Cell Cycle Arrest Biomarkers: New Weapons for A New Battle

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Acute Kidney injury (AKI) is becoming an important health concern not only because the syndrome is a deadly condition in itself but also because it represents a gateway to chronic kidney disease (CKD) [1]. AKI is a syndrome with high mortality due to comorbidities and management challenges, especially in the critically ill patient [2]. AKI, however, is more than that. Even minimal kidney damage due to an insult (exposure) in the tubular or glomerular structure may evolve into progressive apoptosis and fibrosis and possibly a devastating glomerular destruction with inevitable hyper-filtration of the remnant parenchyma. Thus, AKI is a near and present danger that has ramifications for the rest of a patient's life. Several efforts have been made in recent years to standardize the definition/classification of AKI and, above all, to make an early diagnosis of acute kidney damage/dysfunction. This effort has included the discovery and validation of new biomarkers of AKI.

In spite of a growing body of publications, many new biomarkers have not yet transitioned to clinical routine because of a series of unresolved issues [3]. The first is the lack of specificity for AKI of some molecules. The amount of false positive cases associated with the elevation of the biomarkers caused by acute and chronic comorbidities in patients without AKI has often been too high. The second is lack of sensitivity of some markers, particularly at the earliest stages of kidney injury. A third is the absence of

clinically relevant and validated cutoff values that help guide use of the biomarkers to trigger appropriate interventions and changes to patient management. In addition, a major concern has been that once significant damage has occurred, the possibility to modify the clinical course and especially the recovery phase was considered minimal or absent. The extent to which this may or may not be true is unknown, but a significant number of patients with AKI are known to recover kidney function [4]. Therefore, the general consensus is that at least some kidney tissue can be salvaged and earlier detection and intervention are likely to benefit the patient. This may be especially true at the earliest stages of stress and injury when it may be possible to prevent further damage and preserve the remaining renal capacity, for example, by removing potentially injurious exposures such as nephrotoxic drugs and by providing extra supportive measures such as heightened attention to fluid and hemodynamic management [2].

There is unanimous agreement that a specific plan should be undertaken to fight AKI and its consequences. A strategic move of the scientific community to prevent, protect, diagnose, and cure AKI is definitely needed not only to save many lives from the acute disorder but also to avoid the evolution into CKD either by reducing the level of injury or by facilitating healing and recovery of the damaged parenchyma. However, all these approaches

have been hindered by the lack of reliable methods for early diagnosis of the injury and an early identification of the patient at risk.

Recently, the US Food and Drug Administration made an important step forward in the battle against AKI and its consequences. The FDA cleared the marketing of the NephroCheck Test (Astute Medical Inc., San Diego, USA), a rapid test for the quantitative measurement of the cell cycle arrest biomarkers Tissue Inhibitor of Metalloproteinase – 2 (TIMP2) and Insulin-Like Growth Factor Binding Protein – 7 (IGFBP7) [5]. The combination of the two biomarkers ([TIMP2]·[IGFBP7]) measured by the test seems to be highly predictive of which patients will develop moderate to severe AKI in the next 12–24 h.

Early work in the international multicenter Sapphire study of 728 critically ill patients showed that the elevation of the combination of biomarkers measured by the NephroCheck test is specific to AKI (i.e., is not caused by other comorbidities such as sepsis or CKD) and provides a strong signal or ‘renal alarm’ to identify when a patient is at imminent risk of developing AKI [6]. These urinary biomarkers are believed to be elevated in response to renal tubule cell stress or early injury associated with the types of exposures known to cause AKI. A primary clinical cutoff value (0.3) for the combination of the two biomarkers was derived from the Sapphire study data and verified in a new cohort of 153 critically ill patients (Opal study) [7]. This cutoff was selected to have high sensitivity for the primary endpoint of moderate to severe AKI in the next 12 h, with the intent to be used in routine clinical practice to identify patients at high risk for AKI who therefore are candidates for kidney-sparing management strategies such as those outlined in the KDIGO guideline for high-risk patients [2]. A second, high specificity cutoff (2.0) was selected and verified to identify the subgroup of patients who are at the highest risk of AKI and who therefore might be appropriate for more active interventions. Both cutoffs (0.3 and 2.0) were subsequently validated in a 23 site study of 408 critically ill patients in the United States (Topaz study) using clinical adjudication to determine the primary endpoint of moderate-severe AKI [8].

The NephroCheck quantitatively measures the combination of the two-cell cycle arrest biomarkers ([TIMP2]·[IGFBP7]) both by point-of-care techniques and other laboratory platforms, thus expanding the availability of the test worldwide [9].

According to the recent publication of the Acute Dialysis Quality initiative consensus group [10], there is a

need for early identification of damage or risk of AKI especially in those patients in which creatinine is still negative but biomarkers are positive. In this sense, NephroCheck may be used alone or in combination with other biomarkers of AKI as a discriminating test to alert physicians. All these considerations assume that putting the diagnostic clock ahead by 12 to 24 h compared to the clinical clock can make a difference. We are particularly convinced that this is the case. Early diagnoses or assessment of risk of injury may not only contribute to the identification of the cause of AKI and hopefully mitigate its effects but also help to identify patients in which, due to high susceptibility, even a small exposure may cause a severe injury. Even a subclinical (creatinine negative) injury, that may appear to be negligible, can produce a significant parenchymal damage [11]. This may be underestimated due to the presence of a significant renal functional reserve in the kidney and the absence of clinical signs and symptoms [12]. The injury, however, reduces the functioning renal mass and produces a progressive increase in kidney frailty with a remarkable susceptibility to future injuries. This process may be the gateway to CKD.

We must, therefore, use all the tools we have to raise the level of patient care and escalate the battle against AKI. A reliable, validated, and widely available test with a specific cutoff threshold has been requested by clinicians for a long time. A simple urinary biomarker test to screen critically ill patients for risk for AKI is something that is likely to be a useful new weapon in the battle against AKI. In this area, FDA has taken an important step to provide us with a new tool that is an early alert of which patients are at imminent risk. We should take the next step in using this new tool to help us improve the care of our patients.

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