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ARTICLE

Predicting Acute Renal Injury in Cancer Patients Receiving Cisplatin Using Urinary Neutrophil Gelatinase-Associated Lipocalin and Cystatin C

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Acute kidney injury (AKI) limits cisplatin use. We tested whether urine cystatin C (uCyC) and neutrophil gelatinase-associated lipocalin (uNGAL) can preidentify patients at risk for AKI. Patients initiating cisplatin-based chemotherapy were prospectively enrolled. uNGAL/uCyC were measured pre/post-cisplatin administration and compared with serum creatinine (sCr). AKI was defined as sCr increase ≥50% or ≥0.3 mg/dL above baseline. In all, 102 patients were enrolled; 95 provided evaluable data. Twenty-five patients developed AKI. Median baseline and pre-cisplatin uNGAL levels were significantly higher in AKI patients. Although immediate changes in uNGAL/uCyC 2 h after cisplatin were not detectable, post-cisplatin peak values over the course of therapy were markedly and significantly elevated in AKI patients. In multivariate modeling with age, baseline glomerular filtration rate, and histology, maximum uCyC was a significant independent AKI predictor. These findings suggest pre-cisplatin uNGAL and peak uCyC levels can identify patients with increased AKI risk, potentially allowing for tailored modification of cisplatin-based treatment regimens.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Cisplatin use is limited because of the risk for acute kidney injury (AKI). Novel urinary biomarkers, uCyC and uNGAL, have demonstrated the predictability of AKI in some clinical settings.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ Can uCyC and uNGAL provide better prediction for AKI than our current use of sCr and GFR?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✔ Baseline and pre-cisplatin uNGAL levels were significantly higher in patients who developed cisplatin-induced AKI. High peak levels of uCyC also independently identified patients with AKI.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✔ Baseline and pre-cisplatin uNGAL levels, and peak uCyC levels, can identify patients with increased AKI risk, potentially allowing for tailored modification of cisplatin-based treatment regimens.

Cisplatin is commonly used in the treatment of lung, testicular, ovarian, head and neck, and urothelial cancers, among others. Despite recent excitement surrounding novel targeted therapies, cisplatin remains a critical and commonly used tool in the oncologic armamentarium and is critical for the treatment of unresectable and metastatic cancers.[1] One major limitation to wider use of cisplatin is renal toxicity, which occurs in 28–36% of patients who receive even a single dose.[2] In a small number of patients, renal injury is irreversible, necessitating hemodialysis.[3] Nephrotoxicity can result in hospitalization, complicate surgical procedures, impair diagnostic testing, and can delay or limit the spectrum of further cancer and noncancer pharmacotherapies. Even when controlling for determinants of nephrotoxicity risk,[4–6] there is still significant heterogeneity in the development of cisplatin-induced nephrotoxicity.

Compounding the clinical problem is the fact that the primary indicator of nephrotoxicity is an increase in serum creatinine (sCr), which is insensitive and occurs relatively late for intervention to occur.[7,8] Creatinine changes often lag behind the time of initial renal insult by 48–96 h.[9] Therefore, earlier warning of impending renal injury would allow for patient-specific cisplatin dose-modification, alteration of chemotherapy when several equivalent regimens exist, or avoidance

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of cisplatin when toxicity risks outweigh potential benefits. Because of the numerous shortcomings of sCr, significant research toward the discovery of alternative biomarkers of acute kidney injury (AKI) has been initiated.[10]

Two biomarkers of primary interest are urinary cystatin C (uCyC) and urinary neutrophil gelatinase-associated lipocalin (uNGAL). Early evidence involving animal models treated with cisplatin demonstrated earlier rises in both uNGAL and uCyC compared with sCr.[11,12] Human studies have been conducted examining these biomarkers in the postcardiopulmonary bypass setting.[9,13] In a landmark study, uNGAL in children undergoing cardiopulmonary bypass demonstrated a sensitivity of 1.00 and specificity of 0.98 as a predictor of AKI 2 h postbypass.[9] More recently, studies have demonstrated the ability of uNGAL to independently predict mortality in the critically ill and in children with AKI.[14,15] However, only a few small human studies have investigated these biomarkers with respect to cisplatin nephrotoxicity.[16–22] In general, these studies have been underpowered and several were limited to a specific cancer type. Because renal injury is a limiting factor in multiple cancers using cisplatin-based regimens, a better AKI biomarker is necessary. In the most comprehensive prospective study to date including a broad spectrum of cancer types, we aimed to determine whether measurement of uCyC or uNGAL during cisplatin administration would lead to earlier identification of patients at risk for AKI.

METHODS

Trial design

This was a prospective, single-center study designed to examine AKI biomarkers in adult patients who were to begin cisplatin-containing chemotherapy for cancer. The study was Institutional Review Board (IRB)-approved and conducted in agreement with the principles of the Helsinki Declaration (clinicaltrials.gov identifier NCT00984035).

Study participants

Patient enrollment was conducted over a 3-year period. Treating staff identified and approached patients who were scheduled to start anticancer therapy with a cisplatin-containing regimen. Exclusion criteria included prior receipt of cisplatin, prior history of dialysis, uncontrolled hypo- or hyperthyroidism, or inability to provide informed consent. Urinary CyC is an unreliable marker in patients with thyroid disease.[23] Patients were expected to provide routine blood and urine samples at prespecified timepoints during their chemotherapy administration, per the schedule described below. AKI patients had all their samples analyzed, while non-AKI patients had a representative subset of samples from the most relevant timepoints analyzed. Schedules for cisplatin administration were based on standard (i.e., institutional/National Comprehensive Cancer Network) guidelines. For example, the cisplatin administration schedules for the three most common included tumor types were as follows: urothelial carcinoma (70 mg/m^2, day 1 every 21 days), head and neck (100 mg/m^2, day 1 every 21 days), and lung (75 mg/m^2, day 1 every 21 days).

Serum creatinine, glomerular filtration rate, and biomarker measurements

Urine samples for kidney biomarkers consisted of 25 mL samples at each of the following timepoints: i) prior to infusion of cisplatin and intravenous hydration on each day cisplatin was administered; ii) 2($\pm$1) h after each cisplatin infusion; and iii) at midcycle interval visits, occurring 24–72 h after each cisplatin dose (these timepoints occurred if the patient was returning to the medical center for a standard of care visit on nontreatment days). All urine samples were preprocessed at the University of Chicago and analyzed using a prototype assay[24] via a contract with the O'Brien Core Center for AKI research (www.obrienaki.org). All biomarker levels were normalized to urinary creatinine as previously described.[9,13]

Serum creatinine was measured according to standard institutional procedures at all patient visits throughout the study period, defined as the period from the first cisplatin dose until 35 days after the last cisplatin administration. Glomerular filtration rate (GFR) was estimated using the modified MDRD equation.[25] The "baseline" sCr and GFR were defined as the average of the three most recent sCr and GFR values prior to the first cisplatin administration. If there were less than three values, the mean of the available values up to three was used.

AKI definition

Patients were categorized into two predefined groups: AKI or non-AKI, according to the definitions adopted by the Risk, Injury, and Failure; and Loss; and Endstage kidney disease (RIFLE)[26] and Acute Kidney Injury Network (AKIN)[27] criteria. At the time of study development, the updated Kidney Disease Improving Global Outcomes (KDIGO) criteria[28] were not published; thus, the AKIN and RIFLE criteria were used for our AKI definition. Using these composite criteria, "AKI" in this study was defined as an on-study increase in sCr (from baseline sCr to peak on-study sCr) of at least 50% and/or $\geq$0.3 mg/dL above pre-cisplatin baseline. A subset of these patients were labeled "severe AKI" if their sCr rise was $\geq$50%. "Non-AKI" patients were defined as those having no increase in sCr or those having sCr increase of $<$50% during the study. AKI events underwent manual chart review by the study physicians to ensure that an alternative cause of AKI (e.g., hypotension/shock, contrast dye) was not present.

Statistical analysis

The primary end point was the median change between biomarker levels measured pre-cisplatin and 2 h post-cisplatin in AKI patients vs. non-AKI patients. Secondary end points included evaluation of maximum, baseline, and pre-cisplatin biomarker levels between AKI and non-AKI patients. The maximum biomarker level was defined as the single largest biomarker level occurring at any time from first cisplatin dose until 35 days after the final cisplatin dose. Baseline biomarker was the single biomarker level obtained prior to the first cisplatin dose. Pre-cisplatin biomarker was defined as the mean of all biomarker levels drawn prior to each cisplatin dose administration during the treatment course. In the analysis, multiple observations were averaged over the entire course for pre-cisplatin as described. When these were entered into the analysis, they were entered

Table 1 Patient demographics

Variable	Categories	Total population	AKI	non-AKI	*P*-value
Age	Median	60 years	64	59	0.06
	Range	18–83 years	50–80	18–83	
Gender	Male	71 pts (75%)	18	53	0.92
	Female	24 pts (25%)	7	17	
Cancer subtype	Urothelial	48 pts (50%)	17	31	0.30
	Head and neck	12 pts (13%)	2	10	
	Lung	12 pts (13%)	4	8	
	Esophageal	19 pts (10%)	1	8	
	Testicular	6 pts (6%)	0	6	
	Other[a]	8 pts (8%)	1	7	
Race	Caucasian	76 pts (80%)	20	56	0.56
	African-American	14 pts (15%)	5	9	
	Asian	4 pts (4%)	0	4	
	Hawaiian-Pacific Islander	1 pt (1%)	0	1	
Body surface area	Median (m^2)	2.0	2.04	1.96	0.053
	Range (m^2)	1.47–2.61	1.7–2.36	1.47–2.61	
Baseline serum Creatinine	Median (mg/dL)	1.0	1.0	0.98	0.74
	Range (mg/dL)	0.5–1.5	0.7–1.3	0.5–1.5	
Baseline Glomerular filtration rate	Median (mL/min/m^2)	76	72	76	0.32
	Range (mL/min/m^2)	44–120	44–98	47–120	
Cisplatin dose[b]	Median (mg/m^2)	220	210	210	0.31
	Range (mg/m^2)	30–450	70–385	30–450	
On-treatment time[c]	Median (days)	77	77	77	0.48
	Range (days)	36–155	42–154	36–155	

Continuous variables were tested by Wilcoxon Rank sum test, and categorical variables were tested by chi-square test.
Total evaluable patients = 95.
Two patients were excluded due to no demographic information. Five patients were dropped from analysis due to no biomarker measurements. Only two patients had preexisting diabetes.
[a]Other cancer types included mesothelioma ($n = 4$ pts), cholangiocarcinoma ($n = 2$), squamous cell carcinoma of the anus ($n = 1$), and anaplastic central neurocytoma ($n = 1$).
[b]Schedules for cisplatin administration were based on standard (i.e., institutional/National Comprehensive Cancer Network) guidelines. For example, the cisplatin administration schedules for the three most common included tumor types were as follows: urothelial carcinoma (70 mg/m^2, day 1 every 21 days), head and neck (100 mg/m^2, day 1 every 21 days), and lung (75 mg/m^2, day 1 every 21 days).
[c]On-treatment time was defined as the day of first cisplatin dose to 35 days after final cisplatin dose.

as single observations. Using a planned sample size of 98 patients, we conservatively predicted that 20% (20 patients) would have AKI and 78 would not. From Mishra *et al.*,[9] the mean increase in uNGAL 2 h after surgery among patients who developed acute renal failure was 150 μg/L, with a standard deviation (SD) of $\sim$225 μg/L. In patients without renal failure the mean and SD were 10 μg/L and 60 μg/L, respectively. Assuming similar variation, our projected sample size of 20 patients with and 78 without renal toxicity would provide 80% power to detect a true difference between groups similar to that observed in Mishra *et al.*, i.e., from 10 μg/L in patients without AKI to 150 μg/L in patients with AKI.

We analyzed pre/post-cisplatin change in uNGAL as the primary end point, along with secondary end points of baseline, pre-cisplatin, and maximum uNGAL and uCyC to compare AKI and non-AKI patients. Due to inherent skewness in the distributions, Wilcox rank sum tests and bootstrap estimates of the 95% confidence interval (CI) were used. In addition, we developed a series of multivariate logistic regression models including an AKI indicator as a dependent variable and each biomarker as an independent variable. Clinical variables such as age, tumor type, and baseline GFR were adjusted in the model. We used receiver-operating characteristic (ROC) curves, the area under the curve (AUC), and Brier score[29] to assess the discrimination ability between AKI and non-AKI patients. The Brier score is a probability measure of predictive accuracy ranging from 0 for perfect prediction to 1 for worst prediction. There is no study suggesting an acceptable level for the score, but it can be used to compare relative performance among different models. In our analysis, the Brier score along with AUC was used to assess the predictive ability among different statistical models.

RESULTS

Study population

Table 1 demonstrates the baseline characteristics of the patient population. In all, 102 patients were enrolled. Two subjects were excluded due to missing demographic information, and five additional patients could not be included in the analysis because they did not provide urinary biomarker data and/or serial sCr levels. A CONSORT diagram is shown in **Figure 1**. Although the study protocol appropriately mandated that patients with AKI where the renal injury could be attributed to causes other than cisplatin would be excluded

from the analysis (since this study was focused on cisplatin-induced renal injury), no such AKI patients were found to have other attributable causes of AKI upon formal review.

Incidence of AKI

The baseline median sCr and GFR for the entire cohort were 1.0 mg/dL (range 0.50–1.5 mg/dL) and 76 mL/min/m^2 (range 44–120 mL/min/m^2), respectively. As demonstrated in **Figure 2**, 25 of the 95 patients developed AKI (26%), including 15 severe AKI cases (16%). No patient experiencing AKI required renal replacement therapy. The average change in sCr over the entire treatment course was +0.62 mg/dL in AKI patients compared with +0.10 mg/dL in non-AKI patients. Patients developing AKI tended to be slightly older, although this difference was not statistically significant (median 64 vs. 59 years, $P = 0.06$). The odds ratio (OR) of developing AKI for every 5-year interval increase in age was 1.23 (CI: 1.19, 1.28, $P = 0.04$). There were no differences with respect to AKI risk by gender, cancer subtype, race, cumulative cisplatin dose received (median cisplatin dose in AKI patients was 210 mg/m^2 (range 70–385) vs. 210 mg/m^2 (range 30–450) in non-AKI patients, $P = 0.31$), on-treatment time (median 77 days of cisplatin treatment in AKI patients vs. 77 days in non-AKI patients, $P = 0.48$), body surface area (BSA) (median 2.04 m^2 in AKI patients vs. 1.96 m^2 in non-AKI patients, $P = 0.053$), baseline sCr (median 1.0 mg/dL in AKI patients vs. 0.98 mg/dL in non-AKI patients, $P = 0.74$), or baseline GFR (mean 72 mL/min/m^2 in AKI patients vs. 76 mL/min/m^2 in non-AKI patients, $P = 0.31$) (**Table 1**). Characteristics of the severe AKI group (a subgroup of the AKI cohort) are described in **Supplemental Table S1**. This group had overall similar characteristics to all AKI patients; however, urothelial cancer patients made up 67% of the severe AKI cohort, compared with 50% of the entire AKI cohort.

Biomarker changes during cisplatin

The median number of biomarker samples analyzed for AKI patients was 7 (range 3–20) and 2 (range 1–16) for non-AKI patients. In order to determine if the novel biomarkers of interest were predictors of AKI, we analyzed baseline levels (**Table 2**). For uNGAL, the median baseline level in AKI patients was significantly higher than in non-AKI patients, 169 ng/mg (CI: 48, 331) vs. 59 ng/mg (CI: 43, 97), $P = 0.03$ (**Figure 3**). There was no significant difference for uCyC at baseline between AKI and non-AKI patients (median: 63 ng/mg vs. 48 ng/mg, $P = 0.43$).

Table 2 Comparisons of baseline, maximum, and pre-cisplatin values of uNGAL and uCyC between AKI and non-AKI patients

	AKI	Non-AKI	p-value
uNGAL			
Baseline	169 (CI: 48, 331)	59 (CI: 43, 97)	0.030
Maximum	940 (CI: 463, 1713)	97 (CI: 70, 179)	<0.0001
Pre-cisplatin	292 (CI: 97, 352)	63 (CI: 42, 108)	<0.001
uCyC			
Baseline	63 (CI: 20, 126)	48 (CI: 36, 63)	0.43
Maximum	710 (CI: 233, 948)	86 (CI: 63, 154)	<0.0001
Pre-cisplatin	84 (CI: 57, 154)	60 (CI: 39, 79)	0.13

All values are expressed as medians. All units are ng/mg.

Significant changes in both biomarkers were not detectable in the immediate (same-day) pre/post-cisplatin administration period. For uCyC, median levels actually decreased at 2 h post-cisplatin compared with just prior to cisplatin infusion (median decrease −33 ng/mg (CI: −83, −9) for the AKI group vs. median decrease −15 ng/mg (CI:−32, −5) for the non-AKI group, $P = 0.48$). Similarly for uNGAL, the median change in uNGAL during the peri-infusion period was −1.8 ng/mg (CI: −38, 25) for AKI patients and +1.9 ng/mg (CI: −5.1, 12) for non-AKI patients ($P = 0.44$).

However, the maximum (peak) values of uCyC in AKI patients were significantly higher than non-AKI patients: peak medians were 710 ng/mg (CI: 233, 948) in AKI patients compared with only 86 ng/mg (CI: 63, 154) in non-AKI patients ($P < 0.0001$) (**Table 2**). Peak uNGAL levels in AKI patients were similarly strikingly different: 940 ng/mg (CI: 463, 1713) for AKI patients vs. 97 ng/mg (CI: 70, 179) in non-AKI patients ($P < 0.0001$) (**Figure 4**). Biomarker characteristics of the most restrictive severe AKI group followed a similar pattern (**Supplemental Table S2**).

We also explored composite pre-cisplatin biomarker levels to decipher the predictability of AKI over the entire course of chemotherapy (**Table 2**). Pre-cisplatin uCyC was 84 ng/mg (CI: 57, 154) in AKI patients but 60 ng/mg (CI: 39, 79) in non-AKI patients ($P = 0.13$). Pre-cisplatin uNGAL levels showed a significant difference in patients who developed

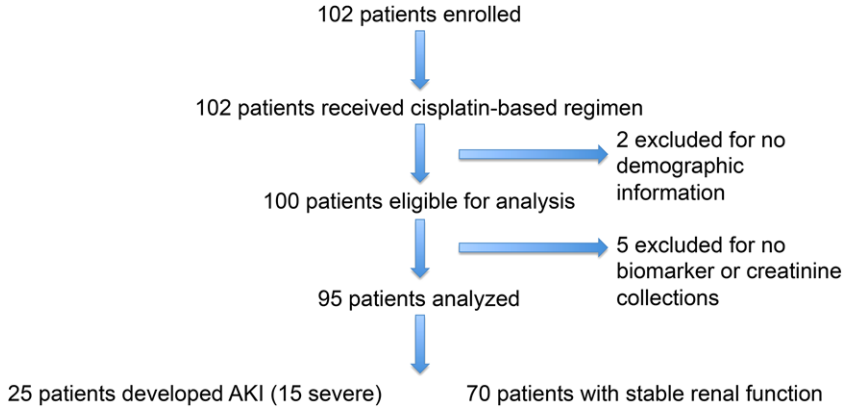

Figure 1 CONSORT diagram showing the analysis of the 102 patients enrolled in this study.

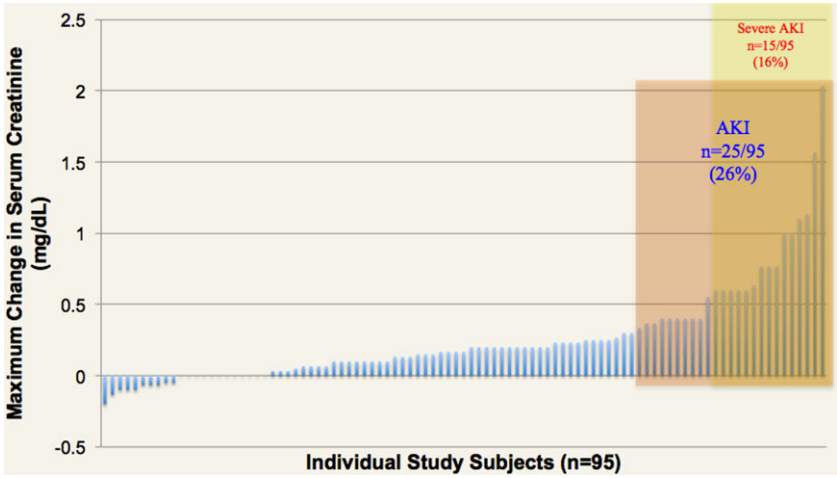

Figure 2 Overall incidence of AKI in the study population. Twenty-five of 95 patients (26%) developed AKI during the study period; 15 had severe AKI. AKI was defined as a change in serum creatinine of at least 50% (severe) and/or ≥0.3 mg/dL above pre-cisplatin baseline.

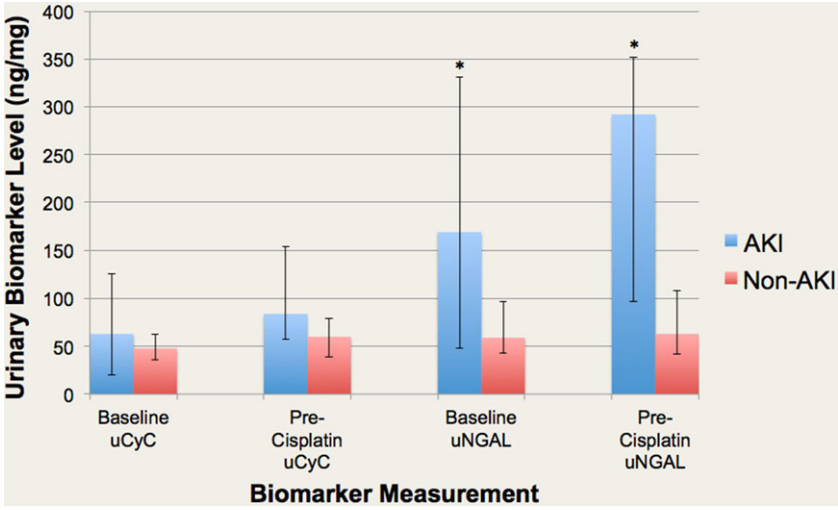

Figure 3 Median baseline and pre-cisplatin uCyC and uNGAL (ng/mg) in AKI patients and non-AKI patients. Significant differences were noted in baseline and pre-cisplatin levels of uNGAL between AKI and non-AKI patients. Baseline and pre-cisplatin uCyC did not show a difference between the two populations. Baseline values refer to the first biomarker level drawn during the study period. Pre-cisplatin values were the composite of all respective biomarker levels drawn prior to every cisplatin dose during therapy. An asterisk (*) denotes a statistically significant difference ($P < 0.05$).

nephrotoxicity: 292 ng/mg (CI: 97, 352) in AKI patients vs. only 63 ng/mg (CI: 42, 108) in non-AKI patients ($P < 0.001$) (**Figure 3**).

Combining clinical predictors of AKI with novel urinary biomarkers of AKI

Given that several of the analyzed urinary biomarker values were significantly predictive on univariate testing, we next sought to interrogate whether combined models including these novel biomarkers alongside clinical factors could provide improved prediction for the development of AKI compared with clinical factors alone. Interestingly, on univariate analysis, none of the analyzed clinical/demographic characteristics (age, race, gender, cisplatin dose, on-treatment time, BSA, baseline GFR, cancer type) were independent risk factors for prediction of AKI in our study. Despite this, we proceeded with a multivariate analysis including age, baseline kidney function, cancer type, and each of the biomarkers of interest to identify independent predictors of AKI. Adding total cisplatin dose to this model did not change the results (data not shown). Two separate sets of analyses were run using either baseline sCr or baseline GFR, respectively, as the traditional measure of baseline renal function within the model.

Most interestingly, using these combined models, maximum uCyC was found to be a strong independent predictor of AKI. Higher maximum uCyC had an OR of 1.42 (CI: 1.16, 1.82, $P = 0.0018$) for association with AKI risk. In addition, when a stepwise variable selection method was employed, maximum uCyC again was identified as an independent, statistically significant biomarker. Higher pre-cisplatin uCyC also was associated in the combined models

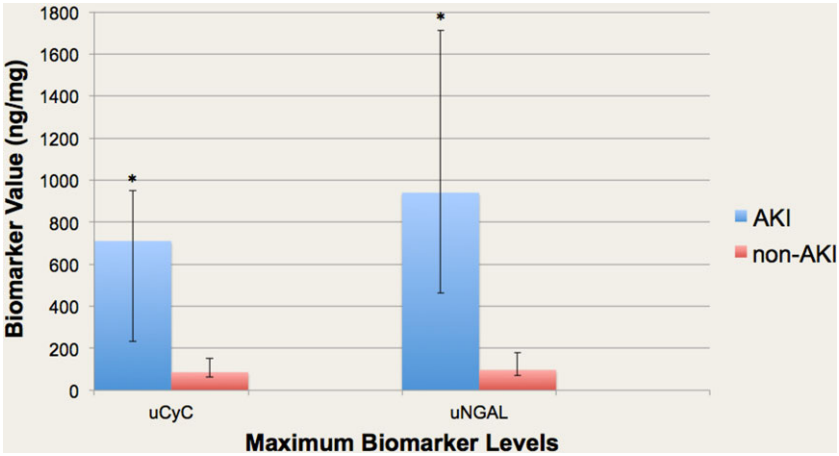

Figure 4 Median maximum uCyC and uNGAL (ng/mg) in AKI patients vs. non-AKI patients. Significant differences were noted with both biomarkers, with patients who developed AKI having dramatically higher peak levels. An asterisk (*) denotes a statistically significant difference ($P < 0.05$).

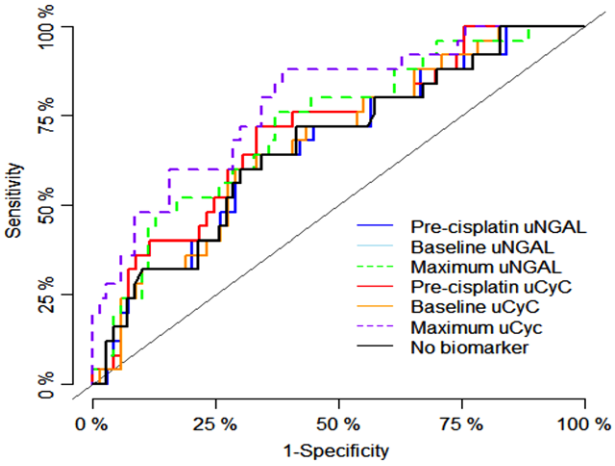

Figure 5 Receiver-operating characteristic (ROC) curves demonstrating area under the curves for the biomarkers of interest adjusted for age, cancer histology, and GFR. The solid black line denotes the ROC curve for the clinical characteristics alone. All models including the biomarkers performed better than the clinical model alone. The model including maximum uCyC performed most robustly compared with clinical characteristics alone.

with an increased OR of developing AKI, with an OR of 2.24 for every 250 unit change, although this result did not reach formal statistical significance (CI: 0.85, 6.55, $P = 0.11$). Baseline uCyC, and the various uNGAL biomarker levels, did not significantly enhance prediction of AKI risk when assessed in these combined clinical-biomarker multivariate models.

To conceptualize these results, ROC curves were developed for each biomarker incorporated along with the selected clinical characteristics, and these clinical-biomarker curves were compared with the ROC curve for the clinical characteristics alone (**Figure 5**). Including only these characteristics without a urinary biomarker provided an AUC of 66.5 with an associated Brier score of 0.181. In comparison, every curve in which a novel biomarker was included along with the clinical characteristics improved the AUC. The respective AUCs (and Brier score) for baseline, maximum, and pre-cisplatin uNGAL were 67.3 (0.182), 72.2 (0.174), and 66.6 (0.183). For uCyC, the baseline, maximum, and pre-cisplatin AUCs (and Brier score) were 67.3 (0.182), 78.7 (0.150), and 70.6 (0.177), respectively (**Figure 5**).

DISCUSSION

There is significant heterogeneity in the development of drug-induced nephrotoxicity across treated patients, and identification of the patients at highest risk is extremely challenging. In patients with malignancies, cisplatin-based chemotherapy regimens are prominently limited by the risk of AKI. In this study, and despite modern supportive care measures designed at minimizing AKI risk, we found that 26% of cancer patients treated with cisplatin developed AKI. We demonstrated that baseline, maximum, and pre-cisplatin levels of uNGAL identified patients at increased risk for AKI. Additionally, maximum uCyC levels associated strongly and independently with patients developing AKI. If further validated, the use of these markers could identify patients with increased AKI risk, potentially allowing for earlier, tailored modifications of cisplatin-based treatment regimens.

The overall rate of renal injury in our study was comparable to previous data.[2] Additionally, the odds of developing AKI with increasing age validates prior data.[30] It was perhaps somewhat surprising that we did not identify other clinical or demographic factors that contribute to AKI risk—but this fact underscores the limitations of current clinical/demographic predictors. This makes the identification of novel AKI prediction biomarkers even more critical and necessary.

We demonstrated a significant difference in maximum levels of biomarkers between AKI and non-AKI patients. For the AKI cohort, 12 of the 25 patients developed peak levels of uCyC and uNGAL after the first dose of cisplatin. The remaining patients developed peak levels at various timepoints throughout cisplatin therapy. Understandably, these patterns make it more difficult to always identify in

practice high-risk patients prior to receipt of cisplatin-based therapy. Thus, while the peak biomarker changes are certainly impressive, using maximum (peak) levels may not be the ideal means of earlier identification of AKI. The utility of peak levels may lie in conjunction with baseline and/or pre-cisplatin values. For example, if a patient had an sCr or GFR that would permit cisplatin use at baseline, but an elevated baseline biomarker level, the measurement of the maximal biomarker level after one dose of cisplatin might be highly informative to guide cisplatin discontinuation or dose reduction even in the absence of immediate significant sCr change—so as to risk-mitigate further kidney injury and potentially avoid the full manifestations of AKI. Such decisions would necessarily balance risk vs. benefit for the continued inclusion of cisplatin in the regimen. Our data suggest that this type of complex decision-making might be augmented and better informed by the integrated use of multiple biomarkers (including traditional and novel ones) rather than just one (like sCr).

Two previous studies suggested similar findings to ours for higher uNGAL levels prior to cisplatin doses in AKI patients.[18,19] However, these studies included half the patients[18] or were limited by examination of only one cisplatin dosing regimen in a single tumor type.[19] We showed that baseline levels of uNGAL were significantly elevated in AKI cancer patients compared with non-AKI cancer patients. This was true despite the fact that baseline renal function was ostensibly the same between the two groups. This underscores the limitations of sCr and GFR in assessing true AKI risk among oncology patients. Our data also indicated uNGAL followed over the course of cisplatin chemotherapy could allow for earlier identification of patients at higher risk for AKI. In current practice, providers perform continued reevaluation throughout a patient's chemotherapy course to weigh the risks and benefits of ongoing cisplatin use. However, sCr does not typically allow maximally informed real-time decision-making to occur because sCr rise is delayed until after injury has already occurred. If uNGAL levels could be drawn prior to cisplatin administration with prompt reporting, it would be possible based on such results to alter the treatment regimen (substitute carboplatin; decrease the cisplatin dose) if a rise in uNGAL was detected, even if the sCr remained normal. Clinical implementation of this strategy would require prospective validation of this approach first, but our results suggest that such a prospective study is justified.

Repeated measurement of novel urinary biomarkers prior to each cisplatin dose is likely the most clinically applicable and useful means of identifying the highest-risk patients. Single measurements, or even comparative pre/post-cisplatin infusion difference measurements, are likely less useful, as indicated by our inability to detect an immediate (2 h postinfusion) difference in biomarker levels when comparing AKI and non-AKI patients. In other clinical settings (cardiopulmonary bypass and vascular surgeries), uCyC rose within 6 h after renal injury and peaked around 48 h, although the levels in those studies were not statistically different between AKI and non-AKI patients when adjusted for other confounding factors.[13,31] In our study, we likely did not capture the true initial timepoint of early AKI detection, since most patients were not seen (after the day of infusion) for at least 1 week, simply because most anticancer treatment schedules are repeated no sooner than weekly. Further studies with collection points on a daily or every-other-day basis could interrogate more closely the question of timing or rises, to try to optimize early detection sampling protocols. Other future investigations could include the effect of agents purported to attenuate cisplatin-induced damage on levels of uNGAL or uCyC.

Our study had several limitations. This was a single-center trial, and nephrotoxicity risk mitigation protocols may vary from institution to institution, although our cancer center adheres to national accepted standards.[32] Because we could not analyze every sample collected from every timepoint on all patients in this study (due to cost limitations of running the assays), we analyzed more sample timepoints from patients with AKI than for controls, as we felt samples from AKI patients would be most informative with respect to identifying changes in the biomarkers. While unlikely, it is therefore possible that this strategy resulted in some detection bias within the AKI group. Future studies could also include the use of serum samples as these have been shown to be promising AKI biomarkers.[33] Additionally, there was observed variability in intrapatient biomarker levels, as well as underlying variance in the number of cisplatin treatment cycles each patient received; however, these differences were accounted for in the formal statistical analyses. Finally, cisplatin is known to work by various mechanisms leading to acute and chronic kidney injury.[34] We were unable to definitively decipher from our data the exact molecular mechanism(s) of kidney injury in our patients.

The need for novel biomarkers to supplement sCr is critical for the risk mitigation of cancer patients at risk for AKI. Our report is the most comprehensive prospectively collected body of evidence to date to demonstrate that novel urinary biomarker detection might have a clinical prediction role during cisplatin therapy for any type of cancer. If validated, real-time measurement of these markers may provide clinicians with enhanced ability to avoid cisplatin and thereby prevent AKI in the highest risk patients—an important unmet need in oncology therapeutics.

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investigate biomarkers of AKI, and is named on a patent by Argutus Medical for Pi-GST to be a biomarker of AKI following cardiac surgery.

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