for continuous variables, while Fisher's exact test was used for categorical variables.

## Results/discussion

Out of 64 patients analyzed, the mean age was 62.5 years (Range: 35-81), with 39.1% (25/69) being female. The most common isotype was IgG and the most common free light chain was kappa, comprising 73.1% (38/53) and 68.8% (44/64) respectively. All patients initiated maintenance after ASCT consisting of a two or three drug combination of daratumumab (30/64, 47.6%), pro-teasome inhibitors (47/64, 74.6%) or immunomodulators (50/64, 78.7%) with steroids (58/64, 92.1%). The first vaccine dose was given at a minimum of 70 days after ASCT and for vaccinations that were given during the maintenance period, treatments were held one week prior and after each vaccine dose. The median follow up duration from 1st transplant to last follow-up was 152 days, [Inter quartile range = 68.8, 254.3] (Table 1).

**Table 1:** Demographic and medical characteristics of N=64 MM patients receiving at least one transplant who subsequently received at least one Covid-19 vaccine. Unless noted otherwise, summaries are reported as % (n).

| Variable | N | Summary |
|---|---|---|
| Age [mean (sd)] | 64 | 62.5 (9.7) |
| Female | 64 | 39.1% (25) |
| Race/Ethnicity | 64 | |
| Caucasian | | 84.4% (54) |
| African American | | 10.9% (7) |
| Hispanic | | 3.1% (2) |
| American Indian | | 1.6% (1) |
| Isotype | 53 | |
| IgA | | 26.9% (14) |
| IgG | | 73.1% (38) |
| Light Chain | 64 | |
| Kappa | | 68.8% (44) |
| Lambda | | 31.2% (20) |
| Time from Last Transplant to Titer (days) [median (IQR)] | 64 | 318.0 (139.3, 453.8) |
| Time from First Transplant to last follow up (days) [Median (IQR)] | 64 | 152.0 (68.8, 254.3) |
| ≥ 3 Vaccines Prior to Titer | 64 | 39.1% (25) |
| IVIG | 61 | 34.4% (21) |
| Dara | 63 | 47.6% (30) |
| PI | 63 | 74.6% (47) |
| Steroids | 63 | 92.1% (58) |
| Chemotherapy | 63 | 50.8% (32) |
| Titer >250 | 64 | 53.1% (34) |

At time point of data collection 25/64 (39.1%) had received at least 3 vaccines post ASCT and prior to titer assessment. Of those, 18/25 (72%) were complete responders compared to 7/25 (18%) partial/non-responders, p=0.02. Considering all patients, we observed 53.1% (34/64) of subjects in the entire cohort mounted a complete response (>250 U/ml) and the rest of the subjects (46.9%, 30/64) had partial response with a median antibody titer of 27.5 U/ml.

Patients received ≥3 vaccines post ASCT had a significantly higher chance of achieving a complete response compared to those receiving <3 vaccines (76.5% vs 23.5%, p=0.03), This difference was regardless of the number vaccines given prior to ASCT, While previous studies have reported higher seroconversion rates in MM patients, most of the investigated patients were not post ASCT. Avivi et al reported seroconversion rates of

76% among MM patients which included both non transplant and prior ASCT patients (n=96, 60%) after only two doses of vaccine [8], while in contrast there were only 53% of complete responders in our cohort. This difference may be due to additional immunosuppression conferred by ASCT.

There was a trend towards more time from transplant to first vaccine being associated with a complete antibody response (median days of 171 for complete responders vs 128 days for non/partial responders), albeit that was not significant, p=0.3.

Factors that adversely impacted antibody response were higher age (>65), p=0.02 and daratumumab containing maintenance, p=0.04. These results were in line with previous studies [10,11]. No significant difference was noted between complete and partial/non responders in regard to sex, race, light chain type, Intravenous Immunoglobulins (IVIG) administration and other maintenance regimens (Table 2).

Intriguingly, we observed significantly better antibody response in patients with Ig A MM isotype compared to IgG Isotype, p=0.03, albeit the numbers were small for this analysis (Ig A n=14/65). At the time point of data collection, a total of three pa-tients developed symptomatic Covid-19 infections, all of which were in the non-responders/partial responders' group; none of them required hospitalization.

**Table 2:** Comparison of titer groups with respect to demographic and medical characteristics.

| Variable | Titer ≤ 250 | | Titer > 250 | | P-value |
|---|---|---|---|---|---|
| | N | Summary | N | Summary | |
| Age [mean (sd)] | 30 | 65.4 (7.5) | 34 | 60.0 (10.72) | 0.0205[a] |
| Female | 30 | 40.0% (12) | 34 | 38.2% (13) | >0.99b |
| Caucasian | 30 | 93.3% (28) | 34 | 76.5% (26) | 0.0885[b] |
| Isotype | 25 | | 27 | | 0.0287[b] |
| IgA | | 12.0% (3) | | 40.7% (11) | |
| IgG | | 88.0% (22) | | 59.3% (16) | |
| Light Chain | 30 | | 34 | | 0.1046[b] |
| Kappa | | 80.0% (24) | | 58.8% (20) | |
| Lambda | | 20.0% (6) | | 41.2% (14) | |
| Time from Last Transplant to Titer (days) | 30 | 261.0 (111.8, 351.3) | 34 | 417.0 (230.5, 522.0) | 0.0126[c] |
| Time from Last Transplant to First Vaccine (days) | 30 | 128.5 (70.8, 225.8) | 34 | 171.0 (71.0, 301.3) | 0.3034[c] |
| ≥ 3 Vaccines Prior to Titer | 30 | 23.3% (7) | 34 | 52.9% (18) | 0.0213[b] |
| IVIG | 29 | 37.9% (11) | 32 | 31.3% (10) | 0.6020[b] |
| Dara | 29 | 62.1% (18) | 34 | 35.3% (12) | 0.0447[b] |
| PI | 29 | 69.0% (20) | 34 | 79.4% (27) | 0.3939[b] |
| Steroids | 29 | 89.7% (26) | 34 | 94.1% (32) | 0.6544[b] |
| Chemotherapy | 29 | 44.8% (13) | 34 | 55.9% (19) | 0.4527[b] |

[a] Welch's t-test [b] Fisher's exact test [c] Wilcoxon rank-sum test

## Conclusions

Taken together, this is the first study to evaluate SARS-CoV-2 mRNA vaccine effectiveness post ASCT in MM patients. We show that the administration of at least 3 mRNA Covid vaccines post ASCT lead to significantly improved antibody titers and should be the minimum standard in this patient population. Furthermore, we emphasize the periodic monitoring of vaccine induced an-tibody titers, especially post ASCT, to identify non responders and to evaluate the need for additional vaccine doses or with dif-ferent vaccine types for adequate protection. In our study elderly patients and daratumumab maintenance were the strongest predictors of a reduced vaccine response and this was not affected by sex, race or light chain type. There were some limitations to our study. This was a retrospective study in which the antibody titers were checked at different time points post vaccination, which could likely impact the titer results to some extent. Furthermore, we focused on quantification of antibody titers against SARS-CoV-2 spike glycoprotein as a measure of vaccine response. Furthermore, we did not measure Vaccine-induced T cell response. Nevertheless, antibody titers have been shown to be predictive of disease severity and none of the complete responders developed a Covid-19 infection during the study period [8]. In conclusion, our study offers valuable clinical guidance and em-phasizes to maximize vaccination strategies post ASCT to achieve optimal protection.

## Declarations

**Author contributions:** Conceptualization, NT,CS and YO; methodology NT and CS; Data Collection, NT, Y O, JS, MH, LY, SG; writing—original draft preparation, N.T and CS; writing—review and editing, N.T, C.S,S.A,S.T,M.Z,J.S,F.Z,J.R,F.V.; supervision, CS; All authors have read and agreed to the published version of the manuscript.

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**Institutional review board statement:** The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University of Arkansas for Medical Sciences (protocol code 260312 and 11/30/2021).

**Informed consent statement:** Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

**Conflicts of interest:** The authors declare no conflict of interest.

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