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Antibody Response in Immunocompromised Patients With Hematologic Cancers Who Received a 3-Dose mRNA-1273 Vaccination Schedule for COVID-19

Sabine Haggenburg, MD; Quincy Hofsink, MD; Birgit I. Lissenberg-Witte, PhD; Annoek E. C. Broers, MD, PhD; Jaap A. van Doesum, MD; Rob S. van Binnendijk, PhD; Gerco den Hartog, PhD; Michel S. Bhoekhan, BSc; Nienke J. E. Haverkate, BSc; Judith A. Burger, BSc; Joey H. Bouhuijs, BSc; Gaby P. Smits, MSc; Dorine Wouters, PhD; Ester M. M. van Leeuwen, PhD; Hetty J. Bontkes, PhD; Neeltje A. Kootstra, PhD; Sonja Zweegman, MD, PhD; Arnon P. Kater, MD, PhD; Mirjam H. M. Heemskerk, PhD; Kaz Groen, MD; Tom van Meerten, MD, PhD; Pim G. N. J. Mutsaers, MD; Tim Beaumont, PhD; Marit J. van Gils, PhD; Abraham Goorhuis, MD, PhD; Caroline E. Rutten, MD, PhD; Mette D. Hazenberg, MD, PhD; Inger S. Nijhof, MD, PhD; for the COBRA KAI Study Team

IMPORTANCE It has become common practice to offer immunocompromised patients with hematologic cancers a third COVID-19 vaccination dose, but data substantiating this are scarce.

OBJECTIVE To assess whether a third mRNA-1273 vaccination is associated with increased neutralizing antibody concentrations in immunocompromised patients with hematologic cancers comparable to levels obtained in healthy individuals after the standard 2-dose mRNA-1273 vaccination schedule.

DESIGN, SETTING, AND PARTICIPANTS This prospective observational cohort study was conducted at 4 university hospitals in the Netherlands and included 584 evaluable patients spanning the spectrum of hematologic cancers and 44 randomly selected age-matched adults without malignant or immunodeficient comorbidities.

EXPOSURES One additional mRNA-1273 vaccination 5 months after completion of the standard 2-dose mRNA-1273 vaccination schedule.

MAIN OUTCOMES AND MEASURES Serum immunoglobulin G (IgG) antibodies to spike subunit 1 (S1) antigens prior to and 4 weeks after a third mRNA-1273 vaccination, and antibody neutralization capacity of wild-type, Delta, and Omicron variants in a subgroup of patients.

RESULTS In this cohort of 584 immunocompromised patients with hematologic cancers (mean [SD] age, 60 [11.2] years; 216 [37.0%] women), a third mRNA-1273 vaccination was associated with median S1-IgG concentrations comparable to concentrations obtained by healthy individuals after the 2-dose mRNA-1273 schedule. The rise in S1-IgG concentration after the third vaccination was most pronounced in patients with a recovering immune system, but potent responses were also observed in patients with persistent immunodeficiencies. Specifically, patients with myeloid cancers or multiple myeloma and recipients of autologous or allogeneic hematopoietic cell transplantation (HCT) reached median S1-IgG concentrations similar to those obtained by healthy individuals after a 2-dose schedule. Patients receiving or shortly after completing anti-CD20 therapy, CD19-directed chimeric antigen receptor T-cell therapy recipients, and patients with chronic lymphocytic leukemia receiving ibrutinib were less responsive or unresponsive to the third vaccination. In the 27 patients who received cell therapy between the second and third vaccination, S1 antibodies were preserved, but a third mRNA-1273 vaccination was not associated with significantly enhanced S1-IgG concentrations except for patients with multiple myeloma receiving autologous HCT. A third vaccination was associated with significantly improved neutralization capacity per antibody.

CONCLUSIONS AND RELEVANCE Results of this cohort study support that the primary schedule for immunocompromised patients with hematologic cancers should be supplemented with a delayed third vaccination. Patients with B-cell lymphoma and allogeneic HCT recipients need to be revaccinated after treatment or transplantation.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The COBRA KAI Study Team members are listed in Supplement 2.

Corresponding Author: Mette D. Hazenberg, MD, PhD, Department of Hematology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands (m.d.hazenberg@amsterdamumc.nl).

COVID-19–vaccinated patients with hematologic cancers have demonstrated reduced SARS-CoV-2 seroconversion rates[1-4] and lowered COVID-19 vaccine effectiveness.[5] Reduced vaccine immunogenicity in patients with hematologic cancers is associated with the disease itself and the therapy thereof.[6,7] It has become common practice to offer immunocompromised patients with hematologic cancers a third vaccination to improve SARS-CoV-2 immunity to levels obtained in healthy individuals after the standard 2-dose vaccination schedule,[8] but data substantiating this are lacking.

Key Points

Question Is a third mRNA-1273 vaccination associated with SARS-CoV-2 antibody concentration levels in immunocompromised patients with hematologic cancers similar to levels in healthy adults after the standard 2-dose mRNA-1273 schedule?

Findings In this cohort study that included 584 immunocompromised patients with hematologic cancers, a third mRNA-1273 vaccination was associated with significantly improved SARS-CoV-2 antibody concentrations comparable to those obtained by healthy individuals after the standard 2-dose mRNA-1273 vaccination schedule. The neutralizing capacity of these antibodies against wild-type SARS-CoV-2 virus and variants of concern also improved.

Meaning The primary COVID-19 vaccination schedule for immunocompromised patients with hematologic cancers should be supplemented with a delayed third vaccination.

Methods

Study Patients and Outcomes

Patient characteristics and inclusion and exclusion criteria are described in detail elsewhere.[1] Study protocols were approved by the institutional review board of the Amsterdam UMC and participating centers. All patients provided written informed consent prior to study onset.

Humoral responses against spike glycoprotein (S1) and nucleoprotein (N) of SARS-CoV-2 were quantified before and 28 days after each vaccination.[1,9] Seroconversion was defined as obtaining an S1-IgG concentration greater than 10 binding antibody units (BAU)/mL, and an adequate response as S1-IgG concentration of 300 BAU/mL or greater.[1,10,11] Reference antibody levels were extracted from randomly selected age-matched Dutch citizens (eMethods in Supplement 1).[1] Antibody neutralization was tested using lentiviral-based pseudoviruses expressing SARS-CoV-2 variants[12] in a selection of patients (eTable 1 in Supplement 1).[1,13]

Statistical Analysis

Differences between groups and time points were analyzed with Mann-Whitney *U* and paired sample *t* tests after ^{10}log-transformation, respectively. Pearson correlation was calculated between serum S1-IgG and pseudovirus neutralization after ^{10}log-transformation of both. Two-sided *P* values of <.05 were considered statistically significant. Analyses were performed using the IBM SPSS Statistics for Windows, version 26.0 (IBM Corporation), and R for Windows, version 4.0.3 (The R Foundation for Statistical Computing).

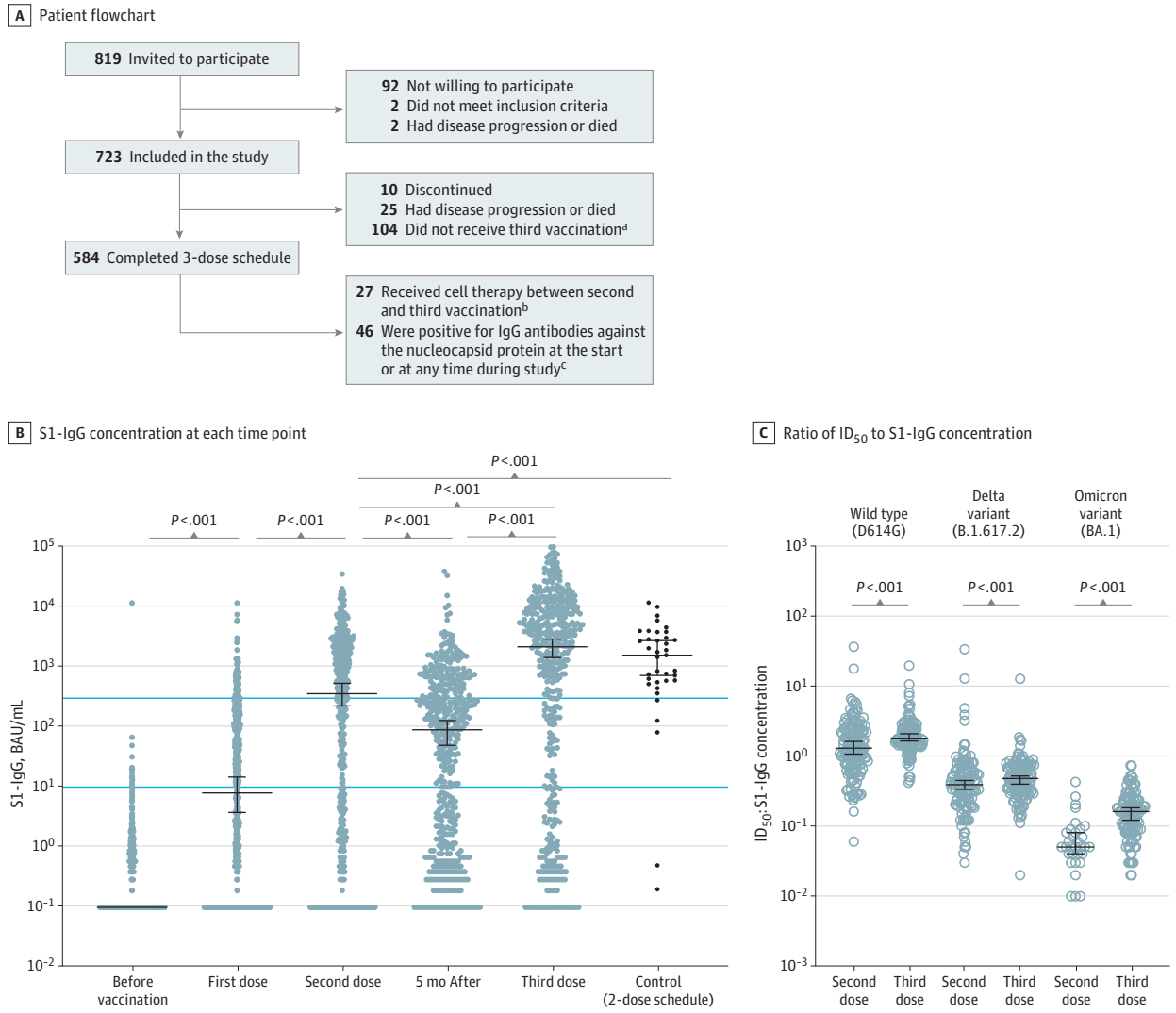
Results

Of 723 study participants, 584 patients received a third dose mRNA-1273, 5 months after completing the standard 2-dose schedule (**Figure 1A**, **Table**). Most of the 104 patients who did not receive a third vaccination deferred because they felt sufficiently protected after 2 mRNA-1273 vaccinations (median S1-IgG 2323 BAU/mL; eTable 2 in Supplement 1). Forty-six patients (7.9%) were excluded from analyses because they had been infected with SARS-CoV-2 (eTable 3 in Supplement 1).

Five months after completion of the standard 2-dose mRNA-1273 schedule, S1-IgG concentrations of evaluable participants had declined significantly to a median of 92.5 BAU/mL, with only 195 of 575 (33.9%) patients maintaining S1-IgG concentration of 300 BAU/mL or greater (Figure 1B). A third mRNA-1273 vaccination was associated with a significant increase in S1-IgG concentration. Seroconversion rates improved from 68.9% (399 of 579) to 78.8% (443 of 562), and 378 of 562 (67.3%) patients obtained S1-IgG concentration of 300 BAU/mL or greater. In 66 of 94 (70.2%) low-responder patients (S1-IgG < 300 BAU/mL), the third vaccination was associated with an S1-IgG concentration of 300 BAU/mL or greater. Median S1-IgG concentration after the third mRNA-1273 vaccination was no longer inferior to the concentration obtained by healthy individuals after the standard 2-dose mRNA-1273 schedule (2171.3 vs 1566.5 BAU/mL; $P = .46$; Table; Figure 1B). Serum S1-IgG concentration correlated significantly with pseudovirus neutralization of SARS-CoV-2 wild-type (D614G; $r = 0.95$; $P < .001$) and variants of concern (Delta [B.1.617.2]: $r = 0.90$; $P < .001$; Omicron [BA.1]: $r = 0.88$; $P < .001$) after the third vaccination (eFigure in Supplement 1). The ratio between pseudovirus neutralization and S1-IgG concentration (a measure of antibody maturation)[14] of wild type and variants of concern per S1-IgG antibody improved significantly after the third vaccination (Figure 1C).

A third mRNA-1273 dose was followed by a significant increase in S1-IgG concentration in all cohorts, with the exception of patients with B-cell non-Hodgkin lymphoma (B-NHL) with ongoing B-cell depletion due to CD20 monoclonal antibody or chimeric antigen receptor (CAR) T-cell therapy, and patients with chronic lymphocytic leukemia (CLL) receiving ibrutinib (**Figure 2**, Table). The few CAR T-cell recipients who did obtain S1-IgG concentration of 300 BAU/mL or greater had low to normal B-cell numbers at the time of the third vaccination. The majority (95 of 112 [84.8%]) of patients who did not seroconvert after the third vaccination (S1-IgG < 10 BAU/mL) had ongoing B-cell depletion (Figure 2B). This included 6 of the 7 allogeneic HCT recipients in whom S1-IgG concentrations remained less than 10 BAU/mL after the third vaccination. No other common denominators to predict responder status after the third vaccination were found. The steepest median increase in S1-IgG concentration was observed in patients with a recovering immune system: 36-fold for patients receiving CD20 antibody therapy less than 12 months prior to the

Figure 1. Included Patients, SARS-CoV-2 Antibody Concentrations, and Antibody Maturation



A, Patient inclusion. B, Spike subunit 1 (S1)-immunoglobulin G (IgG) concentration at each time point for n = 584 evaluable patients. The S1-IgG concentration of age-matched controls measured after the standard 2-dose mRNA-1273 schedule is indicated in black (eMethods in Supplement 1). Blue lines indicate seroconversion (S1-IgG > 10 BAU/mL) and S1-IgG concentration 300 BAU/mL or greater. C, Ratio of ID_{50} to S1-IgG concentration in patients with ID_{50} greater than 20 for SARS-CoV-2 wild type and variants of concern.

[a] Details of patients who did not receive a third vaccination during the time under study are depicted in eTable 2 in Supplement 1.

[b] Details of patients who received cell therapy between the second and third vaccination are depicted in eTable 4 in Supplement 1.

[c] Details of patients who became SARS-CoV-2 infected are depicted in eTable 3 in Supplement 1.

first vaccination, 15-fold for patients with B-NHL who had received autologous HCT less than 12 months prior to the first vaccination, and 49-fold in patients who had received allogeneic HCT less than 6 months before the first vaccination (Figure 2A). This was confirmed in a paired McNemar analysis with S1-IgG concentration less than 300 BAU/mL or 300 BAU/mL or greater as a dichotomous outcome after the second and after the third vaccination (not shown). Significant increases in median S1-IgG concentrations were also observed in patients with ongoing immunodeficiencies, eg, patients with acute myeloid leukemia or myelodysplastic syndrome receiving hypomethylating therapy, patients with myeloproliferative neoplasms receiving ruxolitinib, and patients with chronic graft-vs-host disease using immunosuppressive drugs (Figure 2A). In fact, in 12 of the 16 cohorts, the 3-dose schedule was associated with S1-IgG concentrations similar to or even higher than with the 2-dose mRNA-1273 schedule in healthy individuals (Table).

Twenty-seven patients were analyzed separately because they received cell therapy between completion of the primary 2-dose schedule and the third mRNA-1273 vaccination (eTable 4 in Supplement 1; Figure 2C). The decline in S1-IgG concentration during the 5 months between the second and the third vaccination was comparable to the other cohorts, and all cell therapy recipients maintained S1-IgG antibody concentrations 10 BAU/mL or greater. Patients with multiple myeloma who received an autologous HCT after the second vaccination demonstrated a sig-

Table. Patient Characteristics Stratified by Cohort

Characteristic[a]	No.	Age, mean (SD), y	Sex		Seroconversion, No. (%)[b]		S1-IgG concentration, BAU/mL			
			Women, No. (%)	Men, No. (%)	After second	After third	After second, median	*P* value[c]	After third, median	*P* value[d]
All patients	584	60 (11.2)	216 (37.0)	368 (63.0)	399 (68.9)	443 (78.8)	303.1	<.001	2171.3	.94
Lymphoma										
During aCD20 +/− chemotherapy	40	59 (13.0)	16 (40.0)	24 (60.0)	6 (15.0)	9 (22.5)	0.7	<.001	0.7	<.001
<12 mo After aCD20 +/− chemotherapy	36	62 (11.0)	16 (44.4)	20 (55.6)	14 (40.0)	24 (70.6)	4.2	<.001	292.5	.01
<12 mo After autologous HCT (BEAM)	25	59 (12.0)	9 (36.0)	16 (64.0)	13 (52.0)	14 (58.3)	15.4	<.001	731	.26
Multiple myeloma										
First-line therapy	23	62 (8.0)	9 (39.1)	14 (60.9)	17 (77.3)	20 (95.2)	435.1	.06	411.2	.55
Daratumumab-containing therapy	44	63 (8.0)	17 (38.6)	27 (61.4)	42 (95.5)	43 (97.7)	539.3	<.001	1729	.96
IMiDs	46	60 (8.0)	17 (37.0)	29 (63.0)	41 (89.1)	40 (88.9)	1064.2	.17	3071.8	.17
<9 mo After autologous HCT (HDM)	44	61 (7.0)	12 (27.3)	32 (72.7)	42 (95.5)	43 (97.7)	2457.1	.44	10 589.4	<.001[e]
CLL										
Watch and wait	43	64 (8.0)	19 (44.2)	24 (55.8)	34 (81.0)	34 (85.0)	535.4	.01	3465	.27
Ibrutinib	33	64 (7.0)	12 (36.4)	19 (63.6)	12 (36.4)	18 (54.5)	1.3	<.001	3.9	<.001
CML										
Tyrosine kinase inhibitor	42	54 (14.0)	17 (40.5)	25 (59.5)	42 (100.0)	39 (100.0)	2658.7	.31	7572.1	<.001[e]
AML and high-risk MDS										
Hypomethylating therapy	16	66 (14.0)	3 (18.8)	13 (81.2)	12 (75.0)	14 (93.3)	115.7	<.001	836.3	.16
High-dose chemotherapy	18	52 (15.0)	8 (44.4)	10 (55.6)	16 (94.1)	18 (100.0)	3795.9	.11	11 379.1	<.001[e]
Myeloproliferative disease										
Ruxolitinib	31	58 (11.0)	13 (41.9)	18 (58.1)	30 (96.8)	28 (96.6)	296.2	<.001	1795.9	.73
Allogeneic HCT										
<6 mo After HCT	49	55 (13.0)	19 (38.8)	30 (61.2)	28 (57.1)	39 (84.8)	20.9	<.001	2993.9	.50
Chronic GVHD	51	57 (9.0)	17 (33.3)	34 (66.7)	41 (80.4)	46 (92.0)	1064.6	.04	4830.4	.07
CAR T-cell therapy										
CD19-directed	43	60 (12.0)	12 (27.9)	21 (72.1)	9 (21.4)	14 (35.0)	0.3	<.001	0.5	<.001
Healthy control										
PIENTER cohort[f]	37	57 (10)	25 (68)	12 (32)	35 (94.6)	NA	1566.5	NA	NA	NA

Abbreviations: aCD20, CD20 antibody therapy; AML, acute myeloid leukemia; BEAM: BCNU, etoposide, cytarabine, melphalan; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; GVHD, graft-vs-host disease; HCT, hematopoietic cell transplantation; IMiDs, immunomodulatory imide drugs; MDS, myelodysplastic syndrome; NA, not applicable.

[a] Indicated treatment as per first mRNA-1273 vaccination.

[b] Spike subunit 1 (S1)-immunoglobulin G (IgG) concentration greater than 10 BAU/mL.

[c] Second vaccination vs healthy control.

[d] Third vaccination vs healthy control after second vaccination (see eMethods in Supplement 1 for details).

[e] The S1-IgG concentration after third[f] mRNA-1273 vaccination significantly higher than healthy control values after 2-dose mRNA-1273 vaccination.

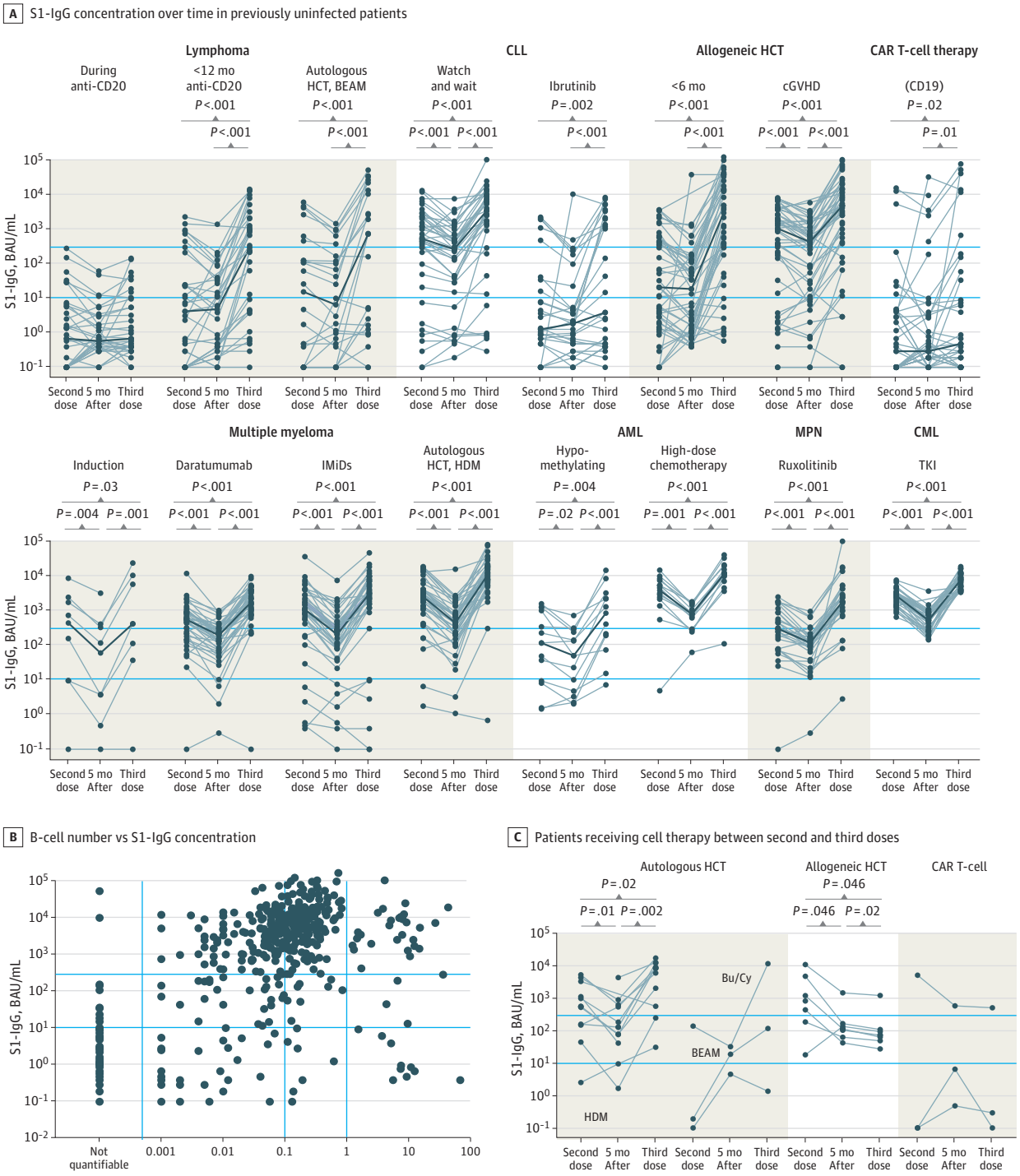
[f] See eMethods in Supplement 1 for details.

nificant increase in S1-IgG concentration after the third vaccination (Figure 2C). A similar S1-IgG dynamic was observed in the 1 patient who received busulfan/cyclophosphamide followed by autologous HCT after the second vaccination as consolidation therapy for acute myeloid leukemia (eTable 4 in Supplement 1). In the few patients with B-NHL who received autologous HCT or CAR T-cell therapy and in patients who received an allogeneic HCT after the second vaccination, S1-IgG concentrations did not increase after the third dose (Figure 2C). With the exception of 1 patient, all new allogeneic HCT recipients had B-cell numbers less than 0.1×10^9/mL and used immunosuppressants (5 patients ≥2 immunosuppressants) at the time of the third dose (eTable 4 in Supplement 1).

Discussion

In this study, we demonstrate that following a third mRNA-1273 vaccination, the majority of immunocompromised patients with hematologic cancers obtained SARS-CoV-2 antibody concentrations similar to healthy individuals after the standard 2-dose mRNA-1273 schedule. Neutralization capacity of SARS-CoV-2 wild

Figure 2. Individual Spike Subunit 1 (S1) Binding Antibody Concentrations and B-Cell Numbers



A, The S1-immunoglobulin G (IgG) concentrations over time of previously uninfected patients. Blue lines indicate thresholds for seroconversion (S1-IgG > 10 BAU/mL) and S1-IgG concentration of 300 BAU/mL; gray lines are individual patients and thick blue lines represent median values for each cohort. Bold lines in HDM and allogeneic HCT panels indicate median values; number of BEAM or Bu/Cy autologous HCT and CAR T-cell recipients was too low for statistical analyses. B, The B-cell number at the time of third vaccination vs S1-IgG concentration 4 weeks after the third vaccination. Blue lines indicate thresholds for seroconversion (S1-IgG > 10 BAU/mL), S1-IgG concentration of 300 BAU/mL, and B-cell detection, and upper and lower limits of normal B-cell numbers. C, Patients who received cell therapy as indicated at any time during the 5 months between the second and the third mRNA-1273 vaccination. See eTable 4 in Supplement 1 for patient details. AML indicates acute myeloid leukemia; BEAM, BCNU, etoposide, cytarabine, melphalan; Bu/Cy, busulfan/cyclophosphamide; CAR, chimeric antigen receptor; cGVHD, chronic graft-vs-host disease; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HCT, hematopoietic cell transplantation; HDM, high-dose melphalan; IMiDs, immunomodulatory imide drugs; MPN, myeloproliferative neoplasm; TKI, tyrosine kinase inhibitor.

type and variants of concern per antibody unit improved significantly after the third vaccination, suggesting antibody maturation over time that was most notable for Omicron.[14]

The additional value of a third vaccination was most pronounced in patients in whom the immune system had to some extent recuperated after receiving the primary 2-dose vaccination schedule. Immune reconstitution did not need to be complete, however, as low numbers of B cells sufficed to produce adequate S1-IgG concentrations.[1] Also in patients with ongoing immunodeficiencies (untreated CLL, patients receiving ruxolitinib or hypomethylating agents), a third mRNA-1273 vaccination often brought antibody concentrations to adequate levels. Only in patients with CLL using ibrutinib[15] and in patients with ongoing B-cell depletion did antibody responses remain low.

Of note, these data demonstrate that autologous and allogeneic HCT did not eliminate pretransplantation-acquired humoral immunity. The number and timing of revaccinations after transplantation may depend on underlying disease, remission-induction therapy, and type of transplantation.

Limitations

This study has limitations. This prospective cohort study started with 723 patients, equally divided over 16 types of hematologic cancers.[1] A total of 139 patients were excluded from the current analysis because they discontinued the study, had progressive disease and/or died, or had deferred a third vaccination, and another 73 patients were analyzed separately because they had COVID-19 or received intercurrent cell therapy (Figure 1A). While these reasons are inherent to the patient group and the pandemic, it reduced the number of evaluable patients considerably.

Conclusions

Results of this cohort study suggest that COVID-19 vaccination in immunocompromised patients with hematologic cancers should be based on a 3-dose mRNA-1273 schedule instead of the standard 2-dose schedule for healthy individuals.

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Author Affiliations: Department of Hematology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (Haggenburg, Hofsink, Bhoekhan, Kater, Rutten, Hazenberg); Amsterdam Institute for Infection and Immunity, Amsterdam UMC, Amsterdam, the Netherlands (Haggenburg, Hofsink, Bhoekhan, Haverkate, van Leeuwen, Kootstra, Hazenberg); Department of Epidemiology and Data Science, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands (Lissenberg-Witte); Department of Hematology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands (Broers, Mutsaers); Department of Hematology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (van Doesum, van Meerten); Centre for Immunology of Infectious Diseases and Vaccines, National Institute for Public Health and the Environment, Bilthoven, the Netherlands (van Binnendijk, den Hartog, Smits); Department of Experimental Immunology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (Haverkate, van Leeuwen, Kootstra); Department of Medical Microbiology and Infection Prevention, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (Burger, Bouhuijs, Beaumont, van Gils); Central Diagnostic Laboratory, Amsterdam UMC, Amsterdam, the Netherlands (Wouters); Laboratory Medical Immunology, Amsterdam UMC, Amsterdam, the Netherlands (Bontkes); Department of Hematology, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands (Zweegman, Groen, Nijhof); Cancer Center Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands (Zweegman, Kater, Hazenberg); Department of Hematology, Leiden UMC, Leiden, the Netherlands (Heemskerk); Department of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands (Goorhuis); Department of Hematopoiesis, Sanquin Research, Amsterdam, the Netherlands (Hazenberg); Department of Internal Medicine-Hematology, St Antonius Hospital, Nieuwegein, the Netherlands (Nijhof).

Author Contributions: Drs Hazenberg and Nijhof had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Haggenburg, Hofsink, Goorhuis, Rutten, Hazenberg, and Nijhof contributed equally.
Concept and design: Lissenberg-Witte, van Doesum, Zweegman, Kater, Heemskerk, Groen, Mutsaers, Goorhuis, Rutten, Hazenberg, Nijhof.
Acquisition, analysis, or interpretation of data: Haggenburg, Hofsink, Lissenberg-Witte, Broers, van Doesum, van Binnendijk, den Hartog, Bhoekhan, Haverkate, Burger, Bouhuijs, Smits, Wouters, van Leeuwen, Bontkes, Kootstra, Kater, Groen, van Meerten, Beaumont, van Gils, Goorhuis, Rutten, Hazenberg, Nijhof.
Drafting of the manuscript: Haggenburg, Hofsink, Lissenberg-Witte, Bouhuijs, Smits, Groen, Goorhuis, Hazenberg, Nijhof.
Critical revision of the manuscript for important intellectual content: Lissenberg-Witte, Broers, van Doesum, van Binnendijk, den Hartog, Bhoekhan, Haverkate, Burger, Wouters, van Leeuwen, Bontkes, Kootstra, Zweegman, Kater, Heemskerk, van Meerten, Mutsaers, Beaumont, van Gils, Goorhuis, Rutten, Hazenberg, Nijhof.
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Supervision: Lissenberg-Witte, Broers, van Doesum, Heemskerk, Beaumont, van Gils, Goorhuis, Hazenberg, Nijhof.

Conflict of Interest Disclosures: Dr Zweegman reported other from Janssen (research funding, participation in advisory board), Takeda (research funding, participation in advisory board), Sanofi (participation in advisory board), Bristol Myers Squibb (BMS) (participation in advisory board), and Oncopeptides (participation in advisory board) outside the submitted work. Dr Kater reported grants and participation in advisory boards from Janssen, AbbVie, Roche/Genentech, and BMS outside the submitted work; in addition, Dr Kater had a patent for Janssen pending and a patent for LAVA issued. Dr van Meerten reported research grants from Genentech, Celgene/BMS; personal fees from Kite/Gilead and Janssen (advisory boards); and honoraria from Celgene/BMS outside the submitted work. Dr Nijhof reported education from Janssen and BMS/Celgene outside the submitted work. No other disclosures were reported.

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