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Incidence of Tumor Lysis Syndrome in Patients with Acute Myeloid Leukemia Undergoing Low-Intensity Induction with Venetoclax

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To the Editor:

Venetoclax, a B-cell lymphoma-2 inhibitor, is approved in combination with a hypomethylating agent or low-dose cytarabine for the treatment of newly diagnosed acute myeloid leukemia (AML) in patients who cannot tolerate intensive induction chemotherapy.¹ While tumor lysis syndrome (TLS) is a significant complication of venetoclax treatment in chronic lymphocytic leukemia (CLL),^{2,3} there have been no reports of clinical TLS (cTLS) in studies of venetoclax in AML patients.^{4,5} While there were three cases of laboratory TLS (lTLS) reported in the VIALE-A trial, there is little information regarding the real-life incidence of TLS in these patients.⁴

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Authorship Contributions

S.D. provided study design, collected and analyzed data, and prepared the manuscript. E.N. provided study design, analyzed data, and reviewed and edited the manuscript. C.D. and M.K. contributed patients, and reviewed and edited the manuscript. J.N. and W.Q. conducted statistical analysis, results interpretation, and reviewed and edited the manuscript. A.M. reviewed and edited the manuscript. A.D. provided study design, collected and analyzed data, and reviewed and edited the manuscript.

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This was a single-center retrospective, cohort study of adult AML patients at The University of Texas MD Anderson Cancer Center between November 2014 and June 2019. The primary objective was to determine the real-life incidence of ITLS. Secondary objectives were to evaluate the incidence of cTLS, describe TLS prophylaxis strategies, and identify potential risk factors associated with ITLS. Included were newly-diagnosed AML patients who received frontline induction therapy with venetoclax and either a hypomethylating agent or low-dose cytarabine. Patients also had at least one laboratory value for TLS blood chemistries per 24-hour timeframe for seven consecutive days post-initiation of venetoclax. Patients with prior exposure to venetoclax were excluded.

TLS was defined by the Cairo-Bishop Criteria, which includes changes in serum uric acid (≥ 8 mg/dL or $\geq 25\%$ increase from baseline), potassium (≥ 6 mEq/L or $\geq 25\%$ increase from baseline), phosphorous (≥ 4.5 mg/dL or $\geq 25\%$ increase from baseline), and calcium (≤ 7.0 mg/dL or $\geq 25\%$ decrease from baseline).⁶ ITLS was defined as having at least two laboratory abnormalities within the same 24-hour timeframe. cTLS was defined as the presence of ITLS in addition to elevated serum creatinine (≥ 1.5 times the upper limit of normal) within the same 24-hour timeframe.⁶ Continuous variables were compared between groups by a Wilcoxon Rank Sum test. Associations between categorical variables were examined by a Fisher's Exact test. A Hosmer-Lemeshow test was used to check the goodness-of-fit for the final model. All computations were carried out in SAS version 9.4. This study was approved by the institutional review board.

There were 148 patients who underwent low-intensity induction with venetoclax-based regimens during the study period. All patients initiated venetoclax and were monitored for the 28-day induction period in the inpatient setting. The median age was 72 years, most patients had *de novo* AML (61.5%) and underwent induction with decitabine 20 mg/m² for 10 days (66.2%) plus venetoclax (Table 1). Fifty-nine patients (39.9%) met criteria for ITLS; however, only 5.4% had laboratory values outside normal institutional reference ranges, and 2.7% met criteria for cTLS. Most cases of ITLS were caused by elevations in both serum uric acid and phosphorous within the first 48-hours post-initiation of venetoclax (76.3%).

Multivariable analysis included all baseline patient and disease characteristics, as well as TLS mitigation strategies. Results indicate the presence of isocitrate dehydrogenase 2 (*IDH2*) mutation and elevated baseline lactate dehydrogenase (LDH) level are potential risk factors for ITLS in this population (Supplemental Table 1). *IDH2*-mutated AML patients were 3.6 times more likely to experience ITLS (OR 3.6, 1.2 – 10.5, $p = 0.021$). One patient with *IDH2* mutation had evidence of cTLS. Clinically, patients harboring *IDH2* mutations have high response rates and durable remissions with venetoclax treatment.⁷ The sensitivity of *IDH2*-mutated cells to venetoclax treatment may predispose these patients to ITLS. Also, in our population, a one natural-log unit increase in LDH value resulted in 1.8 times increased likelihood of ITLS (OR 1.8, 1.1 – 2.9 for each natural-log increase, $p = 0.021$). In other words, a patient with baseline LDH level of 582 U/L (i.e. $\ln = 6.37$) would be 1.8 times more likely to develop ITLS than a patient with baseline LDH level of 214 U/L (i.e. $\ln = 5.37$), the institutional upper limit of normal. LDH is often a surrogate marker of tumor burden, so it is unsurprising that increased LDH may lead to increased risk of ITLS with venetoclax in AML patients. Notably, white blood cell (WBC) count was not significantly

associated with ITLS in the final multivariate model; however, most patients with high WBC count were cytoreduced prior to venetoclax initiation, potentially mitigating this risk.

For TLS prophylaxis, 90.5% of patients received allopurinol (Supplemental Table 2). Notably, 20.3% of patients did not undergo a venetoclax dose ramp-up phase. Of the 79.7% who underwent a dose ramp-up phase, there was variation in the duration of ramp-up before reaching the target dose. A two-day ramp-up period was most common (50.8%), followed by three days (28.8%), five days (17.8%), and four days (2.5%). When utilized in combination with a hypomethylating agent, the venetoclax FDA labeling recommends a three-day dose ramp-up in the absence of concomitant CYP3A4 inhibitors, and a four-day dose ramp-up with concomitant strong CYP3A4 inhibitors.¹ In this study, most patients (60.8%) reached their target dose with either no dose ramp-up or shorter dose ramp-up (i.e. two-day) than currently recommended, suggesting an abbreviated dose ramp-up may be safely implemented for certain AML patients. However, this should be done cautiously, as ITLS occurred in patients who did not undergo venetoclax ramp-up phase at a similar rate to our entire study population (13 of 30 patients, 43.3%). One recent study of TLS risk with venetoclax therapy in AML suggested that dose ramp-up may not be necessary, even with concomitant azoles.⁸ While this may be feasible for certain patients, due to the incidence of ITLS noted in our population, it may be safest to utilize some form of dose ramp-up phase until more real-life data is known.

In this study, venetoclax 100 mg with concomitant posaconazole or voriconazole and venetoclax 200 mg with concomitant isavuconazole or fluconazole were considered the 400 mg equivalent dosages; higher doses of venetoclax in these combinations were considered greater than 400 mg equivalent. The target equivalent venetoclax dose was 100 mg for 1.4% of patients, 400 mg for 68.2%, and 800 mg for 30.4%. Concomitant posaconazole was used in 28.4%, voriconazole in 16.2%, isavuconazole in 18.9%, and fluconazole in 1.4%.

While 93.9% of patients received intravenous (IV) hydration, only 14.4% received at least 1.5 liters of fluid (64 mL/hr) per day at the time of venetoclax initiation, as recommended in the FDA labeling.¹ In fact, 46.6% received 500 milliliters of IV hydration per day, and of those 69 patients, 31 (44.9%) were found to have ITLS, a similar rate to our entire study population. Overall, the proportion of AML patients in our study receiving at least 1.5 liters of IV hydration was lower than reported in CLL populations with a similar incidence of TLS.²⁻³ Therefore, it may be appropriate to consider less aggressive IV hydration for certain AML patients initiating venetoclax, especially for elderly patients with concern for fluid overload.

Most patients received TLS blood chemistries two to three times daily for at least the first 72-hours of venetoclax treatment. Since ITLS occurred within 48-hours post-venetoclax initiation in 76.3% of patients, it may be possible to monitor TLS blood chemistries less frequently after this initial timeframe. Although, frequent monitoring may still be appropriate beyond 48-hours for patients with baseline renal dysfunction and/or higher WBC count since both factors were independently associated with TLS in CLL populations.³ Most patients in this study had adequate baseline renal function (mean serum creatinine of 0.91 mg/dL) and low WBC count (92.6% with WBC < 10 x 10⁹/L).

The majority of patients with elevated WBC count at the time of AML diagnosis were cytoreduced prior to venetoclax initiation; 28.8% of patients who had ITLS and 32.6% of patients with no ITLS were cytoreduced with oral hydroxyurea and/or intravenous cytarabine. While the FDA labeling recommends a WBC count $< 25 \times 10^9/L$ prior to starting venetoclax, utilizing a more stringent WBC threshold may decrease the risk of TLS in AML patients.¹

This study is limited by its retrospective design. Data collection was conducted primarily through review of laboratory values, which hindered the ability to capture a wider scope of clinical and subjective information; due to this, the true incidence of cTLS may be underestimated. While only seven patients received rasburicase, most patients with evidence of ITLS received additional IV hydration and/or phosphate binders, which may have mitigated the development of cTLS. Moreover, many patients were cytoreduced to a WBC count $< 10 \times 10^9/L$ prior to venetoclax initiation, which may have further mitigated incidence of TLS in this AML population. This study included newly diagnosed AML patients receiving venetoclax in combination with low-intensity chemotherapy; therefore, results may not be applicable to patients with relapsed AML or those receiving venetoclax in combination with intensive chemotherapy. Lastly, because all patients underwent induction therapy in the inpatient setting with frequent monitoring and early identification of TLS, the recommendations in this report may not be applicable to patients initiating venetoclax in an outpatient setting.

In conclusion, while a significant portion of our population met criteria for ITLS (59 patients, 39.9%), the majority met criteria based on minor increases in uric acid and phosphorus that were still within normal ranges. In fact, only eight patients (5.4%) had laboratory values outside the normal reference ranges, and four patients (2.7%) met criteria for cTLS. This incidence is still higher than previously reported in AML studies, and is similar to recent real-life populations of CLL patients receiving venetoclax (5.7% ITLS and 2.7% cTLS).³ However, it should be noted this CLL population included one patient requiring hemodialysis and one patient death from TLS-related complications.³ While two patients in our study required short-term hemodialysis, there was no incidence of TLS-related death. Overall, TLS is a risk of venetoclax-based induction in AML patients requiring close monitoring for at least the first 48-hours of therapy. Less stringent prophylactic measures may be adequate to prevent TLS in certain patients, such as those with no pre-existing organ dysfunction and low baseline WBC count ($< 10 \times 10^9/L$). However, prophylaxis and monitoring as recommended by the FDA labeling should be utilized for patients harboring an *IDH2* mutation (or unknown *IDH2* mutational status at treatment initiation), and those with elevated baseline LDH levels, as these were identified as potential risk factors for ITLS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Data Availability Statement

Data available on request from the authors

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Table 1.

Baseline Characteristics for Patients Receiving Venetoclax-Based Low-Intensity Induction

	No Laboratory TLS (N = 89)	Laboratory TLS (N = 59)
Age (years)	72 (56 - 86)	72 (49 - 86)
Male	50 (56.2)	31 (52.5)
AML Etiology		
Newly Diagnosed	56 (62.9)	35 (59.3)
Secondary AML with No Prior Treatment	7 (7.9)	5 (8.5)
Secondary AML with Prior Treatment	12 (13.5)	14 (23.7)
Therapy-Related AML	14 (15.7)	5 (8.5)
Myelomonocytic AML	9 (10.1)	2 (3.4)
Tumor Burden		
Baseline WBC Count (x 10 ⁹ /L)	3.7 (0.3 - 52.6)	4.4 (0.4 - 25.5)
Baseline LDH Level (U/L)	479 (108 - 3594)	689 (167 - 7770)
Genetic Mutations		
<i>NPM1</i>	14 (15.7)	13 (22.0)
<i>CEBPA</i>	3 (3.4)	3 (5.1)
<i>FLT3</i>	13 (14.6)	6 (10.2)
<i>IDH1</i>	9 (10.1)	5 (8.5)
<i>IDH2</i>	6 (6.7)	11 (18.6)
<i>TP53</i>	28 (31.5)	15 (25.4)
<i>RUNX1</i>	13 (14.6)	13 (22.0)
<i>ASXL1</i>	19 (21.3)	12 (20.3)
<i>KMT2A</i>	1 (1.1)	1 (1.7)
<i>GATA2</i>	5 (5.6)	2 (3.4)
Baseline Organ Function		
LVEF (%)	60 (45 - 70)	59 (30 - 70)
Serum Creatinine (mg/dL)	0.92 (0.42 - 1.80)	0.90 (0.46 - 3.23)
Total Bilirubin (mg/dL)	0.6 (0.2 - 2.4)	0.7 (0.2 - 2.5)
Induction Regimen		
Decitabine 20 mg/m ² x 5 Days	21 (23.6)	15 (25.4)
Decitabine 20 mg/m ² x 10 Days	59 (66.3)	39 (66.1)
Azacitidine 75 mg/m ² x 7 Days	8 (9.0)	3 (5.1)
Cytarabine 20 mg BID x 10 Days	0 (0.0)	1 (1.7)
Other*	1 (1.1)	1 (1.7)
Concomitant Interacting Agents		
Posaconazole	29 (32.6)	13 (22.0)
Voriconazole	12 (13.5)	12 (20.3)
Isavuconazole	15 (16.9)	13 (22.0)

	No Laboratory TLS (N = 89)	Laboratory TLS (N = 59)
Fluconazole	1 (1.1)	1 (1.7)

Data presented as mean (range) or N (%), as appropriate

TLS = tumor lysis syndrome; AML = acute myeloid leukemia; WBC = white blood cell

LDH = lactate dehydrogenase; LVEF = left ventricular ejection fraction; BID = twice daily

* Includes Decitabine 10 mg/m² x 5 Days (no TLS) and Decitabine 20 mg/m² x 7 Days (laboratory TLS)

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