Favorable outcome of Covid-19 infection in a pediatric cancer patient receiving an anti-PD-L1/anti-CTLA-4 combination

Gabriel REVON-RIVIERE MD[1,2], Christine SOLER MD[3], Tina ANDRIANARIVONY MD[1], Sarah FILY MD[1], Nicolas ANDRE MD, PhD[1,2]

1- Aix Marseille University, APHM, Department of Pediatric Oncology & Hematology, Marseille, France.
2- Aix Marseille University, APHM, Marseille Early Phases Cancer Trials Center CLIP², Marseille, France.
3- Hematology Department, Hôpital l'Archet, CHU de Nice, Nice, France.

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Correspondence to:
Pr Nicolas ANDRE
Department of Pediatric Oncology & Hematology
AP-HM
Aix Marseille University
Marseille
France
0491386828
Nicolas.andre@ap-hm.fr

To the Editor:

Following the first wave of the COVID pandemic, pediatric oncologists started learning how to handle and advise pediatric patients with COVID-19 infection about their cancer treatment. Initial recommendations regarding the care of such patients have been issued by the leading

pediatric cancer organizations (1). While adult cancer patients appear to be more vulnerable to COVID-19 (2), pediatric oncology reports from Europe (3-5), the USA (6) and the rest of the world (7) suggest a benign clinical course for most children and adolescents with cancer, although a severe form seems to occur more frequently than that reported in the global pediatric population (3). The management of COVID-19 pediatric patients receiving immune checkpoint inhibitors and the risk for such patients, however is unknown. We report the case of a 16-year-old male with a refractory metastatic ossifying fibromyxoid sarcoma harboring a ZC3H7B-BCOR fusion who was infected by COVID-19 while receiving an immunotherapy regimen

The patient had previously received and progressed after several chemotherapy regimens: IVADO (ifosfamide, vincristine, actinomycin D and doxorubicin), VIT (vincristine, irinotecan and temozolomide), and metronomic navelbine and cyclophosphamide. Molecular profiling of the tumor was performed through the MAPPYACTS program (NCT02613962) but did not reveal any suitable alterations for targeted therapy. The patient was referred to our institution for enrolment in a phase I trial (NCT03837899) evaluating the combination of durvalumab (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). The treatment plan involves an initial cycle of durvalumab followed by 4 cycles of the combination of durvalumab and tremelimumab, then followed by durvalumab monotherapy until progression or toxicity.

The patient had no prior history of any other chronic condition, had a normal performance status (Karnofsky index100), and experienced no symptoms. At time of enrollment, radiological evaluation showed a target tumor lesion (20 mm hypodense mass of the left psoas,) and pulmonary abnormalities (infracentimetric right apical lesions and two residual lesions in the right lower lobe, resulting from a tumorectomy performed 18 months earlier). Laboratory screening showed no impairment of hematologic, gastrointestinal or renal function, lack of abnormal inflammatory markers and pre-treatment testing for SARS−CoV−2 by real−time polymerase chain reaction (rtPCR) was negative.

When visiting the clinic on day 8, one week after the first infusion of durvalumab, the patient reported isolated anosmia starting 48 hours before the visit. The clinical exam was otherwise normal with no fever or respiratory symptoms. No laboratory abnormalities were noted. The rtPCR test for COVID-19 was positive. The treatment was held according to guidance

provided by the sponsor, and the patient was closely monitored in agreement with the principal investigator. The patient did not receive any specific treatment for the COVID infection. The patient remained asymptomatic for any infection symptoms, yet the repeat rtPCR was still positive at 1 month.

According to the French experience of pediatric oncology patients with COVID-19, the median time to a negative PCR was 16 days and the median time to resume cancer treatment was 14 days (8). Cases of long-term COVID-19 positive patients who remain asymptomatic have also been reported (5). Considering the risk of not treating the underlying malignancy against the potential risks of exposure to an immune checkpoint inhibitor regimen in an asymptomatic COVID-19 patient, a decision was made to resume the immunotherapy regimen despite still positive rtPCR.

The rtPCR test became negative after 35 days, and the patient had confirmed immunity with a positive IgG for COVID-19 at day 28 after the initial COVID diagnosis. The patient proceeded to receive cycle 2, after a 2-weeks delay, with the combination of durvalumab and tremelimumab and has continued to do well 6 weeks after resuming treatment without any new adverse events concerning for COVID infection or exacerbation of any immune-mediated adverse events.

In adults, the use of immune checkpoint inhibitors did not increase the severity of the reported toxicities in patients with lung cancer (9). Souza et al. (10) reported two cases of interstitial pneumonia in 2 COVID-19 positive patients receiving nivolumab and ipilimumab; it is not possible however, to distinguish an immune-mediated adverse effect associated with the immunotherapy regimen versus a direct effect from the COVID-19 infection. In children, we did not find any reports about the use of immune checkpoint inhibitors in a COVID-19 positive patient. Smith et al, reported a fatal case of a COVID-19 infection in a child with neuroblastoma receiving dinutuximab, granulocyte−macrophage colony−stimulating factor, and isotretinoin (11). Bisogno et al, in a series describing the outcomes of 29 pediatric cancer patients with confirmed COVID-19 infection, reported one case of a patient receiving brentuximab vedotin and nivolumab (13); the specific outcome for this patient, however, is unknown.

As reported by ITCC, the COVID-19 pandemic has deeply impacted the activity of pediatric oncology early phase trial centers in Europe, reflected by a 61% decrease in enrollment (12). Our case however, suggests that immune checkpoint therapy can be resumed safely for a patient with asymptomatic COVID-19 disease. Nonetheless, despite our favorable experience, we recommend that pediatric oncologists exercise caution regarding the administration of immune−activating therapies during the COVID−19 pandemic. This includes comprehensive contact screening prior to treatment initiation and considering the implementation of a treatment interruption of such therapy in infected patients.

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