Research Article

Effect of a third booster dose of COVID-19 mRNA vaccine in patients with haematological cancer after the initial two-dose vaccination - a single centre report

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Abstract

Novel Coronavirus SARS-CoV-2 causing COVID-19 has been subject to intensive interest since its appearance in 2019, with the risk of the severe course being significantly higher for adult patients with hematological malignancy. Results on a two-dose, standard vaccination regimen in patients with hematological cancer have identified risk populations with poor vaccination outcomes (Chronic lymphocytic leukemia, anti-CD20 treatment, etc.). Thus, a booster dose was anticipated with hopes of inducing an immune response in formerly non-respondent individuals. We have vaccinated 394 patients with hematological cancer with the third dose of the mRNA BNT 162b2 COMIRNATY vaccine. Our results show promise, especially for increasing protective antibody levels in patients who retain valid antibody titers. We also identify problematic populations such as chronic lymphocytic leukemia, which still represent a major challenge for prophylaxis and protection against a severe course of COVID-19. Our report brings more insight into vaccination results and behavior. Importantly, we have identified risk groups in which poor outcomes can be anticipated and what extensive preventive measures should be undertaken to avoid COVID-19 infection.

Abbreviations

CLL: Chronic Lymphocytic Leukemia; PCR: Polymerase Chain Reaction; ELISA: Enzyme-Linked Immunospecific Assay; VNT: Virus Neutralization Test; AL/MDS: Acute Leukemia/Myelodysplastic Syndrome; cMPN: chronic Myeloproliferative Neoplasms; MM: Multiple Myeloma

Introduction

Novel Coronavirus SARS-CoV-2 causing COVID-19 has been subject to intensive interest since its appearance in 2019. For adult patients with hematological malignancy and COVID-19, the risk for the severe course and/or death is significantly higher compared to the healthy population [1,2]. Although many new antiviral strategies have been put to use, preventive measures including vaccination remain essential to successfully diminish the risks of a severe course of COVID-19.

Systematic results after initial, two-dose vaccination in patients with hematological malignancy have shown worse vaccination responses in patients with hematological cancer in comparison with a healthy population [3]. Worst results have been reported for Chronic lymphocytic leukemia (CLL) and B-lymphoma and some specific anti-cancer drugs (anti-CD20, Bruton kinase inhibitors) in single reports [4-6] and various meta-analyses [7,8]. Moreover, our recent data have pointed to an accelerated deterioration of serological response in patients with hematological cancer within a few months after vaccination [9].

In late 2021, a 3rd booster dose of the vaccine became available with unconvincing results for hematological patients [10]. However, the long-term effect of the booster dose has not been largely evaluated yet. With the appearance of novel mutant Omicron subvariants of SARS-CoV-2, detailed comprehension...
of vaccine mechanisms, appropriate timing and the impact of specific diagnoses and/or drugs on their outcome becomes crucial.

We report our final results for the 3rd dose of mRNA vaccine administered as a booster in a larger heterogenous single-center cohort.

## Methods and data collection

Since 27th September 2022, all patients of our facility initially vaccinated with two doses of mRNA BNT 162b2 COMIRNATY vaccine (Pfizer/BioNTech) have been offered a third booster dose of the same vaccine regardless of their diagnosis, treatment status, or antibody response to initial vaccination.

First, we prioritized patients with no response to the initial two-dose vaccination along with patients who lost their protective antibody titers 3 months after two standard doses (“low responders”). Next, due to a worsening epidemiologic situation, we aimed to vaccinate all patients of our facility. We vaccinated all patients with PCR-confirmed SARS-CoV-2 negativity.

A testing schedule to evaluate the immune response and its duration has been implemented in accordance with our previous data collection [11]. Blood serum samples were drawn at given timepoints and tested for the detection of IgG, IgM, and IgA anti-S1/S2 antibodies to SARS-CoV-2 using commercial ELISA assays and for the detection of neutralizing antibodies using in-house in-vivo Virus Neutralization Test (VNT) against the Wuhan and delta variant viruses. ELISA assays for the detection of IgG and IgA contained the S1 subunit of the spike protein as antigen and ELISA assay for the detection of IgM contained nucleoprotein (NCP) as antigen (Euroimmun, Lübeck, Germany). A signal-to-cut-off ratio was calculated and values < 0.9 were regarded as negative, ≥ 0.9 to < 1.1 as borderline and ≥ 1.1 as positive seroconversion. The VNT was performed as described in [12]. Baseline VNT positivity was determined as a titer of 20 with a positive correlation with IgG neutralizing activity [13].

For low responders, a positive response to vaccination was determined as VNT higher than the cut-off value with or without positive IgG and / or IgA titers > 21 days after the third dose. For patients with valid IgG and VNT titers at the time of the third dose, a positive response was determined as an increase in both IgG and VNT titers > 21 days after its administration.

Patients with a known history of COVID-19 infection < 4 weeks before the third dose or who contracted COVID-19 during data collection and patients who had a baseline excess positive IgG and VNT serology (> 2.5 fold increase compared to their results 6 months after initial vaccination) or who tested positive for IgM anti–SARS-CoV-2 at the time of third dose administration were excluded from our final analysis.

A written consent for each dose administration and samples collection and evaluation, approved by the local Ethical committee, has been obtained from every participating patient.

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## Results

We have vaccinated a total of 394 patients, of which 32.5% (128/394) were low responders: 21.8% (86/394) were serologically naïve (patients with no response after the initial two doses) and 10.7% (42/394) have lost their antibody titers inside of 3 months after the second dose. The remaining 67.5% (266/394) had valid antibody titers at the time of the third dose.

In Acute leukemia / Myelodysplastic syndrome (AL/ MDS) cohort the overall response was 100% (26/26) and in the Chronic myeloproliferative neoplasms (cMPN) group the overall response was 97.8% (45/46). In the Multiple myeloma (MM) cohort the overall response was 93.9% (108/115), in the Lymphoma group, the overall response was 73% (84/115) with 76.2% (16/21) response in Hodgkin lymphoma and B-Lymphoma 100% (16/16) and 68.7% (68/99), respectively. In the CLL group, the overall response was 13% (6/46).

In the AL/MDS cohort, we have not seen any serologically naïve patients, and 100% (3/3) of patients who lost protective antibody levels after standard two-dose vaccination regained valid titers after the third dose.

In cMPN group, 2.2% (1/46) patients were serologically naïve and did not achieve serological response after the third dose. Zero patients have lost their antibody titers within three months following standard vaccination. We saw an average 1.72-fold increase in antibody titers for all patients with valid titers (97.8%, 45/46) in this cohort.

In the MM cohort, 10.4% (12/115) patients were serologically naïve and 8.7% (10/115) lost their antibody titers after standard vaccination. Of these patients, 58.3% (7/12) and 90% (9/10) responded, respectively. Of 93 patients with valid antibody titers, all but one (98.9%) responded.

In the Lymphoma group, 30.4% (35/115) patients were serologically naïve, of which 91.4% (32/35) received anti-CD20 treatment < 6 months prior to the third dose. The response rate in this sub-cohort was 37.1% (13/35) and 76.9% (10/13) of responders received prior anti-CD20 therapy. The seroconversion rate for patients where anti-CD20 therapy was discontinued > 6 months prior to the third dose of vaccine was 70% (7/10).

Lymphoma patients with loss of protective antibody titers after two doses of vaccine accounted for 15.7% (18/115). The response rate in this sub-cohort was 55.6% (10/18), of which 60% (6/10) received prior anti-CD20 treatment. In 100% (6/6) of these patients, anti-CD20 therapy was discontinued > 6 months prior to third dose administration.

Of 62 Lymphoma patients with valid antibody titers, 98.4% (61/62) responded. One patient with no response started an anti-CD20–based therapeutic regimen shortly before the third dose of the vaccine.

In CLL group 56.5% (26/46) patients were serologically naïve with 7.7% (2/26) response. Of five patients with loss of
protective antibody titers after two doses of vaccine, 40% (2/5) responded to the third dose. Of 15 patients with valid antibody titers, 86.7% (13/15) responded.

**Discussion**

We saw very promising results for AL/MDS, cMPN, and MM cohorts with very high response rates. The response rates after the third dose of vaccine in these cohorts even surpassed our first findings for standard two-dose vaccination [11] and are in accordance with previously published data on encouraging outcomes of third dose booster vaccine [14].

Importantly, nearly 70% of patients vaccinated with the initial two doses of mRNA vaccine had valid antibody titers >6 months after the initial vaccination. Surprisingly, less than 10% of MM patients in our cohort lost their antibody titers >6 months after a two-dose vaccination and 90% saw a rise after a third booster dose of vaccine.

In the Lymphoma cohort, we saw less encouraging results. However, our data clearly show the effect of anti-CD20 lymphodepleting therapy on vaccination response. We saw a major shift in response for patients where anti-CD20 therapy was discontinued > 6 months prior to vaccination. Our findings were in accordance with previous reports on low humoral responses to different types of vaccines [15] as well as mRNA anti–SARS–CoV–2 vaccines [16–18].

We saw worse results for CLL patients with only a 13% response rate in our cohort which is in accordance with our earlier results [9], but worse compared to 23.8% (44/172) reported by Herishanu, et al. [19]. The difference between our cohorts may be due to heavier pretreatment of our patients including a significant proportion of active anti-CD20 and Biritinib treatment. Importantly, the third dose of the vaccine acted as an effective booster for 86.5% of CLL patients with valid antibody titers.

Our findings are in accordance with generally reported poor vaccination results in CLL patients [20,21]. However, an encouraging outcome of a booster vaccine shows surprising promise.

In general, the third dose of vaccine has shown potential in reinforcing anti–SARS–CoV–2 IgG and VNT titers for hematological patients, especially in AL/MDS, cMPN, and MM with very satisfying results. Also, our research has shown the benefit of a booster dose, especially for patients on prior anti-CD20 treatment, provided a 6-month time window is kept. In all, patients with blood cancer show a lesser antibody response compared to the healthy population [22], although a booster in antibody titers have been observed.

Next, our research identifies groups of interest – patients with suboptimal or no response to vaccination who should be regarded as high-risk for the adverse course of COVID–19, especially chronic B-lymphoproliferative neoplasms. For such patients, any accessible preventive and curative measures (e.g. depot monoclonal antibodies) should be strongly recommended in order to mitigate the risk of severe COVID–19 and/or death.

The appearance of the new Omicron subvariants (BA.4, BA.5) with their potential for immune escape put us against new challenges [23]. However, some works have confirmed persisting, albeit diminished efficacy of booster vaccines-induced antibodies against novel Omicron subvariants [24]. In the absence of more sophisticated, subvariant-targeted strategies, vaccination along with commercial prophylactic antibodies and rational personal prevention measures retains a crucial role in the protection against severe COVID–19 breakthrough infections.

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OŠ and BŠ performed the research and data collection, and data analysis and wrote the paper.

RH designed the research study and supervised data collection and paper preparation.

RH is the corresponding author.

This research has been approved by the local Ethics Committee of Faculty Hospital Ostrava, Czech Republic.

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