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RESEARCH LETTER

A Prospective Evaluation of Novel Renal Biomarkers in Patients With Lymphoma Receiving High-Dose Methotrexate

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INTRODUCTION

Methotrexate (MTX)-associated acute kidney injury (AKI) occurs in 3% to 60% of patients at some point during treatment.[1,2] The standard of care for MTX dose derivation and postdose monitoring centers around serum creatinine level as a surrogate for glomerular filtration rate (GFR).[3] As the terminal byproduct of skeletal muscle metabolism, nonrenal determinants, including altered muscle mass, deconditioning, and malnutrition, can decrease the accuracy of serum creatinine-based GFR estimation in patients with cancer.[4] In addition, creatinine level may not rise until 48 hours after the onset of kidney damage, leaving a missed window of opportunity for early intervention.[5]

Novel biomarkers that indicate tubular epithelial cell stress or early damage demonstrate the capacity to identify kidney injury before overt AKI is detected by a rise in serum creatinine level or a decline in urine output.[6,7] Consensus recommendations support the incorporation of damage and stress biomarkers into the detection and management of AKI.[8] Whether these novel biomarkers can predict AKI in patients receiving high-dose MTX (HDMTX) is unclear. Therefore, this study sought to determine whether urinary TIMP2*IGFBP7 and urinary NGAL measurements are predictive for AKI in patients with lymphoma hospitalized to receive HDMTX. Reporting of this observational study has been done according to the Modified STROBE Statement (Supplementary Appendix 1). Methods, including MTX-inclusive combination chemotherapy protocols (Supplementary Table S1) and the leucovorin dose adjustment schema (Supplementary Table S2) are detailed in Appendix 2 of the Supplementary Material.

RESULTS

Baseline Demographics and Clinical Characteristics

Of 137 patients screened for participation, 77 were enrolled (Supplementary Figure S1). Table 1 details baseline demographics and clinical characteristics. Univariate analysis showed no association between age, sex, race, baseline chronic kidney disease, diabetes mellitus, serum creatinine, estimated GFR (eGFR), or predicted 24-hour urine protein and AKI.

Acute Kidney Injury

AKI occurred in 16 patients (21%) within 96 hours of HDMTX. Overall, 5 patients (31%) developed stage 1 AKI, 5 patients (31%) had stage 2 AKI, and 6 patients (38%) experienced stage 3 disease. The median time from the start of HDMTX infusion to AKI onset was 49 (interquartile range: 26–56) hours. No patient required renal replacement therapy for AKI.

The incidence of AKI varied according to the MTX dose prescribed. AKI occurred in 4 patients (11.8%) prescribed 8 g/m^2 as central nervous system lymphoma

Table 1. Comparison of baseline demographics and laboratory values between patients with lymphoma who did and did not develop acute kidney injury within 96 hours of HDMTX administration

Characteristics	All patients ($N = 77$)	Patients who developed AKI ($n = 16$)	Patients who did not develop AKI ($n = 61$)	Odds ratio (95% CI)	*P* value
Age (yr), median (IQR)	68.4 (59–76)	66.4 (61–69)	69.9 (59–76)	1.00 (0.96–1.04)	0.90
Male, *n* (%)	51 (66)	14 (88)	37 (61)	4.54 (0.95–21.78)	0.059
Race, *n* (%)					
Caucasian	71 (92)	13 (81)	58 (95)	Reference	
Other/unknown	6 (8)	3 (19)	3 (5)	4.46 (0.81–24.66)	0.086
Chronic kidney disease	4 (5)	0 (0.0)	4 (7)	0.39(0.01–10.64)	0.57
Diabetes mellitus	14 (18)	2 (13)	12 (20)	0.58 (0.12–2.92)	0.51
Body surface area, median (IQR)	2.0 (1.8–2.1)	2.1 (2.0–2.2)	1.9 (1.8–2.1)	1.22 (0.97–1.54)[a]	0.083
Lymphoma diagnosis subtype, *n* (%)					
DLBCL	43 (58)	9 (60)	34 (58)	Reference	
Primary DLBCL of the CNS	22 (30)	3 (20)	19 (32)	0.60 (0.14–2.47)	0.48
EBV-positive DLBCL of elderly	6 (8)	2 (13)	4 (7)	1.89 (0.30–12.01)	0.50
Other	3 (4)	1 (7)	2 (3)	1.89 (0.30–12.01)	0.50
Bone marrow involvement, *n* (%)	10 (13)	5 (31)	5 (8)	5.09 (1.26–20.60)	0.023
Percent involvement, median (IQR)	15 (10–30)	10 (10–10)	20 (20–30)		
Serum creatinine, mg/dl, median (IQR)	0.9 (0.74–1.08)	0.9 (0.8–1.09)	0.9 (0.72–1.08)	1.07 (0.87–1.31)[a]	0.54
Estimated CrCl, ml/min, median (IQR)	90 (70–120)	96 (78–119)	86 (70–120)	1.01 (0.90–1.13)[b]	0.93
Estimated GFR, ml/min, median (IQR)	92 (77–106)	99 (84–116)	91 (77–106)	1.09 (0.89–1.34)[b]	0.41
Predicted 24-hour urine protein, mg/24 h, median (IQR)	210 (148–306)	235 (155–287)	194 (148–310)	1.00 (0.97–1.03)[b]	0.93
Hemoglobin, g/dl, median (IQR)	11.4 (10.2–13.2)	11.6 (10.0–13.5)	11.3 (10.3–13.1)	1.06 (0.80–1.40)	0.69
Albumin, g/dl, median (IQR)[c]	3.8 (3.5–4.2)	3.9 (3.3–4.3)	3.8 (3.5–4.2)	0.99 (0.88–1.10)[a]	0.80
LDH, median (IQR)	212 (180–277)	218 (183–398)	212 (178–263)	1.04 (0.99–1.09)[b]	0.096

AKI, acute kidney injury; CNS, central nervous system; CrCl, creatinine clearance (per Cockcroft Gault equation); DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; GFR, glomerular filtration rate; HDMTX, high-dose methotrexate; IQR, interquartile range; LDH, lactate dehydrogenase.
[a]Per 0.1 unit increase.
[b]Per 10 unit increase.
[c]Only available in 61 ($n = 14$ who developed AKI and $n = 47$ who did not develop AKI).

treatment. In addition, AKI developed in 10 patients (32%) who received 3.5 g/m^2 (treatment: $n = 4$; prophylaxis: $n = 8$) and 2 patients (22%) given 1.5 g/m^2 as prophylaxis against central nervous system relapse. Patients prescribed MTX dose of 3.5 g/m^2 were significantly more likely to develop AKI than those prescribed 8 g/m^2 (odds ratio = 3.75, 95% CI: 1.07–13.12, $P = 0.039$).

Urinary Biomarkers

Median baseline TIMP2*IGFBP7 concentration was 0.3 (interquartile range: 0.1–0.8). The distribution of baseline TIMP2*IGFBP7 included 40 patients (52%) at <0.3, 23 (30%) between 0.3 and 0.99, and 14 (18%) at ≥1.0. There were 3 patients who had a baseline TIMP2*IGFBP7 ≥ 2.0. Baseline TIMP2*IGFBP7 did not demonstrate any correlation with baseline serum creatinine at $r = -0.08$ (95% CI: −0.30 to 0.15, $P = 0.48$) or eGFR at $r = 0.13$ (95% CI: −0.10 to 0.34, $P = 0.27$).

Patients with a baseline TIMP2*IGFBP7 concentration of ≥0.3 were significantly more likely to develop any AKI (odds ratio = 6.68, 95% CI: 1.72–25.94, $P = 0.006$) or AKI stage 2 or 3 (odds ratio = 6.11, 95% CI: 1.22–30.49, $P = 0.027$). AKI occurred in 7.5%, 30%, and 54% of patients with a baseline TIMP2*IGFBP7 <0.3, between 0.3 and 0.99, and ≥1.0, respectively. The area under the receiver operating characteristic curve (AUC) of TIMP2*IGFBP7 to predict AKI is depicted in Figure 1 (AUC = 0.70, 95% CI: 0.54–0.86, $P = 0.008$).

The median baseline urinary NGAL concentration was 21 ng/ml (interquartile range: 13–44). Urinary NGAL was not significantly associated with any AKI

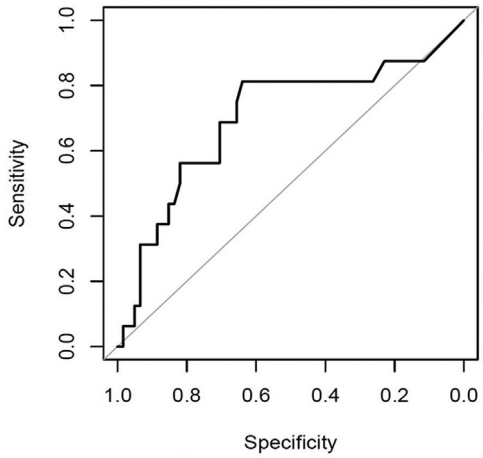

Figure 1. AUC demonstrating the diagnostic performance for baseline urinary TIMP2*IGFBP7 to predict acute kidney injury (AUC = 0.70, 95% CI: 0.54–0.86, $P = 0.008$). AUC, area under the receiver operating characteristic curve.

or severe AKI development. Furthermore, the AUC of urinary NGAL to predict AKI was 0.54 (95% CI: 0.39–0.69).

DISCUSSION

This prospective observational study of patients with lymphoma revealed a 21% incidence of AKI after HDMTX. Notably, 69% of the cases were stage 2 or 3 AKI. Patients with baseline urinary TIMP2*IGFBP7 concentrations of ≥0.3 were significantly more likely to develop any AKI and stage 2 or 3 AKI. Urinary NGAL failed to demonstrate any utility in this cohort.

We did not observe an association between urinary NGAL concentrations and AKI. In addition, the AUC suggests no ability of urinary NGAL to predict AKI in patients with lymphoma prescribed HDMTX. NGAL for assessment of kidney injury after HDMTX has currently been limited to pediatric patients with acute lymphoblastic leukemia or osteosarcoma with variable results.[9,S6,S7] One study of 20 pediatric patients with acute lymphoblastic leukemia prescribed HDMTX at 5 g/m^2 over 24 hours found no utility for plasma or urinary NGAL measurements.[9] Conversely, serum NGAL values were significantly higher after a 24-hour MTX infusion of 3 g/m^2 in children with acute lymphoblastic leukemia who experienced AKI than those who did not.[S6] Furthermore, 12 patients with osteosarcoma receiving HDMTX 12 g/m^2 demonstrated that elevations in AKI biomarkers could reflect HDMTX-associated nephrotoxicity; however, the regimen prescribed also contained cisplatin, a known nephrotoxin.[S7] A younger patient population, longer MTX infusion, different supportive care processes, and different biomarker sample timing preclude direct comparisons to our study. Future studies should confirm our results and investigate whether serial urinary NGAL measurements can identify optimal parameters to predict renal insult after HDMTX.

Our results identified an association between baseline urinary TIMP2*IGFBP7 and any AKI, including stage 2 or 3 AKI, after HDMTX. This differs from studies in critically ill or postsurgical patients where baseline concentrations were similar and increases in those with AKI occurred shortly after a known inciting event.[6,7,S8,S9] Little is known about the role of urinary TIMP2 and IGFBP7 concentrations for AKI prediction in patients with lymphoma receiving HDMTX. TIMP2*IGFBP7 has currently only been studied in adult patients with cancer receiving platinum chemotherapy.[S10,S11] One study in patients with lung cancer demonstrated no TIMP2 and IGFBP7 concentration differences in those with or without AKI after cisplatin.[S11] However, another study in patients receiving cisplatin concluded that urinary TIMP2*IGFBP7 was a useful tool for AKI prediction.[S10] Elevations in baseline urinary TIMP2*IGFBP7 in our population may represent subclinical AKI given the normal serum creatinine and eGFR values.[8,S12,S13] A cancer diagnosis at hospital admission has been associated with moderate-to-severe hospital-acquired AKI.[S14] This risk would only be compounded by administering HDMTX for cancer treatment. In addition, patients with cancer have concurrent, acute risk factors for AKI, such as hypotension and hypovolemia.[4] Given that the AUC demonstrated acceptable discrimination of TIMP2*IGFBP7 to predict AKI, these hypothesis-generating data compel investigations that explore the utility of this biomarker as a component within a screening tool for AKI risk estimation in adult patients with lymphoma who require HDMTX therapy.[S15,S16]

Limitations of this study include the single-center setting and moderate sample size. Second, a full characterization of baseline kidney health, including baseline urine albumin or baseline urine protein, was not part of our protocol and was not always available near the HDMTX administration on electronic health record review; although, assessment beyond serum creatinine is atypical before HDMTX in these patients, especially when the serum creatinine value and corresponding estimated creatinine clearance or eGFR represent normal kidney function. Importantly, few patients in our study had evidence of pre-existing chronic kidney disease based on eGFR, and none fit AKI criteria at admission. In addition, kidney assessment and management after HDMTX-associated AKI lacks standardization with testing and imaging at the discretion of the primary service and requires optimization. Last, three different, protocol-defined doses of HDMTX were prescribed. However, our patient population possessed similar baseline demographics among the dosing tiers. To our knowledge, this is the largest study of urinary TIMP2*IGFBP7 and urinary NGAL in adult patients with lymphoma and the first to attempt evaluating these biomarkers in adult patients with lymphoma receiving HDMTX.

CONCLUSION

AKI occurred frequently in patients with lymphoma receiving HDMTX, and most cases were moderate or severe. Urinary NGAL lacked utility in predicting AKI. Increased baseline urinary TIMP2*IGFBP7 was associated with AKI and severe AKI development.

DISCLOSURE

EFB provides consultation for FAST Biomedical and Wolters Kluwer, unrelated to this work. All the other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The deidentified data supporting this study's findings are available on request from the corresponding author. The data are not publicly available owing to privacy or ethical restrictions.

AUTHOR CONTRIBUTIONS

JNB, KBK, KCM, ADR, JCL, CDG, CAT, NL, TEW, and EFB wrote the manuscript. JNB, KBK, KCM, ADR, JCL, CAT, NL, TEW, and EFB designed the research. JNB, KBK, KCM, ADR, CDG, and EFB performed the research. JNB, JMR, JNB, KBK, KCM, ADR, JCL, CDG, CAT, NL, TEW, and EFB analyzed the data. JNB, KBK, KCM, ADR, JCL, CDG, CAT, NL, TEW, and EFB played an important role in interpreting the results.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Appendix 1. Modified STROBE statement.

Appendix 2. Methods.

Table S1. MTX-inclusive combination chemotherapy regimens.

Table S2. Leucovorin dose adjustment protocol.

Figure S1. Flow diagram of patient enrollment.

Supplementary References.

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