

## Original Article

# COVID-19 infection in patients with acute leukemia; Istanbul experience

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**Abstract:** Coronavirus disease 2019 (COVID-19) has led to a global pandemic that has also challenged the management of various other life-threatening conditions, such as malignant disorders. In this study, we present the clinical features and treatment outcomes of twenty-seven COVID-19 positive patients with leukemia across seven different centers in Istanbul. From March 1st to December 31st 2020, 116 patients were diagnosed with acute leukemia. Thirty-two cases with acute lymphocytic leukemia (ALL), 82 cases with acute myeloid leukemia (AML), and 2 cases with mixed phenotype acute leukemia (MPAL) were identified. Of the 27 patients with the COVID-19 infection, seven patients had ALL, 19 patients had AML and one patient had MPAL. The mortality rate was 37% among the patients with AML, whereas there were no deaths in the ALL group. The mortality rate of AML patients with the COVID-19 infection was higher compared to cases without the infection ( $P < 0.05$ ). We could not detect any significant difference in the ALL cohort. This study, which includes one of the largest acute leukemia series in literature proved that acute myeloid leukemia patients with the COVID-19 infection have worse outcomes than patients without the infection. The high mortality among patients with acute leukemias hospitalized with COVID-19 highlight the need for aggressive infection prevention, increased surveillance and protective isolation and even modification of the therapy, in case of minimal residual disease (MRD) negativity.

**Keywords:** COVID-19, SARS-Cov2, acute leukemia, acute myeloid leukemia, acute lymphoblastic leukemia

### Introduction

Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by the infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It has led to a global pandemic affecting nations worldwide, with more than 189.0000 positive cases and 4.000.000 deaths due to COVID-19 being reported in the world. The virus affects mainly the respiratory tract, causing pulmonary damage and fibrosis. Furthermore, it can also affect other organ systems and present as a multisystem disease [1, 2]. The diagnosis of COVID-19 is made by clinical evaluation and confirmed with the reverse transcription polymerase ch-

ain reaction (RT-PCR) test. In patients where RT-PCR tests are negative but there is still high clinical suspicion, imaging of the chest with computerized tomography (CT) can be of diagnostic value.

It is well known that co-existing comorbidities increase the mortality in COVID-19 infection. The presence of low lymphocyte counts, frequently observed in leukemia, and other comorbidities such as advanced age are positively associated with mortality [1-3]. During the pandemic, many patients with hematological malignancies confronted the virus, either at the time of diagnosis or during the treatment course. It is hypothesized that patients with hematologic

malignancies and concomitant COVID-19 infection may have poorer disease outcomes and worse survival rates compared to patients without the disease.

The management of acute leukemia, which may cause death in days if patients are not promptly treated, became a challenge in the COVID-19 era. Several guidelines were published to decrease the mortality in acute leukemia patients [4-6].

Acute leukemia working party of EBMT (European Society for Blood and Marrow Transplantation) recommended to wait for cytogenetics and molecular biology results to properly stratify the risk of the acute leukemia cases [4]. They also advised screening of COVID-19 infection before initiation of chemotherapy and consideration of omission of one cycle of consolidation in case of MRD molecular remission achievement. They mentioned that outpatient visits should be deferred or performed as telemedicine visits. For AML cases fit for intensive therapy and with favorable and intermediate cytogenetic risk, authors recommended induction with "3+7" and consolidation with reduced dose (1.5 g/m<sup>2</sup>) of cytarabine. In case of adverse cytogenetic risk, consideration of allogeneic hematopoietic stem cell transplantation (allo-HSCT) was supported. For AML patients unfit for intensive therapy, azacytidine or low dose cytarabine monotherapy, hydroxyurea or supportive care were management options. For ALL cases, EBMT supported maintenance of recommended dose of glucocorticoids, specifically during prophase, induction and consolidation. They stated that nonurgent allo-HSCT should be postponed as much as possible. High risk allo-HSCT in refractory disease or in cases with high non-relapse mortality were advised not to proceed to transplantation. Case based discussion of the indication of allo-HSCT was recommended [4]. The participating centers to our study were in agreement with the approach of EBMT acute leukemia working group.

Herein we present the real-life results of acute leukemia patients co-diagnosed with COVID-19 in seven centers across Istanbul. We evaluated their clinical features, the management strategies, the clinic outcomes and the mortality rates to contribute to literature.

### Methods

#### *Study design*

We identified adult patients (aged  $\geq 18$  years) diagnosed with acute leukemia across seven different hospitals that have hematology units in Istanbul from March 1st to December 31st, 2020. Inclusion criteria were the presence of acute leukemia and confirmed COVID-19 infection. Hundred and sixteen patients were diagnosed with acute leukemia (acute lymphocytic leukemia, acute myeloid leukemia, mixed phenotype acute leukemia). Acute leukemias were classified according to the 2016 WHO classification. In the majority of centers, COVID-19 testing via RT-PCR on specimens from nasopharyngeal swabs were performed before treatment initiation. Computerized chest tomography was also performed in some cases. As a result, twenty-seven cases (23%) were found to have the SARS-CoV-2 infection.

#### *Data collection*

Epidemiological, clinical, laboratory and radiological data were collected from clinical charts, and electronic medical records. This study was conducted in accordance with the national pandemic guidelines and the declaration of Helsinki. It was evaluated and approved by the national ethics board of the Turkish Ministry of Health, and by the institutional review board (Ethical Committee of Research, 2021.233. IRB1.077). Informed consent was not required because this was a retrospective case-study, and the need of informed consent was waived by the ethical committee of the institutional review board (Koc University School of Medicine).

#### *Endpoints*

The primary endpoint was the mortality rates among patients diagnosed with acute leukemia and COVID-19. The secondary endpoints were the improvement or worsening of the COVID-19 symptoms, laboratory and radiological parameters. We compared the mortality rates with patients who did not have the COVID-19 infection at the time of acute leukemia diagnosis.

#### *Statistical analysis*

Categorical variables were compared using the chi square test whereas the continuous variab-

les were tested by the t-test. Multivariate analysis was performed by using logistic regression to detect the predictors of fatality. Gender, Age  $\geq 60$ , AML, and COVID-19 positivity were included as independent variables. Statistical significance was accepted as a  $p$  value  $< 0.05$ . STATA version 14.2 was used in the analysis.

### Results

#### *Baseline characteristics of patients*

We analyzed 116 patients with acute leukemia: thirty-two patients were diagnosed with ALL, 82 with AML and two with mixed phenotype acute leukemia (MPAL). Among the AML patients, five had AML M3. There were 53 (46%) female and 63 (54%) male patients. In the entire leukemia population, median age at COVID-19 diagnosis was 46 (range: 17-80).

Seven patients with ALL, 19 patients with AML and one patient with MPAL were SARS-CoV-2 positive. Among the COVID-19 positive acute leukemia patients, the median age was 44 (range: 18-71), specifically among AML and ALL patients the median age was 49 (range: 18-71) and 32 (range: 29-40) respectively. There were 12 (44%) female and 15 (56%) male patients.

#### *Disease status*

Thirteen patients were diagnosed with acute leukemia concomitant with the COVID-19 infection and of which, six were in complete disease remission, five had relapsed disease, two had refractory disease and one patient's disease status was unevaluated. Among the AML cases, one patient had favorable, five had intermediate and 10 had high risk disease according to the European LeukemiaNet criteria. Among the AML M3 patients, two had high risk and one had intermediate risk disease. Among the ALL patients, three had standard and four had high risk. The baseline characteristics and outcomes of the confirmed COVID-19 cases are shown in **Table 1**.

#### *Treatment status of leukemia*

In total, twenty-one patients received chemotherapy. Three patients had not started chemotherapy yet, two patients did not receive any treatment and one patient received best supportive care. Patients's treatment modalities

are described in **Table 1**. The details of the protocols are shown in **Table 2**.

A total of 10 cases had treatment delay due to concomitant COVID-19 infection. Dose modification was performed in two patients and the treatment was stopped in two cases. There was no need to change the treatment protocol in 10 patients.

#### *Treatment of COVID-19 infection*

Favipiravir was suggested as an antiviral agent for the initial treatment for COVID-19 according to the guidelines of the Turkish Ministry of Health. Corticosteroids, Tocilizumab and Anakinra were used as anti-inflammatory agents for patients with impaired oxygen saturation, pulmonary damage, or uncontrolled and persistent fever with pneumonic infiltration. In terms of the severity of the COVID-19 disease, 14 (52%) of the acute leukemia patients had transient conventional oxygen supplementation, five (18%) required noninvasive ventilation support and four (15%) needed invasive mechanical ventilation.

#### *Outcomes of COVID-19 infection*

There was no significant difference between COVID-19 positive and negative patients in terms of gender, age, diagnosis, and mortality (**Table 3**).

Of the 27 patients with COVID-19 disease, seven (26%) died due to COVID-19 and all of them had AML, meaning a mortality rate of 37% among the 19 patients with AML. There were no deaths in the ALL cohort.

The mortality rate was similar between COVID-19 positive and negative acute leukemia cohorts ( $P=0.364$ ). However, it was significantly higher in COVID-19 positive AML patients (seven over nineteen cases; 37%) compared to COVID-19 negative (nine over sixty-three cases; 14%) AML group ( $P=0.028$ ) (**Table 4**).

In the univariate and multivariate analysis, the female gender was the only factor to significantly increase the risk of death (in the univariate analysis,  $P=0.04$  [95% CI: 1.04-7.03] and in the multivariate analysis  $P=0.044$ ; [95% CI: 1.02-7.15]) (**Table 5**).

## COVID-19 infection in acute leukemia patients

**Table 1.** Characteristics and Outcomes of Leukemia Patients with COVID-19

Nr	Age	Sex	Leukemia type	Disease risk score	Disease phase	Treatment protocol	Time to COVID-19 diagnosis (days)	Symptoms	Time to respiratory failure (days)	Treatment for respiratory failure	Anti-viral treatment	Anti-inflammatory treatment	COVID due treatment changes	Outcome of infection	Outcome	Survival (days)
1	29	M	ALL	High	CR	GMALL Consolidation V	22	no	12	Oxygen	Favipiravir	Corticosteroid Tocilizumab	Discontinuation	R	A	24
2	40	F	ALL	High	Onset	GMALL Induction I	19	yes	0	Oxygen	Favipiravir	Corticosteroid Anakinra	Delay	R	A	18
3	30	M	ALL	High	CR	GMALL Consolidation	19	yes	-	-	Favipiravir	Corticosteroid	Delay	R	A	63
4	32	M	ALL	High	CR	BFMA 1A	3	yes	-	-	Favipiravir	Corticosteroid	Delay	R	A	61
5	30	M	ALL	Standard	Onset	GMALL Induction I	6	yes	-	-	Favipiravir	-	Delay	R	A	27
6	34	F	ALL	Standard	CR2	FLAG-IDA	56	no	-	-	Favipiravir	-	No change	R	A	82
7	34	M	ALL	Standard	Relapse	No treatment	-	no	-	-	Favipiravir	-	No change	R	A	80
8	57	M	AML	Favorable	Relapse	FLAG-IDA	12	yes	5	Oxygen, NIV, intubation	Favipiravir	Corticosteroid	No change	P	D	-
9	38	M	AML	Adverse	Onset	3+7 Induction	14	yes	5	Oxygen, NIV, intubation	Favipiravir	Corticosteroid	No change	P	D	-
10	49	M	AML	Intermediate	Onset	3+7 Induction	19	yes	4	Oxygen	Favipiravir	Corticosteroid	Delay	R	A	36
11	51	F	AML	Adverse	Onset	2+5 Induction	13	yes	0	Oxygen	Favipiravir	Corticosteroid Anakinra	Delay	R	A	18
12	33	M	AML M3	High	Onset	Not started yet	-	yes	7	NIV	Favipiravir	Corticosteroid	Delay	R	A	30
13	48	M	AML	Intermediate	CR	3+7 Induction	13	yes	2	Oxygen	Favipiravir	Hyperimmune plasma, Corticosteroid	Delay	R	A	85
14	46	M	AML M3	high	Onset	Not started yet	-	yes	-	-	Favipiravir	Corticosteroid	Dose reduction	R	A	59
15	48	M	AML M3	Intermediate	Refractory	ATRA	6	yes	6	Oxygen, intubation	Favipiravir	Corticosteroid Tocilizumab	Discontinuation	P	D	-
16	63	F	AML	Intermediate	Onset	3+7 Induction	7	yes	20	Oxygen, intubation	Favipiravir	Corticosteroid	No change	P	D	-
17	32	M	AML	Intermediate	Relapse	FLAG-IDA	17	yes	-	-	Favipiravir	-	-	R	A	180
18	71	F	AML	Adverse	Refractory	Azacytidine, Venetoclax	54	yes	?	Oxygen	Favipiravir	-	Delay	R	A	75
19	18	F	AML	Adverse	CR	HD Cytarabine	24	no	-	-	Favipiravir	-	Delay	R	A	131
20	63	F	AML	?	?	No treatment	-	yes	-	Intubation	Favipiravir	Corticosteroid	-	P	D	-
21	51	F	AML	Adverse	Onset	3+7 Induction	25	yes	1	Oxygen, NIV	Favipiravir	-	No change	R	A	266
22	65	F	AML	Adverse	Onset	3+7 Induction	5	yes	1	Oxygen	Favipiravir	-	Dose reduction	R	A	37
23	49	F	AML	Adverse	Relapse	FLAG-IDA	17	yes	0	Oxygen, NIV, Intubation	Favipiravir	Corticosteroid	No change	P	D	-
24	62	F	AML	Adverse	Relapse	Best supportive care	-	?	?	?	?	?	?	P	D	-
25	49	F	AML	Intermediate	Onset	3+7 Induction	35	no	-	-	Favipiravir	-	No change	R	A	14
26	25	M	AML	Adverse	Onset	Not started yet	-	no	-	-	Favipiravir	-	No change	R	A	81
27	53	M	MPAL		Onset	FLAG-IDA	9	yes	5	Oxygen	Favipiravir	-	No change	R	A	19

MPAL: mixed-phenotype acute leukemia; Time to COVID-19 diagnosis: from the first day of the last chemotherapy (days); CR: complete remission; Symptoms at the time of the diagnosis of COVID-19: Yes/No; NIV: non-invasive ventilation; Time to respiratory failure: calculated from COVID-19 diagnosis to respiratory failure (days); Outcome of infection: Progressed (P), Resolved (R); Outcome: Dead (D), or Alive (A); Survival: calculated from the time of recovery to the end of study (days).

## COVID-19 infection in acute leukemia patients

**Table 2.** Details of treatment protocols for acute leukemia

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<b>A. AML treatment protocols</b>
<b>3+7 Induction</b>
Daunorubicin/Idarubicin (60 mg/m <sup>2</sup> ; 12 mg/m <sup>2</sup> ; i.v.) d1-d3
Cytarabine (100 mg/m <sup>2</sup> ; i.v.) d1-d7
<b>2+5 induction</b>
Daunorubicin/Idarubicin (60 mg/m <sup>2</sup> ; 12 mg/m <sup>2</sup> ; i.v.) d1-d2
Cytarabine (100 mg/m <sup>2</sup> ; i.v.) d1-d5
<b>High dose (HD) cytarabine</b>
Cytarabine (3000 mg/m <sup>2</sup> ; i.v., every 12 hours) d1, d3, d5
<b>FLAG-IDA</b>
G-CSF (0.5 mcg/kg; s.c.) d1-d7
Fludarabine (30 mg/m <sup>2</sup> ; i.v.) d2-d6
Cytarabine (2 g/m <sup>2</sup> ; i.v.) d2-d6
Idarubicin (8 mg/m <sup>2</sup> ; i.v.) d4-6
<b>Azacitidine-Venetoclax</b>
Azacitidine (75 mg/m <sup>2</sup> ; s.c.) d1-d7
Venetoclax (start 100 mg, with daily ramp-up to the target dose of 400 mg; p.o.) d1-d28

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<b>B. AML M3 treatment protocols</b>
<b>Induction Therapy</b>
ATRA (22.5 mg/m <sup>2</sup> , every 12 h; p.o.) d1- to max. 60 days
Idarubicin (12 mg/m <sup>2</sup> ; i.v.) d1, d3, d5, d7
<b>Consolidation Therapy</b>
ATRA (22.5 mg/m <sup>2</sup> , every 12 h; p.o.) d1-d15
Idarubicin (5 mg/m <sup>2</sup> ; i.v.) d1-d4
Cytarabine (1000 mg/m <sup>2</sup> ; i.v.) d1-d4
ATRA (22.5 mg/m <sup>2</sup> , every 12 h; p.o.) d1-d15
Mitoxantrone (10 mg/m <sup>2</sup> ; i.v.) d1-d5
ATRA (22.5 mg/m <sup>2</sup> , every 12 h; p.o.) d1-d15
Idarubicin (12 mg/m <sup>2</sup> ; i.v.) d1
Cytarabine (150 mg/m <sup>2</sup> ; i.v.) d1-d4

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<b>C. ALL BFMA treatment protocol</b>
<b>Induction protocol 1A (35 days)</b>
Prednisolone (60 mg/m <sup>2</sup> ; p.o) d1-d28
Methotrexate (12 mg; i.t) d1, d12, d33
Daunorubicin (30 mg/m <sup>2</sup> ; i.v) d8, d15, d22, d29
Vincristine (2 mg; i.v) d8, d15, d22, d29
L-asparaginase (5000 IU/m <sup>2</sup> ; i.v) d12, d15, d18, d21, d24, d27, d30, d33
<b>Consolidation 1B (29 days)</b>
Cyclophosphamide (1000 mg/m <sup>2</sup> ; i.v) d1, d29
Mesna (400 mg/m <sup>2</sup> ) d1, d29
6-mercaptopurine (60 mg/m <sup>2</sup> ; p.o) d1-d28
Cytarabine (75 mg/m <sup>2</sup> ; s.c) d3-d6, d10-d13, d17-d20, d24-d27
Methotrexate (12 mg; i.t) d10, d24
<b>Protocol M (56 days)</b>
6-mercaptopurine (25 mg/m <sup>2</sup> ; p.o) d1-d56
Methotrexate (500 mg/m <sup>2</sup> ; i.v) d8, d22, d36, d50
Methotrexate (4500 mg/m <sup>2</sup> ; i.v) d8, d22, d36, d50
Methotrexate (12 mg; i.t) d8, d22, d36, d50

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Calcium folinate (15 mg/m<sup>2</sup> every 6 hours; i.v) d9, d23, d37, d51

Reinduction Protocol II (50 days)

- Dexamethasone (10 mg/m<sup>2</sup>; p.o) d1-d21
- Doxorubicin (30 mg/m<sup>2</sup>; i.v) d8, d15, d22, d29
- Vincristine (2 mg; i.v) d8, d15, d22, d29
- L-asparaginase (5000 IU/m<sup>2</sup>; i.v) d8, d11, d15, d18
- Thioguanine (60 mg/m<sup>2</sup>; p.o) d36-d49
- Cyclophosphamide (1000 mg/m<sup>2</sup>; i.v) d36
- Mesna (400 mg/m<sup>2</sup> at 0, 4, 8 hours post each cyclophosphamide dose; i.v) d36
- Cytarabine (75 mg/m<sup>2</sup>; s.c) d38-d41, d45-d48
- Methotrexate (12 mg; i.t) d38, d45

High Risk Block I (11 days)

- Dexamethasone (10 mg/m<sup>2</sup>; p.o) d1-d5
- Vincristine (2 mg; i.v) d1, d6
- Methotrexate (500 mg/m<sup>2</sup>; i.v) d1
- Methotrexate (4500 mg/m<sup>2</sup>; i.v) d1
- Methotrexate (12 mg; i.t) d1
- Cytarabine (30 mg; i.t) d1
- Hydrocortisone (50 mg; i.t) d1
- Calcium folinate (15 mg/m<sup>2</sup>, every 6 hours; i.v) d2
- Cyclophosphamide (200 mg/m<sup>2</sup> every 12 hours, 5 doses; i.v) d2-d4
- Mesna (70 mg/m<sup>2</sup> at 0, 4, 8 hours post each cyclophosphamide dose; i.v) d2-d4
- Cytarabine (2000 mg/m<sup>2</sup> twice daily; i.v) d5
- L-asparaginase (25000 IU/m<sup>2</sup>; i.v) d6, d11
- Filgrastim (5 microgram/kg; s.c) d7-until neutrophil recovery

High Risk Block II (11 days)

- Dexamethasone (10 mg/m<sup>2</sup>; p.o) d1-d5
- Vincristine (2 mg; i.v) d1, d6
- Methotrexate (500 mg/m<sup>2</sup>; i.v) d1
- Methotrexate (4500 mg/m<sup>2</sup>; i.v) d1
- Methotrexate (12 mg; i.t) d1
- Cytarabine (30 mg; i.t) d1
- Hydrocortisone (50 mg; i.t) d1
- Calcium folinate (15 mg/m<sup>2</sup>, every 6 hours; i.v) d2
- Ifosfamide (800 mg/m<sup>2</sup> every 12 hours, 5 doses; i.v) d2-d4
- Mesna (300 mg/m<sup>2</sup> at 0, 4, 8 hours post each ifosfamide dose; i.v) d2-d4
- Daunorubicin (30 mg/m<sup>2</sup>; i.v) d5
- L-asparaginase (25000 IU/m<sup>2</sup>; i.v) d6, d11
- Filgrastim (5 microgram/kg; s.c) d7-until neutrophil recovery

High Risk Block III (11 days)

- Dexamethasone (20 mg/m<sup>2</sup>; p.o) d1-d5
- Cytarabine (2000 mg/m<sup>2</sup> twice daily; i.v) d1, d2
- Etoposide (100 mg/m<sup>2</sup> every 12 hours, 5 doses; i.v) d3-d5
- Methotrexate (12 mg; i.t) d5
- Cytarabine (30 mg; i.t) d5
- Hydrocortisone (50 mg; i.t) d5
- L-asparaginase (25000 IU/m<sup>2</sup>; i.v) d6, d11
- Filgrastim (5 microgram/kg; s.c) d7-until neutrophil recovery

Maintenance

## COVID-19 infection in acute leukemia patients

6-mercaptopurine (50 mg/m<sup>2</sup>; p.o) daily

Methotrexate (20 mg/m<sup>2</sup>; p.o) weekly

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### D. ALL GMALL treatment protocol

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#### Prephase (d1-d5)

Methotrexate (15 mg; i.t) d1

Dexamethasone (10 mg/m<sup>2</sup>; p.o) d1-d5

Cyclophosphamide (200 mg/m<sup>2</sup>; i.v) d3-d5

#### Induction I (d6-d20)

Rituximab (375 mg/m<sup>2</sup>; i.v) d6 (if B-ALL and CD20 ≥20%)

Dexamethasone (10 mg/m<sup>2</sup>; p.o) d6-d7+d13-d16

Vincristine (2 mg; i.v) d6, d13, d20

Daunorubicin (45 mg/m<sup>2</sup>; i.v) d6-d7+d13-d14

PEG-Asparaginase (2000 u/m<sup>2</sup>; i.v) d20

#### Induction II (d24-d44)

Rituximab (375 mg/m<sup>2</sup>; i.v) d23, d44

Cyclophosphamide (1000 mg/m<sup>2</sup>; i.v) d24, d44

Cytarabine (75 mg/m<sup>2</sup>; i.v) d26-d29, d33-d36, d40-d43

6-mercaptopurine (60 mg/m<sup>2</sup>; p.o) d31-d44

Methotrexate (15 mg; i.t) d25, d32, d39

#### Consolidation I (d61-d72)

Rituximab (375 mg/m<sup>2</sup>; i.v) d60

Dexamethasone (10 mg/m<sup>2</sup>; p.o) d61-d65

Vindesine (3 mg/m<sup>2</sup>; i.v) d61

Methotrexate (1.5 g/m<sup>2</sup>; i.v) d61

Etoposide (250 mg/m<sup>2</sup>; i.v) d64, d65

Cytarabine (2×2 g/m<sup>2</sup>; i.v) d65

Methotrexate/Cytarabine/Dexamethasone (15/40/4 mg; i.t) d72

#### Consolidation II (w14-w16)

Rituximab (375 mg/m<sup>2</sup>; i.v) d0

Methotrexate (1.5 g/m<sup>2</sup>; i.v) d1, d15

PEG-Asparaginase (2000 U/m<sup>2</sup>; i.v) d2, d16

6-mercaptopurine (25 mg/m<sup>2</sup>; p.o) d1-d7, d15-d21

#### Reinduction (w19)

Rituximab (375 mg/m<sup>2</sup>; i.v) d0

Prednisolone (60 mg/m<sup>2</sup>; p.o) d1-d14

Vindesine (3 mg/m<sup>2</sup>; i.v) d1, d7

Adriamycin (25 mg/m<sup>2</sup>; i.v) d1, d7

PEG-Asparaginase (2000 U/m<sup>2</sup>; i.v) d14

Methotrexate/Cytarabine/Dexamethasone (15/40/4 mg; i.t) w19, w21

#### Consolidation III (w24)

Cytarabine (1000 g/m<sup>2</sup>; i.v) d1, d3, d5

Cyclophosphamide (200 mg/m<sup>2</sup>; i.v) d1, d3, d5

#### Consolidation IV (w27+w29)

Methotrexate/Cytarabine/Dexamethasone (15/40/4 mg; i.t) d1

Rituximab (375 mg/m<sup>2</sup>; i.v) d0

Methotrexate (1.5 g/m<sup>2</sup>; i.v) d1, d15

PEG-Asparaginase (2000 U/m<sup>2</sup>; i.v) d2, d16

6-mercaptopurine (25 mg/m<sup>2</sup>; p.o) d1-d7, d15-d21

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### Consolidation V (w32)

Cytarabine (1000 g/m<sup>2</sup>; i.v) d1, d3, d5

Cyclophosphamide (200 mg/m<sup>2</sup>; i.v) d1, d3, d5

### Consolidation VI (w35+w37)

Methotrexate/Cytarabine/Dexamethasone (15/40/4 mg; i.t) d1

Rituximab (375 mg/m<sup>2</sup>; i.v) d0

Methotrexate (1.5 g/m<sup>2</sup>; i.v) d1, d15

PEG-Asparaginase (2000 U/m<sup>2</sup>; i.v) d2, d16

6-mercaptopurine (25 mg/m<sup>2</sup>; p.o) d1-d7, d15-d21

### Maintenance (w41-w130)

Methotrexate (20 mg/m<sup>2</sup>; i.v) weekly

6-mercaptopurine (50 mg/m<sup>2</sup>; p.o) daily

Methotrexate/Cytarabine/Dexamethasone (15/40/4 mg; i.t) (w41, w53, w65, w77, w89, w101)

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## Discussion

During the COVID-19 pandemic, patients with hematological malignancies were particularly considered as having a high risk of worse disease outcomes because of immunosuppression and long hospital stays for treatment delivery. Here we present the outcomes of this high-risk group, consisting of patients with acute leukemia, with or without the COVID-19 infection.

From the beginning of March to the end of December 2020, 116 cases with acute leukemia were treated. The majority of cases (n=82) were diagnosed with AML. The mortality rate in our entire acute leukemia population was 20%. The mortality rate was 26% among all COVID-19 positive cases and it was 37% among AML cases with COVID-19 infection. There was no significant difference in the mortality rate between COVID-19 positive and negative cases among all patients with acute leukemia. Thirty-seven percent of AML cases with the COVID-19 infection and 14% AML cases without the infection were dead. The mortality rate was significantly higher in the COVID-19 positive group (P=0.028).

In recent studies, heterogeneous groups of patients with various hematological diseases and co-existing COVID-19 infection were presented. Data about treatment outcomes, disease course and mortality for patients with acute leukemia that had the infection were published in the literature. Ferrara et al. reported a mortality rate of 50% in a study including 10 patients with AML that had COVID-19 infection [7]. It was shown that patients with hema-

tological malignancies have an increased risk for being infected with COVID-19 [3] and that patients with cancer and concomitant COVID-19 infection have poorer disease outcomes and may have more severe complications than patients without cancer and COVID-19 infection [8]. In the largest study evaluating COVID-19 infection in hematological malignancies, Passamonti et al. reviewed 536 cases with symptomatic COVID-19 infection and hematological cancer. In their cohort, they had 51 patients with AML (10%) and 16 patients with ALL (3%). Hundred and ninety-eight (37%) of 536 patients died; 11% of the non-survivors had AML and 2% had ALL. They reported that patients with hematological malignancies and COVID-19 infection have a high mortality risk. Older age, progressive disease, having AML, non-Hodgkin's lymphoma or plasma cell neoplasms are shown to have worse outcomes in their cohort [9].

Furthermore, Martin-Moro et al. published the results of 34 cases with hematological malignancies of which seven had leukemia, and a death rate of 36% for patients with the COVID-19 infection was shown [10]. In the study presenting the results of 12 cases with acute leukemia and COVID-19 infection, eight patients (67%) had AML, four patients (33%) had ALL or lymphoblastic lymphoma (LBL). Two of the AML patients died, whereas all ALL/LBL patients survived [11]. In our study, the mortality rate was 37% among 19 AML cases, and none of our ALL patients with COVID-19 infection died. It was hypothesized that the higher median age of AML patients could be associated with increased mortality compared to ALL patients. Furthermore, severe and prolonged neutrope-



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**Table 3.** Characteristics of the patients with COVID-19 (+)

	COVID-19 (+) n=27	COVID-19 (-) n=89	P
Female gender	12 (44)	41 (46)	0.882
Mean age (SD)	44 (13)	46 (18)	0.562
Diagnosis			
AML	19 (70)	63 (71)	0.659
ALL	7 (26)	25 (28)	
MPL	1 (4)	1 (1)	
Dead	7 (26)	16 (18)	0.364

**Table 4.** Mortality of COVID by AML patients

	Death in COVID-19 positive cases (n=7)	Death in COVID-19 negative cases (n=16)	P
AML (n=82)	7/19 (37%)	9/63 (14%)	0.028
ALL (n=32)	0/7 (0%)	6/25 (24%)	0.204
MPL (n=2)	0/1 (0%)	1/1 (100%)	NA

NA: non-applicable.

**Table 5.** Predictors of fatality among acute leukemia patients

	Univariate Analysis			Multivariate Analysis		
	OR	CI	P	OR	CI	P
COVID-19	1.5	0.57-4.41	0.367	1.6	0.58-4.76	0.334
Female gender	2.7	1.04-7.03	0.040	2.7	1.02-7.15	0.044
Age ≥60	1.2	0.46-3.42	0.654	1.1	0.38-3.19	0.839
AML	0.9	0.34-2.52	0.895	0.9	0.33-2.56	0.875

nia is more common in the treatment course of AML compared to ALL, which may also result in higher mortality rate in the AML cohort.

Leukemia patients are immunocompromised and frequently develop multiple complications during their management, such as severe infections due to leukopenia and/or neutropenia, which may also complicate the treatment of COVID-19. There is limited data on the clinical course and outcomes of SARS-CoV-2 infections in patients with leukemia and there are no established guidelines for their treatment. Therefore, the management of COVID-19 becomes more challenging for patients with leukemia and should be based on the individual assessment of the patient.

Postponement of the treatment of hematological malignancies constitutes an option for patients with COVID-19 infection. Nevertheless, leukemia often requires urgent and ag-

gressive treatment at the time of diagnosis. The “watch and wait” strategy may not always be an option, and clinicians must be cautious in the case of treatment delay. Nunez-Torron et al. recommended initiation of chemotherapy for patients with AML following the resolution of COVID-19 symptoms and achievement of a negative PCR test [12]. Raza et al. suggest delay of the induction therapy for up to 14 days in hematologically asymptomatic patients [13]. The risks of treatment delay should be evaluated cautiously based on each individual case.

There are contradicting results about therapy delay in patients with acute myeloid leukemia and COVID-19 disease in the literature. Sekeres et al. found out that delaying treatment for more than 5 days could lower the overall survival among young patients, whereas older cases may benefit from the delay [14]. On the other hand, Bertoli et al. did not report any negative effect of treatment postponement on disease outcome [15]. Hence, there is no consensus on the management of leukemia cases with COVID-19 infection.

Several guidelines were published to optimize the management of acute leukemia patients with COVID-19 disease [4-6]. Brissot et al. from the working party of EBMT recommend to screen the patients for COVID-19 before initiating chemotherapy. An induction therapy with 3+7 is offered for AML patients with a good performance status and favorable or intermediate risk. They advised to discuss omission of one of the three consolidation treatments in case of achievement of minimal residual disease negativity. They offered hypomethylating agents or low dose cytarabine monotherapy for patients with poor performance status, unsuitable for intensive treatment. G-CSF is recommended following each cycle of chemotherapy. For ALL cases, no change in glucocorticoid dosage is recommended during prophase, induction and consolidation. Unurgent allogeneic transplantations are proposed to be deferred [4]. We agree with the EBMT recommendations and we think that their guideline is more suitable within daily practice.

At the beginning of the pandemic, we were looking for the optimal approach for the treatment of leukemia patients. Hematologists became more experienced with time and can now make recommendations about the management of acute leukemia during the pandemic. The patients and their companions should be informed in detail about the COVID-19 infection, its mortality potential and the ways the patient can get the disease. They should be warned about the potential risks of outside contact and visiting the patient should be forbidden. According to our real-life experience, we recommend to perform the regular COVID-PCR tests on all patients before starting each chemotherapy cycle. The results are mostly available within 6-24 hours. In case of strong suspicion of COVID-19 infection or active infection, we recommend delay of leukemia treatment. The regimens to treat acute leukemia induces long term myelosuppression, which can often be life-threatening if viral infections occur. Dose reduction in chemotherapy protocols for AML may be an alternative approach. Induction treatment with curative intend should be initiated in young acute leukemia cases. Allo-HSCT of favorable or intermediate risk acute leukemia cases in complete remission should be postponed, as they are evaluated as nonurgent SCT. Low-intensity regimens such HMA and venetoclax or supportive care may be preferred for the elderly and for patients with poor performance status.

In our daily practice, we do not change the number of planned treatment cycles, their duration or the dosage of the medications in the ALL management. Use of G-CSF to hasten neutrophil count recovery may be beneficial. In our cohort, we did not experience any treatment failure or relapse due to treatment delay. In other words, postponement of the treatment does not always lead to worse outcomes. In contrary, five of the seven patients with AML (71%), who died from the COVID-19 infection, had neutropenia at the time of COVID-19 diagnosis. Four of those patients had chemotherapy related neutropenia and one of them had refractory disease and was receiving supportive care.

### Conclusion

In conclusion, it is evident that the management of leukemia patients with the COVID-19

infection is challenging. Our data presents recent information about the clinical courses and mortality rates among patients with acute leukemia and concomitant COVID-19 infection. Delay in the leukemia treatment does not always result in progressive disease and, sometimes the decision of delaying chemotherapy can even save lives. On the other hand, patients should not lose the chance to receive adequate treatment due to prolonged delays. Because of the increased risk of mortality and morbidity in this group, an effective and multidisciplinary approach should be planned. Clinicians should recognize that the prompt resumption of hematological treatment following the clearance of COVID-19 infection is crucial for the patient's survival. It is evident that larger case series are needed to prepare reliable treatment guidelines for patients with acute leukemia and COVID-19 infection. We think that our case-series will contribute to the establishment of these essential treatment protocols.

### Disclosure of conflict of interest

None.

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