

# **Assessment of acute kidney injury by urinary $\beta$ 2-MG and NAG in childhood cancer patients prescribed with Ifosfamide**

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# Acute kidney injury in malignancy

The progresses in developing anticancer medications, and appropriate management for cancer treatment, lead to the **increased survival rate** of the cancer patients in the last decades.

High dose chemotherapy has both early and late complications, **including kidney injury**

For having a **better quality of life**, we have to be more considerate about preventing the aforementioned complications, and seeking for early diagnosis

# Acute kidney injury (AKI):

- AKI can be defined as the **abrupt loss of kidney function**, leading to a decrease in GFR, and impaired control of acid-base, electrolyte and fluid balance
- It is **a common problem** in children admitted to hospital, especially among those requiring intensive care, and it is an independent risk factor for increased mortality and severe morbidity

**Also AKI usually(not always) is a reversible condition, but:**

- Children who have suffered AKI from any cause are at risk for late development of kidney disease several years after the initial insult
- Also if some nephrotoxic medication is discontinued: the serum creatinine may continue to increase for several days due to ongoing tubular injury from continued high parenchymal levels of the aminoglycoside.



Mammen C, Al Abbas A, Skippen P, *et al.* Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. Am J Kidney Dis 2012;**59**:523–30.

- Surviving patients, **most with short-term recovery from their AKI**, were assessed at 1, 2, or 3 years after AKI.
- **CKD was defined** as the presence of albuminuria and/or GFR <60 mL/min/1.73 m<sup>2</sup>.
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- **Risk of CKD was defined** as having a mildly decreased GFR (60-90 mL/min/1.73 m<sup>2</sup>), hypertension, and/or hyperfiltration
- The **number of patients with CKD** 1-3 years after AKI was **10.3%**
- **46.8%** patients were identified as being at **risk of CKD**

Andreoli SP. Acute kidney injury in children:  
Pediatr Nephrol, 2009 Feb;24(2):253-63

- Medications associated with AKI, at least in part due to toxic tubular injury, include chemotherapeutic agents such as ifosfamide and cisplatin, and carboplatin
- Children with nephrotoxic renal insults, are more likely to have AKI with normal urine output.

# Acute kidney injury (AKI):

- The diagnosis of AKI has traditionally relied on measurements of serum **creatinine as a marker of GFR** and/or monitoring of urine output.
- However, serum creatinine is a **late and insensitive marker of renal damage**; levels only rise significantly once 25–50% of renal function has been lost
- Relatively small changes in serum creatinine levels may reflect significant pathology

There is a clear need to identify more sensitive and earlier biomarkers of AKI:

Thus, recent developments in AKI detection may be divided into:

- ✓ Determining patients who are risk of AKI;
- ✓ Discovery of early and sensitive biomarkers for the assessment of patients deemed at risk of AKI.



# Biomarkers for the assessment of patients deemed at risk of AKI:

- ✓ KIM-1(kidney injury molecule 1 ),
- ✓ and plasma and urinary NGAL(neutrophil gelatinase-associated lipocalin ),
- ✓ TIMP-2 (tissue inhibitor of metalloproteinases 2),
- ✓ IL-18(Interleukin 18)
- ✓ NAG (N-acetyl- $\beta$ -D-glucosaminidase),
- ✓  $\alpha$ 1-microglobulin
- ✓  $\beta$ 2-MG

# $\beta$ 2-MG ( $\beta_2$ -microglobulin)

- ❑ 11.8 kDa proteins
- ❑ Expression: on the cell surface of all nucleated cells
- ❑ Function: as the light chain of MHC I antigen
- ❑ was offered as an indicator of the early and subtle changes in the GFR
- ❑ possesses small molecular weight, so easily filtered via the glomerular wall into the tubule
- ❑ 99.9% of  $\beta$ 2-MG proteins retaken
- ❑ During the renal tubular damage : The augmentation of the urinary  $\beta$ 2-MG

# $\beta$ 2-MG ( $\beta_2$ -microglobulin)

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- Nakajima Y, Hoshi F, Higuchi S, Kawamura S. **Determination of bovine beta2-microglobulin and albumin in urine by a reversed-phase high-performance liquid chromatography.** J Vet Med Sci. 1999 Jul;61(7):725-9.
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- Stefan Schaub, John A. Wilkins, Mihaela Antonovici, Oleg Krokhin, Tracey Weiler, David Rush, Peter Nickerson. **Proteomic-Based Identification of Cleaved Urinary  $\beta$ 2-microglobulin as a Potential Marker for Acute Tubular Injury in Renal Allografts.** American Journal of Transplantation 2005; Pages 729-738
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- Jeong Deok Hong, In Seok Lim. **Correlation between glomerular filtration rate and urinary N acetyl-beta-D glucosaminidase in children with persistent proteinuria in chronic glomerular disease.** Korean J Pediatr. 2012 Apr;55(4):136-42
- Chen CJ, Liao WL, ثف شم. **Urine proteome analysis by C18 plate-matrix-assisted laser desorption/ionization time-of-flight mass spectrometry allows noninvasive differential diagnosis and prediction of diabetic nephropathy.** PLoS One. 2018 Jul 19;13(7)
- Fernanda R Tibu'rcio<sup>1</sup>, Karla E de S Rodrigues<sup>1</sup>. **Glomerular hyperfiltration and  $\beta$ -2 microglobulin as biomarkers of incipient renal dysfunction in cancer survivors:** Future Sci OA. 2018 Aug 10;4(8)



Fernanda R Tibu' rcio<sup>1</sup>, Karla E de S Rodrigues<sup>1</sup>. **Glomerular hyperfiltration and  $\beta$ -2 microglobulin as biomarkers of incipient renal dysfunction in cancer survivors**: Future Sci OA. 2018 Aug 10;4(8)

- Study subjects comprised 41 recruited children, who **were previously diagnosed with a solid malignancy** and had **already completed cancer treatment** for at least 1 month and were in remission
- The patients received at least one of the following potentially nephrotoxic chemotherapy drug: cisplatin, carboplatin, ifosfamide, CPM, and MTX



Fernanda R Tibu' rcio<sup>1</sup>, Karla E de S Rodrigues<sup>1</sup>. **Glomerular hyperfiltration and  $\beta$ -2 microglobulin as biomarkers of incipient renal dysfunction in cancer survivors:**  
Future Sci OA. 2018 Aug 10;4(8)

- B2MG values were higher than reference values in all children
- There was no estimated GFR lower than 60 ml/min/1.73 m<sup>2</sup>.
- 63.4% patients presented glomerular hyperfiltration (GFR  $\geq$  175 ml/min/1.73 m<sup>2</sup>).
- There was a strong positive correlation between B2MG and plasma levels of creatinine (p < 0.001).

## In this study:

- ✓ Two biomarkers including **β2-MG** and NAG for nephropharmacological assessment of childhood malignant patients **treated with Ifosfamide**, were selected

# Materials and Methods

## ✓ Inclusion criteria:

- \* less than 16 years old,
- \* diagnosed by : Ewing sarcoma. Osteosarcoma, BT, Neuroblastoma,
- \* admitted from 2017 to 2018 in Sayed-al-Shohada Hospital.
- \* under the treatment with Ifosfamide,
- \* no kidney involvement or any previous kidney disease
- \* Had a stable disease

✓ The features of these selected patients including age, sex, type of cancer were recorded.

✓ Informed consents were received from all Parents of patients or patients before beginning the study.

# Materials and Methods

## ➤ **Exclusion criteria:**

(A) **Creatinine level of higher than 1.2** mg/dl before the treatment

(B) the patients with fever and **infection** during five days of the treatment who were **prescribed with antibiotics** were excluded

➤ 61 courses of chemotherapy in 40 participants suffering different childhood cancers were examined.



## Materials and Methods

- 61 urine and blood samples of patients collected before the medication and the day six after treatment, then centrifuged at 2000 rpm for 20 minutes to get the precipitants of urine and 5 minutes for blood samples.
- $\beta$ 2-MG and NAG → measured in urine samples using  $\beta$ 2-Microglobulin ELISA Kit (AESKU, Germany) and N-acetylglucosaminidase ELISA Kit (HSL, UK) for the quantitative determination before and after medication.
- BUN and Cr → determined in serum and urine samples using Chemistry Analyzer BT3000 (Biotechnica, Italy) before and after the medication

# Results: Among 61 courses of chemotherapy,

- ❖ According to RIFLE criteria, up to 5 (8.2%) indicated AKI,
- ❖ On the day zero, 37 patients(60% ) had B2MG over the normal rang, and on day 6 increased to 87% (P=0. 001)
- ❖ On the day zero, 43 patients(70% ) had nag over the normal rang, and on day 6 increased to 86% (p=0. 072)
- ❖ The difference between mean levels of the NAG/Cr and β2-MG/Cr at the day 0 the day 6 of the treatment were statically significant (p=0.001 and p=0.003)

# Conclusion

## According to data bases:

- ✓ Serum creatinine concentration is an insensitive tool for evaluating kidney function
- ✓ High level of urine B2MG is associated with glomerular hyperfiltration

## According to our result:

- ✓ There is high prevalence of High urine B2MG and NAG level in patients receiving Ifosfamide,
- ✓ Therefore , it may be suggested that: hyperfiltration is very frequent in pediatric patients under the Ifosfamide treatment

## Suggestion :

- ✓ Since glomerular hyperfiltration has been associated with progressive nephropathy, children receiving Ifosfamide, should be monitored for the risk factor of renal disease, and presence of B2MG in urine, and close follow-up for detecting any kidney complication



