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SHORT REPORT

Infectious Causes of Cancer

Treatment of chronic COVID-19 with convalescent/postvaccination plasma in patients with hematologic malignancies

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Abstract

Immunocompromised patients are at high risk to fail clearance of SARS-CoV-2. Prolonged COVID-19 constitutes a health risk and a management problem as cancer treatments often have to be disrupted. As SARS-CoV-2 evolves, new variants of concern have emerged that evade available monoclonal antibodies. Moreover, antiviral therapy promotes SARS-CoV-2 escape mutations, particularly in immunocompromised patients. These patients frequently suffer from prolonged infection. No successful treatment has been established for persistent COVID-19 infection. Here, we report on a series of 21 immunocompromised patients with COVID-19—most of them hematologic malignancies—treated with plasma obtained from recently convalescent or vaccinated donors or a combination thereof. Repeated dosing of SARS-CoV-2-antibody-containing plasma could clear SARS-CoV-2 infection in 16 out of 21 immunocompromised patients even if COVID-19-specific treatments failed to induce sustained viral clearance or to improve clinical course of SARS-CoV-2 infection. Ten patients were major responders defined as an increase delta(*d*)*Ct* of > = 5 after the first administration of convalescent and/or vaccinated plasma (C/VP). On average, SARS-CoV-2 PCR *Ct* values increased from a median value of 22.55 (IQR = 19.10–24.25) to a median value of 29.57 (IQR = 27.55–34.63; p = <.0001) in the major response subgroup. Furthermore, when treated a second time with C/VP, even 4 out of 5 of the initial nonresponders showed an increase in *Ct*-values from a median value of 23.13 (IQR = 17.75–28.05) to a median value of 32.79 (IQR = 31.75–33.75; p = .013). Our results suggest that C/VP could be a feasible treatment of COVID-19 infection in patients with hematologic malignancies who did not respond to antiviral treatment.

KEYWORDS
COVID-19, prolonged SARS-CoV-2 infection, SARS-CoV-2-antibody containing plasma

What's New?

Hematologic cancer patients still have a high risk of prolonged infection and death from COVID-19. So far, no definitive treatment has been established in this vulnerable patient group. Here, the authors report on a series of 21 immunocompromised patients with COVID-19, most of them with hematologic malignancies, treated with plasma obtained from convalescent or vaccinated donors. The plasma retained activity against SARS-CoV-2 variants that had rendered monoclonal therapies ineffective, with plasma administration constituting a safe and feasible treatment. Virus clearance may allow to continue cancer therapy and decrease risk of infection to staff.

1 | INTRODUCTION

COVID-19 remains a life-threatening disease in immunocompromised patients. A recent review for patients with hematological malignancies indicated a mortality of 34%.[1] Patients with hematological malignancies and especially those with impaired humoral immune response are at risk for viral rebound, and chronic infection.[2] The vast majority of immunocompetent patients (83%) achieve viral clearance within 28 days (median of 7–12 days).[3,4] Numerous studies investigating patients with B-cell malignancies and patients receiving B-cell-depleting therapies highlighted the importance of humoral responses for long-term viral clearance.[2,5–12] A recent study in 368 individuals observed B-cell as well as CD19-directed therapy as basic risk factors for prolonged PCR positivity, and re-hospitalization.[13] Hematological cancer patients with chronic COVID-19 are at risk for subsequent worsening of the underlying disease and often cannot safely undergo treatment for the underlying disease. In addition, CD4-cells appear to be crucial besides B-cells in promoting long-term viral clearance.[14] With the prolonged persistence of virus comes the risk of viral evolution.[2] Persistent SARS-CoV-2 replication also poses a risk for staff, family members, and other patients. With the reduction in COVID-19 restrictions, chronic COVID-19 defined as viral shedding for more than 4 weeks particularly in cancer patients, is an increasing problem that is going to persist with SARS-CoV-2 as an endemic infection.

Unfortunately, no definitive treatment has been established for persistent COVID-19 infection.[2] Because of a lack of randomized controlled trials concerning antivirals in immunocompromised patients, recommendations for treatment management are currently drawn from data obtained for the general population. The antivirals molnupiravir, nirmatrelvir/ritonavir, and remdesivir, as well as monoclonal antibodies, have been implemented in immunocompromised patients. Remdesivir was studied in patients who were at high risk of progressing to severe disease, and it was shown to be highly effective in reducing the risk of hospitalization and death.[15] However, this trial only included a small number of participants who were immunocompromised. Current consensus guidelines recommend nirmatrelvir/ritonavir in hematologic patients.[16] The EPICOVIDEHA trial compared epidemiology and outcome of patients with hematologic malignancies receiving nirmatrelvir/ritonavir with those who did not.[17] The mortality rate in patients treated with nirmatrelvir/ritonavir was lower than in patients with targeted drugs other than nirmatrelvir/ritonavir. In this retrospective analysis, patients with extrapulmonary symptoms at COVID-19 onset and a second vaccine dose are more prone to receive nirmatrelvir/ritonavir as opposed to those with chronic pulmonary disease and obesity. The EPIC-HR trial showed that the use of ritonavir-boosted nirmatrelvir reduced the risk of hospitalization or death when compared with placebo in patients who had a high risk of progressing to severe COVID-19.[18] As the trial did not enroll many participants who were immunocompromised the efficacy of ritonavir-boosted nirmatrelvir was not established for this population. Another retrospective study from Israel analyzed factors associated with mortality in high-risk patients with COVID-19 after receiving nirmatrelvir/ritonavir. Immunosuppressed patients showed increased mortality, adjusted by different comorbidities. However, the authors did not differentiate hematologic malignancies from other reasons for immunosuppression.[19] Current antivirals often fail to eradicate SARS-CoV-2 in these patients. The commercially available monoclonal antibodies are specific for certain variants. Recently, our own randomized clinical trial[20] and a retrospective analysis[21] demonstrated that patients with solid tumors and hematological malignancies with acute, severe COVID-19 can benefit from therapy with convalescent/post-vaccination plasma (C/VP). A systematic review and meta-analysis including three randomized clinical trials, five matched cohort studies, and 138 case series showed an association between use of convalescent plasma and mortality benefit in immunocompromised patients.[22] Within another clinical trial, greatest benefit was observed in patients with low pre-existing anti-SARS-CoV-2 antibody function and associated with a shift toward enhanced nucleocapsid (*N*) humoral responses.[23] Another recent case series also reports clinical benefit associated with transfusion of plasma obtained from vaccinated and convalescent donors in 31 consecutive immunocompromised patients.[24] Although inducing a transient improvement in symptomatology, all COVID-19-specific treatments failed to sustainably improve the clinical course of COVID-19. The optimal timing, frequency, and schedule of plasma administration has yet to be determined. Also, recent trials elucidated the advantages of a combination therapy strategy comprising antivirals and monoclonals or antivirals and CCP in immunocompromised patients.[25–28] Considering the progressive loss of efficacy of monoclonal antibodies, promising regimen options are reserved to combinations of small molecule antivirals and C/VP. Here, we report on a series of C/VP-treated patients with persistent SARS-CoV-2 infection or high-risk for persistent SARS-CoV-2 infection.

2 | METHODS

2.1 | Study population

Inclusion criteria for offering the individual treatments were that the patient was suffering from a life-threatening infection and that there was no other approved treatment available anymore. In total, we consecutively treated 21 patients (for patient characteristics see Table 1), 18 patients with hematologic malignancies, one patient following solid organ transplant, one patient with common variable immunodeficiency disease, and one patient with cardiovascular risk factors between December 2020 and December 2022. Among the hematologic patients, 13 (62%) suffered from B-cell disorders or received B-cell depleting therapy (Figure 1A). We included patients with alpha, delta, and omicron variants, including the omicron variants BA.1, BA.2, and BA.5, depending on the respective phase of the pandemic (Figure 1B). Therapies against SARS-CoV-2 infection before plasma treatment included antivirals and monoclonal antibodies, which $n = 12$ patients received either simultaneously ($n = 2$) or at least 14 days beforehand ($n = 10$). Furthermore, most patients suffered from prolonged virus clearance, which was defined as PCR positivity for > = 28 days according to prior studies showing most patients become PCR negative within 28 days of infection.[3]

2.2 | C/VP treatment and assessment of response

In total, 64 C/VP from $n = 15$ donors were transfused. Patients received at least one unit of AB0-compatible plasma, 238–337 mL each, intravenously in addition to standard of care. Clinical aim of the therapy was to achieve persistent clearance of SARS-CoV-2 and/or an increase in the Ct-value to > 30 which indicates low likelihood of infectious virus and allowed regular patient care. Response was assessed two to 4 days post plasma infusion. Since several patients required more than one cycle of C/VP treatment we graded the response to the first bag of C/VP.[29] Major response was defined as an increase delta(*d*)Ct after first C/VP application of >/= 5. A minor response required a *dCt* between >/= 2 and <5. Nonresponders were patients with *dCt* value <2 (Table 1). Within the major responders, the initial C/VP was CP in 3 cases (30%), VP in one case (10%), and CVP in 6 cases (60%). Similarly, 14 out of 21 patients received CVP for the first plasma treatment (66%).

2.3 | Plasma manufacturing

C/VP was obtained from healthy donors either after confirmed recent SARS-CoV-2 infection or after mRNA-vaccination or a combination thereof at the IKTZ Heidelberg, Heidelberg, Germany as previously described.[20] To determine antibody titers in plasma a live-virus neutralization assay was performed as previously described[30] or a quantitative ELISA (QuatiVac, Euroimmun, Lübeck, Germany). In brief, for the live-virus neutralization assay virus stocks were produced by either amplification of the BavPat1/2020 strain (European Virus Archive) or isolation and amplification of the B.1.617.2 (delta) and the B.1.1.529 (omicron) variants from nasopharyngeal and oropharyngeal swabs of PCR-confirmed SARS-CoV-2 positive patients. BavPat1/2020 and B.1.617.2 (delta) variant were amplified in VeroE6 cells and virus titers of stocks were determined by plaque assay and Tissue Culture Infectious Dose (TCID) 50 assay in VeroE6 cells. Viral loads were semi-quantitatively assessed by nasopharyngeal swabs in our center following the respective SOP.

3 | RESULTS

3.1 | Highest titers of neutralizing antibodies were observed in plasma from vaccinated and recently convalescent donors

Initially, we used plasma from convalescent donors. But higher titers of neutralizing antibodies in the first donations from vaccinated and convalescent donors with a median of 1:640 ($n = 7$, range 1:320–1:2560) compared to plasma donations from convalescent donors ($n = 10$, median = 1:60, range 1:40–1:320; $p = .006$, Figure 1C and Reference [20]) led us to switch to plasma from convalescent and vaccinated donors. However, a tendency to higher titers was also observed for vaccinated donors ($n = 5$, median = 1:80, range 1:80–1:320) compared to convalescent donors ($p = .163$). As we aimed to make use of advantages of both types, we prioritized plasma from vaccinated and recently convalescent donors. No specific adverse events or side effects were observed. Nevertheless, when comparing change in viral load, no difference between vaccinated (and convalescent) and convalescent-only plasma was observed ($p = .52$, Figure 1C).

3.2 | Study population—response groups

The distribution of sex and age was equal in non- and major responders (Figure 1D). Also, underlying diseases were equally distributed in all three groups (Figure 1A). The cohort of major responders showed a shorter time interval from PCR positivity to C/VP treatment (mean = 19 days) when compared to minor responders (mean = 62 days, $p = .043$, Figure 1D). Compared to non-responders, the major responders showed a tendency to a shorter time interval from PCR positivity to C/VP treatment ($p = .058$, Figure 1D).

The major responders ($n = 10$) were at median 59 years of age, showed a median time for SARS-CoV-2 PCR positivity for 18 days (mean = 19 days), and cleared with the virus within a median time of 25 days following first administration of plasma in eight out of 10 cases. Two patients died and could not be assessed for eventual virus clearance. Within the collective of major responders, five patients have been critically ill and administered to an ICU. Only one

TABLE 1 Patient characteristics and SARS-CoV-2 determinants.

ID	Age	Sex	Main diagnosis	Variant	Previous B-cell-depleting agents	Symptoms	Critically ill	Anti-spike mAbs or small molecule antivirals	Positive (days)	C/VP's until PCR negativity	Days until clearance	Response
20	44	m	Burkitt's lymphoma	BA.5	Rituximab, obinutuzumab	Fever	No	Remdesevir[a]	36	2	NA	No
18	75	m	AML, allo SCT	BA.2	None	Fever, coughing, fatigue	No	Nirmatrelvir/ritonavir[b]	38	2 × 3, 1 × 2	160	No
19	53	m	AML, allo SCT	BA.5	None	None	No	Nirmatrelvir/ritonavir	11	2	NA	No
11	39	m	DLBCL	B.1.1.529	Rituximab	None	No	Sotrovimab	47	2	26	No
26	66	w	Follicular B-cell lymphoma	B.1.617.2	Unknown	ARDS, multiorgan dysfunction	Yes	No	63	Death	NA	No
7	45	f	B-ALL	Unknown	Blinatumomab	Fatigue	Yes	No	56	2	3	Minor
1	63	f	follicular B-cell lymphoma	B.1.160	Obinutuzumab	Gastrointestinal, colitis	No	No	180	3	29	Minor
16	26	m	Histiocyte-rich T-cell lymphoma	BA.1	Tafasitamab	Pneumonia, fever, sepsis	Yes	No	31	1	60	Minor
15	52	f	AML	BA.2	None	Pneumonia	No	Nirmatrelvir/ritonavir	35	2	19	Minor
3	66	f	Multiple myeloma	B.1.617.2	Daratumumab	Fatigue	No	No	42	1	2	Minor
21	46	f	MDS, allogeneic SCT	BA.5	Rituximab	Respiratory distress, pneumonia	Yes	2× nirmatrelvir/ritonavir	28	1	Unknown	Minor
2	78	m	Renal transplant recipient	B.1.1.7	No	Fatigue	Yes	No	51	2	31	Major
8	60	m	Mantle cell lymphoma	B.1.1.529	Rituximab	Pneumonia	Yes	Remdesevir and sotrovimab	21	4	21	Major
28	64	m	Pulmonary fibrosis	Unknown	None	ARDS, fibrotic interstitial pneumonia with alveolar damage	Yes	No	2	Death (1 × 2)	NA	Major
9	58	m	DLBCL	B.1.1.529	Rituximab	None	No	No	41	2	180	Major
24	65	m	CMML, allogeneic SCT	B.1.1.529	None	Pneumonia, bad overall condition	No	Remdesevir and sotrovimab	30	Death	NA	Major
4	8	f	Pre-B-ALL	Unknown	Blinatumomab	Respiratory distress, pneumonia	Yes	Casivirimab/imdevimab	16	1	30	Major
17	34	m	AML	Unknown	None	Fever, throat pain, rhinitis	No	Nirmatrelvir/ritonavir and sotrovimab	7	1	17	Major
5	56	m	Multiple myeloma	BA.1	High-dose chemotherapy	None	No	Remdesevir and sotrovimab	16	1	3	Major
25	60	m	CVID	Unknown	none	Respiratory distress	Yes	Remdesevir, simultaneously	3	1 × 2	16	Major
6	7	m	Allogeneic SCT following myeloablation, pre-ALL	Unknown	Rituximab	Rhinitis	No	Casivirimab/imdevimab	1	7 × 2	176	Major

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; CVID, common variable immunodeficiency; DLBCL, diffuse large B cell lymphoma; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; NA, not applicable; SCT, stem cell transplant.
[a]Remdesivir was applicated for 3 days: 200 mg on day 1 and 100 mg on day 2 and day 3.
[b]Nirmatrelvir/ritonavir was prescribed for 5 days.

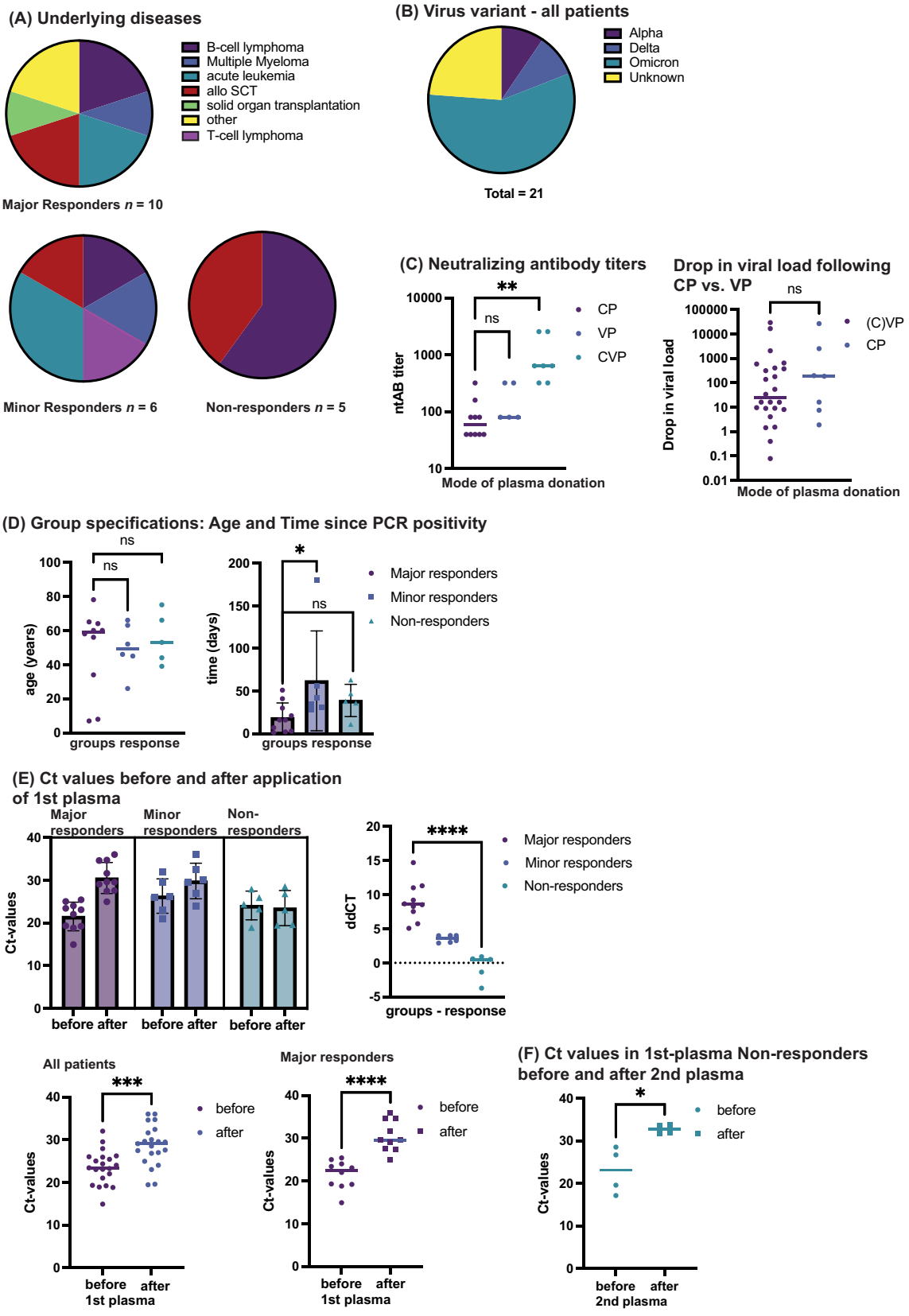

FIGURE 1 Legend on next page.

patient received nirmatrelvir/ritonavir before being treated with C/VP (10%). The patients with minor response ($n = 6$) were at median 49 years of age, showed a median time for SARS-CoV-2 PCR positivity for 38 days (mean = 62 days), and cleared with the virus within a median time of 19 days following first administration of plasma in all cases. Two patients received nirmatrelvir/ritonavir before being treated with C/VP (33%). The non-responders ($n = 5$) were at median 53 years of age, showed a median time for SARS-CoV-2 PCR positivity for 38 days (mean = 39 days), and experienced full virus clearance within 26 and 160 days following first administration of plasma in only two out of 5 cases. Three patients within the group of non-responders were lost to follow-up. Two patients received nirmatrelvir/ritonavir before being treated with C/VP (40%). In total, 16 out of 21 patients cleared with SARS-CoV-2, three died and two were lost to follow-up.

3.3 | Response following administration of C/VP

After the first administration of C/VP, we observed a rise in SARS-CoV-2 PCR Ct-values (within 2–4 days) from a median value of 23.40 (IQR = 20.15–25.96) to a median value of 29.07 (IQR = 25.88–32.02; $p = .0005$, Figure 1E). In the subgroup of major responders, the SARS-CoV-2 PCR Ct values increased from a median value of 22.55 (IQR = 19.10–24.25) to a median value of 29.57 (IQR = 27.55–34.63; $p = <.0001$, Figure 1E). SARS-CoV-2 antibody titers in C/VP administered to patients belonging to each of the three defined response groups were approximately equal. Nonetheless, when treated a second time with C/VP, 4 out of 5 of the initial non-responders responded with an increase in *Ct*-values from a median value of 23.13 (IQR = 17.75–28.05) to a median value of 32.79 (IQR = 31.75–33.75; $p = .013$, Figure 1F).

3.4 | Repetitive treatment with C/VP might cure chronic SARS-CoV-2 infection

We repeatedly treated 11 out of 19 patients with C/VP who did not show full clearance of SARS-CoV-2 virus after the first C/VP. The remaining eight patients either improved clinically or/and showed a rise in *Ct*-values >30 ($n = 3$), were lost to follow-up ($n = 2$), or died from COVID-19 pneumonia ($n = 3$). We repeatedly treated two patients in whom virus clearance was prolonged for more than 100 days. As Focosi et al. suggested it would be reasonable to repeat the treatments once a week in these patients.[31] These patients received two units of C/VP every 2–4 weeks until clearance of SARS-CoV-2 (Table 1). Up to 8 plasma bags were administered per patient. For one patient (Figure 2A) suffering from mantle cell lymphoma with interruption of therapy over 3 weeks, we observed virus clearance following 4 administrations of C/VP (Figure 2A). Interestingly, sequencing results revealed that the patient was infected with the omicron variant BA.1,[32] while initial C/VP was obtained from a post-vaccination donor convalescent from infection with the delta variant. Eventually, the patient died due to refractory lymphoma shortly after achieving virus clearance.

3.5 | C/VP is equally effective in SARS-CoV-2 omicron sub-variants

As the SARS-CoV-2 omicron (sub)variants are the ones of current concern, we also performed analyses on these patients. Twelve out of 21 patients included in the present study were infected with SARS-CoV-2 omicron (sub)variants. In both groups, the rise in Ct-values post-C/VP administration were similarly significant. In patients with an omicron variant, the SARS-CoV-2 PCR Ct values increased from a

FIGURE 1 Patient characteristics and determinants of response to C/VP treatment. (A) Distribution of underlying diseases in the three response groups indicated by color code. (B) Distribution of SARS-CoV-2 variants within the overall patient cohort ($n = 21$). (C) Left: SARS-CoV-2 neutralizing antibody titers (ntAB) per plasma donation transfused to the first 8 patients treated. A live-virus neutralization assay was performed as previously described.[30] The ntAB in C/VP from convalescent donors (CP, $n = 10$, median = 1:60, range = 1:40–1:320) was compared with plasma from vaccinated donors (VP, $n = 5$, median = 1:80, range = 1:80–1:320) and plasma from convalescent and vaccinated donors (CVP, $n = 7$, median 1:640 range 1:320–1:2560). Statistical significance was assessed using a two-tailed Student's unpaired *t*-test. $^{**}p = .006$. Right: Fold-changes in viral load following first and second transfusions of C/VP in all patients from vaccinated ($n = 24$, median = 24.80, IQR = 8.22–396.43) and convalescent donors ($n = 7$, median = 186.11, IQR = 7.46–2521.28). Statistical significance was assessed using a two-tailed Student's unpaired *t*-test, $p = .516$. (D) Left: Age distributions in the three response groups. Median age in major responders: 59 years; median age in minor responders: 49 years; median age in non-responders: 53 years. Right: Time from disease onset (first detected PCR-positivity) until first C/VP transfusion in days. The cohort of major responders showed a shorter time interval from PCR positivity to C/VP treatment (mean = 19 days) when compared to minor responders (mean = 62 days). Compared to non-responders (mean = 39 days) the group of major responders showed a tendency to a shorter time interval from PCR positivity to C/VP treatment. Statistical significance was assessed using a two-tailed Student's unpaired *t*-test. $^{*}p = <.043$ (E) Upper left: *Ct*-values before and after first transfusion of plasma. Upper right: delta*Ct* after first transfusion of C/VP according to the defined response groups (major response: *dCt* >5, median 8.60, minor response: *dCT* between >2 and < =5, median 3.62, nonresponse: *dCt* <2, median = 0.52). Statistical significance was assessed using a two-tailed Student's unpaired *t*-test. $^{****}p = <.0001$. Lower left: *Ct*-values before (median = 23.40, IQR = 20.15–25.96) and after (median = 29.07, IQR = 25.88–32.02) first C/VP transfusion in all patients. Statistical significance was assessed using a two-tailed Student's paired *t*-test $^{***}p = .0005$. Lower right: *Ct*-values before (median = 22.55, IQR = 19.10–24.25) and after (median = 29.57, IQR = 27.55–34.63) first C/VP transfusion in major responders. Statistical significance was assessed using a two-tailed Student's paired *t*-test. $^{****}p = <.0001$. (F) *Ct*-values in nonresponders before (median = 23.13, IQR = 17.75–28.05) and after (median = 32.79, IQR = 31.75–33.75) second C/VP transfusion. Statistical significance was assessed using a two-tailed Student's paired *t*-test. $^{*}p = .013$.

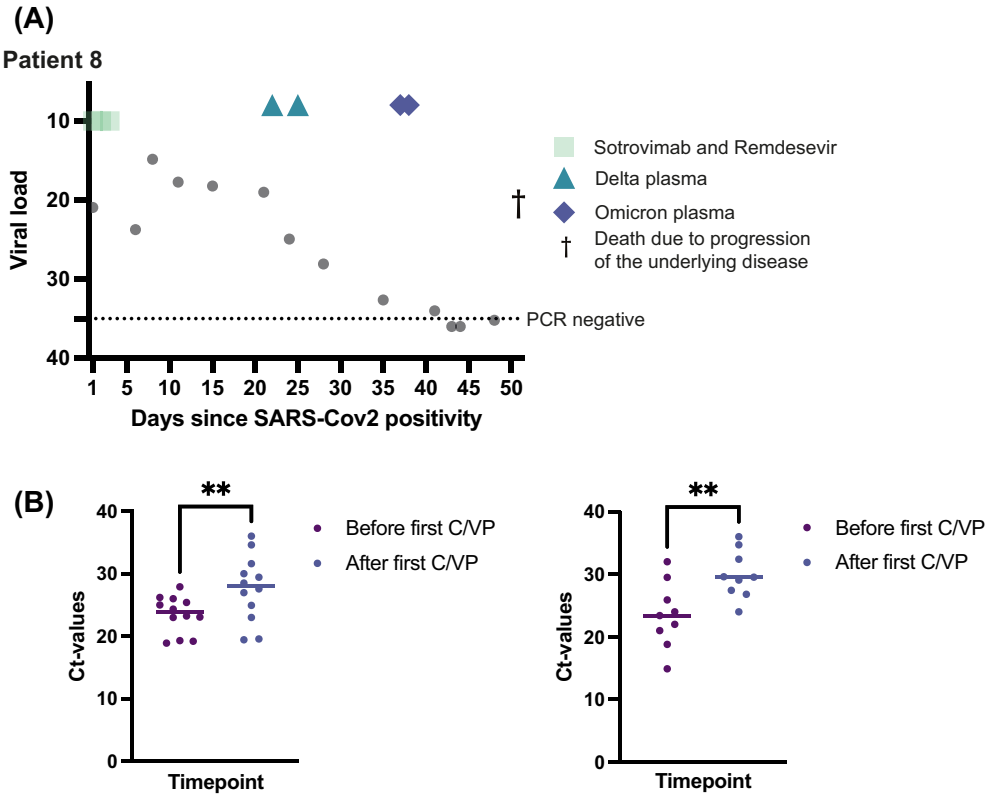

FIGURE 2 Determinants of response to C/VP in omicron variants. (A) Course of treatment of a patient (8) suffering from mantle cell lymphoma with interruption of therapy over 3 weeks due to SARS-CoV-2 infection. Virus clearance was observed following 4 administrations of CVP. Sequencing results revealed that the patient was infected with the omicron variant BA.1, while initial CVP was obtained from a post-vaccination donor convalescent from infection with the delta variant. In total, the patient received two times plasma from a vaccinated donor convalescent of the delta variant and two times plasma from a vaccinated donor convalescent of the omicron variant. The patient died due to refractory lymphoma shortly after achieving virus clearance. (B) Left: *Ct*-values before (median = 23.81, IQR = 20.23–25.85) and after (median = 28.04, IQR = 23.49–31.22) first C/VP transfusion in all patients tested positive for the SARS-CoV-2 omicron variant. Two-tailed Student's paired *t*-test $^{**}p = .0090$. Right: *Ct*-values before (median = 23.40, IQR = 19.90–27.71) and after (median = 29.54, IQR = 27.14–33.55) first C/VP transfusion in all patients tested positive for SARS-CoV-2 variants other than the omicron variant. Two-tailed Student's paired *t*-test $^{**}p = .0026$. C/VP, convalescent/post-vaccination plasma; CVP, convalescent and post-vaccination plasma.

median value of 23.81 (IQR = 20.23–25.85) to a median value of 28.04 (IQR = 23.49–31.22; $p = .0090$, Figure 2B). In patients with any other than an omicron variant, the SARS-CoV-2 PCR *Ct* values increased from a median value of 23.40 (IQR = 19.90–27.71) to a median value of 29.54 (IQR = 27.14–33.55; $p = .0026$, Figure 2B).

4 | DISCUSSION

Recent studies investigated combination therapy strategies in immunocompromised patients. Gentile and colleagues treated 11 patients with 10 days of intravenous remdesivir plus 5 days of nirmatelvir/ritonavir and observed 100% viral clearance.[26] Out of the 11 patients, 7 were in an early phase and 4 patients were in a late phase of COVID-19. The latter experienced significantly higher disease severity. Mikulska et al. investigated a triple combination therapy regiment with 2 antivirals alone or combined with monoclonal antibodies in 22 immunocompromised patients.[27] Eighteen out of the 22 patients suffered from a hematologic malignancy. Four patients of the total collective received antivirals only. Day 14 and 30 response rates were significantly higher when combination therapy included mAbs. Similarly, in a recent review it was reported that combinations of either small molecule antivirals or small molecule antiviral plus passive immunotherapies are safe and effective in small cohorts reported so far.[28] The authors concluded that in light of the progressive loss of efficacy of all authorized anti-spike monoclonal antibodies, promising regimen options are reserved to combinations of small molecule antivirals and COVID-19 convalescent plasma from vaccinated donors. In our patient cohort, some have been treated sequentially with antivirals and C/VP. Three out of 21 patients have been pretreated with a combination of one antiviral and a monoclonal antibody without achieving viral clearance before receiving C/VP. A promising option for immunocompromised patients might be to combine antivirals with C/VP which should be investigated in future trials.

Limitations of the current study are the non-systematic selection of the patients and the lack of a control group. Overall, this study

suggests succesful treatment by C/VP of chronic COVID-19. Although the patients within the present study were pretreated, 16 out of 21 cleared of the virus following plasma treatment. With the lack of a control group, we are not able to determine if these patients might have cleared of the virus by themselves without having received plasma. At least in most patients, we observed a rise in *Ct*-values and clinical improvement.

In conclusion, patients with hematological malignancies who received C/VP were cured of chronic SARS-CoV-2 infection. Administration of plasma with high titers of neutralizing SARS-CoV-2 antibodies is safe and can facilitate clearance of infection in patients with hematological malignancies. Thus, C/VP obtained ideally from recently convalescent and/or vaccinated donors might constitute an effective therapy in chronic SARS-CoV-2 infection in immunocompromised patients. In the setting of long-term virus persistence, repeated treatment cycles with change of donor might be necessary. Virus clearance allows to continuation cancer therapy and decreases risk of infection for staff and household members of patients.

AUTHOR CONTRIBUTIONS

MJ, RFS, CMD, and CMT designed the study and wrote the manuscript; PD and MS co-supervised the study and wrote the manuscript; MJ and CMT analyzed the data; JB, SS participated in patient recruitment and edited the manuscript; AL, CW, MSt produced and provided plasma, wrote a standard operating procedure on plasma production and wrote the manuscript; MB performed experiments. The work reported in the paper has been performed by the authors unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

CMT reports potential conflict of interests as follows: research funding from Pfizer, Bioline RX, and BMBF. RFS is a member of the advisory boards of Daiichi Sankyo, Pfizer, Astellas, and Novartis. RFS received research funding from PharmaMar, Astra Zeneca, Pfizer, Roche, Boehringer Ingelheim, Daiichi Sankyo. RFS received travel accommodations from Daiichi Sankyo. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

All data supporting the findings will be available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The individual treatments were approved by the Regierungspräsidium Karlsruhe and performed in accordance with all regulatory guidelines. The study was performed in accordance with the Declaration of Helsinki. Informed consent for the individual treatments was obtained from all participants.

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