as a RF[5] could not be validated in our cohort. In addition, we could demonstrate that absolute increase exhibited a better discriminatory ability compared to a relative increase. It could be argued that relative increases could overestimate the impact of a dynamic biomarker, particularly in patients with low levels at diagnoses.

Anemia is one of the hallmark symptoms in symptomatic MM. Hence, a decrease in hemoglobin during the first year of diagnosis as a RF of progression in SMM has been suggested in previous studies (Table S3B in Appendix S1). We could not confirm that the decrease of hemoglobin by ≥ 5 g/L during the first year of follow-up as a RF. Moreover, this cut-off could include values within the intra-individual variation of hemoglobin.

The findings in our retrospective study support that dynamic changes in MP can identify patients at high risk of progression. In conclusion, BMPCs > 20% and MP > 20 g/L at diagnosis, were independent RFs for the progression. Moreover, eMP > 5 g/L and eFLCr > 4.5 were significant predictors of progression during the follow-up. With a median TTP of 5 months after an evolving pattern is observed, patients with evolving RF should be closely monitored. However, as these findings are exploratory, they should be validated in future prospective studies. The observed high risk of progression in patients with either or both evolving biomarkers may advocate a closer monitoring of these patients as well as possibly inclusion in future prospective early intervention trials.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

C.G and H.N. conceived the study and oversaw overall direction and planning. C.G, J.B.B and V.L. collected the data. C.G., E.A., J.B.B., S.U. and H.N. wrote the manuscript with input from all authors. C.G., J.L. and H.N. analyzed the data. E.A. and H.N. supervised the project. All authors critically revised the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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Incidence of tumor lysis syndrome in patients with acute myeloid leukemia undergoing low-intensity induction with venetoclax

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]

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 lTLS. Secondary objectives were to evaluate the incidence of cTLS, describe TLS prophylaxis strategies, and identify potential risk factors associated with lTLS. 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 ≥25% increase from baseline), potassium (≥6 mEq/L or ≥25% increase from baseline), phosphorous (≥4.5 mg/dL or ≥25% increase from baseline), and calcium (≤7.0 mg/dL or ≥25% decrease from baseline).[6] lTLS was defined as having at least two laboratory abnormalities within the same 24-hour timeframe. cTLS was defined as the presence of lTLS 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/m^2 for 10 days (66.2%) plus venetoclax (Table 1). Fifty-nine patients (39.9%) met criteria for lTLS; however, only 5.4% had laboratory values outside normal institutional reference ranges, and 2.7% met criteria for cTLS. Most cases of lTLS 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 lTLS in this population (Supplemental Table SS1). *IDH2*-mutated AML patients were 3.6 times more likely to experience lTLS (odds ratio [OR] = 3.6, 1.2-10.5, P = .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

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 ($\times 10^9$/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		
NPM1	14 (15.7)	13 (22.0)
CEBPA	3 (3.4)	3 (5.1)
FLT3	13 (14.6)	6 (10.2)
IDH1	9 (10.1)	5 (8.5)
IDH2	6 (6.7)	11 (18.6)
TP53	28 (31.5)	15 (25.4)
RUNX1	13 (14.6)	13 (22.0)
ASXL1	19 (21.3)	12 (20.3)
KMT2A	1 (1.1)	1 (1.7)
GATA2	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 × 5 d	21 (23.6)	15 (25.4)
Decitabine 20 mg/m^2 × 10 d	59 (66.3)	39 (66.1)
Azacitidine 75 mg/m^2 × 7 d	8 (9.0)	3 (5.1)
Cytarabine 20 mg BID × 10 d	0 (0.0)	1 (1.7)
Other[a]	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)
Fluconazole	1 (1.1)	1 (1.7)

Note: Data presented as mean (range) or N (%), as appropriate.
Abbreviations: AML, acute myeloid leukemia; BID, twice daily; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; TLS, tumor lysis syndrome; WBC, white blood cell.
[a]Includes Decitabine 10 mg/m^2 × 5 days (no TLS) and Decitabine 20 mg/m^2 × 7 days (laboratory TLS).

patients to lTLS. Also, in our population, a one natural-log unit increase in LDH value resulted in 1.8 times increased likelihood of lTLS (OR = 1.8, 1.1-2.9 for each natural-log increase, P = .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 lTLS 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 lTLS with venetoclax in AML patients. Notably, white blood cell (WBC) count was not significantly associated with lTLS 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 S2). 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 lTLS 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 lTLS 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 L of fluid (≥64 mL/hour) per day at the time of venetoclax initiation, as recommended in the FDA labeling.[1] In fact, 46.6% received ≤500 mL of IV hydration per day, and of those 69 patients, 31 (44.9%) were found to have lTLS, a similar rate to our entire study population. Overall, the proportion of AML patients in our study receiving at least 1.5 L 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 lTLS 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. However, 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 $<10 \times 10^9$/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 lTLS and 32.6% of patients with no lTLS 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 lTLS 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 lTLS (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% lTLS 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 lTLS.

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AUTHOR CONTRIBUTIONS

Stacy Diao provided study design, collected and analyzed data, and prepared the manuscript. E Dan Nichols provided study design, analyzed data, and reviewed and edited the manuscript. Courtney DiNardo and Marina Konopleva contributed patients, and reviewed and edited the manuscript. Jing Ning and Wei Qiao conducted statistical analysis, results interpretation, and reviewed and edited the manuscript. Abhishek Maiti reviewed and edited the manuscript. Adam J. DiPippo provided study design, collected and analyzed data, and reviewed and edited the manuscript.

CONFLICTS OF INTEREST

S.D., E.N., J.N., W.Q., and A.D. have no disclosures. C.D. served as a consultant for AbbVie, Agios, Celgene, Daiichi Sankyo, Jazz, and Notable Labs. M.K. served as a consultant for AbbVie, Genentech, F. Hoffman La-Roche, Stemline Therapeutics, Amgen, Forty-Seven, and Kisoji. M.K. received research funding and clinical trial support from AbbVie, Genentech, F. Hoffman La-Roche, Eli Lilly, Cellectis, Calithera, Ablynx, Stemline Therapeutics, Agios, Ascentage, and AstraZeneca. M.K. received royalties from Reata Pharmaceutical. A.M. received research funding from Celgene. The current affiliation for S.D., E.N., C.D., M.K., J.N., W.Q., A.M., and A.D. is The University of Texas MD Anderson Cancer Center.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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Natural history of multiple myeloma patients refractory to venetoclax: A single center experience

To the Editor:

Over the last decade, a drastic survival improvement for multiple myeloma (MM) was observed and most patients live beyond 10 years. Nevertheless, in the constant quest for a functional cure, a demand for novel modern therapies exists.[1] Venetoclax, a selective BCL-2 inhibitor, has emerged as a potential treatment option for relapsed refractory MM (RRMM) with its benefit more prominently seen in RRMM patients with the cytogenetic abnormality t(11;14).

So, BCL2, an anti-apoptotic protein, is critical for myeloma cell survival.[2] in vitro data confirmed MM samples positive for the t(11;14) were highly sensitive to ABT-737, a cell-permeant compound that binds to Bcl-2 and Bcl-x(L) but not to Mcl-1and had higher ratios