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 venetoclax2; 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...
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 at day 14 of follow-up | SARS-CoV-2 viremia at baseline and shortly before and during COVID-19, date of therapy start |
|----|----------|-----------------------------------------------|-----------------------------------------------------------------|----------------------------------------|----------------------------|---------------------|-------------------------|--------------------------------|---------------------------------|-----------------------------|--------------------------------|--------------------------------------------------------------------------------|
| 1  | 34, M    | Ph⁻ common B-ALL, 3/13/20                     | GMALL 8/13 trial: 1. Prephase: 3/13/20 2. Induction: 3/19/20 | MRD¹ 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), 3/9/20       | Induction 1: 3+7, 3/13/20                                      | Unknown (death)                        | Felty 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  | 48, F    | MRD⁺ Ph⁻ common-B-ALL, 12/6/19               | Binatumab: 1. First cycle: 3/31/20 2. Second cycle: 5/12/20 | MRD² 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 + midostarbin, 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: 4/14/20 | 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 + midostarbin: 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/m², days 1, 3, and 5 plus cytarabine 100 mg/m² days 1-7; admit, admission; aplasia, neutrophil count < 0.5 x 10⁹/L; Aza, azacytidine; CPX351, CPX351 100 U/m² days 1, 3, and 5; sunitinib and venetoclax analog per DiNardo et al²; DVT, deep ven thrombosis; F, female; FLAG-Ida, fludarabine 30 mg/m² days 1-4, cytarabine 2000 mg/m² days 1-4, idarubicin 10 mg/m² days 1 and 3; GMALL, German Multicentre ALL Study Group; HDAC, high-dose cytarabine, 2000 mg/m² 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 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/Admission max 72 h | Severity of ARDS (Horowitz index) | Complications during ICU stay | Chest CT results per Simpson et al4,6 | SARS-CoV-2 viremia at baseline and 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                               | 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, 4/15/20                          | MRD* after reinduction None      | None                           | No/NA                           | NA                                       | NA                                  | NA                               | ND                            | Baseline 4/9/20; ND; day 14, no |

*AML risk stratification according to the European LeukemiaNet classification.†SOFA score according to Singer et al.‡Preexisting myelodysplastic syndrome.

Results and discussion

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 viral detection by real-time reverse transcriptase (RT)-PCR tests. SARS-CoV-2 immunoglobulin (IgG) antibodies were tested against viral spike protein (S1/S2) and nucleoprotein (N).

Participants

All patients (for treated characteristics, see Table 1). All included patients were treated at the German Multicenter Study Group on Adult ALL (NCT number 02881086).

Support

This study was supported by the German Multicenter Study Group on Adult ALL (NCT number 02881086).
| Pt | Experimental treatment | ICU treatment | Type of MV (days) | Vasopressor therapy | Renal replacement therapy | 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 mg/L (normal <0.5) | Highest ferritin level in mg/L (normal male: 22-322, normal female: 10-291) | Days until no detectable SARS-CoV-2 RNA in nasopharyngeal swabs* |
|----|------------------------|---------------|------------------|---------------------|--------------------------|-----------------------------------|------------------------|-------------------------------|------------------------------------|------------------------------------|-------------------------------------|----------------------------------|------------------------------------------|
| 1  | Lopinavir/ritonavir, Pentaglobin | HFNC (1), MV (4) | Yes | No | 7.7 | Grade 3 | Grade 3 | 246 | 526 | 0.8 | 1514 | Negative/ negative | 32 |
| 2  | None | HFNC (1), MV (8) | Yes | Yes | 0.1 | Aplasia | Grade 4 | 259 | 5350 | 11.84 | 12436 | ND/ND | Positive until death |
| 3  | COVID-19 convalescent plasma | NA | NA | No | 1.5 | Grade 3 | Grade 3 | 183 | 109 | 0.09 | 4006 | Positive/ positive | 22 |
| 4  | None | None | No | No | 0.1 | Aplasia | Grade 4 | 215 | 447 | 0.59 | 6268 | Positive/ positive | 22 |
| 5  | Tocilizumab, Pentaglobin | HFNC (1), MV (9), ECMO (8) | Yes | Yes | 0.3 | Aplasia | Grade 4 | 291 | 8452 | 2.87 | 21173 | ND/ND | Positive until death |
| 6  | None | None | No | No | <0.1 | Aplasia | Grade 4 | 292 | 287 | 1.87 | 3204 | Negative/ negative | 22 |
| 7  | None | HFNC (1), MV (12) | Yes | Yes | 1.13 | Aplasia | Grade 3 | 368 | 1513 | 6.71 | 4431 | Positive/ positive | 36 |
| 8  | None | None | No | No | 0.1 | Aplasia | Grade 3 | 163 | 72 | 0.27 | 2413 | Positive/ positive | 33 |
| 9  | None | None | No | No | 0.1 | Aplasia | Grade 4 | 270 | 1338 | 4.76 | 11911 | Positive/ positive | 29 |
| 10 | None | HFNC (5) | No | No | 0.6 | Aplasia | Grade 4 | 333 | 768 | 16.7 | 15357 | Positive/ positive | 29 |
| 11 | None | MV (4) | Yes | No | 1.1 | Aplasia | Grade 3 | 361 | 538 | 4.86 | 2888 | Positive/ negative | 12 |
| 12 | None | NA | NA | No | 1.2 | Grade 3 | Grade 3 | 4 | 1.6 | 0.1 | 1385 | Negative/ negative | 29 |

Neutropenia: grade 2, \( <1.5 \times 10^9/L \) to \( 1.0 \times 10^9/L \); grade 3, \( 0.5 \times 10^9/L \) to \( 0.8 \times 10^9/L \); grade 4, \( <0.5 \times 10^9/L \). Lymphopenia: grade 1, \( 1.1 \times 10^9/L \) to \( 0.8 \times 10^9/L \); grade 2, \( 0.8 \times 10^9/L \) to \( 0.5 \times 10^9/L \); grade 3, \( <0.5 \times 10^9/L \). 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.
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. 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. In unselected patients in China, mild and moderate courses have been described in ~80%, almost 14% had severe disease, and 6% critical courses. We scored mild and moderate courses have been described in infections in patients with hematological malignancies.

To be able to draw firm conclusions on the treatment of AL from the international series are necessary.

Conflict-of-interest disclosure: P.K. is a shareholder of Abbvie Inc. S.K. received research support by Ambu, E.T. View Ltd, Fisher & Paykel, Pfizer, and Xenios; received lecture honoraria from Arjo-Huntleigh, Astellas, Astra, Basilea, Bard, Baxter, Biotest, CSL Behring, Cytosorbents, Fresenius, Gilead, Merck Sharp & Dohme ( MSD), Orion, Pfizer, Philips, Sedana, Sorin, Xenios, and Zoll; and received consultant honoraria from AMODEM, Astellas, Baxter, Bayer, Fresenius, Gilead, MSD, Pfizer, and Xenios. H.R. received speaker honoraria from MSD, Pfizer, Infectopharm, Correvio, Accelerate Diagnostics and as an advisor for MSD, Pfizer, and Shionogi. K.W. received speaker honoraria from Amgen, Adaptive, Bristol Myers Squibb (BMS), Celgene, Janssen, GlaxoSmithKline (GSK), Karyopharm, Takeda, and Sanofi; has participated in advisory boards/has a consulting role for Amgen, Adaptive, BMS, Celgene, Janssen, GSK, Karyopharm, Takeda, and Sanofi; and received research funding from Amgen, Celgene, Sanofi, and Janssen. C.B. received speaker honoraria from Merck KGaA, Sanofi, Roche, Bayer, BMS, AstraZeneca, and MSD; has a consulting or advisory role for Lilly/ImClone, Merck Serono, Sanofi, Bayer Schering Pharma, MSD, GSO, and AOK Health Insurance; received research funding from AbbVie, ADC Therapeutics, Agile Therapeutics, Alexion Pharmaceuticals, Amgen, Apellis Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, BerGenBio, Blueprint, Medicines, BMS, Boehringer Ingelheim, Celgene, Daichi Sankyo, Eisai, Gilead Sciences, Glycotope GmbH, GSK, Incyte, IO Biotech, Isosol Medical, Janssen-Cilag, Karyopharm Therapeutics, Lilly, Millennium, MSD, Nektar, Novartis, Rafael Pharmaceuticals, Roche, Springworks Therapeutics, and Taiho Pharmaceutical; and received travel accommodations and expenses from Merck Serono, Sanofi, Pfizer, and BMS. D.W. reports personal fees from Correvio, Gilead, Pfizer, and MSD. W.F. has participated in advisory boards for Amgen, Pfizer, Novartis, Jazz Pharmaceuticals, Celgene, Morphosys, and Ariad/Incyte; received research funding from Amgen; received support for meeting attendance from Amgen, Jazz Pharmaceuticals, Daiichi Sankyo Oncology, and Servier; and has received support in medical writing from Amgen, Pfizer, and AbbVie. F.M. received support for meeting attendance from Servier, Incyte, Gilead, Jazz Pharmaceuticals, Novartis, Teva, Pfizer, and Amgen; received a research grant from Daiichi Sankyo; and received a speaker honorarium from Servier. The remaining authors declare no competing financial interests.

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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