PROLONGED COVID-19 INFECTION IN A CHILD WITH LYMPHOBLASTIC NON HODGKIN LYMPHOMA: WHICH IS THE BEST MANAGEMENT?

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CP	Convalescent plasma
COVID-19	Coronavirus disease 2019

ABSTRACT

During SARS-CoV-2 pandemic, oncologists manage patients at higher risk of having a severe course of this infection. This raises new questions about their correct management, as well as the difficulty of distinguishing tumor/treatments complications from those related to Coronavirus disease 2019 (COVID-19).

We report a case of an 11 year-old boy undergoing treatment for T cell lymphoblastic lymphoma who experienced a prolonged SARS-CoV-2 infection. Oncological therapy was continued without significant changes compared to the initially planned treatment. No relevant complications occurred. COVID-19 convalescent plasma (CP) was administered, resulting in a positive antibody titer after 24 days.

INTRODUCTION

SARS-CoV-2 pandemic led healthcare professionals to face new challenges. Oncologists have to manage patients with cancer, known to be at higher risk of severe COVID-19.[1–3] Although it is recognized that children have a more favorable course of the disease from SARS-CoV-2,[4] pediatric patients with cancer have potentially a higher risk of morbidity and mortality from viral respiratory infections.[1,5] Since a consistent proportion of children and adolescents with cancer are potentially curable, a key issue in case of SARS-CoV-2 infections how to balance the risk of immunosuppression due to oncological treatments and the risk of tumor failure in case of delay or major treatment deviations.[6]

International guidelines that help clinicians to manage these situations have recently been drawn up, as well as some works of reaction to the pandemic's initial experiences.[7,8]

For each positive patient a careful balance between the aggressiveness of the oncological disease and the risk and severity of the viral infection should however be made.[9]

CASE DESCRIPTION

We report the case of a 11-year-old male with a T-cell lymphoblastic lymphoma (stage III St.Jude's - Murphy's) treated with intravenous and intrathecal polichemotherapy according to the Italian guidelines (after the EURO-LB02 Protocol[10]) from October 2020.

On November 9, 2020, he performed a naso-pharyngeal surveillance molecular test, that resulted positive for SARS-CoV-2 (the contemporary anti-SARS-CoV-2 antibody titer was negative).

Despite his good clinical conditions, because of known significant immunosuppression, he was hospitalized in order to continue the induction phase (Fig.1a) in a safer setting knowing that induction is the most intense part of the treatment and with the greatest risk of infectious complications.[10]

No antibiotic nor antiviral drugs were administered except for the continuation of usual prophylaxis (oral trimethoprim-sulfamethoxazole and acyclovir).

However, in order to reduce the risk of possible severe COVID-19, the patient received CP on days 11 and 12 from the first positive swab.

He did not developed SARS-CoV-2-related symptoms, nor signs of severe organ disease. We could not find however an explanation for a transient episode of acute pancreatitis associated with hypertransaminasemia and for a prolonged antithrombin III deficiency after the Peg-Asparaginase administration. Furthermore a CT scan performed for other indication showed basal bilateral parenchymal disventilative areas without any evidence of ground-glass opacities.

The anti-SARS-CoV-2 antibody titer (total IgG-IgM) was found finally positive 24 days after plasma administration.

After 47 days of hospitalization, the patient completed the induction phase and was discharged.

Due to the previous pancreatic and hepatic toxicity and the concomitant and persistent SARS-CoV-2 positivity we decided to reduce the dose of methotrexate (3 g/m^2) for the first administration (protocol M) (Fig.1b), while, given the absence of toxicity, the subsequent courses were

administered at full doses but reducing the infusion time to 6 hours instead of 24; the clearance of the drug was normal and no toxicity was observed.

At the time of writing this report the child is still on treatment and the COVID-19 swab has just become negative, 107 days after the first positive swab.

DISCUSSION

We have described the case of a child with an aggressive lymphoma and protracted SARS-CoV-2 infection.

The concomitance of these two conditions aroused several problems: did the immunosuppression expose our patient to the risk of a severe infection? Continuing chemotherapy had more advantages or disadvantages? Using one of the therapies suggested for severe COVID-19 infection would have been of some help? How to distinguish between the comorbidities related to the tumor and chemotherapy from those related to infection?

A large multicenter Italian study on COVID-19 in 759 children revealed that older age (>5 years old) and underlying chronic diseases (including cancers) are risk factors for symptomatic COVID-19.[11] However, the few data on pediatric cancer population seem to suggest that in these subjects, compared to adults, COVID-19 appears with a lower severity or even asymptomatic. Although the limited information do not yet allow to draw up guidelines on pediatric oncological treatments, the literature reports on different experiences in SARS-CoV-2-positive children who continued chemotherapy.[5,12,13]

A case series on 15 Spanish children with cancer and COVID-19 reported a mild course of the disease, with only 13% requiring oxygen and a few receiving specific therapies; interestingly, 60% of patients did not delay chemotherapy.[12] Conversely, a recent study of the French Society of Pediatric Oncology reported a less encouraging experience on 37 patients with cancer and COVID-19: 76% patients were symptomatic for SARS-2-CoV infection and 65% had received

chemotherapy a month prior to COVID-19 diagnosis. 14% required intensive care unit admission because of COVID-19 (2/5 had undergone autologous stem cell transplantation within 2 months before COVID-19 diagnosis) and one died.[13]

It must be considered that the immunosuppression could be associated with a prolonged infection and delayed viral clearance,[14–16] so waiting the negativization of the swab to resume treatments could lead to significant delays and reductions in dose density/intensity that is crucial for many pediatric cancers. If children and young adults treated for cancer may be at risk for severe COVID-19 disease, and should be closely monitored, it seems also desirable to continue oncological treatments to prevent any delay which can negatively affect the prognosis.[6]

In our patient management the absence of virus-related symptoms prevented us from starting any specific treatment for COVID-19 at the time of its diagnosis. We decided however to administer CP, even if the data on its efficacy were discordant.[17–19] The state of immunodepression justified the late antibody response.[20] Several trials fail to demonstrate the clinical improvement by CP administration if compared to placebo arm;[19,21] a recent report showed instead that an early administration of high-titer CP against SARS-CoV-2 to mildly ill infected patients significantly reduced the progression of COVID-19.[22] Starting from these considerations and following the favorable experience with CP in adult patients with COVID-19 and severe humoral deficiency,[20] we treated our patient with two courses of CP to prevent the progression of infection, continuing chemotherapy.

Though after a longer time, the anti-SARS-CoV-2 antibody titer of our patient became measurable. We cannot assert with certainty whether seroconversion occurred thanks to the CP but we feared that the child's immune system was too compromised to independently guarantee the production of antibodies.[20]

Since the first positive swab, the clinical course of the patient was generally regular. We had twice the dilemma of whether the unexpected manifestations that we observed were of iatrogenic or of

infectious origin. The acute pancreatitis we observed could be due either to the therapy with Peg-Asparaginase for lymphoma or to SARS-CoV-2 infection, as reported in the literature.[23–26]

We also observed a prolonged antithrombin III deficiency which is known to be associated with Asparaginase and Peg-Asparaginase[23] but that in our case was more severe and more protracted than expected. The infection could have indeed played a role, also considering the evidence on thrombotic alterations related to COVID-19.[27,28]

Overall, the management of the child was not complicated by the infection and continuing the treatment proved to be the correct choice.

We believe that our report could be useful for all those professionals facing the challenge of treating pediatric hemato-oncological patients during COVID-19 pandemic. The aggressiveness of most pediatric cancers imposes to balance the continuation of the chemotherapy and the potential risk of severe COVID-19 course.

The Authors declare that there is no conflict of interest.

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LEGENDS

Fig.1 Flow-chart from the treatment plan EURO-LB 02 for Lymphoblastic Lymphoma. A) Induction phase; B) Protocol M

Fig.2 Timeline of treatments and diagnostic tests.

PA: Peg-Asparaginase; AT: antithrombin III; P: plasma; CP: convalescent plasma; red square: negative anti-SARS-CoV-2 antibody titer; green square: positive anti-SARS-CoV-2 antibody titer; red circle: positive anti-SARS-CoV-2 swab; green circle: negative anti-SARS-CoV-2 swab.