

Covid-19 in patients with chronic lymphocytic leukemia: Clinical outcome and B- and T-cell immunity during 13 months in consecutive patients

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INTRODUCTION

- Patients with CLL have an increased risk of severe infections due to disease- and treatment related immunodeficiency.
- During the Covid-19 pandemic early international surveys reported a high fatality rate among CLL patients admitted to hospital due to severe Covid-19.
- Also, CLL patients might not respond sufficiently to Covid-19 vaccination.
- We report on the clinical and immunological outcome of Covid-19 in consecutive patients with CLL from a well-defined area during the first 13 months of the pandemic.

Objectives

- To investigate hospitalization, ICU-admission and fatality rates during months 1-6 vs month 7-13 of the pandemic, and identify possible prognostic factors.
- To investigate B- and T cell immunity during long-term follow-up

METHOD

- Patients with CLL at three hematology centers in Stockholm (covering >95% of patients with CLL in the region) who had a history of PCR-verified, symptomatic Covid-19 during March 1 2020 until March 31 2021 were included (n=60).
- Baseline clinical characteristics included age, gender, CIRS, CLL treatment history, CLL status, blood counts and Ig levels.
- Data was also collected on Covid symptoms, hospitalization/ICU admittance and its length, Covid-19 treatment and clinical outcome.
- Convalescent blood samples were obtained from most survivors at 3-6 months and up to 12 months post infection and analyzed for SARS-CoV-2 antibodies.
- In depth immunological analyzes was performed in a subset of convalescents and included whether antibodies had neutralizing capacity (competitive bead-based binding assay), if SARS-CoV-2 specific antibodies could be found in saliva (self sampling kit) and whether T-cell immune response occurred (IFN-gamma ELISpot assay).

RESULTS

Baseline characteristics and clinical outcome

	All patients (n=60)	Requiring hospitalization (n=46)	ICU admission (n=11)	Death (n=14)
Median age, years (range)	71 (43-97)	71 (43-97)	71 (50-76)	81 (43-97)
≥75 y	32% (19/60)	35% (16/46)	18% (2/11)	57% (8/14)
Male	65% (39/60)	70% (32/46)	64% (7/11)	64% (9/14)
CIRS median (range) (n=60)	8 (4-20)	9 (4-20)	8 (4-17)	10 (4-20)
CIRS > 6	75% (45/60)	80% (37/46)	73% (8/11)	86% (12/14)
BMI, median (range)(n=49)	25 (19-42)	25 (20-42)	25 (23-30)	24 (20-30)
Diabetes	30% (18/60)	30% (14/46)	36% (4/11)	14% (2/14)
Never smoker	53% (31/59)	50% (23/46)	45% (5/11)	50% (7/14)
IgG (g/L), median (range)	7.9 (2.1-13.4)	8.3 (2.1-13.4)	8.3 (5.8-9.6)	5.4 (2.1-10.6)
CLL treatment at Covid-19 diagnosis (n=60)				
Never treated	63% (38/60)	63% (29/46)	55% (6/11)	64% (9/14)
Previously treated ^a	20% (12/60)	15% (7/46)	9% (1/11)	7% (1/14)
Ongoing therapy ^b				
Current BTKi	70% (7/10)	70% (7/10)	50% (2/4)	75% (3/4)
CLL status at Covid-19 diagnosis (n=60)				
SD	63% (38/60)	69% (32/46)	64% (7/11)	64% (9/14)
CR/PR	25% (15/60)	22% (10/46)	27% (3/11)	36% (5/14)
PD	12% (7/60)	9% (4/46)	9% (1/11)	0% (0/14)

- 60 patients were included with a median age of 71 years, median CIRS 8, median BMI 25, and 65% were men.
- Patients had indolent CLL (n=38), were previously treated (n=12, all >12 months ago) or had ongoing therapy (n=10, among which 7 received BTKi).
- 46 patients (77%) were hospitalized due to severe Covid-19, of these 11 (24%) were admitted to ICU.
- Severe Covid-19 was equally distributed across subgroups irrespective of age, gender, BMI, CLL status and CLL treatment except CIRS (p<0.05).
- 14 patients (23%) died; age ≥75 years was the only significant risk factor (p<0.05, multivariate analysis).

Outcome month 1-6 vs 7-13 and Covid management

- ICU admission and death rates were numerically reduced in the second time period (37% to 15% and 32% to 18%, respectively) while hospital admission remained frequent (86% vs 71%).
- 85% of admitted patients needed supplemental oxygen (both time periods).
- There was a numerical increase in the use of remdesivir in the second time period (5% vs 41%).
- Corticosteroids became more widely applied during month 7-13 of the pandemic (from 47% to 78%).

Immunological results

Patient number	Serology ^a			Neutralizing antibodies	Antibodies in Saliva ^c	ELISpot assay (IFN-gamma) ^d			
	3 mo ^b Pos/Neg	6 mo ^b Pos/Neg	12 mo ^b Pos/Neg			Spike specific T cells/CD3+ (%)	Spike specific SFUs	Spike specific T cells/uL	Pos/Neg ^e
003	Pos	Pos	Pos	++ (7)	Pos (13)	0.09	44	1	Pos (7)
007	-	Pos	Pos	++ (7)	Pos (13)	0.2	46	3	Pos (7)
015	-	Pos	-	+++ (5)	Pos (11)	1.4	1032	59	Pos (5)
012	Pos	Pos	Pos	+ (5)	Neg (10)	0.35	380	1.5	Pos (5)
011	Pos	Pos	Pos	+++ (6)	Pos (12)	0.15	32	2	Pos (6)
024	-	Pos	Pos	+ (8)	Neg (13)	0.1	26	1.5	Pos (8)
014	Pos	Pos	-	+++ (6)	-	0.7	292	16	Pos (6)
017	Pos	Pos	-	+++ (4)	-	0.6	562	3.5	Pos (4)
030	Pos	Pos	Pos	+++ (7)	-	0.1	42	3.5	Pos (7)
020	Pos	Neg	Neg	Neg (8)	-	0.5	456	4.5	Pos (8)
010	Neg	Neg	Neg	Neg (6)	Pos (12)	2.2	2712	9.5	Pos (6)
013	-	Pos	-	++ (5)	Pos (10)	0.2	26	2.5	Pos (5)
023	Pos	Pos	-	+ (3)	Pos (6)	0.02	4	0.6	Neg (3)
009	Neg	Neg	Neg	Neg (7)	Neg (11)	0.04	18	0.3	Neg (7)
004	-	Neg	Pos ^a	Neg (9)	Pos (13)	0	0	0	Neg (9)
052	Pos	Pos	-	-	Pos (4)	-	-	-	-
058	Pos	-	-	-	Pos (3)	-	-	-	-
060	Pos	Pos	-	-	Pos (4)	-	-	-	-
043	Pos	Pos	-	-	Pos (6)	-	-	-	-
019	-	Pos	Pos	+++ (7)	Pos (12)	0	0	0	Pos ^f (7)
026	Pos	-	-	-	Neg (5)	-	-	-	-
035	Pos	-	-	-	Pos (4)	-	-	-	-
027	Pos	-	-	-	Neg (5)	-	-	-	-
047	Pos	-	-	-	Pos (4)	-	-	-	-
059	Pos	-	-	-	Neg (2)	-	-	-	-
037	-	Pos	-	-	Pos (6)	-	-	-	-
032	Neg	-	-	-	Neg (4)	-	-	-	-
025	Neg	-	-	+ (3)	Neg (6)	0.15	32	4	Pos (3)
018	Neg	Neg	-	-	-	-	-	-	-
036	Pos	-	-	-	-	-	-	-	-
038	Pos	-	-	-	-	-	-	-	-
044	Pos	-	-	-	-	-	-	-	-
046	Pos	Pos	-	-	-	-	-	-	-
051	Neg	-	-	-	-	-	-	-	-
055	Pos	-	-	-	-	-	-	-	-
057	Pos	-	-	-	-	-	-	-	-
061	Pos	-	-	-	-	-	-	-	-
062	Pos	-	-	-	Pos (3)	-	-	-	-
034	Pos	-	-	-	Pos (3)	-	-	-	-
029	Neg	-	-	-	-	-	-	-	-
040	-	-	-	-	Pos (6)	-	-	-	-
048	Pos	-	-	-	Neg (4)	-	-	-	-

^a nucleocapsid and/or spike – see Methods; ^b number indicate time (months) from Covid-19 diagnosis to test; ^c saliva antibody reactivity against the Spike S1S2 trimer. For MFI (median fluorescence intensity) value, see supplementary table; ^d ELISpot was considered positive if >20 SFUs in Spike-based and/or M+N+E –based tests; ^e negative at 6 months against Nucleocapside, positive at 12 months against Spike; ^f positive due to 40 spots in the M+N+E analysis; - no data available

- Seroconversion occurred in 34/41 (83%) of convalescents and anti-SARS-CoV-2 antibodies remained detectable at 6 and 12 months of follow-up in 17/22 and 8/11 patients, respectively.
- Immunological analyzes also revealed that 13/17 tested patients had neutralizing antibodies (of which 1 patient was negative in conventional serology).
- 19/28 patients (68%) had SARS-CoV-2 specific antibodies in saliva.
- SARS-CoV-2 specific T-cells were detected in 14/17 patients (82%) and was generally paralleled by seroconversion.

CONCLUSIONS

- Covid-19 continued to result in high admission and fatality rates even among consecutive and young early-stage CLL patients.
- Risk of severe Covid-19 was independent of age, CLL status and CLL treatment.
- The only significant risk factor of death was age ≥75 years.
- Risk of death and ICU admission declined in the second time period.
- A robust and durable B- and/or T-cell immunity was observed in most convalescents.

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