

Case Report

Viral Clearance with Neutrophil Recovery in a Patient with Active COVID-19 Infection and Refractory Acute Myeloid Leukemia Who Underwent Successful Reinduction with Cytarabine/Idarubicin

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Keywords

Acute myeloid leukemia · Myelosuppressive chemotherapy · Complete remission · Active COVID-19 infection · Viral clearance

Abstract

Administering myelosuppressive chemotherapy to patients with aggressive malignant hematologic disorders typically poses serious infectious complications, which can be exacerbated by the presence of active COVID-19 infection. We report on a case of a successfully treated fit elderly woman with refractory acute myeloid leukemia (AML) who also had mild COVID-19 infection and detectable viral load at the time she was found to have recurrent disease. Prior to initiation of reinduction treatment with cytarabine/idarubicin, this 2-dose COVID-19-vaccinated patient received antiviral therapy with remdesivir with resolution of upper respiratory symptoms. This was followed by sotrovimab on the third day of chemotherapy. Throughout her hospital course, she remained hemodynamically stable with one episode of neutropenic fever without other identified infections. Symptomatic reactivation of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 was not observed. After achieving biopsy-confirmed morphologic remission of AML and with neutrophil recovery, the patient gradually cleared the virus, eventually testing negative on polymerase chain reaction test of the nasopharynx. This case underlines the importance of considering initiation

of timely chemotherapy, although myelosuppressive, in appropriate patients with aggressive hematologic malignancies and concomitant SARS-CoV-2. It demonstrates management of active COVID-19 infection in this group of patients and the dynamics of SARS-CoV-2 viral load during leukemia treatment.

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Introduction

The COVID-19 pandemic, which started in early 2020, has created challenges with regards to effective and timely treatment of many patients, especially those who are infected with the novel coronavirus and in need of immediate cancer treatment that can be myelosuppressive. Active COVID-19 infection gives most oncologists a pause when it comes to starting treatment for infected patients' malignant hematologic disorders. Prior studies have indicated worse COVID-19 outcomes in patients with acute myeloid leukemia (AML) receiving cancer treatment [1, 2]. Weighing the risks and benefits of withholding treatment until infection clearance in an already immunocompromised host is done on a case-by-case basis with careful consideration of the best outcome for patients. Here, we present the case of a patient in need of life-saving AML reinduction treatment, who had active COVID-19 infection.

Case Presentation

A 68-year-old woman with medical history significant only for recently diagnosed AML presented with 80% blasts on bone marrow biopsy, white blood cell count 175,000 with 27% peripheral blasts, normal karyotype on cytogenetics, and positive for DNMT3, NPM1, PTPN11, and two TET2 pathogenic mutations next-generation sequencing test. Induction chemotherapy included decitabine and venetoclax and was complicated by nonsustained ventricular tachycardia with rapid atrial fibrillation and bacterial pneumonia. She appeared to be in remission but presented for her second cycle of this regimen with a new maculopapular rash involving the torso and upper extremities (shown in Fig. 1). Biopsy revealed leukemia cutis, and peripheral blood showed 44% monocytic blasts. The following day, the patient reported to clinic complaining of a nonproductive cough along with rhinorrhea and sore throat. She was afebrile. Respiratory viral polymerase chain reaction (PCR) panel from a nasopharynx swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), supporting a new diagnosis of COVID-19. Of note, the patient had received two doses of the mRNA-1273 vaccine, 26 days apart, 9 months earlier (prior to her AML diagnosis). The patient was admitted to the medicine service, where she spent 1 week with care focused on management of COVID-19. Computed tomography of the chest showed no definitive findings of pneumonia. She did not require supplemental oxygen or intubation. She completed a 3-day course of remdesivir. Although she remained positive for SARS-CoV-2 on nasopharyngeal PCR testing, she was otherwise hemodynamically stable with resolved upper respiratory symptoms, and a decision was made for her to be transferred to the malignant hematology service to undergo urgent treatment for refractory AML. She received 7+3 reinduction chemotherapy with cytarabine 170 mg (100 mg/m²) IV daily for 7 days and idarubicin 20 mg (12 mg/m²) IV daily for 3 days, as well as prophylactic intrathecal cytarabine 50 mg on day 28 of chemotherapy. She was retested every 3–5 days for COVID-19 by nasopharyngeal PCR test. On day 3, given the persistent SARS-CoV-2 positivity

Fig. 1. A rash on the patient's back, biopsy confirmed as leukemia cutis on a 3.5-mm punch biopsy, at the start of cycle 2 of decitabine/venetoclax, supporting a diagnosis of refractory AML.



on testing, the patient received further treatment for COVID-19 with sotrovimab. However, she remained positive for the virus throughout the entire admission. On day 7, she experienced chest pain, and computed tomography of the chest demonstrated evidence of pericarditis. As compared to a prior study from the end of cycle 1 of decitabine/venetoclax, a 2D echo showed a slightly larger pericardial effusion without hemodynamic compromise. Per cardiology recommendations, the patient started a 3-month course of daily colchicine with quick resolution of her chest pain. Blood cell counts reached nadir on day 9 with absolute neutrophil count (ANC) of 0. The patient developed neutropenic fever on day 20. She was otherwise asymptomatic. Infectious workup, including a chest x-ray, was negative. She completed a 7-day course of empiric cefepime on day 26. While ANC remained below 500, she received antimicrobial prophylaxis with valacyclovir, isavuconazole, and levofloxacin (while not on empiric cefepime). Counts started recovering on day 25 with ANC of 170. Infectious control monitored the patient's COVID-19 threshold (CT) count via GeneXpert2[®] system on the nasopharyngeal COVID-19 PCR test, as shown in Table 1. On discharge, day 36, COVID-19 PCR was retested and remained positive. A recovery bone marrow biopsy performed on the same day was consistent with a morphologic complete remission but with persistent mutations involving DNMT3 and TET2. By discharge, the patient's leukemia cutis rash had cleared.

In the outpatient setting, the patient's COVID-19 PCR became negative on day 42. The patient went on to complete one cycle of high-dose cytarabine consolidation (6 doses of cytarabine 1,000 mg/m² every 12 h) on a clinical trial, with plans for a second cycle, followed by allogeneic hematopoietic stem cell transplantation with curative intent. She received tixagevimab/cilgavimab 600 mg intramuscularly once for COVID-19 prophylaxis 2.5 weeks after initiation of consolidation chemotherapy. She tolerated chemotherapy well and has remained SARS-CoV-2-negative.

Discussion

The case described here of an elderly patient without significant comorbidities successfully treated for refractory AML while infected with SARS-CoV-2 demonstrates several important points related to the dynamics of viral activity and load in this group of patients. First, despite several layers of defense against the virus, including vaccination, remdesivir, and sotrovimab, the patient did not clear the virus promptly, and this was likely due to immunocompromise related to AML as well as to the chemotherapy she received. Her symptoms likely due to COVID-19 resolved quickly. Second, there was no progression of the viral infection during the time period of chemotherapy-induced severe neutropenia.

Table 1. Viral detection and load from the time of COVID-19 diagnosis to viral clearance with reference to chemotherapy time points

Time point	Decitabine/venetoclax cycle 2 day 3	Day prior to reinduction	7+3, day 9	7+3, day 25	7+3, day 29	7+3, day 36	7+3, day 42
SARS-CoV-2, NAA, nasopharynx (detected+ /not detected-)	First+	+	+	+	+	+	-
CT value	19.3	17.9	28.4	26.3	32.5	N/A	N/A
WBC	9.8	19.6	0.3	0.7	1.2	2.6	3.1
ANC	3.33	3.53	0	170	220	1.39	1.67
Peripheral blood blasts, %	21	18	0	0	0	0	0
Marrow blasts		Marrow not performed				0	

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NAA, nucleic acid amplification; CT, cycle threshold; WBC, white blood cell count; ANC, absolute neutrophil count; 7+3, cytarabine/idarubicin chemotherapy; N/A, not available/not applicable.

While she experienced neutropenic fever, the patient did not show any symptoms of upper or low respiratory infection to suggest the fever was due to COVID-19. Third, once her ANC became detectable upon count recovery, her viral load decreased as measured indirectly by rising CT of the COVID-19 PCR nasopharyngeal test. Finally, with full recovery of the neutrophil count, the patient cleared the virus entirely without repeat infection with subsequent chemotherapy.

Infection with SARS-CoV-2 leads to the COVID-19 immune syndrome, which is characterized by three distinct clinical and genomic phases that may be used to describe the clinical course of this and other infected patients [3]. The initial phase is the “asymptomatic/presymptomatic phase,” in which the virus affects the respiratory system through the receptor angiotensin-converting enzyme 2 (ACE2) and/or the gastrointestinal system through the co-receptor aminopeptidase N (ANPEP) [3]. This patient had involvement of the respiratory system only. The propagating phase, associated with the EGF receptor (EGFR) and IGF2R gene pathways, is the “respiratory phase with mild/moderate/severe symptoms,” in which there may be lower respiratory, cardiovascular, renal, hematopoietic, or other organ system involvement [3]. The complicated phase can lead to acute respiratory distress syndrome, sepsis, as well as multiorgan failure and septic shock, and is believed to be driven by multiple genes, including interferon (IFN) genes, RSAD2, CXCL10, CXCL11, OAS2, and SAMD9 [3]. In our patient, the COVID-19 immune syndrome did not progress to the propagating or complicated phase.

Management of this patient’s COVID-19 infection was made possible through frequent viral testing. Availability of these tools to fight SARS-CoV-2 is essential for patients who are moderately or severely immunocompromised due to receiving active cancer treatments. Nasopharyngeal swabs using PCR, a type of nucleic acid amplification test (NAAT), generate rapid results within 15–30 min, allowing point-of-care testing, and have accuracy close to 100% [4]. NAAT is thus preferred over antigen tests in hospitals given the ability to rapidly and reliably detect very small amount of viral genetic material. The CT value generated with the PCR test indirectly measures the viral load by indicating how many attempts are made to copy the viral genetic material in a sample before detection, with lower values suggesting higher viral loads [2]. A CT value of less than 32 is consistent with a sample containing replicating virus as it has adequate genetic material for whole genome sequencing [5]. For our patient, the PCR test with CT was repeated every 3 days and results were closely monitored by the cancer hospital’s infectious control team who provided guidance for proper isolation techniques and personal protective equipment for the clinical team members. While immunocompetent patients with CT >32 are considered noninfectious, there are no data regarding this in patients with AML [5]. To determine if a patient is truly noninfectious, testing beyond the PCR/CT test must be performed to show there is no actively replicating virus. This can be accomplished by different methods including viral culture that can detect replicating virus 8–15 days from symptom onset, a subgenomic viral RNA assay that can identify the virus up to 14 days, or a 2-step strand-specific reverse transcription PCR test specific to the minus strand of the envelope gene that can detect the minus-strand RNA up to 30 days [6]. These diagnostic tools were not utilized in this case, and the patient was followed with repeat PCR/CT testing as per hospital policy during myelosuppression. Subsequently, upon neutrophil recovery, our patient’s negative PCR test allowed for her to be seen in our outpatient clinic, where only SARS-CoV-2-negative patients are permitted. NAAT was positive for close to 50 days, which is typical for patients with AML [7].

Beyond close monitoring of the virus, this patient with refractory AML benefited from various effective antiviral pharmaceuticals. Prior to her AML diagnosis, she had completed the two-dose mRNA vaccine series. In a small observational study of patients with AML and myelodysplastic syndrome, this series was shown to lead to 95.7% seropositivity after the

second vaccine [8]. As treatment, she also received a course of remdesivir, an antiviral that inhibits the SARS-CoV-2 RNA-dependent RNA polymerase, which in a randomized trial improved time to recovery by 5 days from 15 to 10 days [9]; as well as sotrovimab, a monoclonal antibody used for mild to moderate COVID-19 infection for viral subtypes preceding the Omicron BA.2 subvariant in patients who were at high risk for progression to severe infection with 85% reduction in hospitalization or death [10, 11]. Once SARS-CoV-2-negative, our patient received tixagevimab/cilgavimab, a combination of two monoclonal antibodies that serves as COVID-19 prophylaxis and provides up to 6 months of protection from pre-Omicron SARS-CoV-2 variants for immunocompromised patients or those who cannot receive vaccination [12]. Although the patient's exact SARS-CoV-2 variant was unknown, the predominant variant in the community at the time was Omicron. Her infectious symptoms remained mild, resolved quickly, and did not recur with the antiviral pharmaceuticals she received.

Overall, the patient tolerated AML therapy well, although her treatment was not without complications. Throughout her inpatient reinduction, she remained on the malignant hematology floor without need for medical intensive care unit care. Her performance status and energy were excellent prior to discharge from the hospital. End of treatment bone marrow biopsy showed complete morphologic response and clearance of at least two out of five pathologic mutations that were present initially.

Given the ongoing pandemic, many patients worldwide with malignant hematologic diseases have required and received cancer therapy just prior or while infected with SARS-CoV-2. The outcome has varied based on the type of cancer, kind and timing of cancer therapy, severity of COVID-19 infection, patient's age, and comorbidities. In a retrospective European study of 59 patients with concurrent COVID-19 infection and hematologic disorders of whom 34% had myeloid malignancies and nearly half had received chemotherapy or immunotherapy within 30 days, the mortality rate was 34% with higher mortality in patients over the age of 60 years [13]. In the first published case report that detailed the clinical course of a patient with both AML and COVID-19, the patient's reported respiratory and systemic symptoms of infection remained mild, but AML did not respond to induction therapy with daunorubicin/cytarabine [14]. Overall, these studies suggest that patients with leukemia and mild to moderate active COVID-19 may continue to have controlled infection allowing them to receive chemotherapy. It is important to note that those two studies predate advances in antiviral pharmaceuticals and focused mainly on the course of SARS-CoV-2 in an immunocompromised host. While COVID-19 was diagnosed in patients who were already undergoing treatment or in need of urgent treatment, the latest recommendations of the Centers for Disease Control and Prevention are still to try to delay therapy for cancer until clearance of the virus if possible [15]. However, for patients with acute leukemia, significant delay is seldom possible.

Conclusion

In this case, as suspected, the immune state of a patient with active malignant hematologic disease correlated with viral load and symptoms. Surprisingly, myelosuppressive chemotherapy did not cause severe illness, likely because of protection from immunity due to vaccination and antiviral medications and myelosuppression being temporary. Based on this patient's experience, we conclude that lifesaving chemotherapy should be considered in the setting of mild COVID-19 infection in an otherwise medically stable patient with AML who had been vaccinated and/or can receive the latest recommended antiviral treatment with close monitoring of the viral load.

Statement of Ethics

The University of Florida Institutional Review Board has determined that a case report is a retrospective analysis of one to three clinical cases and does not constitute human-subjects research; therefore, it does not require prospective IRB approval. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The completed signed consent form is available with the editor if requested.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Erin A. Dean wrote the manuscript. Danielle V. Casaus provided infectious disease data. Randy A. Brown, Pavneet Kaur, and Danielle V. Casaus reviewed and edited the manuscript.

Data Availability Statement

All data necessary for this manuscript are included in this article. Further inquiries can be directed to the corresponding author.

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