Renal Biomarker Levels in a Child Presenting with Newly Diagnosed Acute Lymphoblastic Leukemia and AKI Secondary to Tumor Lysis Syndrome

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Background

Acute lymphoblastic leukemia is the most common pediatric malignancy with approximately 2,400 new diagnoses made each year.
Although survival has risen dramatically for childhood leukemia and lymphoma, morbidities, both short term and long term are not infrequent. One of these morbidities is acute kidney injury (AKI). Children with acute leukemia and lymphoma are at risk for AKI for multiple reasons. These include infiltration of the kidneys with malignant cells, dehydration and/or sepsis, or the use of nephrotoxic medications including antibiotics and chemotherapy. In addition, tumor lysis syndrome (TLS), which has the potential to cause AKI from hyperuricemia and hyperphosphatemia occurs in up to 8.4% of acute leukemia and lymphoma patients (1).
The incidence of AKI is not well characterized either at the time of diagnosis, or during treatment of pediatric leukemia and lymphoma. Long term renal function is also important to assess as 20-40% of children exhibit abnormal GFR or renal scans when assessed as long as 8 years after cessation of therapy (2).
The traditional biomarkers of AKI, BUN and creatinine, are somewhat insensitive early markers of tubular and glomerular injury. Multiple renal and nonrenal factors affect BUN and creatinine serum levels leading to an inaccurate picture of AKI and its time course (3). Specifically, pediatric patients with malignancies may have had experienced malnutrition and cachexia prior to their diagnosis. A decrease in fluid or protein intake may affect serum creatinine measurements.
Emerging renal biomarkers, such as, NGAL, IL-18, and KIM-1 may offer earlier evidence of renal injury and might provide insight into those children who may be at greatest risk for developing AKI and needing RRT, particularly in the subgroup of patients presenting with TLS.

Methods

All patients 0-21 years old presenting to HDVCH Pediatric Hematology Oncology Program for treatment of new onset acute leukemia or lymphoma were eligible for enrollment. Previous history of renal insufficiency, past renal trauma, known renal or urinary anomaly affecting function, or previous course of chemotherapy prior to the onset of the current illness were criteria for exclusion. The study was IRB approved and Informed consent as well as, assent where appropriate were obtained prior to enrollment .
Urine for KIM-1, IL-18, and NGAL were collected prior to initiation of chemotherapy, every 6 hours for the first 24 hours of therapy and daily for the next 6 days of therapy. Thereafter, urine was collected and analyzed for biomarker levels weekly during the induction cycle of chemotherapy (4 weeks total). Samples were stored at 4 degrees Centigrade for up to 48 hours before centrifugation. The supernatant was then taken off and frozen in a -80 degree Centigrade freezer until analysis.

Urine biomarkers were assayed by ELISA at the CCHMC biomarker laboratory and data were normalized for urine creatinine.
Of 25 patients enrolled in the study only one presented with TLS and had evidence of AKI. The patient presented with newly diagnosed ALL with hyperuricemia, hyperphosphatemia, hyperkalemia, and RIFLE-I AKI. The patient was given rasburicase and required CRRT for about 24 hours prior to beginning chemotherapy. Study consent was not obtained until just prior to beginning chemotherapy and the patient was no longer on CRRT, therefore, no urine samples were obtained before or during CRRT.

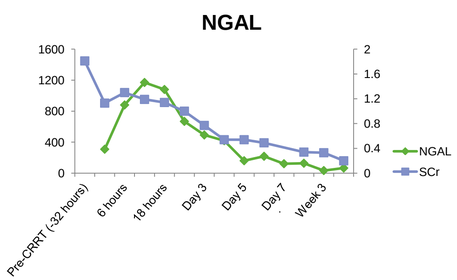
Results

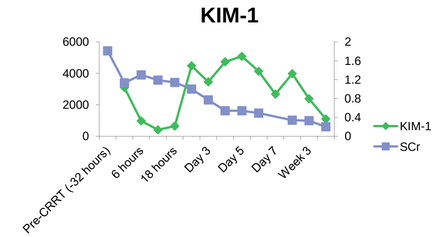
Urine NGAL peaked at 1170 ug/mg Cr (4-fold rise) 12 hours post chemotherapy and returned to baseline by day 7. KIM-1 peaked at 5083 pg/mg Cr (12-fold rise) on day 5 and returned to baseline by week 4. IL-18 peaked at 180 pg/mg Cr on day 3 (2-fold rise), returning to near baseline by day 7 but increased again at week 2 which was temporally associated with pseudomonas bacteremia (Table 1). Serum creatinine consistently declined throughout the course of chemotherapy despite these changes in other renal biomarkers. The patient's renal function by RIFLE criteria was RIFLE-I at the start of chemotherapy and returned to normal by day 4 of induction chemotherapy.

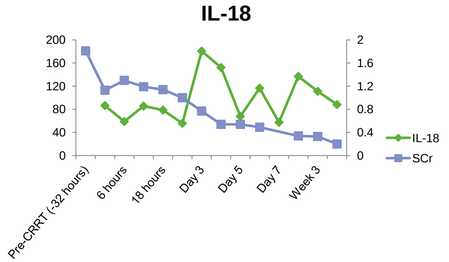
Table 1:

Biomarker	Pre-Chemotherapy	Post Induction Peak
eCCL by Schwartz	51*	58*
NGAL[1]	309	1170
KIM-1[2]	3098 (406 at 12 hrs induction)	5083
IL-18[2]	86	180

1- microgram/ mg Cr
2- picogram/ mg Cr
*- lowest clearance value post induction in mL/min/m2







Conclusions

In this child with new onset ALL and AKI secondary to TLS, a significant elevation in novel renal biomarkers was noted following initiation of IV chemotherapy despite improving estimated creatinine clearance (eCCL). We postulate that this change represents subtle, secondary tubular injury by nephrotoxic agents in an already vulnerable host. The role of novel renal biomarkers in elucidating renal injury in children with TLS at time of induction chemotherapy deserves further investigation.

References

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Acknowledgement- The authors would like to thank Michael Bennett, PhD. and his staff at the CCHMC Biomarker Laboratory for the analysis of the renal biomarkers.