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Risk of Acute Kidney Injury and Cytopenias During Treatment of Chronic Lymphocytic Leukemia in a Nationwide Real-World Cohort

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BACKGROUND & AIM

Adverse events (AEs) from treatment of chronic lymphocytic leukemia (CLL) affects quality of life, treatment adherence, and survival.
Our aim was to **identify risk factors of acute kidney injury and cytopenias** for CLL patients receiving treatment.

METHODS

We used data from **Danish nation-wide health registers**, linked on an individual level.

- Cohort: Patients with **CLL or SLL receiving first-line treatment between 2005 and 2023**, identified in the Danish CLL Register and Danish Lymphoma Register.
- Adverse events: Defined using **CTCAE v5**. Based on laboratory values from The Clinical Laboratory Information System Database.

We included following events:

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hgb <LLN - 6.2 mM	Hgb <6.2 - 4.9 mM	Hgb <4.9 mM	-
White blood cell decreased (leukopenia)	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased (neutropenia)	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased (lymphopenia)	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Platelet count decreased (thrombocytopenia)	<LLN - 75.0 x 10e9 /L	<75.0 - 50.0 x 10e9 /L	<50.0 - 25.0 x 10e9 /L	<25.0 x 10e9 /L
Creatinine increased (proxy for AKI)	>ULN - 1.5 x ULN	->1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN

Table 1: CTCAE definitions of acute kidney injury and cytopenias
- Grade ≥3 anemia, thrombocytopenia, leukopenia (neutropenia/lymphopenia)
- Grade ≥2 acute kidney injury (AKI), based on creatinine increase

Follow-up: 6 months from treatment start. Last follow-up: June 2023.

Primary outcome:
- Cumulative incidence of adverse events within 180 days of treatment initiation, with death as competing risk (Aalen-Johansen).
- Risk factors analyzed with Cox proportional hazards models.

RESULTS

Baseline characteristics	
Number of patients	2 646 patients
Type	CLL = 2 355 patients SLL = 291 patients
Age at diagnosis	Median = 69 (range 22-98)
Sex (male)	1 725 (65.2%)
Time from diagnosis to treatment	Median = 1.1 years
First-line treatment	
Bendamustine-based	638 (24.1%)
Chlorambucil-based	606 (22.9%)
Fludarabin-based	431 (16.3%)
CD20 antibody	328 (12.4%)
Venetoclax	211 (8.0%)
Other	169 (6.4%)
BTK-inhibitor	159 (6.0%)
Venetoclax-ibrutinib	32 (1.2%)
Missing	72 (2.7%)

Table 2: Baseline variables

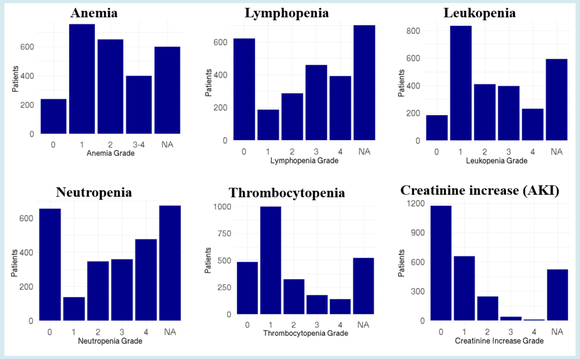

Figure 1: Selected adverse events by CTCAE-grade. 55% experienced ≥1 AE within 6 months of first-line treatment. Most common AEs: neutropenia (42%), lymphopenia (44%), and leukopenia (31%).

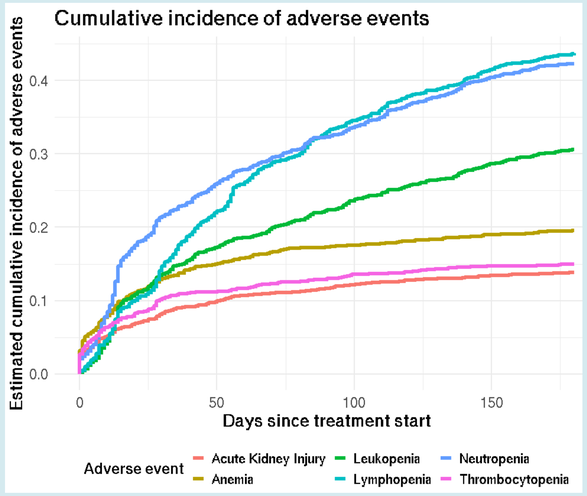

Figure 2: Cumulative incidence of selected adverse events with death as the only competing risk, estimated using the Aalen-Johansen method. Adverse events are not treated as competing risk.

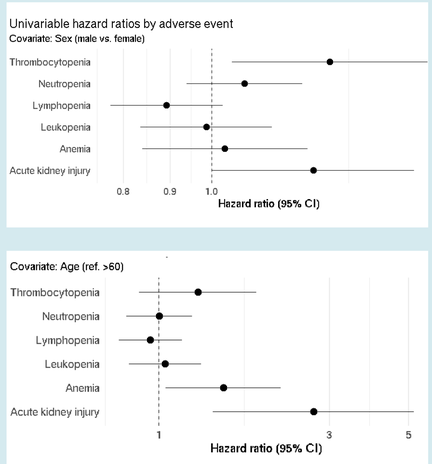

Figure 3+4: Forest plot showing univariable hazard ratios (HR) with 95% confidence intervals for each adverse event, estimated using separate Cox proportional hazards models. Reference groups: female (sex) and ≤60 years (age).

Multivariable analyses were fully adjusted for age, sex, treatment type, IGHV status, TP53 mutation, and del17p status.

Selected results:
Anemia: the association with age disappeared.
Lymphopenia: sex and age were significant.

Treatment type (reference = BTK-inhibitor)
- **Chemo-based regimens (bendamustine, chlorambucil, fludarabine)** → increased risk of neutropenia, lymphopenia, leukopenia, and thrombocytopenia.
- **Venetoclax** → increased risk of neutropenia, lymphopenia and leukopenia.
- **CD20 antibody** → increased risk of lymphopenia, thrombocytopenia and leukopenia.
- **Venetoclax + ibrutinib** → increased risk of thrombocytopenia.
- **No significant differences for anemia**
- Only **fludarabine** → increased risk of **AKI.**

CONCLUSION

Over half of CLL and SLL patients experienced an AE within six months of first-line treatment in routine care.

Risk patterns differ by treatment type, age, and sex, emphasizing the importance of **tailoring treatment strategies** to individual patient characteristics.

AE risk was highest with bendamustine (76%) and venetoclax (72%), and **lowest** with BTK inhibitors (40%).

Venetoclax-treated patients had significantly higher risk of neutropenia and lymphopenia compared to **BTK-inhibitors.**

FUTURE WORK

Inclusion of **cardiovascular events and infections**. This will provide a more comprehensive understanding of age- and treatment-related adverse event patterns.

ADDITIONAL INFORMATION

CONTACT INFORMATION
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