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High Dose Methotrexate-Induced Acute Kidney Injury: Incidence, Risk Factors, and Recovery

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INTRODUCTION

High dose methotrexate (HD MTX) (>1 g/m^2) remains the first line therapy for many malignancies. The reported incidence of acute kidney injury (AKI) ranges from 1.8% to 38.6% because of varied definitions of AKI.[1-3] The risk factors for AKI, long-term renal outcomes, the safety of redosing HD MTX following AKI, and survival when HD MTX is continued after AKI are not known. Because HD MTX is a life-extending and life-saving therapy, and because AKI can result in delays or termination of therapy with this drug, we took advantage of the large adult cohort at our cancer center to evaluate the rate of and risk factors for AKI, and the effect of AKI on long-term renal function and on survivorship when HD MTX is redosed following AKI.

RESULTS

Separate analyses were performed for the overall group (OG) and the survivorship group (SG). AKI occurred in 32.1% in OG and 37.4% of SG. Demographics for OG are outlined in Table 1. In OG, patients with AKI were significantly older (mean ± SD, 60.5 years ± 16.3 vs. 55.3 ± 17.1; $P < 0.001$), had a significantly lower BLCr (mean ± SD, 0.7 mg/dl ± 0.2 vs. 0.9 ± 0.2; $P < 0.001$) and baseline eGFR (BLeGFR) (mean ± SD, 95.1 ml/min ± 21.8 vs. 90.0 ± 22.0; $P < 0.001$), and received a significantly higher CD (median [IQR], 25750 mg [14100–35000] vs. 20000 [9425–34300]; $P < 0.01$] than the non-AKI group. Demographic data on SG are shown in Supplementary Table S1. The same analyses in SG showed similar significant differences for age, BLCr, and BLeGFR as observed in OG. CD was significantly higher among those with a BLeGFR >60 ml/min than in those with a BLeGFR <59 ml/min (median [IQR] 24000 [11000–35000] vs. 16660 [5820–268800]; $P < 0.01$). CD was not significantly different among survivors with and without AKI.

In OG, univariate model showed that age, BLCr, BLeGFR, and CD were associated with an increased risk for AKI (Supplementary Table S2). Each 1-year increase in age increased AKI risk by 2%. Each 1 mg/dl increase in Cr reduced AKI risk by 91%. BLeGFR >60 ml/min had a 2.5-fold higher risk of AKI than a BLeGFR ≤ 59 ml/min. Higher CD (≥22500 mg) showed a 1.44-fold higher risk of AKI than lower CD (<22500 mg). Multivariable logistic regression model showed that age (odds ratio [OR] = 1.02 per year [95% CI = 1.01–1.03]) and BLCr (OR = 0.07 per mg/dl [95% CI = 0.03–0.16]) remained significantly associated with risk of AKI after adjusting for BLGFR and CD. Univariate analyses in the SG showed that only age and BLCr were associated with the risk of AKI (Supplementary Table S3). Multivariable logistic regression model showed that age (OR = 1.02 [95% CI = 1.01, 1.04]) and BLCr (OR = 0.02 [95% CI = 0.01, 0.10]) remained significantly associated with the risk of AKI after adjusting for BLeGFR and CD.

In OG, 279 patients developed AKI. Of these, Cr levels returned to within 20% of the baseline in 160 (57.3%). Among the 160 who recovered, 102 (63.8%) continued HD MTX. Respective values in the SG were 62.2% and 75.6%. Those who recovered renal function were younger (mean ± SD, 57.9 ± 17 years vs. 64.1 ± 14.7 years; $P < 0.005$), had a higher BLCr (mean ± SD, 0.8 ± 0.2 mg/dl vs. 0.7 ± 0.2 mg/dl; $P < 0.005$), and received a higher CD (median [IQR], 28000 mg [14800–36365]

Table 1. Overall group: demographic characteristics

	AKI		Summary	
Data	**No (*N* = 587)**	**Yes (*N* = 278)**	**Total (*N* = 865)**	***P* value**
Age				
Mean (SD)	55.3 (17.1)	60.5 (16.3)	57.0 (17.0)	<0.001
Gender				
Female	287 (67.4%)	139 (32.6%)	426 (49.2%)	0.76
Male	300 (68.3%)	139 (31.7%)	439 (50.8%)	
Race				
White	496 (67.3%)	241 (32.7%)	737 (85.2%)	0.45
Black	31 (66.0%)	16 (34.0%)	047 (5.4%)	
Other	60 (74.1%)	21 (25.9%)	081 (9.4%)	
Baseline creatinine value				
Mean (SD)	0.9 (0.2)	0.7 (0.2)	0.8 (0.2)	<0.001
eGFR				
Mean (SD)	90.0 (22.0)	95.1 (21.8)	91.6 (22.0)	0.001
eGFR				
High (>60)	537 (66.7%)	268 (33.3%)	805 (93.1%)	0.008
Low (≤59)	50 (83.3%)	010 (16.7%)	060 (6.9%)	
Cum dose				
Median (IQR)	20000 (9425–34300)	25750 (14100–35000)	22500 (11000 –34500)	0.003
Cum_cat				
High (≥22500)	278 (63.9%)	157 (36.1%)	435 (50.3%)	0.012
Low (<22500)	309 (71.9%)	121 (28.1%)	430 (49.7%)	
Cum dose before AKI if AKI occurred				
Median (IQR)	20000 (9425–34300)	11000 (6440–20000)	15500 (6510–31000)	
Recovery				
No		119 (42.8%)		
Yes		159 (57.2%)		
Recovery value				
Mean (SD)		0.8 (0.2)		
Median (IQR)		0.8 (0.7–1.0)		
Survive_5 yr				
No	450 (69.7%)	196 (30.3%)	646 (74.7%)	
Yes	137 (62.6%)	082 (37.4%)	219 (25.3%)	
Death				
No	269 (66.1%)	138 (33.9%)	407 (47.1%)	
Yes	318 (69.4%)	140 (30.6%)	458 (52.9%)	
SEER1				
Bones and Joints	5 (62.5%)	3 (37.5%)	8 (0.9%)	
Brain and other nervous system	62 (77.5%)	18 (22.5%)	80 09.2%)	
Breast	1 (100.0%)	0 (0.0%)	1 (0.1%)	
Female genital system	4 (80.0%)	1 (20.0%)	5 (0.6%)	
Leukemia	96 (80.7%)	23 (19.3%)	119 (13.8%)	
Lymphoma	417 (64.5%)	230 (35.5%)	647 (74.8%)	
Myeloma	0 (0.0%)	1 (100.0%)	1 (0.1%)	
Sarcoma	2 (50.0%)	2 (50.0%)	4 (0.5%)	
HD_MTX_after_AKI				
No		97 (34.9%)		
Yes		181 (65.1%)		
HD				
No	578 (67.8%)	274 (32.2%)	852 (98.5%)	1.00
Yes	9 (69.2%)	4 (30.8%)	13 (1.5%)	
Glucarpidase				
No	587 (67.9%)	277 (32.1%)	865 (99.9%)	
Yes	0 (0.0%)	1 (100.0%)	1 (0.1%)	

AKI, acute kidney injury; Cum, cumulative; eGFR, estimated glomerular filtration rate; HD, high dose; IQR, interquartile range; MTX, methotrexate; SEER1, Surveillance, Epidemiology and End Results.

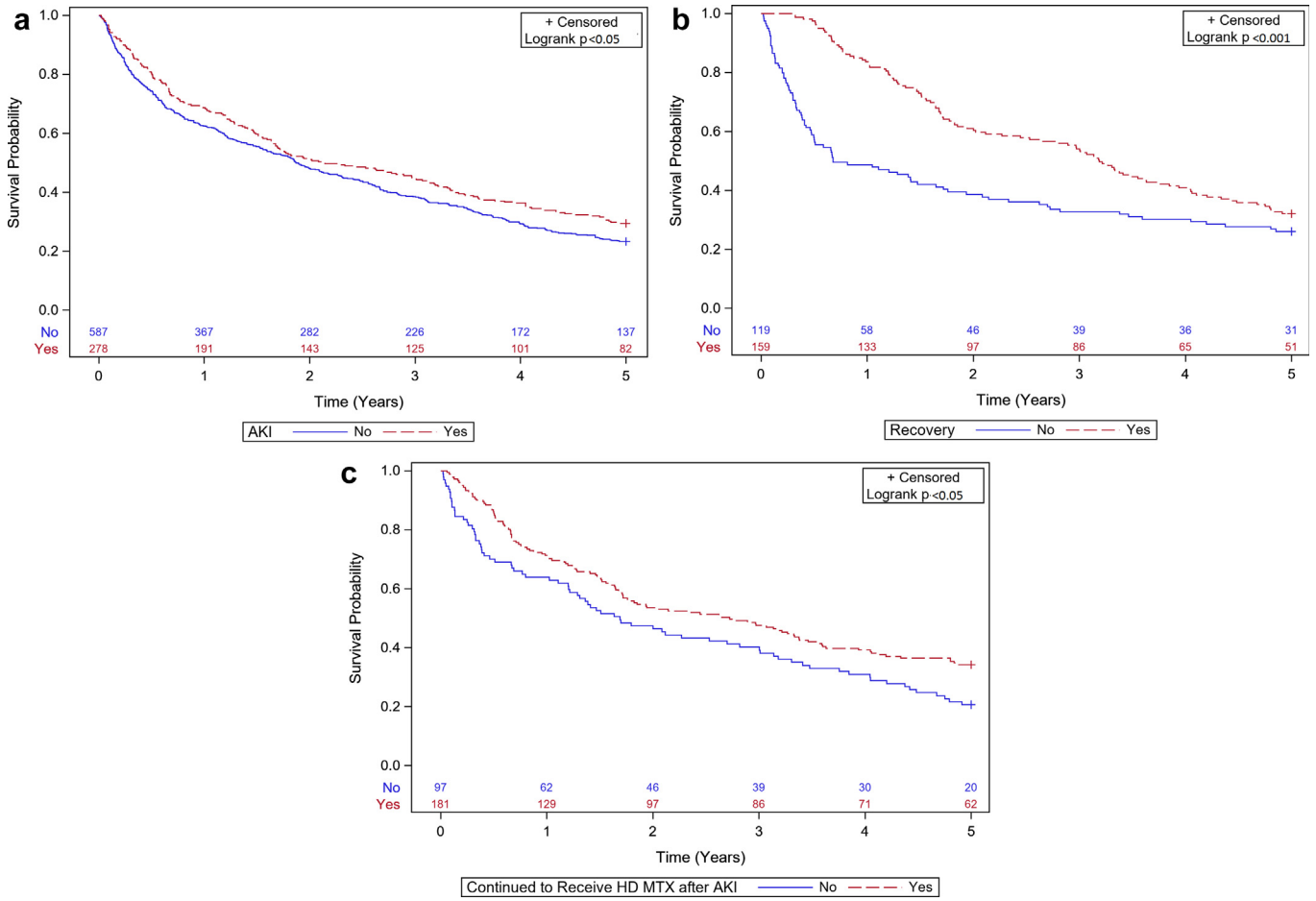

Figure 1. (a) Kaplan-Meier estimates of survival in years for patients on the basis of whether they had AKI with number of subjects at risk (censored at 5 years). (b) Kaplan-Meier estimates of survival in years for patients on the basis of whether they had recovery from AKI with number of subjects at risk (censored at 5 years). (c) Kaplan-Meier estimates of survival in years for patients on the basis of whether they continued to receive HD MTX following AKI with number of subjects at risk (censored at 5 years). AKI, acute kidney injury; HD, high dose; IQR, interquartile range; MTX, methotrexate.

vs. 22500 [12500–32285]; $P < 0.05$) than those who did not recover. AKI rates were similar in males and females (31.7% vs. 32.6%). Males were more likely to recover kidney function (64% vs. 50.4%; $P < 0.05$).

The 5-year OS among patients who developed AKI was significantly higher than in those who did not ($P < 0.05$) (Figure 1a). Patients who recovered from AKI to within 20% of the baseline Cr had significantly higher 5-year OS than those who did not ($P < 0.001$) (Figure 1b). Patients who continued to receive HD MTX after AKI had significantly higher 5-year survival than those who did not ($P < 0.05$) (Figure 1c).

When compared with OG, survivors were younger (mean ± SD 53.2 ± 18 years vs. 57 ± 17 years), received a higher CD of MTX (median [IQR], 31000 mg [21000–37470] vs. 22500 [11000–34500]) and had a higher rate of AKI (37.4% vs. 32.1%). Male sex, low CD of HD MTX, and AKI are significantly associated with higher 5-year OS after adjusting for age and baseline eGFR (Supplementary Table S4). One patient with AKI received glucarpidase and 4 required hemodialysis.

DISCUSSION

This is the largest single-center study using Kidney Disease: Improving Global Outcomes criteria to evaluate the rate of AKI, its risk factors, and long-term renal and survivorship outcomes when HD MTX is resumed following AKI. The rate of AKI was similar for the overall (32.1%) and survivor (37.1%) groups. Observational studies have demonstrated that AKI is associated with higher mortality than in the general population.[4,5] Our analyses revealed that the 5-year OS was significantly higher in those who experienced AKI, those who recovered from AKI, and in those who continued to receive HD MTX after AKI. There are several possible explanations for these observations.

Leukemic and lymphomatous infiltration of the kidney has been observed in 33% to 63% of cases.[6,7] Thus, patients with underlying lymphomatous or leukemic infiltration in the kidneys would be more susceptible to renal injury from HD MTX and recovery from AKI could indicate that the infiltration resolved following HD MTX with consequent improved survival in such patients. Improved survival among those who recovered renal function may also indicate that these individuals had better baseline health and functional status, and that this allowed them to continue to receive HD MTX following AKI and were thus able to complete therapy. Those who did not recover from AKI or had other complications from HD MTX may have had their treatment terminated. Indeed, SG was significantly younger, had a higher baseline Cr, and received a higher CD of MTX. The observation that males had a 1.47-fold increase in mortality compared with females is likely not related to AKI events. Leukemias and lymphomas are more common in males than in females and men with these diseases have worse survival.[8]

Multivariate analysis of both OG and SG demonstrated that older age, lower BLCr, and higher BLeGFR were significantly associated with an increased risk for AKI. These counterintuitive findings have several potential explanations. First, older cancer patients may have relatively lower muscle mass and thus a lower BLCr and higher BLeGFR. We did examine the interaction between age and eGFR, and the result was insignificant ([$P = 0.31$] for eGFR continuous and [$P = 0.81$] for dichotomized scale), indicating that there was no significant interaction between age and eGFR in the current model. Second, older patients generally have more comorbidities and thus are more likely to be on medications which can make them more susceptible to renal injury.

Cancer stages, complications of the underlying disease, and therapy complicate the interpretation of all retrospective data analyses. Indeed, the observation that low CD of HD MTX was significantly associated with higher 5-year OS after adjusting for age and baseline eGFR suggests that SG may also have had a lower disease burden, but we did not have data on the stage of the disease. This retrospective analyses is useful to generate hypotheses for future studies to prospectively evaluate risk factors and mitigation strategies for HD MTX associated AKI. Large clinical databases can be used to develop machine learning tools that identify patients at risk for AKI and, in an effort to improve survival probability, patients who can continue to receive HD MTX after AKI.

CONCLUSION

The 5-year survival is significantly higher in patients with AKI after HD MTX, when there is recovery of renal function and when HD MTX is continued after AKI.

DISCLOSURE

Edgar A Jaimes is a shareholder and Chief Medical Office of Goldilocks Therapeutics, Inc. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary Files (Word)

Table S1. Baseline demographic characteristics among cancer patients who survived at least 5 years after HD MTX.

Table S2. Overall group: univariate and multivariate model for risk factors for AKI among cancer patients who received HD MTX.

Table S3. Cancer survivor group: univariate and multivariate models for risk factors of AKI among cancer patients who survived at least 5 years after receiving HD MTX.

Table S4. Cancer survivor group: univariate and multivariate cox proportional hazards regression model to evaluate independent factors for survival.

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