Risk of Tumor Lysis Syndrome Among Patients With Chronic Lymphocytic Leukemia or Mantle Cell Lymphoma Treated with Venetoclax: A Real-World Study

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Background: Tumor lysis syndrome (TLS) is a life-threatening oncological emergency caused by the rapid destruction of malignant cells that can result in renal failure, cardiac arrhythmias, or death. Venetoclax, a B-cell lymphoma 2 inhibitor, has been associated with TLS in clinical trials. The incidence of TLS events ranges from 1.8% to 3.0% across clinical trials evaluating the efficacy and safety of venetoclax in patients with B-cell malignancies. However, data on TLS among patients treated with venetoclax in routine clinical practice are limited. This study aimed to describe the incidence of TLS among patients with chronic lymphocytic leukemia (CLL) or mantle cell lymphoma (MCL) treated with venetoclax in routine clinical practice in the United States.

Methods: Deidentified data from patients with CLL or MCL who initiated venetoclax from April 2016 to December 2024 were identified from the TriNetX Dataworks-USA Network electronic health record database. Patient demographics, comorbidities, and concomitant medications were described. The primary outcome was the 3-month TLS risk following venetoclax initiation. A 3-month follow-up was selected to encompass the dose ramp-up period in patients with CLL or MCL. TLS was identified using two definitions: (1) the presence of the *International Classification of Diseases, Tenth Revision, Clinical Modification* diagnosis code E88.3 and (2) receipt of rasburicase treatment. The secondary outcome was the incidence of all-cause mortality in patients experiencing TLS, defined as the presence of TLS diagnosis within the same month as death or the month prior, with no trauma-related diagnosis recorded during the same period.

Results: A total of 4747 patients with CLL and 408 patients with MCL initiated venetoclax therapy and were included in this analysis; 68.7% of patients with CLL and 67.2% of patients with MCL were aged ≥65 years. Approximately 54.1% of patients with CLL and 55.9% of patients with MCL had at least 1 comorbidity. Venetoclax was administered in combination with either rituximab or obinutuzumab in 44.3% and 40.7% of patients with CLL and MCL, respectively. Antihyperuricemic prophylaxis with either allopurinol or febuxostat at baseline was observed in 58.2% of patients with CLL and 63.7% of patients with MCL. Using the *ICD-10* diagnosis code-based definition, TLS occurred within 3 months of venetoclax initiation in 5.6% (n=265) of patients with CLL and 8.6% (n=35) of patients with MCL, with median time to onset of 17 and 16 days, respectively. Using the definition based on rasburicase use, TLS incidence was 3.9% (n=186) among patients with CLL and 5.9% (n=24) among patients with MCL, with a median time to onset of 14 and 11 days, respectively. All-cause mortality occurred in 0.3% (n=12) of patients with CLL and 2.2% (n=9) of patients with MCL who were

identified as having TLS; median time to mortality was 47 and 43 days after the start of therapy with venetoclax, respectively.

Summary/Conclusion: This real-world study demonstrated that the risk of TLS was common among patients treated with venetoclax and generally occurred shortly after treatment initiation. The risk appeared to be relatively higher among patients with MCL than in those with CLL. These findings underscore the importance of close monitoring during venetoclax therapy, particularly during the dose ramp-up period.

Table. TLS Risk in Patients With CLL or MCL Receiving Treatment With Venetoclax

3-month TLS risk		**CLL (n=4747)**	**MCL (n=408)**
***ICD-10* diagnosis code-based definition**	n (%)	265 (5.6)	35 (8.6)
	Median (IQR) time to onset, days	17 (7-37)	16 (8-31)
Rasburicase use-based definition	n (%)	186 (3.9)	24 (5.9)
	Median (IQR) time to onset, days	14 (7-26)	11 (7-30)
Incidence of mortality in patient with TLS[a]	n (%)	12 (0.3)	9 (2.2)
	Median (IQR) time to onset, days	47 (36-60)	43 (29-50)

[a]Includes all-cause mortality; cause of death was not available in the data source.
CLL, chronic lymphocytic leukemia; *ICD-10*, *International Classification of Diseases, Tenth Revision, Clinical Modification*; IQR, interquartile range; MCL, mantle cell lymphoma; TLS, tumor lysis syndrome.