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ORIGINAL ARTICLE

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Lack of efficacy of convalescent plasma in COVID-19 patients with concomitant hematological malignancies: An Italian retrospective study

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Abstract

A multicenter retrospective study was designed to assess clinical outcome of COVID-19 in patients with hematological malignancies (HM) following treatment with anti-SARS-CoV-2 convalescent plasma (CP) or standard of care therapy. To this aim, a propensity score matching was used to assess the role of non-randomized administration of CP in this high-risk cohort of patients from the Italian Hematology Alliance on COVID-19 (ITA-HEMA-COV) project, now including 2049 untreated control patients. We investigated 30- and 90-day mortality, rate of admission to

intensive care unit, proportion of patients requiring mechanical ventilatory support, hospitalization time, and SARS-CoV-2 clearance in 79 CP recipients and compared results with 158 propensity score-matched controls. Results indicated a lack of efficacy of CP in the study group compared with the untreated group, thus confirming the negative results obtained from randomized studies in immunocompetent individuals with COVID-19. In conclusion, this retrospective analysis did not meet the primary and secondary end points in any category of immunocompromized patients affected by HM.

KEYWORDS
convalescent plasma, COVID-19, disease severity, hematological malignancy, survival data

1 | INTRODUCTION

The use of convalescent plasma (CP) from subjects recovered from Coronavirus 2 (SARS-CoV-2) infection has been considered a therapeutic modality for patients affected by mild or severe acute respiratory syndrome associated with Coronavirus disease 2019 (COVID-19).[1–10] Three recent meta-analyses of randomized clinical trials and matched-control data showed that the use of CP was not associated with a lower mortality rate compared to patients treated with standard drugs.[11–13] Interestingly, a lower mortality was demonstrated in patients who were treated with high titer CP within 3 days of hospital admission, thus supporting a possible overall benefit of COVID-19 CP in homecare patients as well as in non-critical hospitalized patients.[14–19] As far the clinical implication of COVID-19 infection in patients with concomitant hematological malignancies (HM) is concerned, several studies have reported a high mortality rate and the Italian Hematology Alliance on HM and COVID-19 has found that HM patients with COVID-19 have a more aggressive clinical course than patients with either HM or COVID-19 alone.[20–23] In particular, the preexistence of COVID-19 in patients with B-cell lymphoma is associated with impaired generation of neutralizing antibody titers and reduced clearance of SARS-CoV-2.[24] A recent study has shown that CP treatment was able to neutralize antibody titers in this patient category and to improve clinical response in 80% of patients examined.[2] In a recent study from Visco et al, a high mortality rate in patients with lymphoma and COVID19 has been observed.[25] The clinical outcome may be easily predicted both in hospitalized and not hospitalized patients by demographics or hematological parameters.[25]

In this paper we assessed the association of CP use with 30- and 90-day mortality in COVID-19 infected patients affected by HM. Secondary end points were represented by the rate of admission to intensive care unit, proportion of pts requiring mechanical ventilatory support, hospitalization time, and virus clearance. A propensity score matching analysis was performed using the Italian Hema-COV data base including 2049 COVID-19 patients with hematological malignancies.

1.1 | Material and methods

This multicenter non-interventional study, was based on a retrospective data analysis (previously published by Passamonti et al,[22,26] Visco et al,[25] and a second retrospective cohort study, aimed at evaluating the impact of the use of CP in reducing mortality in COVID-19-infected Italian patients. This sub-analysis was performed in the same Italian Institutions reporting data over the last 18 months (April 2020- October 2021). The present study involved 64 hematology Institutions in Italy. The ITA-HEMA-COV (the ITAlian HEMatology Alliance on COVID-19) worked on behalf of 5 Italian societies, namely SIE (Società Italiana di Ematologia), SIES (Società Italiana di Ematologia Sperimentale), GITMO (Gruppo Italiano Trapianto Midollo Osseo), SEIFEM (Sorveglianza Epidemiologica Infezioni nelle Emopatie), and FIL (Fondazione Italiana Linfomi). All patients (aged ≥18 years) with an established diagnosis of hematological malignancies and being treated with CP were registered by single centers between 25 Feb 2020 and 1 October 2020 (retrospective cohort), and then between April 2020 and October 2021 (retrospective/prospective cohort including the use of CP). Disease severity for COVID-19 was classified according to the following categories; 1) Mild (non-pneumonia and mild pneumonia); 2) Severe (dyspnea, respiratory frequency 30/min, SpO2 93%, PaO_2/FiO_2 <300 and/or lung infiltrates >50%); 3) Critical (respiratory failure, septic shock, and/or multiple organ dysfunction or failure).

Seventeen Italian Institutions provided data on the use of CP in COVID-19 patients with HM. CP was prepared according to national and international guidelines. Serum titer of specific neutralizing antibodies was >160 in all cases and >320 in 50% of preparation using the EIA method. Pathogen (viral) inactivation treatment of the plasma was performed in all CP preparations, in view of presence of viral DNA in donor population, according to national legislation. The plasma volume used was 200 mL of CP for two consecutive days (400 mL in total). CP was used in hospitalized patients. The levels of neutralizing antibody titers in the treated patients-group were available in a small number of cases (no. 8).

Inclusion criteria were a diagnosis of hematological malignancy, according to standard WHO-criteria and laboratory-confirmed SARS-CoV-2 infection, tested by RT-PCR on nasopharyngeal swabs following standardized national recommendations. The trial was approved by the institutional review board of Varese Hematology unit. Written informed consent was collected from all patients.

1.2 | Statistical analysis

The baseline characteristics of the cohort of patients who received the CP were compared with those obtained from controls using a bivariate analysis and the Student's *t*-test, Mann-Whitney test, and Chi square test. Given the observational nature of the study, and considering that the treatment variables were not assigned in a randomized way, we created a propensity score in order to match controls with similar baseline characteristics of patients treated with CP.

The individual propensity score to receive plasma treatment was estimated through a multivariate logistic regression model using as covariates the baseline characteristics of the patients potentially influencing the outcomes: age, disease-type, disease status, COVID severity. For the matching, the nearest-neighbor method was used with a ratio of 1: 2 between treated and controls.

Survival was studied through Kaplan-Meier curves and compared through log-rank between CP and controls, considering both the overall cohort and the matched control sample. The significance threshold was 0.05 and the tests were all two-sided.

Analyses were performed with the STATA software, version 14.2.

TABLE 1 Main clinical characteristics of CP-treated versus untreated control patients, obtained from ITA-HEMA Covid registry (*n* 2490 patients with COVID-19 and concomitant HM)

Variable	Convalescent plasma recipient group (*n* 79)	Control group (*n* 2490)	*p* value
Median age	62.1 years	63.7 years	
Sex	Male 61.54% (*n* 48)	Male 59.46% (*n* 1477)	0.713
	Female 38.46% (*n* 30)	Female 40.54% (*n* 1007)	
Charlson index (m)	4.53	4.24	0.190
HM subtype:			
AML/ALL	16.88% (*n* 13)	11.33% (*n* 282)	0.000
MPN/CML/MDS	5.19% (*n* 4)	21.49% (*n* 535)	
Aggressive NHL/HL	42.86% (*n* 33)	22.65% (*n* 564)	
Indolent NHL/CLL	23.38% (*n* 18)	23.78% (*n* 592)	
Plasma cell neoplasm	11.69% (*n* 9)	23.78% (*n* 517)	
HM status at the time of Covid-19 infection			
CR	34.85% (*n* 23)	41.62% (*n* 857)	0.002
PR	34.85% (*n* 23)	19.87% (*n* 396)	
PD	19.07% (*n* 13)	13.55% (*n* 270)	
SD	10.14% (*n* 7)	24.74% (*n* 493)	
Pneumonia			
	Yes 53.52% (*n* 38)	Yes 39.29% (*n* 855)	0.016
	No 46.48% (*n* 33)	No 60.71% (*n* 1321)	
Severity of Covid-19			
Mild	32.00% (*n* 24)	63.99% (*n* 1477)	0.0001
Severe	53.33% (*n* 40)	26.86% (*n* 620)	
Critical	14.67% (*n* 11)	9.14% (*n* 211)	
ICU admission			
	Yes 26.58% (*n* 21)	Yes 11.33% (*n* 282)	0.0001
	No 73.42% (*n* 58)	No 88.67% (*n* 2208)	

Abbreviations: ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; CML, Chronic Myeloid Leukemia; CR, Complete Remission; HL, Hodgkin Lymphoma; HM, Hematological Malignancy; ICU, Intensive Care Unit; MDS, Myelodysplastic Syndrome; MPN, Chronic Myeloproliferative Neoplasm; NHL, Non Hodgkin Lymphoma; PD, Progressive Disease; PR, Partial Remission; SD, Stable Disease; WW, Watch and Wait.

1.3 | Results

This multicenter retrospective analysis has been conducted in 64 hematology Institutions in Italy, belonging to ITA-HEMA-COV (the ITAlian HEMatology Alliance on COVID-19) network. The main aim of this study was to assess the clinical efficacy related to the use of convalescent plasma in the treatment of SARS-CoV-2 infected patients affected by concomitant HM. The main clinical and laboratory features of the treated and untreated patient subgroups are given in Table 1. Treated group was constituted by 79 patients, while the control group was initially composed by 2490 patients. In order to make a better comparison between treated and untreated patient groups, a propensity score matching analysis was performed. Based on this subanalysis, 79 CP recipients were compared with 158 matched untreated control patients (Table 2).

In the CP-treated group, no adverse events were detected following the administration of convalescent plasma therapy.

The statistical analysis performed on the comparative assessment of the whole Ita-Hema-COV series (n 2490) and CP -treated cases (n 79) has shown that CP was mainly used in patients having a more severe COVID-19 infection (advanced pulmonary infection 53.52% vs. 39.29% -p 0.016- as well as those hospitalized with several complications 53.33% vs. 26.86% -p 0.001) compared with the untreated group. Furthermore, CP was mainly used in patients having a more aggressive stage of hematological disease (i.e., aggressive LNH 42.86% vs. 22.65%; *p* 0.0001), who were treated with

TABLE 2 Main clinical characteristics of CP-treated versus untreated propensity score-matched control patients

Variable	Plasma convalescent-treated group (*n* 79)	Control group (*n* 158)	*p* value
Age (median)	62.1 years	61.2 years	
Sex	Male 61.54% (*n* 48)	Male 59.87% (*n* 94)	0.806
	Female 38.46% (*n* 30)	Female 40.13% (*n* 63)	
Charlson index (m)	4.53	3.86	
HM subtype:	16.88% (*n* 13)	12.03% (*n* 19)	0.222
AML/ALL	5.19% (*n* 4)	12.66% (*n* 20)	
MPN/CML/MDS	42.86% (*n* 33)	35.44% (*n* 56)	
Aggressive/CLL	23.38% (*n* 18)	22.15% (*n* 35)	
Plasma cell neoplasia	11.69% (*n* 9)	17.72% (*n* 28)	
HM status at time of Covid infection			
CR	33.33% (*n* 23)	31.48% (*n* 68)	0.481
PR	33.33% (*n* 23)	30.09% (*n* 65)	
PD	18.84% (*n* 13)	18.52% (*n* 40)	
SD	10.14% (*n* 7)	10.19% (*n* 22)	
WW	4.35% (*n* 3)	9.72% (*n* 21))	
Pneumonia			0.627
	Yes 53.52% (*n* 38)	Yes 39.29% (*n* 855)	
	No 46.48% (*n* 33)	No 60.71% (*n* 1321)	
Severity of Covid-19			
Mild	32.00% (*n* 24)	63.99% (*n* 1477)	0.353
Severe	53.33% (*n* 40)	26.86% (*n* 620)	
Critical	14.67% (*n* 11)	9.14% (*n* 211)	
ICU admission			
	Yes 26.58% (*n* 21)	Yes 25.95% (n 41)	0.0917
	No 73.42% (*n* 58)	No 74.05% (*n* 117)	

Abbreviations: ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; CML, Chronic Myeloid Leukemia; CR, Complete Remission; HL, Hodgkin Lymphoma; HM, Hematological Malignancy; ICU, Intensive Care Unit; MDS, Myelodysplastic Syndrome; MPN, chronic myeloproliferative neoplasm; NHL, Non Hodgkin Lymphoma; PD, Progressive Disease; PR, Partial Remission; SD, Stable Disease; WW, Watch and Wait.

more aggressive chemotherapy courses and not yet achieving a remission phase of the disease (partial response: 34.85% vs. 19.87%; *p* 0.002).

Based on this preliminary statistical analysis, a propensity score-matched analysis was performed. The Propensity score-matched control group was composed by 156 cases fully matched for all clinical and laboratory variables (including type of HM). Individual propensities considered several variables, including sex, age, race, ECOG performance status, obesity, hypertension, renal comorbidities, presence of type 2 diabetes, pulmonary impairment, hematologic cancer type, clinical stage and histologic variant, type of treatment, remission phase achieved after treatment, receipt of cytotoxic chemotherapy within 3 months of COVID-19 diagnosis.

In brief, no statistical difference was seen in the two groups (treated vs. untreated group) in terms of 30- and 90-day survival, severity of COVID-19 disease.

Survival data were comparable in the two groups (treated vs. untreated - Figure 1, *p*, not significant values).

Reasons for death and follow-up data were comparable in the two groups and are given in Table 3.

Furthermore, the statistical analysis failed to show meaningful differences between the two groups (treated vs. untreated) in terms of the rate of admission to intensive care unit (26.58% vs. 25.95%; *p* 0.0001), proportion of patients requiring mechanical ventilatory support 47,2% versus. 54,4%; *p* 0.319), hospitalization time (71,2 days vs. 38,8 days; *p* 0.4), and timing of virus clearance (*p* 0.91) (Tables 1 and 3).

Furthermore, there was no meaningful difference in the mortality in patients receiving early versus late administration of convalescent plasma therapy.

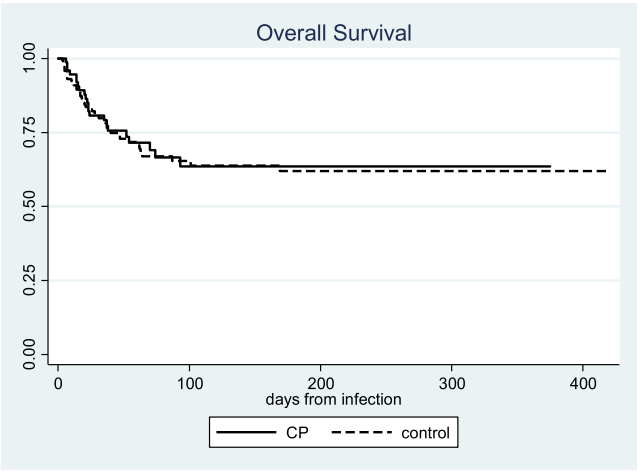

FIGURE 1 Survival analysis curves obtained from CP-treated patient group (*n* 79) versus untreated matched patient group (*n* 158). No differences were seen. CP was used in hospitalized patients

2 | DISCUSSION

The administration of convalescent plasma (CP) has been recently proposed in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected individuals characterized by severe acute respiratory syndrome.[1–10] However, three recent meta-analyses of randomized clinical trials and matched-control data clearly showed that the use of CP was not associated with a lower mortality rate compared to patients treated with standard drugs.[11–13] However, a lower mortality was documented in patients who were treated with high titer CP within 3 days of hospital admission, thus supporting a possible overall benefit of COVID-19 CP in homecare patients as well as in non-critical hospitalized patients.[14–19]

As far the clinical implication of COVID-19 in patients with concomitant hematological malignancies (HM) is concerned, several studies have reported a high mortality rate and the Italian Hematology Alliance on HM and COVID-19 has demonstrated that this patient category is characterized by an aggressive clinical course in most of the examined cases.[20–23] In particular, the pre-existence of COVID-19 in patients with B-cell lymphoma is associated with an impaired production of neutralizing antibody titers and reduced clearance of SARS-CoV-2.[24–28] Recent studies have shown that CP treatment was able to neutralize antibody titers in this patient category and to improve clinical response in a significant number of patients examined.[27,29–39] Furthermore, a recent study indicates an impaired production of SARS-CoV-2- neutralizing antibodies in an immunosuppressed individual treated with CP, possibly supporting the notion that virus escape, particularly in immunocompromized individuals where prolonged viral replication occurs, and this may limit the efficacy of CP treatment in at least some HM patients.[40]

Although most randomized controlled trials have shown negative results on the use of CP for the treatment of COVID-19, we thought to be wise to conduct a retrospective analysis aimed at evaluating the role played by CP for adults with COVID-19 and concomitant HM.[11–13,20–24]

TABLE 3 Reason for death and length of Covid-19 in the various patient groups

		CP-treated *n.* (%)	CP-untreated *n.* (%)	Total *n.* (%)	*p* value (chi^2 test)
Reason of death	HM	2/19 (10.5)	5/46 (10.9)	7/65 (10.8)	0.806
	Covid-19	16/19 (84.2)	40/46 (87.0)	56/65 (86.2)	
	Other	1/19 (5.3)	1/46 (2.2)	2/65 (3.1)	
Recovery_from Covid-19 (follow-up)	Yes	34/72 (47.2)	81/149 (54.4)	115/221 (52.0)	0.319

In our series, a propensity score matching was used to better assess the role played by the non-randomized administration of CP in SARS-CoV-2 infected patients affected by concomitant HM. Individual propensities took into account clinical characteristics such as sex, age, race, ECOG performance status, obesity, hypertension, renal comorbidities, presence of type 2 diabetes, pulmonary impairment, hematologic cancer type, clinical stage and histologic variant, type of treatment, receipt of cytotoxic chemotherapy within 3 months of COVID-19 diagnosis.

The association of CP use with 30- and 90-day mortality, rate of admission to intensive care unit, proportion of patients requiring mechanical ventilatory support, hospitalization time, and SARS-CoV-2 clearance was investigated in a series of Italian patients affected by COVID-19 and HM. 79 convalescent plasma recipients were firstly compared with 2049 untreated control patients affected by COVID-19 and concomitant HM, obtained from the Italian Hematology Alliance on HM and COVID-19. A second analysis was performed using a propensity score matching to better assess the role played by the non-randomized administration of CP in SARS-CoV-2 infected patients with concomitant hematological malignancies. Results indicate a lack of efficacy of CP in the study group compared with a fully matched untreated group (n. 158 cases). Unfortunately, the levels of SARS-CoV-2 antibodies on patients examined were available in a few cases, thus not allowing us to correlate the efficacy of CP with antibody response to COVID-19 infection and/or previous vaccination. Furthermore, in our series, early administration of CP was not associated with an improvement in survival rates and did not meet secondary end points. These data failed to show an improvement in patients' clinical status and did not result in faster clearance of the virus.

In conclusion, this retrospective analysis conducted in a large series of COVID-19 patients with hematological malignancies seem to confirm the negative results obtained from randomized studies in SARS-CoV-2-infected individuals. Although this survey has some limitations, due to its retrospective nature, the lack of antibody titers against Sars-CoV-2, and avoidance of a standardized use of CP in combination with other treatment measures, we do believe that this study may be informative for the medical community. Prospective randomized clinical trials may provide further insights in this high-risk population.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in SIE - Società Italiana Ematologia at https://www.siematologia.it/.

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PEER REVIEW

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