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CASE REPORT

Trends in Pulmonary and Respiratory Medicine

Rapid Clinical Improvement and Negativization in Symptomatic Patient with Secondary Hypogammaglobulinemia and Sars-CoV-2 Respiratory Infection after COVID-19 Convalescent Plasma Transfusion

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Abstract

The novel coronavirus disease pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a global public health issue. Neoplastic and immunosuppressed patients with haematological disorders are at high risk for COVID-19 complications. This patients are unable to develop neutralizing antibodies due to an underlying disease and persistent SARS-CoV-2 RNA shedding has been documented for long time. Convalescent plasma transfusion (CPT) should be usefull in patients who are unable to produce neutralizing antibodies, like patients whose immune systems have been compromised by an haematological or autoimmune underlying disease. We report the case of a 61-year-old man with chronic lymphocytic leukemia previously treated with chemotherapy and in current disease progression that undergoes periodic immunoglobulin infusions with long positivity to SARS-CoV-2. In this report we highlight how the administration of CPT has been determinant on the significant change in the course of our patient's disease. In the case described, it is evident that the persistent positivity to SARS-CoV-2 over time has worsened the fragile clinical condition of our patient due to persistence of fever and worsening of interstitial lung involvement. The rapid clinical improvement is temporally correlated to the rapid viral clearance as well as the rapid improvement of the interstitial radiological picture. In our opinion, in patients with haematological disorders early treatment can have significant advantages and avoid a worsening of clinical conditions related to SARS CoV-2 infection.

Introduction

OThe novel coronavirus disease pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), represents a global public health issue. COVID-19 clinical spectrum varies from asymptomatic infection to interstitial pneumonia, and even acute to respiratory distress syndrome (ARDS), often combined with multiple organ failure [1]. The case fatality rate (CFR) varies considerably across different countries, and is particularly high for elder patients and patients with severe comorbidity (COVID-19) [2-5]. Neoplastic and immunosuppressed patients with haematological disorders are at high risk for COVID-19 complications [6,7]. Patients diagnosed with hematologic malignancies were at an especially higher risk with mortality rates exceeding 30%. An example is a series from a single hospital in New York, with CFR of 37% in patients with hematologic malignancies compared with 25% in patients with solid cancers [8,9].

In addition, patients with hematological disorders have previously been found to be vulnerable to infection with other coronavirus types following stem cell transplantation [10]. The duration of SARS-CoV-2 RNA shedding is generally between 3 and 46 days after symptom onset [11,12] with no correlation with severity of illness. Asymptomatic individuals shed SARS-CoV-2 RNA comparably with symptomatic patients [12]. Persistent SARS-CoV-2 RNA shedding has been documented, with patients remaining qRT-PCR-positive for up to 63 days [13].

This is particularly possible in patients unable to develop neutralizing antibodies due to an underlying disease that impairs the function of the immune system, as for in patients affected by hematological disorders. These patients have also been shown to develop prolonged shedding of infectious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), often lasting several months, and have been implicated in being sources of novel SARS-CoV-2 variants [14,15]. In the past, convalescent plasma transfusion (CPT) has been employed in numerous viral epidemics, such as severe acute respiratory syndrome, Middle East respiratory syndrome, or influenza [16].

A recent statement from the National Institutes of Health underscored that CPT is not the standard of care for patients with COVID-19 and that well-powered randomize controlled trials (RCTs) are needed to determine whether CPT is an effective treatment, especially in patients with normal immune system function [17]. A recent systematic review and meta-analysis of RCTs in patient with confirmed COVID-19 in any treatment setting concluded that treatment with convalescent plasma was not significantly associated with a decrease in all-cause mortality among patients with COVID-19, when compared to a placebo in combination with standard of care or only standard of care [18]. However, this approach should be of particular interest in patients who are unable to produce neutralizing antibodies, and thus the

administration of CPT may be a useful approach for the treatment of patients whose immune systems have been compromised by an haematological or autoimmune underlying disease. Currently, only one case series exists that reports the clinical benefit of CPT in 17 consecutive patients with profound B-cell lymphopenia and protracted COVID-19 disease. In these patients COVID-19–specific treatments failed to improve sustainably the course of the disease, whereas CPT was associated with a striking improvement of clinical symptoms and biological parameters in 16 out of 17 patients, and a decrease of SARS-CoV-2 RNAemia within 7 to 14 days [19].

Case Report

AWe report the case of a 61-year-old man with chronic lymphocytic leukemia previously treated with chemotherapy and in current disease progression that undergoes periodic immunoglobulin infusions. The patient was hospitalized on 28/12/2020 for persistent fever for a few days, in known long positivity to SARS-CoV-2. We confirmed SARS-CoV-2 positivity by antigenic swab for SARS-CoV-2 and specific reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab and in bronchial wash sample. He is also affected by atrial fibrillation in oral anticoagulation with warfarin and COPD with bronchiectasis with periodic exacerbations. His first SARS-CoV-2 positivity was detected on 30/11/2020 by SARS-CoV2–specific RT-PCR in nasopharyngeal swab following the confirmation of his wife positivity. Since then and up to 5 days after hospitalization, the patient had not experienced any symptoms attributable to SARS-CoV-2 infection.

Upon admission, the patient had fever and dyspnea, he underwent biohumoral tests that showed low indices of inflammation, negative blood cultures and HRTC highlighting parenchymal consolidation areas in correspondence of lingula, middle lobe and lower lobes with a ground glass appearance. The patient presented also consolidation with thickening of the bronchial structure and a global involvement of 25% of parenchyma.

Therapy started with dexamethasone, 6 mg/day, and enoxaparin, 200 IU/kg/day. The patient was also treated with immunoglobulin infusion and a bronchoscopy with broncholwashing was performed, showing positivity for Pseudomonas aeruginosa, Pneumocystis jiroveci and Cytomegalovirus with high viral load (60000cp). Hence, we started therapy with ceftazidime, sulfamethoxazole/trimethoprim, ganciclovir and fluconazole. Dexamethasone was discontinued after 6 days.

During hospitalization we observed persistence of febrile episodes with persistently positive antigenic swab for SARS-CoV-2, slightly increased inflammation markers, while blood cultures were always negative. We performed a new CT scan with evidence of diffuse interstitial thickening in both lungs, major on the right, with consolidation features in the dorsal sectors of the left lower lobe (with an involvement of 75% of the lung parenchyma). In consideration of the lack of response to treatment, after collegial discussion among specialists, and after obtaining the consent of the patient and of the ethics committee, we started high-dose cortisone therapy (methylprednisolone 80 mg/day) and convalescent plasma infusion (administered on 19, 20 and 21 January 2021). After the beginning of the new therapeutic scheme, we got stable defervescence and negativity of the antigenic swab for SARS-CoV-2 dated 26/01/2021

On January 28, a second administration of Immunoglobulins was performed. On January 30, new fever onset with negative blood cultures but severe granulocytopenia and thrombocytopenia probably due to sulfamethoxazole/trimethoprim cytotoxicity. For this reason we started therapy with granulokines and antibiotic therapy with piperacillin/tazobactam and caspofungin for 7 days, obtaining stable defervescence already from the third day of therapy. A new CT control was performed with evidence of marked reduction of all previously evident thickening. Minimal oxygen support was provided during hospitalization at low flow rates with no need for escalation to higher oxygen volumes. The patient was discharged apyretic, eupnoic and in periodic hematological follow-up.

Discussion

In this report we highlight how the administration of CPT has been determinant on the significant change in the course of our patient's disease. A reduction in severe disease has been demonstrated in approximately 48% of COVID-19 patients, particularly with high titre plasma, especially when administration occurred in the early stage of the disease because limited the host's immune response and avoided clinical worsening due to cytokine storm [19].

However, the current published data have not shown a significant benefit from the use of CPT on the reduction of all causes of death or on other clinical outcomes in all patients with COVID-19 [18].

Current data suggest that patients with hematologic malignancies have limited immune responses to COVID-19 [20]. Patients who do not mount a strong immune response against SARS-CoV2 are likely to shed the virus for a longer time and be a source of continued unintended exposure infecting other persons and being unable to react effectively to a viral infection, may be susceptible to potentially fatal bacterial or fungal superinfections.

Hueso et al. showed that treatments currently used for COVID-19 in patients with severe B lymphopenia are able to temporarily reduce fever or inflammation but are unable to change the course of the disease. On the contrary the administration of CPT could change the clinical course with a marked improvement in clinical symptoms and biological parameters [19]. Clinical improvement also strongly correlated with viral clearance, supporting the concept that passive immunotherapy in such patients provides the antibodies needed to neutralize SARS-CoV-2.

In the case described, it is evident that the persistent positivity to SARS-CoV-2 over time has worsened the fragile clinical condition of our patient due to persistence of fever and worsening of interstitial lung involvement evident on CT. The rapid clinical improvement is temporally correlated to the rapid viral clearance (negativization after 7 days from the first administration of the first CPT dose), as well as the rapid improvement of the interstitial radiological picture.

The use of convalescents plasma from COVID-19 is limited by the possible reduced availability of plasma from donors and by the reduced information regarding the timing of administration. However, in our opinion, there is a group of patients (table 1) whose early treatment can have significant advantages in the administration of CPT for which we have provided a dedicated protocol in order to treat them quickly and avoid a worsening of clinical conditions related to SARS CoV-2 infection.

Haematological patients population reflecting several comorbidities may be particularly vulnerable and would benefit from priority vaccination. Therefore, it is reasonable to recommend that patients receiving cancer immunotherapies should be considered for priority COVID-19 vaccination regardless of receiving this therapy. Data in many studies support the recommendation to provide priority COVID-19 vaccination to

Table 1: *Early treatment patients with convalescent plasma transfusion (CPT)*

Type 1	< 70 year + < 10 days onset of symptoms + 1 of the following • Ongoing chemotherapy with non-palliative intent • transplant • severe neutropenia (<500 mmc) • Common variable CVID immunodeficiency with hypogammaglobulinemia (IgG <500 mg/dl)
Type 2	< 70 year + positive antigenic swab for > 21 days + 1 of the following • Ongoing chemotherapy with non-palliative intent • transplant • severe neutropenia (<500 mmc) • Common variable CVID immunodeficiency with hypogammaglobulinemia (IgG <500 mg/dl)

patients with cancer due to their increased risk of mortality with COVID-19 infection.

This recommendation should result in early vaccination to patients who are currently receiving treatment for cancer, or have an advanced cancer that may result in increased risk of complications from COVID-19. There are currently not enough data to evaluate the interactions between active oncologic therapy with the ability to induce protective immunity to COVID-19 with vaccination [20].

Given the evidence that the COVID-19 vaccines may provide greater levels of neutralizing antibodies than SARS-CoV2 infection in a substantial number of patients, it would be of high importance to offer priority vaccinations to patients receiving cytotoxic chemotherapy, in particular for hematologic malignancies [21,22]. The performance of COVID-19 mRNA vaccines in hematological malignancy patients is unknown, as these individuals were excluded from COVID-19 vaccine clinical trials [23,24].

One study measured SARS-CoV-2 antibody responses in 67 patients with hematological malignancies who have received two doses of either the mRNA-1273 (Moderna) or the BNT162b2 (Pfizer) vaccine. Underlying malignancies were B-cell chronic lymphocytic leukemia (CLL, 19.4%), lymphomas (31.3%), multiple myeloma (43.3%), and other myeloid malignancies (5.97%). Thirty patients (44.8%) were undergoing therapy for their cancers, whereas 37 (55.2%) were under observation. Among the 62 patients whose vaccine type was available, 50.8% (34/67) and 41.8% (28/67) had received the BNT162b2 or mRNA-1273 vaccines, respectively. In total, 31/67 patients (46.3%) had a negative antibody result after vaccination and were therefore considered to be vaccine non-responders. Older patients were more likely to be vaccine non-responders than younger patients [25].

This data show that nearly half of patients with hematological malignancies do not generate antibodies after completing their COVID-19 vaccine series, which is in stark contrast with the results of phase 1 mRNA vaccine immunogenicity trials, in which robust antibody responses were seen in essentially 100% of participants [26,27]. This lack of response was particularly pronounced among patients with CLL, in whom the results of qualitative testing demonstrated significantly lower antibody signals compared to patients without CLL, suggesting that patients with CLL are unable to develop any antibody response after COVID-19 vaccination. These findings cannot be explained by age, cancer therapy, or IgG levels, and are therefore likely a result of the humoral defects that are characteristic of CLL [28].

Therefore, the case for vaccinating patients with certain cancers who have limited ability to mount a natural neutralizing antibody response to COVID-19 infection is further strengthened to prevent spread to others, in particular given their need for frequent visits to clinics to continue with their cancer care. It is possible that patients with certain cancers receiving anti-CD20 or cytotoxic therapies may not demonstrate an antibody response to the COVID-19 vaccination, but because the current vaccines demonstrate a strong T-cell response, it is possible that they would still result in protective T-cell immunity.

A hypothetical alternative option may be treatment with monoclonal antibodies against Sars-CoV-2 spike proteins casirivimab and imdevimab. providing neutralizing SARS-CoV-2 Abs (mAbs), lead to an effective and well balanced immune response, as reported in recent case series [29].

In haematological patients, combined therapy (steroids, mAbs and remdesivir) leads to reduced viral load, activation of T lymphocytes and inflammatory cytokines without affecting the functionality of the response of specific peripheral blood T lymphocytes.

Further studies are needed to understand the best clinical and therapeutical management of this patients such as the use of antiviral agents, systemic steroid, passive and active immunotherapy, and their impact on anti-SARS-CoV-2-specific antibody production.

These findings underscore the importance of adherence to non-pharmaceutical interventions to prevent COVID-19 in hematological malignancy patients, particularly in the context of the limited arsenal of SARS-CoV-2 antiviral therapies, the high mortality rates of cancer patients with COVID-19, and the emerging risk of prolonged SARS-CoV-2 replication and variant generation in cancer patients [30].

Conclusion

Although several papers have shown no decrease in all-cause mortality or any benefit for other clinical outcomes among patients with normal immune system function, passive transfer of COVID-19- neutralizing antibodies through CPT proved to be efficient and safe in patients with protracted COVID-19 diseases presenting with severe humoral immunity impairment. The benefit in the administration of CPT in our patient is clear, so we assume that, in this specific population like patients with hematological disorders, the use of CPT should be considered earlier, before a clinical worsening. Although immunological correlates of vaccine protection may be more complex than the presence or absence of antibody responses, these patients should be advised to wear masks and observe social distancing regardless of vaccination status.

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