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Antibody responses to SARS-CoV-2 vaccination in patients with acute myeloid leukaemia and high risk MDS on active anti-cancer therapies

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To the editor

Encouraging seroconversion rates to SARS-CoV-2 vaccination in acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS) patients have been reported in large cohort studies[1,2,3,4] ; however, the majority of these patients were not receiving active systemic anti-cancer therapy (SACT) and its impact on vaccine responses remains to be fully elucidated. Mori *et al.*[5] report seroconversion rates of 94.7% and 100% respectively in Japanese patients with AML and MDS after two doses of mRNA SARS-CoV-2 vaccine, of which 39% received SACT. We report SARS-CoV-2 antibody responses following vaccination in a UK cohort of AML and HR-MDS patients all receiving or recently completed SACT and stratify by prior SARS-CoV-2 infection. Demographics, SACT history and laboratory parameters were collected from electronic health records for patients following two doses of SARS-CoV-2 vaccine (BNT162b2 or ChAdOx1nCoV-19) between December 2020 and July 2021. Serological

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjh.18248

testing was performed using Roche Elecsys anti-SARS-CoV-2 enzyme immunoassays. Thirty nine (85% AML, 15% HR-MDS, median age 63 [21-76]), underwent serological testing after receiving two vaccine doses, Table 1. All were tested for anti-S antibodies after two doses (median 40 days post-dose) and 59% after first dose (median 39 days). Thirty-three (85%) underwent testing for anti-N antibodies, identifying 7 (21% of those tested) had previous SARS-CoV-2 infection. Eleven patients (28%) received intensive chemotherapy, 51% venetoclax-combination therapy (with azacitidine, low-dose cytarabine or gilteritinib) and 21% non-intensive azacitidine. Seropositivity rates and antibody titres increased with consecutive vaccine doses, from 74% in all patients (75% AML, 67% MDS) to 95% (94% AML, 100% MDS), with a median anti-S titre of 5.90U/ml [IQR 0.58-56.7] after dose one, rising to 333U/ml [IQR 86.8-1971] post dose two. Significantly higher titres were detected after dose two in AML patients, but not in MDS, though numbers are small (Fig.1B). We report similar seroconversion rates following two doses as seen by Mori *et al* (Fig.1A, Table1), despite all our patients receiving SACT compared to 39% of their cohort; however, we found no difference in anti-S titres between AML and HR-MDS patients receiving SACT after 2 vaccine doses (333IU/ml [IQR 105.9-1896] versus 495.9IU/ml [IQR 82.15-2320], p=0.99). These patterns persisted in patients with no prior SARS-CoV-2 infection and negative anti-N serology (Fig.1C, Table1), although seroconversion rates and median anti-S titres were somewhat reduced. Previous SARS-CoV-2 infection was associated with higher titres after two vaccinations (median 2500U/mL [IQR 141-2500]), consistent with higher post-vaccination antibody titres in healthy individuals with prior natural infection[6,7]. This highlights the importance of measuring antibody titres, as opposed to seropositivity alone, and considering prior SARS-CoV-2 infection to delineate vaccine responses. Mori *et al* reported lower antibody titres after 2 doses in those AML/MDS patients receiving active SACT as treatment or maintenance therapy (majority received HMA) compared to those receiving non-chemotherapeutic treatments or completed treatment[5]. We observe no significant difference in seropositivity or anti-S titres was seen in AML patients receiving intensive (28%) compared to non-intensive chemotherapy (21%); however, anti-S titres were significantly reduced in venetoclax-based regimens (55% AML patients, 33% HR-MDS), median

158.5U/mL [IQR 34.85-873], p=0.04), independent of previous SARS-CoV-2 infection (Figure 1E, 1F). Reduced serological responses in patients receiving venetoclax has been reported in mature B-cell neoplasms and myeloma, but not in AML or MDS[3,8,9]. Further work to define the impact of SACT regimens on the magnitude/duration of humoral and T cell responses to SARS-CoV-2 vaccination will have clear implications for this vulnerable group and should be priority questions for larger studies.

Contributions

JO conceived of the study, performed data collection, data analysis, literature search, and manuscript writing and revision; WC data collection, data analysis, manuscript writing, and revision; CZ performed data collection, manuscript review and revision; EP conceived of study, manuscript review and revision; ES data collection, manuscript review and revision; AF, AK, RG, manuscript review and revision.

Declaration of interest: All authors declare no conflicts of interest.

Acknowledgements

We are extremely grateful to all the patients who participated in this study and to the NHS staff that provided their clinical care. EMP is supported by a CRUK Advanced Clinician Scientist Fellowship (Grant No. A24873). RG acknowledges funding from Cure Cancer@ UCL.

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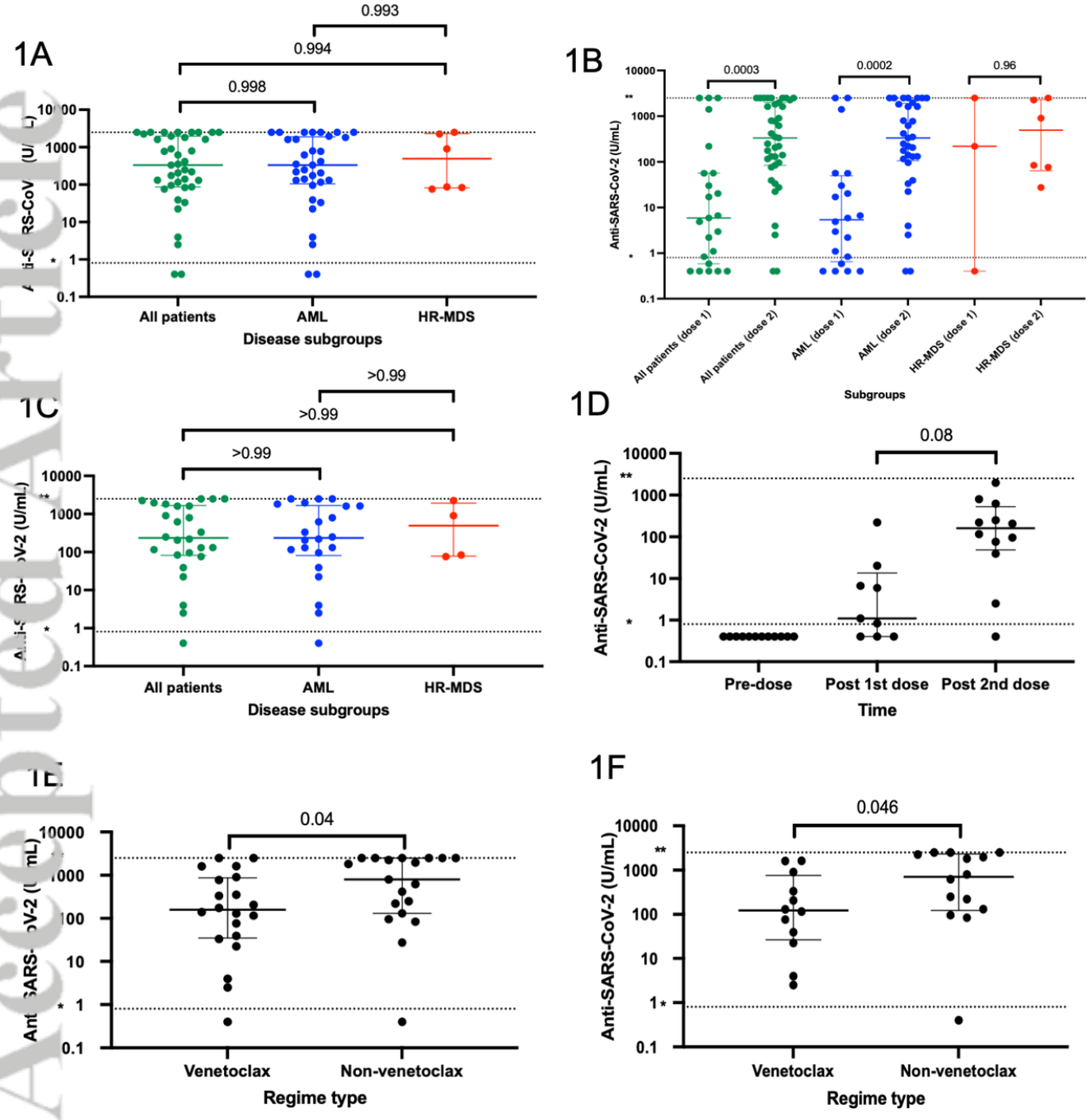
Figure legend

Figure 1: Serological responses in patients with AML and HR-MDS after SARS-CoV-2 vaccination

All figures are presented with a Log10 scale on the y-axis. ***lower limit of assay, **upper limit of assay, HR-MDS High Risk MDS***

1A: Seropositivity for anti-S antibodies in all patients following two doses of SARS-CoV-2 vaccine, categorized by disease subtype . **1B:** Anti-S antibody titres following the first and second vaccine doses by disease category. **1C:** Serological response to two vaccination doses in patients with no previous SARS-CoV-2 infection**. 1D:** Seroconversion rates in patients with no previous SARS-CoV-2 infection, after one and two doses of vaccine (Paired pre dose, post first dose and second dose); in all patients**. 1E:**Serological response following two doses of vaccine in all patients treated with venetoclax-based regimens. **1F:** Serological response following two doses of vaccine in AML/HR-MDS treated with venetoclax-based regimens and no evidence of previous SARS-CoV-2 infection



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The following changes have been made to the revised version of the manuscript from the original submitted manuscript.
New text which has been added has been highlighted in red font. In summary, all data and reference pertaining to acute lymphoblastic leukaemia has been removed and areas of direct comparison (both similarities and differences) with Mori at al's study have been emphasised. The figures and table have been amended to reflect this.

- The correspondence has been shortened from a 1000-word limit to an approximate 500-word limit (560 words).
- All reference to the included Acute Lymphoblastic Leukaemia (ALL) cohort has been removed
- Lines 17-21 of the original manuscript has been moved to lines 13-16 and amended to remove ALL.
- Lines 13-14 in the original manuscript has been moved to line 16-17 and edited to include reference to seroconversion rates in Mori *et al.*
- Lines 21-23 in the original manuscript has been moved to lines 18-20 and edited to remove reference to ALL.
- Line 27 and 29 has been removed
- Line 31 to 38 has changed in percentage references to reflect the change in the cohort due to removal of ALL patients.
- Line 39 to 48 has been removed as it makes comparisons with ALL patients.
- Line 49 has moved to line 35-36.
- Line 50-57 has been summarised in line 37-39 with reference to ALL removed.
- Line 57-61 has been summarised in lines 39-41
- Lines 62-70 has been summarised in lines 46-51 with reference to ALL and ALL-type therapies removed.
- Lines 71-90 has been summarised in lines 51-53.
- Line 77-79 has been moved to line 41-43.

Table 1: Patient demographics, disease and treatment characteristics.

Characteristics	All patients *n=39*	AML *n=33*	HR-MDS *n=6*	Negative baseline *n=26*	Positive baseline *n=7*
Gender (% male)	21 (54)	17 (52)	4 (67)	13 (50)	3 (43)
Median age [range]	63 [21-76]	58 [21-76]	70 [50-76]	60 [21-76]	47 [22-73]
Diagnosis (%):					
AML	33 (85)	33 (100)	-	22 (85)	6 (86)
HR MDS	6 (15)	-	6 (100)	4 (15)	1 (14)
SARS-CoV-2 infection*(%)	7/33 (21)	6/28 (21)	1/5 (20)	-	-
Treatment (%):					
Intensive AML chemotherapy	11 (28)	11 (33)	0 (0)	8 (31)	3 (27)
Venetoclax based regimens	20 (51)	18 (55)	2 (33)	12 (34)	3 (27)
- Ven & Aza	16	14	2	10	2
- Ven & LDAC	2	2	-	1	0
- Ven & Gilt	1	1	-	1	0
- Ven, Gilt & Aza	1	1	-	0	1
Azacitidine therapy	8 (21)	4(12)	4 (67)	6 (23)	1 (10)
Seropositive**, 1 dose (%)	17/23 (74)	15/20 (75)	2/3 (67)	10/13 (77)	6/7 (86)
Seropositive**, 2 doses (%)	37/39 (95)	31/33 (94)	6/6 (100)	25/26 (96)	6/7 (86)
Seroconversion*** post 2 doses (%)	25/26 (96)	21/22 (95)	4/4 (100)	25/26 (96)	-
Vaccine type (%):					
BNT162b2	26 (67)	21 (64)	5 (83)	16 (62)	7 (100)
ChAdOx1 nCoV-19	8 (21)	7 (21)	1 (17)	6 (23)	0 (0)
Unknown	5 (13)	5 (15)	0 (0)	4 (15)	0 (0)
Median time (days) from first dose to serology [range]	39 [24-79]	35 [24-79]	42 [31-68]	31 [24-79]	44 [29-68]
Median time (days) from second dose to serology [range]	40 [13-133]	40 [13-133]	51.5 [29-78]	40 [13-133]	41 [15-72]
Median titres post first dose in all patients U/mL (IQR)	5.90 U/mL (0.58-56.70)	5.395U/mL (0.64-49.85)	220 U/mL (0.4-2500)	5.90 U/mL (0.62-38.35)	1412 U/mL (2.2-2500)
Median titres post first dose in patients with negative baseline U/mL (IQR)	5.90 U/mL (0.62-38.35)	4.43U/mL (0.51-19.50)	130.1U/mL (40.2-220)	-	-
Median titres post second dose in all patients U/mL (IQR)	333 U/mL (86.80-1971)	333 U/mL (105.9-1896)	495.9 U/mL (82.15-2320)	235U/mL (82.15-1670)	2500 U/mL (141-2500)
Median titres post second dose in patients with negative baseline U/mL (IQR)	235U/mL (82.15-1670)	235 U/mL (81.65-1670)	494.6 U/mL (78.25-1921)	-	-

*SARS-CoV-2 infection defined by presence of anti-N (nucleocapsid) antibodies.

**SARS-CoV-2 seropositive defined by presence of anti-S (Spike) antibodies.

***Seroconversion defined by the detection of anti-S antibodies in patients who had previously undetectable anti-S antibodies.

Patients received two doses of SARS-CoV-2 vaccine, with 8 to 12 weeks between doses as per UK vaccination programme. All patients consented for excess serum to be stored and used as part of the "UCL Biobank for Studying Health and Disease – Haematology Project", reference no NC10.13

Definitions: AML, acute myeloid leukaemia; HR-MDS, high risk MDS; Ven, venetoclax; Aza, azacitidine; LDAC, low dose cytarabine; Gilt, gilteritinib