195 Characterization of the Early Humoral and Cellular Response Developed in Oncohematological Patients Post-Vaccination with One Dose Against COVID-19.

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Background: Oncohematological patients present a variable immune response against many vaccines, due to the immunodeficiency caused by the disease and its treatment. The experience of vaccination against COVID-19 in oncohematological patients is low and mostly limited to studies of humoral immunity. However, the humoral and cellular immune responses between different oncohematological diseases (OHD) have not been compared.

Objective: To compare the humoral and cellular immune responses in four groups of patients with OHD after receiving the first dose of one COVID-19 vaccine.

Materials & methods: We recruited 53 patients in four groups according to diagnosis: Chronic Lymphatic Leukemia (CLL) (n=14), Chronic Myeloid Leukemia (CML) (n=11), Multiple Myeloma (MM) (n=15), and Allogeneic Hematopoietic Stem Cell Transplantation (ASCT) (n=13) (Table 1). Samples were collected prior to vaccination and 3 weeks after receiving one dose of COMIRNATY (BioNTech-Pzifer), mRNA-1273 (Moderna), or AZD1222 (AstraZeneca). Twenty-six healthy donors with similar vaccination pattern were recruited. IgG titers against SARS-CoV-2 were quantified by Euroimmun-Anti-SARS-CoV-2 ELISA. Direct cellular cytotoxicity (DCC) was determined against Vero E6 cells infected with pseudotyped SARS-CoV-2, measuring caspase-3 activation after co-culture with PBMCs, in which cytotoxic populations were phenotyped by flow cytometry. Antibody-dependent cellular cytotoxicity (ADCC) analyses were performed using Annexin V on Raji cells as a target.

Results: 1) Early humoral response against COVID-19 vaccination in patients with CML was 5.1- ($p<0.0001$), 2.8- ($p=0.0027$), and 3.2-fold ($p<0.0001$) higher than in patients with

CLL, MM and HSCT, respectively, and 3.5-fold higher than in healthy donors (p=0.0460) (Fig. 1). 84% of CLL patients did not develop detectable IgG titers. Individuals with OHD developed lower titres of neutralizing antibodies than healthy donors. 2) Unspecific ADCC was overall reduced in patients with OHD, mostly in individuals with ASCT (3.2-fold lower (p<0,0001)), whereas ADCC was reduced 2.2- (p<0.0001), 1.8- (p=0.0040), and 2.2-fold (p<0.0001) in individuals with CLL, CML and MM, respectively (Fig. 2A). However, specific DCC was increased 4.7-, 8.1- (p=0.0189), and 2.1-fold, respectively, in PBMCs from patients with CLL, MM, or ASCT, in comparison with healthy donors, whereas patients with CML showed a very similar response than healthy donors (Fig. 2B). 3) Levels of CD3+CD8+TCRγδ+ T cells were increased 2.2-, 2.1-, 2.7-, and 4.3-fold (p=0.0394) in patients with CLL, CML, MM, and ASCT, respectively, in comparison with healthy donors. CD3+CD8-TCRγδ+ T cells were also increased in patients with OHD, expressing high levels of the degranulation marker CD107a. However, the levels of CD3-CD56+CD107a+ NK cells were reduced 4.2- (p=0.0003) and 3.6-fold (p=0.0010) in PBMCs from patients with MM and ASCT, respectively, in comparison with healthy donors.

Conclusions: We found significant differences in the early humoral immune response after one single dose of COVID-19 vaccine depending on the OHD analyzed. It was observed for the first time that the early cytotoxic immune response is efficient in all groups of patients, although superior in those who were not exposed to ASCT. Most cytotoxic activity relied on CD8+ T cells. These data can be useful to determine the efficacy of COVID-19 vaccines in patients with OHD.

Table 1. Patient's clinical characteristics

	CLL (n=14)	CML (n=11)	MM (n=15)	SCT (n=13)
DEMOGRAPHIC CHARACTERISTICS				
Age, median (IQR)	66 (65-76)	62 (56-76)	72 (60-77)	58 (44-66)
Sex: male, n (%)	9 (64.3)	7 (63.6)	9 (60)	8 (61.5)
Days since first dose vaccination, median (IQR)	21 (18-33)	27 (21-28)	23 (18-27)	23 (20-28)
First-line treatment, n (%)	2 (14.28)	9 (81.8)	11 (73.3)	5 (38.5)
Treatment, n (%)	- Active treatment 7 (50) - No treatment 7 (50)	- TIKs discontinuation 5 (45.5) - TKIs 6 (55.5)	- Maintenance treatment after ASCT 9 (60) - Not-ASCT candidates 6 (40)	- Immunosuppresive treatment 6 (46.2) - Non-immunosuppressive treatment 7 (53.8)
BONE MARROW TRANSPLANT PATIENTS				
Type, n (%)	N/A	N/A	Autologous 6 (40)	Allogeneic 13 (100)
Months since transplant, median (IQR)	N/A	N/A	32 (23-60)	36 (21-44)
cGvHd, n (%)	N/A	N/A	N/A	8 (61.5)
VACCINES AND ANALYTICS PARAMETERS				
Vaccine, n (%)				
- AZD1222 (A. Zeneca)	3 (31.4)	3 (28.3)	0	0
- mRNA-1273 (Moderna)	7 (50%)	7 (63.6%)	7 (46.7%)	0
- COMIRNATY (Pfeizer)	4 (28.6%)	1 (9.1%)	8 (53.3%)	13 (100%)
Pre-vaccine, median (IQR) $x10^3$/mL				
- Neutrophils	3.2 (1.6-4.9)	3.4 (2.8-3.9)	2.4 (1.4-2.9)	3 (2.3-4.4)
- Lymphocytes	18 (1-80)	2.6 (2-2.9)	1.7 (1.2-2.4)	2.1 (1.3-2.8)
- Monocytes	0.5 (0.3-0.9)	0.5 (0.4-0.7)	0.5 (0.4-0.7)	0.6 (0.4-0.8)
- Plathelets	115 (91.1-146)	245 (191-344.2)	160 (144-199.4)	201 (122-271)
Post-vaccine, median (IQR) $x10^3$/mL				
- Neutrophils	4 (2-4.9)	4.6 (1.7-4.6)	2.3 (1.7-2.6)	3,2 (2,2-7,2)
- Lymphocytes	18.9 (5.3-112.6)	1.8 (0.1-3.5)	1.7 (1-2.2)	1,7 (0,2-7,4)
- Monocytes	0.9 (0.7-5.3)	0.5 (0.4-0.9)	0.5 (0.4-0.8)	0,6 (0,1-1)
- Plathelets	166 (122.7-255)	199 (134-361)	166.5 (122.2-203.5)	262.5 (195 -477)

IQR, interquartile range; cGvHd, chronic graft-versus-host disease; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MM, multiple myeloma; SCT, stem cell transplant; TKI, tyrosine kinase inhibitors; ASCT, autologous stem cells transplant; N/A, not applicable.

Figure 1. Levels of IgGs against SARS-CoV-2 in the different groups of patients and against healthy donors.

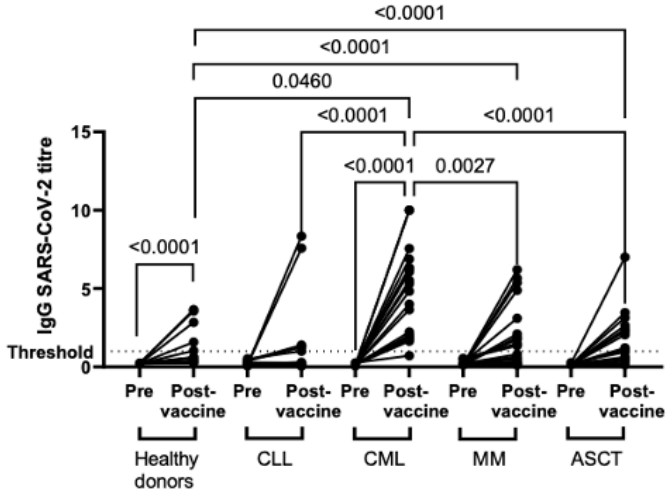
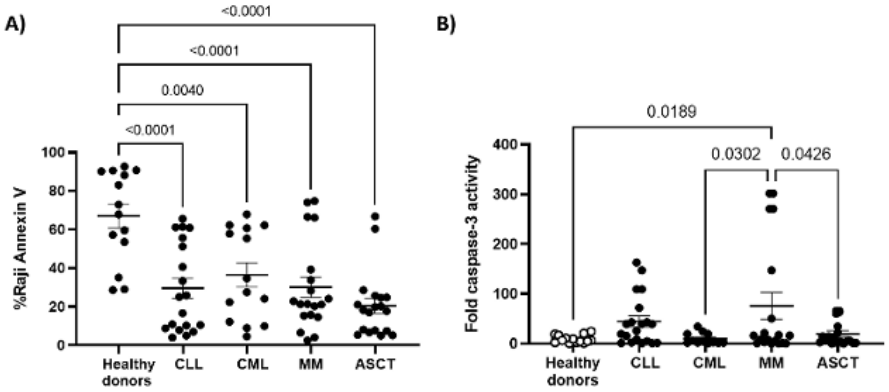


Figure 2. Unspecific ADCC (A) and specific DCC (B) responses in the different groups of patients in comparison with healthy donors.



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