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Preventive strategies for acute kidney injury in cancer patients

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ABSTRACT

Acute kidney injury (AKI) is a common complication of cancer that occurs in up to 50% of neoplastic patients during the natural history of their disease; furthermore, it has a huge impact on key outcomes such as overall prognosis, length of hospitalization and costs. AKI in cancer patients has different causes, either patient-, tumour- or treatment-related. Patient-related risk factors for AKI are the same as in the general population, whereas tumour-related risk factors are represented by compression, obstruction, direct kidney infiltration from the tumour as well by precipitation, aggregation, crystallization or misfolding of paraprotein (as in the case of multiple myeloma). Finally, treatment-related risk factors are the most common observed in clinical practice and may present also with the feature of tumour lysis syndrome or thrombotic microangiopathies. In the absence of validated biomarkers, a multidisciplinary clinical approach that incorporates adequate assessment, use of appropriate preventive measures and early intervention is essential to reduce the incidence of this life-threatening condition in cancer patients.

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INTRODUCTION

Acute kidney injury (AKI), probably the most common form of renal disease diagnosed in cancer patients, leads to a number of negative consequences in this particular patient population, including hindering active cancer treatment, worsening overall prognosis, increasing length of hospitalization (for inpatients) as well as increasing costs.

The global burden of acute kidney failure has been estimated to be 13.3 million cases per year. According to the UK National Institute for Health and Care Excellence, the relevance of AKI is a major problem for public health and its prevention could avoid as many as 42 000 deaths every year [1].

Indeed, oncologic patients, and particularly elderly ones, have an increased risk of developing AKI within the first year from the diagnosis of cancer, and this combination negatively affects their survival [2]. Also concerning is the increased mortality observed in cancer patients who have developed AKI on top of a pre-existing chronic kidney disease (CKD), as compared with those without kidney disease.

The relationship between kidney disease and cancer has been defined as 'circular' [3]. Indeed, AKI may disturb the bioavailability and/or safety profile of many oncological drugs, potentially leading to suboptimal treatments, or enhance the risk for drug-induced toxicities. Finally, some very effective anticancer agents may be avoided as a potential option in patients with AKI due to the lack of specific information on their pharmacokinetic properties in this setting [3].

Knowledge of specific risk factors and their modification is crucial to prevent AKI; indeed, since we presently do not have effective treatments for AKI, as highlighted by Rosner and Perazella, its prevention should be regarded as a key clinical priority [4].

DEFINITION OF AKI

The definition of AKI varies according to different classifications, either nephrological [i.e. , Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) or Acute Kidney Injury Network (AKIN)] [5] or oncological [National Cancer Institute - Common Terminology Criteria for Adverse Events v5.0 (NCI-CTCAE v5.0)] [6]. These classifications are reported in Table 1.

EPIDEMIOLOGY OF AKI

The largest study addressing the bulk of AKI in cancer patients is a Danish population study [2] in which 1.2 million people were followed from 1999 to 2006. During the whole observation period, >37 000 incident cancers were evidenced; the 1-year risk of AKI—defined by the RIFLE criteria—in this population was 17.5%, with a 27% risk over 5 years. The most common malignancies in which AKI was observed were renal cell cancer (44%), multiple myeloma (MM) (33%), liver cancer (32%) and leukaemia (28%); notably, patients with metastatic disease were at the highest risk of developing AKI. Even more severe AKI [corresponding to failure in RIFLE criteria and reflecting a tripling of serum creatinine (SCr) or absolute rise >4 mg/dL] was seen in 4.5 and 7.6% of patients at 1 and 5 years, respectively. Among cancer patients with any stage of AKI (9613 total), 5.1% required dialysis within 1 year of AKI onset [2]. Notably, the 28-day mortality of cancer patients who require dialysis has been estimated to be 66–88% [7].

AKI is particularly prevalent in the inpatient setting; notably, oncological units, together with intensive care, cardiac surgery and transplantation units, are characterized by extremely high AKI rates of ≥50% [8].

Furthermore, a recent study [9] investigated the incidence of AKI in 163 071 patients receiving systemic chemotherapy or targeted agents for their cancer and identified 10 880 patients who experienced AKI; the rate of AKI was thus 27/1000 person-years, with an overall cumulative incidence of 9.3%. Malignancies with the highest 5-year AKI incidence were myeloma [26.0%, 95% confidence interval (CI) 24.4–27.7%], bladder (19.0%, 95% CI 17.6–20.5%) and leukaemia (15.4%, 95% CI 14.3–16.5%). Advanced cancer stage, CKD and diabetes were associated with increased risk of AKI (adjusted hazard ratios =1.41, 95% CI 1.28–1.54; 1.80, 95% CI 1.67–1.93; and 1.43, 95% CI 1.37–1.50, respectively). In patients aged ≥66 years, diuretic and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker co-prescription was associated with higher AKI risk [9].

Another large study from China recently reported an incidence of AKI in cancer patients of between 14% and 20% [10].

CAUSES OF AKI IN CANCER PATIENTS

AKI in cancer patients has different causes, which can be either patient-, tumour- or treatment-related.

Patient-related causes are mainly represented by comorbidities, which overall increase the risk of episodes of AKI. Causes of AKI in cancer patients may also be differentiated in prerenal, renal and postrenal, as reported in Table 2.

As far as tumour-related causes, they are mainly represented by urinary compressions/obstructions or by kidney involvement (especially in lymphoma and myeloma).

Finally, different oncologic treatments may induce AKI, either through a direct injury to the kidney (as in the case of chemotherapy-induced AKI) or through indirect causes, as in the case of tumour lysis syndrome (TLS).

As for TLS and thrombotic microangiopathies (TMAs), they will be addressed separately since they have multiple, and often overlapping, causes.

PATIENT-RELATED RISK FACTORS FOR AKI

Substantially, patient-related risk factors for AKI are the same in the general population as in patients with cancer, although the latter may present other specific risk factors, as discussed below [11].

In 2013, a multicentre prospective observational study was performed in the acute medical units of 10 hospitals in England and Scotland to identify the main risk factors for AKI [12]. Age, hypotension, sepsis, hypovolaemia, pre-existing CKD, concomitant vascular disease (including atherosclerosis) and congestive heart failure—either past or acute—diabetes mellitus, jaundice as well as the use of nephrotoxic medications used in

Table 1. Different definitions of AKI, according to the most commonly used nephrological and oncological classifications

RIFLE			AKIN			NCI-CTCAE v5.0	
	Cr/GFR criteria	UO criteria		Cr criteria	UO criteria	Grade 1	>ULN – 1.5 × ULN
Risk	Increased Cr × 1.5 or GFR decreases >25%	UO < 0.5 mL/kg/h × 6 h	Stage 1	Increased Cr × 1.5 or ≥0.3 mg/dL	UO <0.5 mL/kg/h × 6 h	Grade 2	>1.5–3.0 × baseline; >1.5–3.0 × ULN
Injury	Increased Cr × 2 or GFR decreases >50%	UO < 0.5 mL/kg/h × 12 h	Stage 2	Increased Cr × 2	UO <0.5 mL/lg/h × 12 h	Grade 3	>3.0 × baseline; >3.0–6.0 × ULN. Hospitalization indicated
Failure	Increased Cr × 3 or GFR decreases >75% or Cr ≥4 mg/dL (with acute rise of ≥0.5 mg/dL)	UO < 0.3 mL/kg/h × 24 h or anuria × 12 h	Stage 3	Increased Cr × 3 or Cr ≥4 mg/dL (with acute rise of ≥0.5 mg/dL)	UO <0.3 mL/kg/h × 24 h or anuria × 12 h	Grade 4	>6.0 × ULN. Life-threatening consequences, dialysis indicated
Loss	Persistent ARF = complete loss of renal function for >4 weeks		Patients who received RRT are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT			Grade 5	Death
ESRD	End-stage renal disease						

UO, urine output; ULN, upper limit of normal; ARF, acute renal failure; RRT, renal replacement therapy.
Definition: a disorder characterized by the acute loss of renal function (within 2 weeks) and is traditionally classified as prerenal (low blood flow into kidney), renal (kidney damage) and postrenal causes (uretheral or bladder outflow obstruction).

Table 2. Main causes of AKI in patients with haematological malignancies and solid tumours

Haematologic malignancies	Solid tumours
Prerenal	
Nausea, vomiting and diarrhoea	
Stomatitis and cachexia	
'Third spacing' (including hepatorenal syndrome)	
Neutropenia and resulting sepsis	
Capillary leak syndrome (from interleukin-2 treatment)	
Renal	
Antineoplastic agents (either cytotoxics, targeted agents or immune checkpoint inhibitors)	
Contrast medium	
BPs	
NSAIDs	
TMA	
Paraneoplastic glomerulonephitis	
Immunomediated nephritis	
Hypercalcaemia	
VOD (less common in solid tumours)	
TLS (less common in solid tumours)	
Light-chain-associated glomerular disease	
Cancer infiltration	
HSCT	
Postrenal	
Compression/obstruction (tumour-related or radiotherapy-related)	

BPs, bisphosphonates; NSAIDs, non steroidal anti-inflammatory drugs; TMA, thrombotic microangiopathies; VOD, veno-occlusive disease; TLS, tumor lysis syndrome; HSCT. hematopoietic stem cell transplantation.

Table 3. Risk factors of AKI in patients with haematological malignancies and solid tumours

Haematologic malignancies	Solid tumours
Age >65 years	
Congestive heart failure (primitive or caused by oncological treatments)	
Pre-existing CKD (primitive or caused by oncological treatments)	
Diabetes	
Uncompensated cirrhosis/hepatic failure	
Nephrotic syndrome	
Volume depletion (hypovolaemia, hypotension, dehydration due to vomiting, diarrhoea, stomatitis, etc.)	
Sepsis (often central vascular device-related)	
Multiple myeloma	Urinary tract (renal cell as well as urothelial) carcinomas
Leukaemia and lymphoma	Hepatocellular carcinoma and cholangiocarcinoma

Table 4. Causes of AKI and possible preventive measures in haematological cancer patients

Causes	Possible preventive measures
General non-specific	Adequate hydration to maintain euvolaemia
Volume depletion (secondary to nausea, vomiting and diarrhoea)	Use of prophylactic antibiotics and haematopoietic growth factors in case of neutropenia/febrile neutropenia
Sepsis	
Iodinated contrast nephrotoxicity	Avoid repeated and frequent use of contrast medium
Concomitant use of nephrotoxic drugs	Avoid the use of potentially nephrotoxic agents
Tumour-specific	Beyond TLS (see the text), there are no specific preventive measures to implement in the case of tumour-specific AKI
Tumour infiltration of the kidney	
Obstructive nephropathy	
Lysozymuria	
Disseminated intravascular coagulation	
Hypercalcaemia	
Glomerular disease	
Chemotherapy-related nephrotoxicity	
TLS	

AKI, acute kidney injury; TLS, tumor lysis syndrome.

Table 5. Patterns of tissue injury and mechanisms responsible for AKI in dysproteinaemias

Type of tissue injury	Mechanism
Glomerular injury	Multiple myeloma can induce multiple patterns of glomerular damage, some of them associated with AKI due to endocapillary proliferative GN or crescentic GN. Amyloidosis is associated with nephrotic syndrome, which can determine AKI in severe cases
Ischaemic nephropathy, initially reversible but potentially leading to tubular injury/acute tubular necrosis	Prerenal azotaemia, induced by volume depletion (nausea/vomiting, diarrhoea and renal salt and water loss)
Tubulo-interstitial injury	Deposition of light chains in proximal tubular cells and in the interstitium
Myeloma cast nephropathy	Most common cause of AKI in Multiple myeloma patients. After binding to uromodulin (Tamm–Horsfell protein), light chains precipitate in distal tubules inducing tubular obstruction and interstitial inflammation and fibrosis. Light chains precipitation and tubular obstruction reduce single nephron glomerular filtration, resulting in loss of function and atrophy of the nephron
Drug-induced nephrotoxicity	NSAIDs, contrast media, chemotherapy, targeted and immunomodulating agents
Nephrotoxic injury due to MM-associated metabolic derangement	Hypercalcaemia and TLS

GN, glomerulonephritis; AKI, acute kidney injury; GN, glomerlonephritis, NSAIDs, non steroidal anti-inflammatory drugs; TLS, tumor lysis syndrome.

the week before admission to the hospital, were found to be potentially associated with the development of AKI. When a logistic regression model was used, among the above 10 risk factors, only hypovolaemia [adjusted odds ratio (OR) = 6.21, 95% CI 3.55–10.84; $P < 0.0001$], pre-existing CKD (OR = 3.92, 95% CI 2.39–6.42; $P < 0.0001$), diabetes (OR = 2.75, 95% CI 1.32–5.72; $P = 0.007$) and sepsis (OR = 2.34, 95% CI 1.05–5.23; $P = 0.038$) remained significant [12]. As a whole, risk factors for AKI in patients affected by solid or haematologic malignancies are reported in Table 3.

Therefore, prevention of AKI consists of general measures such as volume optimization, haemodynamic stabilization and improved cardiac performance, as well as correction of anaemia [8].

TUMOUR-RELATED AKI

Compression and obstruction: mechanisms and prevention

As already highlighted, compressions and obstructions are among the main causes of tumour-related AKI; they are caused by the primary tumour mass itself or by its metastases (e.g. enlarged abdominal or retroperitoneal lymph nodes). More than by an acute onset of AKI, these patients are characterized by a gradual development of CKD; indeed, a retrospective analysis of 117 consecutive patients with malignant ureteral obstruction showed that, before any intervention, as many as 91 patients had already CKD Stages 1–3 and 26 patients were CKD Stages 4 and 5 [13].

Despite the fact that no clear-cut preventive measures are available, a strict monitoring of both urinary outflow and renal function is mandatory, as is the prompt relief of the obstruction itself, to prevent the progression of renal damage from early to late stage.

This can be achieved by means of the placement of a percutaneous nephrostomy tube, of a ureteric stent or, more rarely, of a more complex open disobstructive surgical procedure. Nephrostomy tubes offer excellent drainage and can be placed under local anaesthesia, although they do require a bag, which can have a negative impact on patients' quality of life. JJ stents have a higher failure rate due and usually require a general anaesthesia for placement [14].

In cancer patients, internal ureteral stenting proved to be effective in maintaining renal function but it did not restore it; since renal function is related to the prognosis of the patients, to really improve patients' renal function and prognosis, patients who require stenting must be quickly identified and treated [13].

AKI in leukaemia and lymphoma: mechanisms and prevention

Patients with leukaemia and lymphoma are at risk for developing AKI from several causes different from direct involvement of the kidney: hypotension, sepsis, administration of radiocontrast, antifungal and antibacterial agents, cytotoxic chemotherapy, immunosuppressive drugs, haematopoietic stem cell transplantation (HSCT) or TLS (Table 4).

A direct leukaemic infiltration of the kidney from leukaemia and lymphoma is less rare than expected and is most commonly seen in highly aggressive and disseminated disease [15].

Indeed, autopsy studies have suggested that renal involvement occurs in ~90% of patients with lymphoma. Based on renal biopsy series from patients with lymphomas, patients who present with AKI have predominantly bilateral interstitial infiltration of the kidneys by lymphoma cells and often present an increased renal size on radiographic imaging [16]. These findings suggest an increased interstitial pressure leading to reduced intrarenal blood flow with subsequent renal tubular compression and disruption. In the presence of proteinuria, the local release of permeability factors and cytokines by lymphomatous cells has been suggested as its main pathophysiological mechanism.

Regarding leukaemia, autopsy studies have showed that 60–90% of leukaemic patients have renal involvement. On biopsy, cells are usually located in the renal interstitium, although occasional glomerular lesions are noted. Such as in the case of lymphomas, an increased interstitial pressure leads to vascular and tubular compression and subsequent tubular injury.

Given the above pathogenesis, AKI from direct involvement of lymphoma and leukaemia cannot be prevented.

AKI in MM: mechanisms and prevention

In dysproteinaemic states, an abnormal clone of B-lymphocytes secretes a paraprotein, most commonly a light-chain fragment of an immunoglobulin and more rarely an intact monoclonal immunoglobulin. The most severe form of dysproteinaemia is MM, where an uncontrolled proliferation of B cells develops and large quantities of paraprotein are produced, inducing increased serum levels of the abnormal light chain.

The paraproteins produced by B-lymphocyte clones are nephrotoxic and they represent the main cause of AKI in MM [17]. However, the mechanisms responsible for AKI in dysproteinaemias and specifically in MM are multiple and diverse [18], showing different patterns of tissue injury at various kidney locations, where precipitation, aggregation, crystallization or misfolding of the paraprotein may occur. Glomerular filtration delivers large amounts of free light chains to the proximal tubular cells, determining direct injury due to excessive endocytosis through the cubilin–megalin complex and consequent apoptosis, inflammation and fibrosis. In addition, in the distal tubules free light chains will bind to uromodulin (Tamm–Horsfall protein) leading to myeloma cast nephropathy, the most common cause of AKI in MM patients [19].

Importantly, haemodynamic abnormalities, metabolic disturbances and drug toxicity should also be kept in mind as possible causes of or contributors to acute derangement of kidney function (Table 5).

Myeloma cast nephropathy is the most common cause of AKI in MM patients [19]. AKI with decreased glomerular filtration rate develops in about 50% of patients before or within 30 days of MM being diagnosed. Among those who experience kidney failure, 10% will require dialysis.

A recent study investigated the incidence of AKI in cancer patients undergoing treatment [9]. Among 163 071 observed patients, 10 880 (6.7%) experienced AKI, accounting for an overall incidence of 27/1000 person-years; MM patients had an incidence of 21% (event rate: 90.8/1000 person-years). Considering the 5-year AKI cumulative incidence, a sharp difference was confirmed: 26% in MM patients, compared with 7.8% in the total cohort [9].

Prevention of AKI from cast nephropathy has been hypothesized through interference with the binding interaction between free light chains and uromodulin [20]. A competitor binding peptide was tested *in vitro* and in a rodent model of cast nephropathy, demonstrating inhibition of intraluminal cast formation and preventing AKI *in vivo*. However, no further developments have appeared in the literature regarding this approach. The best prevention of AKI is timely initiation of MM treatment with the newest therapeutic approaches, as reviewed elsewhere [21]. In addition, supportive treatment is of the utmost importance. It should be directed at avoiding or at least containing the exposure to nephrotoxic agents, correction of dehydration and hypercalcaemia, which are well-known risk factors for AKI. Dehydration also facilitates the precipitation of free light chains with uromodulin. Among drugs, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) are more often associated with worsening of kidney function.

Based on animal studies, the hypothesis that low-urinary pH may intensify myeloma nephrotoxicity was proposed. In rats, alkaline urine reduces the interaction of free light chains and uromodulin [22], but there are no clinical data to support this approach in humans.

The common-sense assumption that a rapid reduction in the concentration of free light chains may improve kidney function or prevent further kidney damage in patients with cast nephropathy has sparked interest in extracorporeal removal of free light chain. The two main approaches proposed by investigators are therapeutic plasma exchange and haemodialysis with high cut-off membranes. Results reported with both techniques are controversial, and although retrospective studies showed significant reductions in free light-chain concentrations and improved kidney function, randomized controlled trials did not confirm a significant advantage [23].

AKI in renal cell carcinoma: mechanism and preventive strategies

Cancers of renal parenchyma or of urinary tract (from renal pelvis to bladder) are often associated with AKI, due to both intrinsic and extrinsic causes [11].

Kidney cancer, irrespective of its histology, remains the only malignancy where surgical removal of the primary tumour, by means of either total or partial nephrectomy, is indicated not only when the disease is localized but also in the presence of distant metastases [24], although a recent randomized controlled trial challenged this old paradigm [25].

Despite this, the numbers of cytoreductive nephrectomies in metastatic renal cell carcinoma patients have been decreasing in recent years, mainly due to the superior activity of novel systemic treatments as compared with those used in the past [26].

Of course, among operated patients (irrespective of tumour stage, localized or metastatic), those undergoing radical nephrectomy are at increased risk of developing AKI [27], especially in the presence of certain comorbidities or of an acute worsening a pre-existent CKD, which is highly prevalent in these patients prior to surgery.

Partial nephrectomy is usually considered to be nephron-sparing, irrespective of the dimensions of the tumour [28, 29], although we should acknowledge that it may also cause AKI, depending on the amount of non-neoplastic parenchyma removed [30] as well as on the underlying conditions of the renal parenchyma (not discounting possible, although fortunately rare, surgical complications). After accounting for pre-surgery individual characteristics, such as age, obesity and comorbidities (e.g. hypertension or diabetes), partial nephrectomy independently protects against severe CKD [31]. Notably, in comparison with CKD induced by medical causes, surgically induced CKD is associated with a lower risk of progressive annual renal function decline [32]. Screening patients at higher risk for post-surgical AKI is key and should be done by estimating baseline renal function, measuring albuminuria, and optimizing glycemic and blood pressure control; in this way, we could minimize renal function decline after surgery. Furthermore, prevention of AKI includes avoidance of nephrotoxic drugs and renal hypoperfusion to reduce the risk for renal function decline post-operatively [33].

ONCOLOGICAL TREATMENT-RELATED AKI

Cytotoxic chemotherapy, targeted agents, as well as immune checkpoint inhibitors are often nephrotoxic and account for a number of cases of AKI in patients receiving these treatments.

Among cytotoxic chemotherapeutic agents, the ones most commonly related to the development of AKI are cisplatin (CDDP), mitomycin-C (MM-C), gemcitabine, methotrexate (MTX), ifosfamide and pemetrexed.

CDDP: mechanisms and prevention

CDDP is one of the most commonly used cytotoxic, being used—as a monotherapy or in combination with other agents—to treat a wide spectrum of tumours such as lung, ovarian, head and neck, bladder, cervical, testicular and other cancers.

CDDP-induced nephrotoxicity is multifactorial [34]. CDDP induces the production of reactive oxygen species (ROS) and inhibits several antioxidant enzymes, leading to massive oxidative stress injury and tubular cell apoptosis [35].

Renal injury from CDDP is dose-dependent and is first characterized by a decrease in renal blood flow leading to a decline in estimated glomerular filtration rate (eGFR) within 3 h of CDDP administration; these changes are probably due to increased vascular resistance secondary to tubulo-glomerular feedback and increased sodium chloride delivery to macula densa [34].

Acute tubular toxicity of CDDP causes mitochondrial dysfunction, decreased ATPase activity, impaired solute transport and altered cation balance; as a result, sodium and water reabsorption is decreased, and salt and water excretion are increased, often leading to polyuria [34].

Rare cases of TMAs have been reported in patients treated with CDDP, especially when co-administered with other agents.

As for many other cytotoxics, quite often AKI in CDDP-treated patients is caused by indirect toxicities, such as nausea and vomiting leading to volume depletion.

Although renal function improves in most patients, a subgroup of patients developed non-reversible renal impairment.

As far as preventive measures, hyper-hydration and forced diuresis (eventually with the use of mannitol) [36] have been shown to reduce the incidence of AKI in patients receiving CDDP, while the role of loop diuretics is much more debated. A systematic review on strategies to prevent CDDP-induced nephrotoxicity [37] concluded that (i) hydration is essential for all patients, (ii) short-duration (>2–6 h), low-volume (2–4 L of normal saline) and outpatient hydration regimens appear to be safe and feasible, even in patients receiving intermediate- to high-dose CDDP [37], (iii) intravenous (i.v.) magnesium supplementation (8–20 mEq) may limit renal damage [38, 39], and (iv) although a prospective randomized trial, conducted in cancer patients receiving 50–80 mg/m^2 of CDDP, showed that adequate oral prehydration with diuresis is not inferior to i.v. hydration in preventing CDDP-induced nephrotoxicity [40], i.v. hydration is usually preferred. As for mannitol, it may be considered only in the case of use of high-dose CDDP and/or in patients with pre-existing hypertension, while forced diuresis may be appropriated in some patients.

In a pharmacokinetic–pharmacodynamic analysis of CDDP with hydration and mannitol diuresis, forced diuresis treatment did not significantly alter the plasma CDDP pharmacokinetics but dramatically decreased the urine concentration of unbound CDDP and its accumulation into the kidneys in a dose-dependent manner, thus attenuating kidney injury [41].

Only the ROS scavenger amifostine has been approved by US Food and Drug Administration (FDA) for protection against cumulative nephrotoxicity from CDDP therapy [42]. Amifostine is protective by increasing the binding of ROS to thiol groups [43]. Side effects, cost and concerns that it also diminishes antitumour effect have limited its use in clinical practice.

Finally, a huge number of natural compounds [44] and drugs (e.g. allopurinol and statins) has been proposed to prevent CDDP- and other cytotoxics-related nephrotoxicity, but the level of evidence for all of them appears to be low; despite this, 'modulation of CDDP-induced nephrotoxicity still represents a balance on the knife-edge between renoprotection and tumour toxicity' [35].

MTX: mechanisms and prevention

Regarding MTX, despite its large therapeutic range, only high-dose MTX (HD-MTX), that is, MTX given at doses >500 mg/m^2, has the potential for becoming nephrotoxic, due to direct precipitation of the drug as well as to direct toxic effects on renal tubules.

In a large clinical trial of 3887 patients treated with HD-MTX, renal dysfunction occurred in 1.8% of the subjects, leading to a 4.4% mortality [45], although an higher incidence (up to 12%) has been reported, especially in patients with risk factors (e.g. history of renal dysfunction, volume depletion, acidic urine and drug interaction) [46]. Affected patients usually develop nonoliguric or, in more severe cases, oliguric AKI shortly after HD-MTX administration with a urinalysis, which is generally bland and shows no proteinuria. Because MTX is excreted in the urine, renal impairment affects the clearance of the drug; therefore, prolonged exposure to toxic levels of MTX may lead to life-threatening non-renal toxicities, such as prolonged cytopenias, mucositis, neurotoxicity and hepatic dysfunction. MTX solubility is 10-fold higher in urine with a pH of 7.5 than in acidic urine, and therefore urinary alkalinization and aggressive hydration (2.5–3.5 L/m^2/24 h, starting 12 h prior to chemotherapy administration) are important steps to establish brisk diuresis and prevent MTX precipitation in the tubules [47].

Prevention of renal and extra-renal toxicities, together with MTX titres monitoring, is thus crucial.

Leucovorin rescue, the only treatment that proved to be useful in this setting, is used in patients who develop nephrotoxicity and is aimed at prevention of non-renal complications, acting as an antidote by bypassing blocked Dihydrofolate reductase (DHFR) pathway; leucovorin rescue should be started 24 h after completion of each HD-MTX infusion (but should not be delayed beyond 42–48 h) and serum MTX concentrations should be measured daily [47].

Because MTX is acidic, drug crystals are not present in urine with an alkaline pH, as alkalinization greatly increases MTX solubility and excretion. Alkalinization is thus key to reduce intratubular crystal formation; thus, administration of fluids with 40 mEq/L sodium bicarbonate is recommended during and after HD-MTX administration.

Since >90% of MTX is excreted by the kidneys, the use of hydration to promote high urinary ouput is recommended.

Glucarpidase (carboxypeptidase-G2), a recombinant bacterial enzyme that rapidly metabolizes MTX to inactive compounds, is able to decrease MTX plasma level >98% within 15 min after administration and is effective as a single dose; MTX concentration rebounds occurred in 60% of the patients, usually with an increase not more than 10% in plasma MTX concentrations. Glucarpidase only affects extracellular levels of MTX, which may explain the delay in renal recovery after MTX removal from circulation.

Once again, MTX plasma levels should be monitored closely; indeed, for an HD-MTX infusion ≤24 h, if the 36-h concentration is >30 μM, the 42-h concentration is >10 μM or the 48-h concentration is >5 μM and the SCr is significantly elevated relative to the baseline, glucarpidase may be indicated. After a 36- to 42-h HD-MTX infusion, glucarpidase may be indicated when the 48-h MTX concentration is >5 μM. As a whole, glucarpidase administration should optimally occur within 48–60 h from the start of HD-MTX, because life-

threatening toxicities may not be preventable beyond this time point [48]. Unless absolutely necessary, medications that inhibit folate metabolism (e.g. trimethoprim–sulfamethoxazole), exhibit intrinsic renal toxicity (e.g. non-steroidal anti-inflammatory agents and contrast agents) or decrease the fraction of MTX bound to albumin (e.g. aspirin) should not be administered in patients receiving HD-MTX.

Haemodialysis and haemoperfusion have been used with an attempt to remove MTX from circulation; although both modalities result in lower MTX plasma levels immediately after treatment, there is a significant rebound effect (as high as 210%) of pre-procedure MTX concentrations. Because MTX is highly protein-bound, regular dialysis will not clear the drug efficiently, and high doses of leucovorin are needed to prevent systemic toxicity [49]. The successful use of different dialysis modalities has been reported, but available evidence supports in particular haemodialysis with high-flux membranes.

MM-C: mechanisms and prevention

MM-C is often associated with clinical manifestations of TMA, characterized by progressive renal failure. Kidney pathophysiological changes observed in patients developing MM-C-induced TMA are due to the direct toxic effects of the oncological agent on the endothelium [50].

Since MM-C nephrotoxicity is dose-dependent, with the risk of TMA being 1.6% with cumulative doses >40 mg/m^2 and as high as 30% at doses exceeding 70 mg/m^2, doses exceeding 40 mg/m^2 should be avoided. To prevent MM-C-related TMAs, current practice restricts its administration to 2–3 months.

Other chemotherapeutic agents

Although gemcitabine, ifosfamide and pemetrexed are potentially nephrotoxic, no measures to prevent AKI from these agents have been established to date, except those general interventions used to prevent AKI in non-oncological patients. Together with MM-C, gemcitabine, among cytotoxic agents, may cause TMA with relative frequency. While they represent the cornerstone for the treatment of anticancer drug-related TMA, there is no preventive place for either plasmapheresis or eculizumab, although the latter proved useful to prevent the evolution of a spurious or atypical TMA towards its overt manifestations [51].

Targeted therapies and immune checkpoint inhibitors: mechanisms and prevention

Targeted agents are anticancer drugs designed to specifically inhibit surface proteins or the product of specific gene alterations present in a given cancer, leading to the inhibition of the resulting signaling cascades causing tumour growth, angiogenesis and resistance to apoptosis [3]. Despite their efficacy and activity against different cancers, these agents are often associated with a number of renal adverse events, including AKI, proteinuria, hypertension and electrolyte disturbances. In many cases, this is due to the fact that the inhibited oncogenic pathways have overlapping functions in the kidney.

Immune checkpoint blockade removes inhibitory signals of T-cell activation, which enables tumour-reactive T cells to overcome regulatory mechanisms and mount an effective antitumour response [52]. Although usually well-tolerated, these agents may cause immune-mediated adverse events, which may also include interstitial nephritis and acute tubular necrosis, often presenting with AKI [53, 54].

No specific preventive measures for AKI from these novel anticancer agents are available; one should just follow the generic recommendations from the American Society of Nephrology, which suggested volume status optimization and avoidance of nephrotoxic medications [55].

Thus, one should often consider the possibility of renal damage from either targeted therapies or immune checkpoint inhibitors in any patients with unexplained worsening of kidney function as well as the opportunity of performing a kidney biopsy [4], to make a prompt diagnosis and to start adequate treatment.

Despite the fact that no recommendations to prevent AKI in immune checkpoint inhibitors-treated cancer patients exist, since proton pump inhibitor use was independently associated with an increased risk of immune checkpoint inhibitor-associated AKI [56], their use should be limited as much as possible, especially in patients receiving combinations of immune checkpoint inhibitors (another independent risk factor for the development of AKI).

BPs: mechanisms and prevention

Bisphosphonates (BPs) inhibit malignant osteolysis, as well as bone resorption, thus preventing bone destruction [57], lead to a positive calcium balance and increase bone mineral content. Furthermore, preclinical as well as indirect clinical evidence suggests that nitrogen-containing BPs, like zoledronic acid (ZA), might possess antitumour and anti-angiogenic properties [57, 58].

In September 2011, the US FDA issued a drug safety communication warning about the risk of AKI in patients treated with ZA; manufacturers were thus subsequently required to modify the package insert for BPs to warn for this risk. BPs-related renal adverse events proved to be related to dose, infusion duration and total number of infusions of ZA [59].

The mechanisms of nephrotoxicity of BPs in still not completely understood; since nitrogen-containing BPs exert their effect on osteoclasts through direct inhibition of farnesyl diphosphate synthase, an enzyme present in the mevalonate pathway, it has been proposed that the same inhibition of this key enzyme (i.e. farnesyl diphosphate) in proximal tubular cells may contribute to BPs toxic effect on the kidney [60].

BPs are also able to impair cytoskeleton assembly within osteoclasts; since podocytes, similar to osteoclasts, have a highly complex cytoskeleton, its disruption has also been proposed as one of the mechanisms of renal toxicity from BPs, leading to collapsing focal segmental glomerular sclerosis [59].

Prevention of BPs-related AKI mainly consists of dose reductions, depending on the baseline kidney function of the treated patients as well as on prolongation of the BPs infusions.

Table 6. BPs dosing according to renal function [61]

BP	Estimated CrCl, cm^3/min	Dose/infusion time	Interval, weeks
Pamidronate	>60>60	90 mg >2–3 h	3–4
Zolendronate		4 mg >15 min	3–4
Pamidronate	30–60	90 mg >2–3 h	3–4
Zolendronate	50–60	3.5 mg >15 min	3–4
	40–49	3.3 mg >15 min	3–4
	30–39	3 mg >15 min	3–4
Pamidronate	<30	90 mg >4–6 h	3–4
Zolendronate	<30	Contraindicated	

Concerning dose reductions, those suggested by the American Society of Oncology guidelines [61] are reported in Table 6.

AKI in HSCT: mechanisms and prevention

AKI is common following HSCT and can lead to long-term effects. Aetiology of HSCT-associated kidney injury is often multifactorial, including the direct toxicity of conditioning chemotherapy, the concomitant use of radiotherapy or of other nephrotoxic medications, the occurrence of sepsis, sinusoidal obstruction syndrome (SOS), transplantation-associated TMA and graft-versus-host disease (GVHD), not discounting the possibility of a pre-existing kidney disease [62]. In particular, HSCT-associated TMA is described in detail below. As HSCT-associated SOS often present hepatorenal syndrome with painful hepatomegaly, jaundice, oliguria and ascites, preventive and treatment strategies include prostaglandin E, pentoxiphylline and low-dose heparin [63]. Acute GVHD is a well-known independent factor for AKI; GVHD-related AKI is caused by cytokines-mediated inflammation and cyclosporin exposure, as well as by gastrointestinal (GI) involvement by GVHD causing vomiting and diarrhoea [64].

The incidence of AKI varies based on the definition of AKI, type of HSCT and of the chemotherapeutic conditioning regimen. When AKI is defined as a doubling of SCr during the first 100 days after stem cell infusion, the prevalence ranges from 21% to 73%. Severity of AKI also varies. In a study of paediatric and adult allogeneic Hematopoietic cell transplantation (HCT) recipients, up to a third of all patients doubled their SCr in the first 100 days and 5% required acute dialysis [65]. Severity of AKI is associated with increased risk of morbidity and mortality.

Owing to a propensity for increased GI fluid losses and poor oral intake, HSCT patients are highly susceptible to volume depletion. Close tracking of fluid intake, urine output, fluid losses via the GI tract and insensible losses, and daily weight measurement are thus mandatory, as the only and generic preventive measures available.

The management of AKI is mainly supportive and specific to the underlying cause. For situations of renal hypoperfusion, prompt administration of i.v. fluids is required to restore effective circulating volume. For those not responsive to medical interventions, dialysis is used as supportive therapy for the management of AKI-related fluid and metabolic derangements. The most recent literature cites a risk of dialysis ranging from 0% to 30%, higher in patients treated with myeloablative, as compared with those receiving reduced intensity, regimens [66]; in these patients, an extremely high mortality rate often approaching 80–100% has been reported. In terms of dialysis modality, continuous therapies may be more desirable in the intensive care setting, allowing for fluid removal in haemodynamically unstable patients. Furthermore, continuous haemofiltration offers a convective removal of larger inflammatory molecules, which cannot be cleared using the diffusive properties of continuous haemodialysis, and this could improve survival [67].

TLS: CAUSES AND PREVENTIVE STRATEGIES

TLS results from either spontaneous or chemotherapy-induced tumour cell death, leading to development of hyperuricaemia, hyperphosphataemia, hypocalcaemia and hyperkalaemia. Clinically, this results in multiorgan dysfunctions such as AKI, cardiac arrhythmias and seizures. TLS is the most common oncologic emergency, and without prompt recognition and early therapeutic intervention, morbidity and mortality are high [68]. TLS is most commonly described in haematologic malignancies, although it has also been described in patients with solid malignancies such as small-cell carcinoma of the lung and germ-cell tumours.

While limited options are available for treating TLS, identifying patients at high risk for developing it is crucial; risk factors for TLS include cancer- and patient-specific factors [69]. Tumour burden is the most relevant cancer-specific risk factor but elevated lactate dehydrogenase, white blood cell count >50 000/mm^3, massive liver metastasis, bone marrow involvement, cancer stage, proliferation rate of cancer cells and cell sensitivity to cytotoxic therapy can also play a key role. Patient-related factors include age, volume depletion, pre-existing CKD, hyperuricaemia and hyponatraemia.

Patients at the highest risk of developing TLS require intensified monitoring with more frequent electrolyte checks [70]. Patients with high-risk disease may be prone to lactic acidosis from massive tumour cell necrosis; because acidosis inhibits uric acid excretion, prompt recognition and correction of acidosis may prevent or ameliorate uric acid nephropathy. Additionally, NSAIDs, iodinated radiocontrast dye and other potentially nephrotoxic therapeutic agents should be avoided to abrogate the risk of AKI from TLS.

In terms of prevention, volume expansion supports adequate intravascular volume and renal blood flow, which maintain glomerular filtration. This is the cornerstone of uric acid, potassium and phosphate excretion, and may delay and prevent the need for renal replacement measures [70]. High-dose i.v. saline up to 3 L has been recommended. Diuretics may be necessary if patients develop volume overload, but routine use is not recommended to avoid volume depletion.

The formerly widespread use of urinary alkalinization is now a controversial practice. Alkalinization makes physiologic sense, as increasing urine pH from 5 to 7 can increase the solubility of uric acid >10-fold; however, urinary alkalinization decreases calcium–phosphate solubility, thereby exacerbating its precipitation and deposition. Furthermore, if urinary alkalinization results in rising serum pH, free calcium may bind albumin more avidly and further exacerbate hypocalcaemia. Thus, urinary alkalinization is not recommended in the management of TLS.

Allopurinol and febuxostat are the pillars of TLS prevention.

As a xanthine analogue, allopurinol, which is converted *in vivo* to oxypurinol, acts as a competitive inhibitor of xanthine oxidase and blocks the conversion of purines to uric acid, thus preventing hyperuricaemia; unfortunately, however, it does not treat pre-existing hyperuricaemia. Administration of allopurinol is recommended for prophylaxis in patients with low and intermediate risk of developing TLS [70]. Because oxypurinol is excreted by the kidney, dose adjustments are necessary for patients with CKD and AKI.

Febuxostat is a novel xanthine oxidase inhibitor lacking the hypersensitivity profile of allopurinol; it has been recently approved for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of developing a TLS [71]; it should be administered at the dose of 120 mg/day, starting 2 days before the administration of chemotherapy and for a duration of at least 7 days.

A recent meta-analysis of six studies which enrolled a total of 658 patients showed that, compared with allopurinol, febuxostat achieved a similar response rate (OR = 1.39, 95% CI 0.55–3.51) and TLS incidence (OR = 1.01, 95% CI 0.56–1.81);

furthermore, serum uric acid levels did not differ between the two agents at the second and seventh day of treatment [72]. Because it is metabolized to inactive metabolites by the liver, adjustment for reduced eGFR is not necessary.

As far as rasburicase is concerned, it is a recombinant version of urate oxidase, an enzyme that metabolizes uric acid to allantoin. Urate oxidase is known to be present in many mammals but does not naturally occur in humans [73]; therefore, rasburicase is produced by a genetically modified *Saccharomyces cerevisiae* strain.

Although mainly used to treat TLS once developed, rasburicase is approved by both the US FDA as well as by European Medicines Agency, not only for the treatment of TLS but also for its prevention. However, it is still unclear whether it is really cost-effective, since a decreased incidence of AKI or a decreased risk of death has not been documented. Indeed, in 2010, a randomized controlled trial comparing rasburicase (0.20 mg/kg/day i.v. Days 1–5), rasburicase plus allopurinol (rasburicase 0.20 mg/kg/day Days 1–3, followed by oral allopurinol 300 mg/day Days 3–5) or allopurinol (300 mg/day orally Days 1–5) was published, which demonstrated just a quicker control of plasma uric acid for rasburicase, as compared with allopurinol; the combination of the two yielded the same result as rasburicase alone [74]. Despite the fact that guidelines recommend rasburicase for all high-risk patients, a recent multisite retrospective chart review showed that the preventive use of allopurinol, i.v. bicarbonate and furosemide is similar irrespective of the level of risk for TLS (intermediate or high), while rasburicase is used in just 36% of high-risk patients, thus highlighting the doubts surrounding its real efficacy [75].

Once developed, TLS is treated by means of either rasburicase or renal replacement therapy, when required by the severity of AKI.

TMA: CAUSES AND PREVENTIVE STRATEGIES

TMA is a spectrum of disorders between the two classical entities of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (HUS); TMA may be associated with the cancer itself, with cancer chemotherapy or with HSCT [76]; although overall rare, they are relatively common causes of AKI in cancer patients. Indeed, the incidence of cancer drug-induced TMA during the last few decades is >15%, primarily due to the introduction of anti-vascular endothelial growth factor (VEGF) agents.

Thrombocytopenia with microangiopathic haemolytic anaemia and no alternative diagnosis is considered sufficient to establish a presumptive diagnosis of TMA.

In general, TMA in cancer patients can be classified as follows [50]:

(i) Cancer-related TMA;
(ii) Cancer drugs-induced TMA;
  Type I—caused by chemotherapy regimens;
  Type II—mainly caused by anti-VEGF agents;
(iii) HSCT-related TMA.

Cancer-related TMA can occur in patients with solid tumours, the most common type being adenocarcinomas (of the stomach, breast and lung); however, TMA has been also reported in patients with other solid tumours or haematological malignancies [77]. The pathophysiology of the TMA–malignancy association remains controversial. Several potential pathophysiological mechanisms have been proposed over time. Because cancer-related TMA occurs primarily in patients with mucin-producing adenocarcinomas, it has been speculated that mucin may exert a direct deleterious effect on the injured endothelium, affecting the production and release of von Willebrand factor. TMA may also be caused or aggravated by direct contact between erythrocytes and circulating carcinoma cells, as well as by tumour emboli within small blood vessels, which have been observed at autopsy. Cancer-related TMA may also develop due to injury to the vascular endothelium associated with a decreased ADAMTS13 activity, without the presence of anti-ADMTS13 antibody [78].

The differences between Type I and Type II drug-induced TMA are reported in Table 7.

Table 7. Characteristics of drug-induced TMA

Feature	Type I	Type II
Causative agents	MM-C, gemcitabine, platinum salts and combination regimens of cytotoxic chemotherapeutics	Targeted therapies
Timing of onset	Usually 6–12 months after starting therapy	Occurs any time after the initiation of treatment and may be observed after prolonged treatments
Dose relationship	Yes	No
Localization of pathological alterations	Arteriolar and glomerular capillary thrombosis	Exclusive glomerular capillary thrombosis
Clinical manifestations	Haematologic manifestation usually present Hypertension AKI Pulmonary oedema ARDS	Haematologic manifestations only in half patients Hypertension Varying degrees of proteinuria without kidney failure
Outcome	Irreversible damage Increased morbidity and mortality High incidence of acute mortality (4-month mortality up to 75%) and CKD requiring dialysis despite drug discontinuation, steroids or plasma exchange	High likelihood of recovery after interruption (reversible) Reportedly, does not impact on mortality Patients' and kidney survival rates are excellent after stopping causative agent(s)

MM-C, Mitomycin-C; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease.

There is continued speculation about the pathogenesis of chemotherapy-related TMA. In Type I drug-induced TMA, microvascular thrombosis is the key event, but it is not clear whether this results from direct endothelial toxicity or from immune-mediated effects on ADAMTS13 levels or other potentially damaging activity [78]. Different chemotherapeutic agents have been associated with Type I drug-induced TMA. In Type II drug-related TMA, VEGF/(vascular endothelial growth factor receptor) VEGFRs pathway inhibitors have been linked with the development of a syndrome characterized by new-onset hypertension (or exacerbation of pre-existing hypertension), AKI, with or without proteinuria and histopathologic features of kidney TMA. Half of the TMA cases were limited to the kidney without microangiopathic haemolytic anaemia or thrombocytopenia [79].

Pathologic TMA features limited to the glomerular structures differentiate anti-VEGF-induced TMA from other causes of TMA, including those secondary to chemotherapeutics. Kidney function can be usually preserved combining anti-hypertensive agents with the withdrawal of the anti-VEGF/VEGFRs agent [80].

TMA is also a common cause of late-onset AKI in patients who have undergone high-dose chemotherapy followed by HSCT. TMA after these complex (and toxic) procedures resemble HUS and usually occur 20–99 days post-transplant, more frequently allogeneic (8–12%) as compared with autologous transplantation [81].

The pathogenesis of TMA after HSCT is not well-understood, but damage to renal endothelial cells likely plays a key role [82].

It is unclear whether transplantation-associated microangiopathy is a complication of allogeneic HSCT di *per se*, because TMA can often be attributed to prior chemotherapy, GVHD, high-dose chemotherapy, total-body irradiation and/or disseminated infections [83].

No specific preventive measures are available for TMA in cancer patients; however, avoidance of risk factors possibly contributing to AKI (e.g. nephrotoxic medications, including antibiotics antifungal agents), use of reduced intensity-conditioning regimen, early identification, and effective management of sepsis, TLS, marrow infusion toxicity and hepatic SOS could help in reducing the incidence of AKI in HSCT recipients.

Furthermore, one should often consider the possibility in any patients with worsening of kidney function, hypertension, thrombocytopenia and haemolytic anaemia; biopsy is often required to make a prompt diagnosis and to start adequate treatment.

Accordingly, prevention, early recognition and prompt treatment of kidney injury are essential to improving kidney and patient outcomes after HSCT and for realizing the full potential of this therapy [84].

POST-CONTRAST-AKI IN CANCER PATIENTS: CAUSES AND PREVENTIVE STRATEGIES

Intravascular administration of iodinated contrast is associated with the development of post-contrast-AKI (PC-AKI). Risk factors include underlying CKD, diabetes mellitus, volume depletion and co-administration of other nephrotoxins.

Preventive measures should be used in patients with an eGFR <30 mL/min [85], including limiting contrast volume, using iso-osmolar contrast, pre- (and post-)hydration with normal saline, while the discontinuation of concurrent nephrotoxic agents is presently no longer recommended. Several meta-analyses have examined the use of *N*-acetylcysteine in the prevention of PC-AKI but results remain to date inconclusive, as in the case for bicarbonate administration. There is insufficient evidence to recommend haemodialysis or haemofiltration for the prevention or treatment of PC-AKI.

Notably, since in cancer patients, AKI is usually multifactorial, and the administration of contrast medium is often just one of many different concomitant causes contributing to the onset of AKI; indeed, the use of nephrotoxic agents such as CDDP or BPs in close proximity (i.e. within 24–48 h) to the administration of contrast medium may greatly increase the likelihood of PC-AKI. Thus, an important issue is how to deal with these potentially nephrotoxic agents when a contrast-enhanced radiological procedure (usually a CT scan) is scheduled, in particular, if and when such therapies should be stopped prior to the administration of contrast medium.

THE SEARCH FOR BIOMARKERS OF AKI IN CANCER PATIENTS

Several biomarkers for AKI as a whole have been proposed over time, but unfortunately limitation in specificity (especially in cancer patients) and in some cases also sensitivity have meant that damage markers are used mainly in a research setting.

In cancer patients, the only proposed biomarkers aimed at early detection of AKI have been evidenced only in the setting of CDDP-induced kidney damage [86].

Several proteins, mainly of urinary origin (e.g. beta-2-microglobulin, *N*-acetyl-D-glucosaminidase, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin and cystatin C) have been proposed as biomarkers for CDDP-induced AKI. Many of these well-studied proteins as well as emerging biomarkers (e.g. calbindin, monocyte chemotactic protein-1 and trefoil factor 3) display distinct patterns of time-dependent excretion after CDDP administration. Despite encouraging preliminary studies, the implementation of these biomarkers in the everyday practice has been hampered by the lack of validation studies and of accurate cut-off values and ranges [86].

CONCLUSIONS

AKI is a common and serious complication of cancer and/or of its treatments, being responsible for additional morbidity, mortality and of waste of resources. Prevention of AKI would thus be mandatory in patients with cancer to improve oncological outcomes, preventing unnecessary dose reductions or interruptions of potentially life-prolonging oncological treatments. Identification of those patients at risk and implementation of preventive strategies (whenever feasible) are indeed as important as adequate therapeutic interventions. Hopefully, the development of biomarkers predictive of AKI may lead in the future to an overall better identification and management of these patients.

Finally, a multidisciplinary approach that incorporates adequate assessment, use of appropriate preventive measures and early intervention is essential to reduce the incidence of life-threatening AKI in patients with cancer; collaboration between specialists is indeed of the utmost importance also in this area of onconephrology.

CONFLICT OF INTEREST STATEMENT

None declared.

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