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LETTER TO THE EDITOR

Successful early treatment combining remdesivir with high-titer convalescent plasma among COVID-19-infected hematological patients

1 | INTRODUCTION

Immunocompromised patients with hematological malignancies are at high risk for a severe course of COVID-19 (Coronavirus Disease 2019) with a deadly outcome.[1,2] With remdesivir use, several randomized trials have recorded abbreviated recovery periods, lower mortality, and positive consequences of early treatment initiation.[3,4] Based on randomized trial results, the FDA has approved remdesivir for the treatment of COVID-19. Regarding convalescent plasma (CP), evidence from recently published large trials implies that early administration of high-titer CP is most efficacious.[5]

However, no published studies assessing the effect of remdesivir or CP in COVID-19 have included a substantial proportion of hematooncology patients, and available data are limited to case reports.[6,7] In view of this dearth of data, we decided to analyze the efficacy of early combination therapy of remdesivir and high-titer CP among hematological patients. This treatment strategy was implemented after observing several grim COVID-19 outcomes among these patients.

2 | METHODS

Our retrospective study from 30 December 2020 through 29 March 2021 included unselected consecutive hematological patients diagnosed with COVID-19 (presence of SARS-CoV-2 verified by Reverse Transcription Polymerase Chain Reaction, RT-PCR, or antigen from nasopharyngeal swab) and subsequently treated with a remdesivir and high-titer CP combination at our hospital. Disease severity was assessed according to adapted definitions.[8] Data were obtained from source medical documentation covering comorbidities, pulmonary imaging, COVID-19 diagnostics, therapy, and outcome. High-titer CP was manufactured from plasma of convalescent male donors with SARS-CoV-2 anti-S antibody levels at least 200 U/ml (Elecsys® Anti-SARS-CoV-2 S) at the time of plasma collection.

All patients received intravenous remdesivir 200 mg on day 1, followed by 100 mg daily for a total of 5 days. Two units of high-titer CP (SARS-CoV-2 neutralizing antibodies at a titer 1:160 and higher) were administered per one treatment cycle. Several underwent retreatment due to either prolonged SARS-CoV-2 positivity or re-positivity, eventually supported by culture virus viability, or as a secondary prophylaxis during ongoing oncological treatment. A descriptive analysis was conducted separately for two divided cohorts: "Pneumonia Cohort" versus "No Pneumonia Cohort" at the onset of combination therapy. Pneumonia was diagnosed based on chest x-ray pulmonary infiltrates or high-resolution computer tomography. Our research was undertaken in accordance with relevant guidelines and regulations. All patients involved signed an informed consent form.

Basic statistical methods describing absolute and relative frequency for categorical variables, mean, median, minimum and maximum for continuous variables, respectively, were employed. Categorical parameter relations were evaluated using Fisher's exact tests; continuous variables were compared using the Mann–Whitney U test with $\alpha = 0.05$ as a level of statistical significance.

3 | RESULTS

A total of 32 hematological patients (75% not in remission), with acute leukemias, lymphomas, and myeloma as the most frequent underlying diagnoses (81%), were evaluated with a median follow-up of 36 days (min—15, max—92). Baseline characteristics are described in Table 1. In both cohorts, median time from SARS-CoV-2 positivity to treatment onset was 1 day. When initiating remdesivir, 56% of patients already had evidence of pneumonia. The SARS-CoV-2 diagnosis was primarily determined by RT-PCR test (72%). While not substantial, our "Pneumonia Cohort" exhibited more comorbidities and worse white blood cell parameters than the "No Pneumonia Cohort." When COVID-19 was diagnosed, our "Pneumonia Cohort" had a remarkably higher stage of disease severity (moderate–severe–critical) compared to the "No Pneumonia Cohort" (83% vs. 14%; $p < 0.001$) (Table 1). Corticosteroids and low-molecular-weight heparins were employed among 47% and 91% of study patients, respectively, without a considerable difference between cohorts. During the first treatment cycle,

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TABLE 1 Characteristics of patients enrolled in the study stratified according to the presence of pneumonia at the time of COVID-19 diagnosis

	Total	Pneumonia cohort	No pneumonia cohort	*p*-value
Number of patients, *n* (%)	32 (100)	18 (56)	14 (44)	NA
Age at the time of COVID-19 diagnosis, years, *median; mean* (*range*)	60; 57.7 (25-86)	62; 61.1 (44-86)	56; 53.6 (25-77)	0.303
Sex, male, *n* (%)	19 (59)	10 (56)	9 (64)	0.725
SARS-CoV-2 RT-PCR positive test, *n* (%)	23 (72)	15 (83)	8 (57)	0.132
SARS-CoV-2 antigen positive test, *n* (%)	9 (28)	3 (17)	6 (43)	0.132
Underlying disease at baseline, *n* (%)				
Acute leukemia	10 (31)	3 (17)	7 (50)	0.062
Lymphoma	10 (31)	5 (28)	5 (36)	0.712
Multiple myeloma	6 (19)	4 (22)	2 (14)	0.672
Chronic lymphocytic leukemia	3 (9)	3 (17)	0 (0)	NA
Chronic myelogenous leukemia	1 (3)	1 (6)	0 (0)	NA
Polycythemia vera	1 (3)	1 (6)	0 (0)	NA
Autoimmune leukopenia	1 (3)	1 (6)	0 (0)	NA
Active hematological disease, *n (%)*	24 (75)	14 (78)	10 (71)	0.704
Last hematological therapy 2 years prior to COVID-19, *n* (%)				
Induction of acute leukemia	8 (25)	3 (17)	5 (36)	0.252
First cycle of chemotherapy	6 (19)	4 (22)	2 (14)	0.672
>1 cycle of chemotherapy	9 (28)	4 (22)	5 (36)	0.453
Daratumumab in myeloma	3 (9)	2 (11)	1 (7)	1.0
Cyclosporin A after allo HSCT	1 (3)	1 (6)	0 (0)	NA
Corticosteroids	1 (3)	1 (6)	0 (0)	NA
Hydroxyurea	1 (3)	1 (6)	0 (0)	NA
No therapy	3 (9)	2 (11)	1 (7)	1.0
Number of days between last hematological therapy and COVID-19 diagnosis, *median; mean* (*range*)	4; 18 (0–287)	6; 8 (0–32)	2; 31 (0–287)	0.617
Serious comorbidities, *n* (%)	19 (59)	12 (67)	7 (50)	0.473
Hypertension	13 (41)	7 (39)	6 (43)	1.0
Diabetes	8 (25)	6 (33)	2 (14)	0.412

TABLE 1 (Continued)

	Total	Pneumonia cohort	No pneumonia cohort	*p*-value
Coronary heart disease	3 (9)	3 (17)	0 (0)	NA
Hyperlipidemia	5 (16)	3 (17)	2 (14)	1.0
Pulmonary disease	3 (9)	2 (11)	1 (7)	1.0
Chronic renal failure	1 (3)	1 (6)	0 (0)	NA
COVID-19 severity at the time of the start of therapy, *n* (%)				
Asymptomatic	5 (16)	1 (6)	4 (29)	**<0.001**
Mild	10 (31)	2 (11)	8 (57)	
Moderate	1 (3)	0 (0)	1 (7)	
Severe	16 (50)	15 (83)	1 (7)	
Critical	0 (0)	0 (0)	0 (0)	
Blood count parameters at the time of remdesivir start, $\times 10^9$/L, *median (range)*				
White blood cell count	3.8 (0.08–139)	3.6 (0.08–139)	5.54 (0.69–21.81)	0.992
Absolute lymphocyte count	0.7 (0.03–127)	0.6 (0.03–127)	0.9 (0.3–4.4)	0.689
Absolute neutrophil count	2.4 (0.0–17.4)	2.1 (0.0–11.0)	4.0 (0.1–17.4)	0.459
Platelet count	99 (5–392)	116 (5–284)	83 (12–392)	0.849

Note: The significance level $p < 0.05$ is depicted in bold.

Abbreviations: allo HSCT, allogeneic human stem cell transplantation; ; COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus-2.

significantly, a higher number of patients in our "Pneumonia Cohort" developed severe or critical COVID-19 compared to the "No Pneumonia Cohort" (89% vs. 29%; $p < 0.001$). Nine patients (28%) received, in total, 12 retreatment cycles either for prolonged SARS-CoV-2 positivity (66%), eventually supported by viral culture positivity (63%), as a secondary prophylaxis (17%), or for SARS-CoV-2 re-positivity (17%). No patient developed direct adverse reactions requiring treatment reduction. Final evaluation recorded three deaths (9%), all in the "Pneumonia Cohort" and attributed to critical COVID-19. No further significant differences were noted between the two cohorts. Data concerning therapy and outcome are available in Tables 2 and S1.

TABLE 2 Characteristics of treatment combination and outcome in patients stratified according to the presence of pneumonia at the time of COVID-19 diagnosis

	Total	Pneumonia cohort	No pneumonia cohort	*p*-value
First treatment cycle in COVID-19 positive patients, *n* (%)	32 (100)	18 (56)	14 (44)	NA
Total length of remdesivir treatment, days, *median; mean (range)*	5; 5.0 (NA)	5; 5.0 (NA)	5; 5.0 (NA)	1.0
Number of days between COVID-19 diagnosis and remdesivir start, *median; mean (range)*	1; 2.3 (0–11)	1; 2.4 (0–10)	1; 2.1 (0–11)	0.912
Total number of high-titer CP administration, *median; mean (range)*	2; 2.0 (2–3)	2; 2.0 (NA)	2; 2.1 (2–3)	1.0
Number of days between high-titer CP administration and remdesivir start, *median; mean (range)*	0; −0.25 (−5–1)	0; −0.30 (−5–0)	0; −0.20 (−4–1)	0.803
Concomitant corticosteroids use, *n* (%)	15 (47)	10 (56)	5 (36)	0.308
Concomitant LMWH use, *n* (%)	29 (91)	18 (100)	11 (79)	0.073
COVID-19 highest degree of severity on treatment during first treatment cycle, *n* (%)				
Asymptomatic	2 (6)	0 (0)	2 (14)	**<0.001**
Mild	8 (25)	0 (0)	8 (57)	
Moderate	2 (6)	2 (11)	0 (0)	
Severe	15 (47)	11 (61)	4 (29)	
Critical	5 (16)	5 (28)	0 (0)	
Total length of hospitalization during first treatment cycle, *median (range)*	13 (5–91)	15 (6–91)	12 (5–26)	0.574
Total number of treatment cycles, *n*	44	27	17	NA
Number of cycles per patient, *median; mean (range)*	1; 1.4 (1–4)	1; 1.5 (1–4)	1; 1.2 (1–2)	0.337
Number of patients with 2nd cycle, *n* (%)	9 (28)	6 (33)[a]	3 (21)	0.694
Number of patients with 3rd cycle, *n* (%)	2 (6)	2 (11)	0 (0)	NA
Number of patients with 4th cycle, *n* (%)	1 (3)	1 (6)	0 (0)	NA
Reason for retreatment, *n* (%)				
SARS-CoV-2 prolonged positivity	8 (66)	7 (78)	1 (33)	0.236
Secondary prophylaxis	2 (17)	1 (11)	1 (33)	0.455
SARS-CoV-2 re-positivity (new positivity after negativity)	2 (17)	1 (11)	1 (33)	0.455
SARS-CoV-2 culture performed during all treatment cycles, *n* (%)	8 (18)	4 (15)	4 (24)	0.690
Time from remdesivir start to sampling, days, *median (range)*	6 (0–30)	6 (0–18)	7 (0–30)	NA
Positive SARS-CoV-2 culture, *n* (%)	5 (63)	4 (100)	1 (25)	NA
Alive at the time of data cutoff, *n* (%)	29 (91)	15 (83)	14 (100)	0.238
Death attributed to COVID-19, *n* (%)	3 (100)	3 (100)	NA	NA

Note: The significance level $p < 0.05$ is depicted in bold.

Abbreviations: COVID-19, coronavirus disease 2019; CP, convalescent plasma, LMWH, low molecular weight heparin; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus-2.

[a]One patient received 10-day remdesivir treatment.

4 | DISCUSSION

Our study highlighted efficacy of early concomitant use of remdesivir and high-titer CP in hematological patients with newly diagnosed COVID-19, irrespective of incidental pneumonia.

In literature, a number of multicenter analyzes are published, including meta-analyses, describing high mortality attributed to COVID-19 in patients with hematological malignancies.[1,2,9,10]. A meta-analysis evaluating more than 3000 hematology patients with COVID-19 augmented mortality evidence of 34%, 53%, 41%, 34%, 33%, 32%, and 31% among the entire cohort evaluated, in acquired bone marrow failure syndromes, acute leukemias, myeloproliferative neoplasias, plasma cell dyscrasias, lymphomas, and chronic lymphocytic leukemias, respectively.[1] Similarly, an extensive retrospective study indicated a high probability of death (34%) from COVID-19 in 650 patients with plasma cell disorders.[2] Moreover, large retrospective studies evaluating infection course in a total of 327 patients with chronic myeloid leukemia recorded high mortality of up to 14%.[9,10]

Remdesivir and preferably high-titer CP affected, in general, benefit related to shortened recovery periods among hospitalized patients with lower respiratory tract infection and mortality reduction, with early treatment initiation being the most important attribute.[3–5] Prolonged remdesivir administration did not manifest significant benefit among the general population. Nevertheless, these determinations could not be extrapolated to immunocompromised patients with a high risk of persistent viral replication among patients with severe SARS-CoV-2 infection.[6,7]

Regarding hematological patients, no large clinical trial reports detailing effects of both remdesivir and CP therapy upon COVID-19 have been recorded. However, several case reports affirmed severe protracted courses of SARS-CoV-2 infections resulting from inability to produce virus neutralizing immunity, with prolonged shedding of viable virus up to 2 months following symptom onset and SARS-CoV-2 reinfection.[6,7] Similar to our data, prolonged remdesivir therapy, including retreatment, and, ultimately, in combination with CP, evidenced effectiveness, in vivo, among immunocompromised hematological patients.[6,7]

Our study's major strength is its focus on a uniform single-center cohort comprised exclusively of hematological patients and limited only in terms of sample size and control group participation.

5 | CONCLUSION

COVID-19 infections notably pose a high risk of morbidity and mortality for immunocompromised hematooncology patients in comparison with the general population. While robust data on remdesivir and CP treatment in this specific group of patients are not yet available in literature, published case reports and our substantial actual clinical records indicate remarkable efficacy of a high-titer CP/remdesivir combination initiated immediately following COVID-19 diagnosis. We believe that this treatment strategy is especially effective in patients who have not yet developed pneumonia.

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CONFLICT OF INTEREST

The authors declare no competing or conflicting interests.

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AUTHOR CONTRIBUTIONS

Barbora Weinbergerova and Jiri Mayer contributed to study conception and design; implemented material preparation, data collection and analysis; composed and revised manuscript. Tomas Kabut, Stepan Hrabovsky, Jirina Prochazkova, Zdenek Kral, Vladimir Herout, Rita Pacasova, Lenka Zdrazilova-Dubska, Petr Husa, Petr Bednar, Daniel Ruzek, and Martina Lengerovacontributed to study conception and design; effected material preparation, data collection and analysis; commented on previous manuscript versions; reviewed and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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TRANSPARENT PEER REVIEW

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