EXCEPTIONAL CASE REPORT

blood advances

Challenges in treatment of patients with acute leukemia and COVID-19: a series of 12 patients

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Key Points

- Patients with acute leukemia present with a prolonged and severe course of COVID-19, which is paralleled by high rates of viremia.
- Low-intensive chemotherapy seems to be more feasible in patients with acute myeloid leukemia and concomitant SARS-CoV-2 infection.

Introduction

Since January 2020, >30 million cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have been confirmed globally.[1] Yet, there is almost no information on the clinical impact of coronavirus disease 2019 (COVID-19) in adults with acute leukemia (AL). Because untreated newly diagnosed or refractory/relapsed AL is fatal, these patients require immediate chemotherapy in spite of concomitant SARS-CoV-2 infection. We report a series of 12 patients with AL and SARS-CoV-2 infection who were treated in our department between 18 March and 18 May 2020.

Case description

Eight patients (67%) had acute myeloid leukemia (AML); 4 patients (33%) had acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL).

Characteristics of AML patients

At SARS-CoV-2 diagnosis, 3 patients had untreated, newly diagnosed AML; 4 patients had refractory/relapsed AML. One patient was in complete remission with incomplete hematologic recovery (CRi) and received high-dose cytarabine for consolidation. All 4 refractory/relapsed patients had been treated with intensive chemotherapy before SARS-CoV-2 confirmation. After SARS-CoV-2 infection, 6 patients received therapy with azacytidine and venetoclax[2]; 1 patient with newly diagnosed AML received induction therapy with daunorubicin and cytarabine (3+7).

Clinical course of AML patients

The only AML patient who was in remission started 12 days after SARS-CoV-2 diagnosis with high-dose cytarabine consolidation therapy. He died 23 days after SARS-CoV-2 infection due to severe acute respiratory distress syndrome (ARDS) despite extracorporeal membrane oxygenation (ECMO) in deep aplasia. All three AML patients with newly diagnosed AML developed severe ARDS: the only one who was treated with intensive chemotherapy died. None of the 4 refractory AML patients treated with azacytidine/venetoclax developed ARDS.

Characteristics of ALL patients

One patient had newly diagnosed untreated Philadelphia chromosome–positive common B-cell ALL (B-ALL) and received prephase treatment 5 days before SARS-CoV-2 infection, and continued with induction therapy. Three patients were already under ALL-specific treatment at SARS-CoV-2 diagnosis: 1 elderly patient with T-cell ALL (T-ALL) received induction therapy. The patient with T-cell LBL (T-LBL) in complete remission after induction and consolidation therapy received 1 course of reinduction therapy. One minimal residual disease–positive patient with B-ALL received continuous infusion of

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Table 1. Overview of each patient's characteristics: part 1

Pt	Age, sex	Underlying disease,* date of first leukemia diagnosis	Systematic therapy shortly before and during COVID-19, date of therapy start	Remission status after current therapy	Relevant secondary diseases	Duration of aplasia, d	Admit to ICU/ invasive ventilation (duration, d)	SOFA score† at ICU admit/ max 72 h	Severity of ARDS (Horovitz index)	Complications during ICU stay	Chest CT results per Simpson et al,[6] total severity score per Li et al[7]	SARS-CoV-2 viremia at baseline and at day 14 of follow-up
1	34, M	Ph^+ common B-ALL, 3/13/2020	GMALL 8/13 trial: 1. Prephase: 3/13/20 2. Induction: 3/19/20	MRD^+ after induction I	None	None	Yes (13)/yes (4)	2/9	Severe (75)	Septic shock, DVT	Typical appearance, 10	Baseline 3/18/20, yes; day 14, no
2	76, M	De novo AML (intermediate risk), 3/6/20	Induction 1: 3+7, 3/13/20	Unknown (death)	Follicular thyroid carcinoma 2007	15	Yes (12)/yes (8)	11/12	Severe (72)	Septic shock	Typical appearance, 8	Baseline 3/18/20, yes; day 14, yes
3	46, F	MRD^+ Ph^- common-B-ALL, 12/6/19	Blinatumomab: 1. First cycle: 3/31/20 2. Second cycle: 5/12/20	MRD^- after first cycle, second cycle ongoing	Hypothyroidism, bronchial asthma, allergic rhinitis	None	No/NA	NA	NA	NA	Typical appearance, 5	Baseline 4/6/20, ND; day 14, no
4	64, F	T-ALL, 3/13/20	GMALL recommendations for patients >55 y: 1. Prephase: 3/13/20 2. Induction 1: 3/19/20 3. Induction 2: 4/15/20	CR after induction II	None	4	Yes (9)/no	3/3	No ARDS	None	ND	Baseline 4/5/20, yes; day 14, no
5	47, M	De novo AML (favorable risk), 3/9/20	AMLSG21-12 trial: 1. Induction 1: 3+7, 3/12/20 2. Consolidation 1: HDAC, 4/17/20	1. CRi after induction I 2. Unknown (death)	None	7	Yes (11)/yes (10)	3/11	Severe (55)	Septic shock, stroke, subarachnoid hemorrhage	Typical and indeterminate appearance, 19	Baseline 4/5/20, yes; day 14, yes
6	50, M	De novo AML (adverse risk), 2/19/20	1. Induction 1: 3+7 + midostaurin, 2/21/20 2. FLAG-Ida + sunitinib: 3/27/20 3. Aza and Ven: 5/2/20	Refractory to 1. and 2. 3. Ongoing Aza/ Ven treatment	None	43	Yes (5)/no	4/5	No ARDS	None	Typical appearance, 5	Baseline 4/5/20, yes; day 14, no
7	62, M	De novo AML (adverse risk), 4/2/20	1. First-cycle Aza and Ven: 4/7/20	CRi	None	7	Yes (23)/yes (12)	2/4	Severe (85)	Septic shock	ND	Baseline 4/5/20, yes; day 14, yes
8	60, M	Secondary AML,‡ 2/27/20	1. Induction 1: CPX351, 3/2/20 2. First-cycle Aza and Ven: 4/16/20	Refractory after induction I and Aza/ Ven	Lung emphysema, smoker	34	Yes (3)/no	5/6	No ARDS	None	ND	Baseline 4/5/20, yes; day 14, no
9	64, M	Therapy-associated AML, 2/27/20	1. Induction 1: refractory to CPX351, 3/2/20 2. First-cycle Aza and Ven: 4/7/20	1. Refractory after induction I 2. CRi	Primary CNS lymphoma 2010	36	Yes (2)/no	4/4	No ARDS	None	Typical appearance, 6	Baseline 4/5/20, yes; day 14, yes
10	60, M	De novo AML (adverse risk), 3/5/20	1. Induction 3+7 + midostaurin: 3/9/20 2. First-cycle Aza and Ven: 4/14/20	Refractory after induction I and Aza/Ven	None	37	Yes (9)/no	3/4	No ARDS	None	ND	Baseline 4/5/20, yes; day 14, no

3+7, daunorubicin 60 mg/m^2, days 1, 3, and 5 plus cytarabine 100 mg/m^2 days 1-7; admit, admission; aplasia, neutrophil count $<0.5 \times 10^9$/L; Aza, azacytidine; CPX351, CPX351 100 U/m^2 days 1, 3, and 5, azacitidine and venetoclax analog per DiNardo et al[2]; DVT, deep vein thrombosis; F, female; FLAG-Ida, fludarabine 30 mg/m^2 days 1-4, cytarabine 2000 mg/m^2 days 1-4, idarubicin 10 mg/m^2 days 1 and 3; GMALL, German Multicentre ALL Study Group; HDAC, high-dose cytarabine, 2000 mg/m^2 twice per day, days 1-3; ICU, intensive care unit; M, male; max, maximum; MRD, minimal residual disease; NA, not applicable; ND, not done; Ph, Philadelphia chromosome; Pt, patient; sunitinib, 25 mg/d ongoing; TCL, T-cell lymphoma; Ven, venetoclax.

*AML risk stratification according to the European LeukemiaNet classification.[11]

†SOFA score according to Singer et al.[12]

‡Preexisting myelodysplastic syndrome.

Table 1. (continued)

Pt	Age, sex	Underlying disease,* date of first leukemia diagnosis	Systematic therapy shortly before and during COVID-19, date of therapy start	Remission status after current therapy	Relevant secondary diseases	Duration of aplasia, d	Admit to ICU/ invasive ventilation (duration, d)	SOFA score† at ICU admit/ max 72 h	Severity of ARDS (Horovitz index)	Complications during ICU stay	Chest CT results per Simpson et al,[6] total severity score per Li et al[7]	SARS-CoV-2 viremia at baseline and at day 14 of follow-up
11	69, F	De novo AML (adverse risk), 4/2/20	1. First-cycle Aza and Ven: 4/3/20 2. Second-cycle Aza and Ven: 5/15/2020	1. CRi	None	33	Yes (8)/yes (4)	5/13	Severe (83)	Septic shock	ND	Baseline 4/1/20, yes; day 14, no
12	32, M	Lymphoblastic TCL, 11/5/19	GMALL 08/13 trial: reinduction, 4/16/20	MRD$^+$ after reinduction	None	None	No/NA	NA	NA	NA	ND	Baseline 4/9/20, ND; day 14, no

3+7, daunorubicin 60 mg/m^2, days 1, 3, and 5 plus cytarabine 100 mg/m^2 days 1-7; admit, admission; aplasia, neutrophil count $<0.5 \times 10^9$/L; Aza, azacytidine; CPX351, CPX351 100 U/m^2 days 1, 3, and 5, azacitidine and venetoclax analog per DiNardo et al[2]; DVT, deep vein thrombosis; F, female; FLAG-Ida, fludarabine 30 mg/m^2 days 1-4, cytarabine 2000 mg/m^2 days 1-4, idarubicin 10 mg/m^2 days 1 and 3; GMALL, German Multicentre ALL Study Group; HDAC, high-dose cytarabine, 2000 mg/m^2 twice per day, days 1-3; ICU, intensive care unit; M, male; max, maximum; MRD, minimal residual disease; NA, not applicable; ND, not done; Ph, Philadelphia chromosome; Pt, patient; sunitinib, 25 mg/d ongoing; TCL, T-cell lymphoma; Ven, venetoclax.

*AML risk stratification according to the European LeukemiaNet classification.[11]

†SOFA score according to Singer et al.[12]

‡Preexisting myelodysplastic syndrome.

blinatumomab (for patients characteristics, see Table 1). All ALL patients were treated according to recommendations of the German Multicenter Study Group on Adult ALL (NCT number 02881086).

Clinical course of ALL/LBL patients

One patient with newly diagnosed ALL developed severe ARDS and deep vein thrombosis during COVID-19. None of the remaining 3 ALL/LBL patients developed ARDS. None of the 4 ALL/LBL patients died. The patient with deep vein thrombosis did not receive further pegylated asparaginase.

Methods

Data of the clinical course were collected from the patient's electronic medical records. Diagnosis of SARS-CoV-2 infection was based on virus detection by real-time polymerase chain reaction (SARS-CoV-2 E-gene RT-PCR) in respiratory tract specimens.[3] SARS-CoV-2 immunoglobulin G (IgG) antibodies were tested against viral spike protein (S1/S2) and nucleoprotein (N).

Results and discussion

The median age of patients was 60 years (*r*, 32-76 years). Seventy-five percent (n = 9) were male. Four patients (33%) were asymptomatic at SARS-CoV-2 diagnosis, but later on, all patients became symptomatic. Ten patients (83%) were admitted to the intensive care unit (ICU). Eleven patients (92%) developed COVID-19 pneumonia. None of the 4 refractory AML patients developed ARDS. However, all 4 patients with newly diagnosed AL (patients 1, 2, 7, and 11) and the AML patient in CRi developed severe ARDS (median Pa_{O_2}/Fi_{O_2} [Horovitz index] of 75 [*r*, 55-85])[4] and septic shock. Overall, 5 patients were intubated (50%): 1 patient received high-flow oxygen and 1 ECMO therapy. Median duration between the beginning of symptoms and diagnosis of ARDS was 8 days (*r*, 4-20 days).

Deep vein thrombosis was observed in 1 patient despite adequate anticoagulation.[5] The median stay at the ICU was 9 days (range, 2-23 days). Overall, 9 of 12 patients (75%) had aplasia (grade 4 neutropenia) during SARS-CoV-2 infection with a median duration of 33.5 days (*r*, 4-43 days). Six of 12 patients (50%) had grade 4 lymphopenia during clinical course (for laboratory values, see Table 2).

At diagnosis, SARS-CoV-2-RNA was detected in the upper respiratory tract samples of all patients (12 of 12) by RT-PCR at high concentrations (average 1×10^7 RNA copies per milliliter).[3] All 10 tested patients showed viremia with an average of 1×10^3 RNA copies per milliliter at diagnosis. At day 14, viral loads in respiratory samples and blood decreased overall by 1 log. Four patients still showed viremia after 14 days. Only 7 of 10 tested patients (70%) developed reactivity in SARS-CoV-2 serology (IgM and IgG) after a median follow-up of 43 days (range, 12-61 days): 1 of these patients received COVID convalescent plasma. At the end of follow-up, 2 of 10 alive patients still had detectable SARS-CoV-2 RNA in nasopharyngeal swabs (20%).

All cases in which chest computed tomography (CT) scanning was performed showed bilateral, mainly peripheral, ground-glass opacities with (n = 4) or without (n = 2) consolidation, matching the typical finding of SARS-CoV-2 infection (according to Simpson et al and Li et al[6,7]). At time of CT scanning, 3 patients were in aplasia

Table 2. Overview of each patient's characteristics: part 2

Pt	Experimental treatment	ICU treatment			Absolute count of neutrophils at baseline, $\times 10^9$/L	Highest grade of neutropenia	Highest grade of lymphopenia	Highest CrP level in mg/L (normal <5)	Highest IL−6 level in ng/L (normal <7)	Highest PCT level in μg/L (normal <0.5)	Highest ferritin level in μg/L (normal male: 22-322, normal female: 10-291)	SARS-CoV-2 IgM/IgG	Days until no detectable SARS-CoV-2 RNA in nasopharyngeal swabs*
		Type of MV (days)	Vasopressor therapy	Renal replacement therapy									
1	Lopinavir/ritonavir, Pentaglobin	HFNC (1), MV (4)	Yes	No	7.7	Grade 3	Grade 3	246	526	0.8	1 514	Negative/negative	32
2	None	HFNC (1), MV (8)	Yes	Yes	0.1	Aplasia	Grade 4	259	5250	11.84	12 436	ND/ND	Positive until death
3	COVID-19 convalescent plasma	NA	NA	No	1.5	Grade 3	Grade 3	183	109	0.09	4 006	Positive/positive	Positive until end of study
4	None	None	No	No	0.1	Aplasia	Grade 4	215	447	0.59	6 268	Positive/positive	22
5	Tocilizumab, Pentaglobin	HFNC (1), MV (9), ECMO (5)	Yes	Yes	0.3	Aplasia	Grade 4	291	8452	2.87	21 173	ND/ND	Positive until death
6	None	None	No	No	<0.1	Aplasia	Grade 4	292	287	1.87	3 204	Negative/negative	22
7	None	HFNC (1), MV (12)	Yes	Yes	11.3	Aplasia	Grade 3	368	1513	6.71	4 431	Positive/positive	36
8	None	None	No	No	0.1	Aplasia	Grade 3	163	72	0.27	2 413	Positive/positive	33
9	None	None	No	No	0.1	Aplasia	Grade 4	270	1338	4.76	11 911	Positive/positive	Positive until end of study
10	None	HFNC (5)	No	No	0.6	Aplasia	Grade 4	333	768	16.7	15 357	Positive/positive	29
11	None	MV (4)	Yes	No	1.1	Aplasia	Grade 3	361	538	4.86	2 888	Positive/negative	12
12	None	NA	NA	No	1.2	Grade 3	Grade 3	4	1.6	0.1	1 385	Negative/negative	29

Neutropenia: grade 2, $<1.5 \times 10^9$/L to 1.0×10^9/L; grade 3, $<1.0 \times 10^9$/L to 0.5×10^9/L; aplasia, $<0.5 \times 10^9$/L. Lymphopenia: grade 1, 1.1×10^9/L to 0.8×10^9/L; grade 2, $<0.8 \times 10^9$/L to 0.5×10^9/L; grade 3, $<0.5 \times 10^9$/L to 0.2×10^9/L; grade 4, $<0.2 \times 10^9$/L.

CrP, C-reactive protein; HFNC, high-flow nasal cannula; IL-6, interleukin-6; MV, mechanical ventilation; PCT, procalcitonin. See Table 1 for expansion of other abbreviations.

*Two negative PCR results >24 hours.

(patients 2, 6, and 9). Nevertheless, they were able to mount the typical infiltrates.

Three of 5 patients with ARDS were successfully extubated after invasive ventilation with a median time of 7 days (*r*, 4-12 days). Overall, 8 patients have been discharged from the ICU. Two patients have died (17%; patients 2 and 5). In contrast to the other patients, these patients showed no reduction in viral load in EDTA plasma at day 14 (see visual abstract).

In 7 cases, leukemia-specific treatment was adjusted. In 2 fit patients with newly diagnosed untreated AML (patients 7 and 11), the decision was made against intensive chemotherapy in favor of azacytidine/venetoclax. In all refractory patients (patients 6, 8, 9, and 10), the usual treatment plan was changed from intensive salvage chemotherapy to azacytidine/venetoclax. With this treatment strategy, comparable remission rates to those in non–SARS-CoV-2–infected patients could be observed.[2] The patient with newly diagnosed B-ALL had to discontinue pegylated-asparaginase treatment due to COVID-19–associated deep vein thrombosis.

Clinical symptoms of COVID-19 range from mild symptoms to critical courses and even death.[8] In unselected patients in China, mild and moderate courses have been described in ~80%, almost 14% had severe disease, and 6% critical courses.[8] We scored mild or moderate courses of COVID-19 in 3 patients (25%) and severe and critical courses in 9 patients (75%), including 2 deaths and 42% of severe ARDS. This corresponds to an almost 7 times higher rate of severe and critical courses of COVID-19 in patients with AL and LBL. In April 2020, He et al reported more severe SARS-CoV-2 infections in patients with hematological malignancies.[9]

The prolonged and severe course of clinical disease is paralleled by the virological findings showing that, during the long observation period in 2 patients, SARS-CoV-2 is still detectable and just 60% developed SARS-CoV-2 IgG/IgM. Remarkably, 4 of our patients had persistent viremia on day 14. Increasing RNA titers over the observation period were observed in the 2 patients who had a fatal outcome, which highlights the importance of monitoring RNA load in plasma.

The American Society of Hematology recommends treatment with intensive chemotherapy in patients with newly diagnosed AML and eligibility for intensive therapy.[10] Although the number in our case series is small, only 1 of 4 patients with ALL/LBL developed a critical disease state. In all 4 patients, ALL-specific therapy could be administered with only small delays or modifications. All patients with newly diagnosed AML developed critical courses with ARDS, especially those treated with intensive chemotherapy. None of the 4 refractory AML patients who were all treated with azacytidine/venetoclax developed ARDS. This combination may be less toxic than intensive chemotherapy and may be used as a bridge to further therapy. Meanwhile, after full recovery from COVID-19, 6 patients with indication for stem cell transplantation could receive transplants without SARS-CoV-2 reactivation; another 2 patients are scheduled for transplantation.

To be able to draw firm conclusions on the treatment of AL from the pooled shared experience of the SARS-CoV-2–infected patients, international series are necessary.

Authorship

Contribution: S.G., K.R., P.S., P.K., O.B., S.K., S.S., K.W., C.B., D.W., W.F., D.J., and F.M. collected the clinical and epidemiological data and summarized all data; S.P., H.R., and M.L. performed the virological and RT-PCR assays; H.I. was responsible for radiological assessment and analysis; S.G., S.P., K.R., D.W., W.F., D.J., and F.M. drafted the manuscript; S.G., C.B., D.W., W.F., and F.M. revised the final version; and all authors reviewed and approved the manuscript.

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