REVIEW ARTICLE

Acute kidney injury in cancer patients

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SUMMARY

The increasing prevalence of neoplasias is associated with new clinical challenges, one of which is acute kidney injury (AKI). In addition to possibly constituting a clinical emergency, kidney failure significantly interferes with the choice and continuation of antineoplastic therapy, with prognostic implications in cancer patients. Some types of neoplasia are more susceptible to AKI, such as multiple myeloma and renal carcinoma. In cancer patients, AKI can be divided into pre-renal, renal (intrinsic), and post-renal. Conventional platinum-based chemotherapy and new targeted therapy agents against cancer are examples of drugs that cause an intrinsic renal lesion in this group of patients. This topic is of great importance to the daily practice of nephrologists and even constitutes a subspecialty in the field, the onco-nephrology.

KEYWORDS: *Acute Kidney Injury. Neoplasia. Malignant tumor. Chemotherapy.*

INTRODUCTION

With the epidemiological transition of recent decades, cancer has become the object of several clinical studies that resulted in more options for the diagnosis and treatment of the disease. Thus, there was an increase in the survival of patients, and handling complications of the disease and treatment adverse effects also became more common[1].

The association between cancer and kidney disease has been known for a long time[2,3]. The kidney toxicity of antineoplastic drugs, renal lesions in multiple myelomas (MM), malignant obstructive uropathy, and oncologic emergencies, such as tumor lysis syndrome (TLS), are examples of renal diseases that affect cancer patients[4]. Acute kidney injury (AKI) increases the risk of toxic effects of chemotherapy (CT), compromises the continuation of treatment, and limits the participation of patients in studies with new drugs.

EPIDEMIOLOGY

Among hospitalized patients, AKI is a common complication. Among those with cancer, the incidence reaches up to 12% of cases, and, often, the AKI develops within the first 48 hours of admission[5,6]. A Danish study with 37,257 cancer patients had 17.5% of AKI incidence, per the definitions of the Rifle classification (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease)[7]. In an environment of intensive therapy in cancer

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hospitals, the incidence increases to approximately up to 50%[4].

CANCERS WITH A HIGHER RISK OF AKI

The risk of AKI is greater in hematological neoplasias, especially in MM and neoplasms of the urinary tract, with emphasis on renal and bladder carcinomas[4,7,8]. In cases of renal carcinoma treated with radical nephrectomy, 34% presented AKI, that this procedure was also a predictor of the development of chronic kidney disease (CKD)[9]. Among other hematological neoplasias, in a cohort of 537 patients with acute myeloid leukemia (AML) and high-grade myelodysplastic syndrome, 36% developed AKI[10].

Risk factors

In addition to certain types of cancer being more prone to renal injury, there are factors that increase that risk, among them: age (>65 years), female gender, chronic kidney disease, diabetes, hypertension, renal artery stenosis, advanced-stage cancer, hypoalbuminemia, hyponatremia, leukopenia, absolute (vomiting, diarrhea) or relative (congestive heart failure, cirrhosis or nephrotic syndrome) hypovolemia, use of contrast agents, chemotherapy, antibiotics, mechanical ventilation, vasoactive drugs, use of oral drugs - diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-II-converting enzyme inhibitors II (ACEI) or angiotensin II receptor blockers (ARB)[6,8,10-12].

Evaluation of renal function in cancer patients

Equations that estimate the glomerular filtration rate (GFR) as those of the MDRD (*Modification of Diet in Renal Disease*) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) studies use as reference the iothalamate clearance and are currently the bedside methods available that offer the best accuracy and convenience for the evaluation of renal function. The Cockcroft Gault (CG) equation, since it is based on the creatinine clearance, may underestimate the glomerular filtration rate in elderly and malnourished patients, common characteristics among cancer patients. However, it is still used because it was the method chosen by the FDA (Food and Drug Administration) in 1998 as the standard for dose correction in patients with kidney failure and cancer[13].

Cancer patients often present alterations in the GFR that are not detected by the physician. In a multicenter study with 4,684 patients, the use of creatinine alone underestimated the diagnosis of CKD, since 60% of patients with GFR estimated at <90 ml/min/1.73 m² had creatinine values within the limits of normality[14]. Therefore, the search for more accurate biomarkers is the target of research. That is the case of cystatin C, produced in constant concentrations by all nucleated cells and freely filtered at the glomerulus, is not relevantly influenced by the nutritional state and muscle mass, which makes its use promising, although there have been contradictory preliminary studies estimating the GFR in cancer patients[15].

Regarding the definition of renal injury in these patients, most clinical studies published used the 2004 Rifle criteria. In 2012, the Kdigo (Kidney Disease Improve Global Outcomes) classification established a new system for defining and classifying acute kidney injury (Table 1). For the calculation, it is necessary to know the value of the baseline creatinine, which is the value reviewed from the last 7 to 365 days prior to hospital admis-

TABLE 1. CRITERIA FOR ACUTE KIDNEY INJURY

		RIFLE* 2004	AKIN 2007		KDIGO 2012
Criteria Stages	Diuresis (Same criteria in all three classifications)	GFR (Estimated decrease)	Creatinine clearance		
1	<0.5 ml/kg/h in 6h	>25%	**Risk:** ≥1.5xCr(s)	≥1.5x or increase ≥0.3 mg/dl	≥1.5x or increase ≥0.3mg/dl
2	<0.5 ml/kg/h in 12h	>50%	**Injury:** ≥2x Cr(s)	≥2x	≥2x
3	<0.3 ml/kg/h in 24h or anuria for 12h	>75%	**Failure:** ≥3x Cr(s)	≥3x or ≥4 mg/dl + increase of ≥0.5 mg/dl or TRS	≥3x or increased to values ≥ 4mg/dl** or RRT
Time	In hours	In the last 7 days		in 48h	≥1.5x in up to 7 days ≥0.3 mg/dl in 48h

*The Rifle Classification also has the following stages: Loss: loss of function for >4 weeks. ESRD - need of RRT for >3 months. ** Provided there is an increase ≥0.3 mg/dl in 48h or ≥1.5x in up to 7 days

sion; or the lowest value recorded during hospitalization. When the baseline value is unknown, the calculation of the creatinine value corresponds to the GFR estimated by a MDRD of 75 ml/min/1.73 m². However, in patients with previous CKD, this type of calculation may overestimate the incidence of AKI and its severity[16].

New biomarkers of acute kidney injury are under study, among which those related to inflammation are especially noteworthy, such as neutrophil gelatinase-associated lipocalin (NGAL) and those involved in cell cycle, like the tissue inhibitors of metalloproteinases (TIMP-2) and the IGF binding proteins (IGFBP-7), which require further studies involving cancer patients[17].

CAUSES OF AKI IN CANCER PATIENTS

In a cohort study, the most frequent causes of AKI were ischemia/shock, sepsis, contrast/nephrotoxins, obstruction, post-nephrectomy (renal carcinoma), and TLS[18]. In another study with hematological cancer patients, 68.5% presented AKI, and the main causes were hypoperfusion, TLS, acute tubular necrosis, and nephrotoxic agents[19]. In addition to the etiologies that are common among the general population (sepsis, NSAIDs, antibiotics, and contrast), cancer patients have a higher incidence of injuries due to antineoplastic drugs, post-renal injuries (genitourinary tumors), paraneoplastic syndromes, and TLS after chemotherapy.

In a systematic approach, we can separate the AKI etiologies associated with pre-renal, renal (intrinsic), and post-renal cancer, as is already done in the general population (Tables 2, 3, and 4).

Pre-renal

It is the most common cause of acute kidney injury in this group. The low oral intake, vomiting, and diarrhea after chemotherapy are responsible for most of the cases[20]. Fluid loss can also occur due to diabetes insipidus (DI) (nephrogenic - due to hypercalcemia, chemotherapic, post-renal - or central due to brain injury), third spacing, formation of cavitary effusion, and insensible losses (febrile neutropenia).

Post-renal

Cases of post-renal lesions are more common in cancer patients than in the general population[21]. The tumors were most frequently involved are those of the urinary tract, such as of the prostate and bladder, and those the adjacent systems, such as gynecological and gastrointestinal, and previous local therapeutic interventions such as surgery and radiotherapy increase the risk. This lesion may become irreversible; thus, prompt intervention is necessary. Before definitive surgery, maneuvers to decompress the urinary tract can be used, with ureteral catheters or nephrostomy. The decision on the use of decompression can be based on the presence of clinical parameters that compromise survival, such as hypoalbuminemia, degree of hydronephrosis, and metastatic events[22]. After reducing the obstruction, the tubular cells can be insensitive to vasopressin (nephrogenic DI), with possible polyuria and loss of electrolytes. Thus, it is of fundamental importance to control the hydroelectrolytic balance[23].

Although infrequent, anuria, flank pain, and a palpable mass are the clinical triad of post-renal AKI. Other possible signs are hematuria, abdominal distension, vesical dysfunction, and urinary tract infection. Urinary sediment is usually harmless and may contain red blood cells, crystals (uric acid), and cylinders (light chains). In addition to DI, hyperchloremic acidosis with hyperkalemia is suggestive of type IV

TABLE 2. CAUSES OF PRE-RENAL LESION IN CANCER

Absolute hypovolemia
Low food intake, vomiting, diarrhea - Gastrointestinal effects of chemotherapy - Obstructive abdomen (primary tumors or distant metastasis, adherence due to surgery/previous radiotherapy) - Injuries of the gastrointestinal mucosa of graft-versus-host disease Polyuria - Diabetes insipidus Insensible Losses - Sepsis/febrile neutropenia Others - Losses due to ostomies and drains
Relative hypovolemia
Vasodilation/hypotension. - Sepsis - Veno-occlusive disease/ Hepatorenal syndrome - Iatrogenic (antihypertensives) Renal vasoconstriction - Drugs (NSAIDS, calcineurin inhibitors) Decreased cardiac output - Heart failure due to coronary disease or cardiotoxic drugs Third Spacing - Metastases implants and cavitary effusion - Hypoalbuminemia/ nephrotic syndrome
Vascular compression
- Intra-abdominal hypertension/ abdominal compartment syndrome

renal tubular acidosis[12]. The definitive diagnosis of post-renal AKI is confirmed by radiological examination. Kidney ultrasonography (USG) is an excellent tool for the rapid detection of hydronephrosis/hydroureter. Occasionally, the findings may be negative, if the obstruction is of short duration or when there is renal entrapment due to cancer/retroperitoneal fibrosis. Computed tomography or magnetic resonance imaging are examinations that give more details on the obstruction, guiding the appropriate treatment.

In addition to tumors that compress the urinary tract, intraluminal causes should also be remembered, such as intratubular cylinders (light chain myeloma) and ureterolithiasis (Table 3).

TABLE 3. CAUSES OF POST-RENAL LESIONS

Intraluminal obstruction
Intratubulares crystals - TLS (uric acid, calcium phosphate, xanthine) - Drugs (Methotrexate) Intratubular cylinders *(light chains)* Ureterolithiasis *(hyperuricemia, hypercalcemia)* Urinary bladder clot *(bladder cancer, hemorrhagic cystitis)*
Extraluminal obstruction
Primary tumors of the urinary tract *(Bladder, Prostate)* Gynecological tumors *(uterus, ovary)* Metastases/ adenomegaly compressive of the urinary tract Retroperitoneal fibrosis

Renal (intrinsic)

Acute tubular necrosis due to sepsis and nephrotoxic agents such as antibiotics and contrast are important intrinsic etiologies in this group of patients. However, other causes specific of cancer patients should be remembered, among them nephrotoxicity caused by chemotherapy, TLS, renal injury related to MM, and renal carcinoma (post-nephrectomy).

TABLE 4. INTRINSIC RENAL INJURY

Sepsis Nephrotoxic drugs - Chemotherapy drugs, targeted therapy against cancer, immunotherapy - Bisphosphonates - Antibiotics, antivirals Contrast Ischemia/ pre-renal progression Tumor lysis syndrome Paraproteinemias Infections (pyelonephritis, viral infection - BK and Adenovirus) Renal carcinoma (post-nephrectomy) Tumor infiltration (lymphoma and leukemia) Glomerulopathies - Membranous, thrombotic microangiopathies, amyloidosis and others Endogenous nephrotoxins - Hyperuricosuria, hemoglobinuria, and myoglobinuria

Antineoplastic drugs

Table 5 shows the classes of drugs most frequently involved with nephrotoxicity in daily practice.

Platinum-based drugs are the most frequently involved in cases of nephrotoxicity. The class prototype is the cis-diamminedichloroplatinum (II) (CDDP) or cisplatin. This drug is commonly used in tumors of the lung, head and neck, bladder, testicles, and ovary[24]. Acute kidney injury occurs in approximately one-third of the patients. The drug affects several renal compartments and presents clinical manifestations, from renal injury to thrombotic microangiopathy and tubulopathies, with various electrolyte disturbances during its course, among them hypomagnesemia, proximal tubulopathy, and nephrogenic DI[25]. Renal injury can be prevented by adjusting the dose and maintaining adequate hydration; some studies showed benefits with the use of amifostine (free radical binder) and with a magnesium infusion during preparation for CT[26,27]. Analog substances, such as carboplatin and oxaliplatin, seem to be less nephrotoxic.

The ifosfamide is an alkylating agent used in the treatment of sarcomas, lymphomas, and testicle tumors. It is also associated with increased tubular injury and can manifest in the form of Fanconi Syndrome and even nephrogenic DI. The drug metabolite, chloroacetaldehyde, is the great responsible for the injury. In cyclophosphamide, another drug of the same class, this compound is formed in smaller quantities, and acrolein is produced, whose main side effect is hemorrhagic cystitis. The Mesna synthetic compound binds to and prevents cystitis[24].

The evolution of research in therapeutic tools to fight cancer has led to the emergence of drugs that act more directly on the tumor and have a lower effect against other cells. Among these are the target agents against cancer. The vascular endothelial growth factor (VEGF) and its receptor (VEGFR) and tyrosine kinase inhibitors - who act against the VEGFR and also against the platelet-derived growth factor receptor (PDGFR) - are some of the examples of targets of this new class of drugs, which ends up acting in the tumoral angiogenesis. The VEGF and its receptor are also present in podocytes, the endothelium, mesangium, and kidney tubular cells[28]. Thus, the glomerular lesions most frequently observed are endotheliosis, focal and segmental glomerulosclerosis, and thrombotic microangiopathy. Thus, patients who use these drugs commonly develop hypertension (which is actually a marker

TABLE 5. EXAMPLES OF ANTINEOPLASTIC DRUGS RELATED TO RENAL LESION

Antineoplastic drugs	Examples
Conventional chemotherapy agents	
Platinum-based Alkylating Antimetabolites	Cisplatin, carboplatin, oxaliplatin Ifosfamide, cyclophosphamide Methotrexate, gemcitabine
Targeted therapy	
Anti-VEGF antibodies Tyrosine kinase inhibitors EGFR inhibitors Checkpoint inhibitors - Anti-PD1 antibodies - Anti-CTL-4 antibodies mTOR	Bevacizumab, Aflibercept Sunitinib, Pazopanib, Sorafenib, Imatinib Cetuximab, Panitumumab Pembrolizumab, Nivolumab Ipilimumab Everolimus, Temsirolimus
Others IL2, IFN, Bisphosphonates, Denosumab	

of adequate antitumor response) and mild proteinuria. They can also develop nephrotic syndrome, AKI, and thrombotic microangiopathy, which should be monitored. Proteinuria should be treated with ACEI/ARB, and hypertension with the same drugs or dihydropyridine calcium channel blockers, such as nifedipine. Acute kidney injury with thrombotic microangiopathy is an indication to suspend the antineoplastic drug[28,29].

CONCLUSION

In addition to the etiologies briefly explored in this review, it is worth stressing the importance of acute kidney injury related to the transplantation of hematopoietic cells and renal carcinoma. The emergence of the onco-nephrology subspecialty caters to the need to integrate the treatment of patients with cancer and renal dysfunction. Interaction with other specialties is mandatory: oncology, hematology, urology, clinical pharmacy, a multi-professional team, and others.

Contribution of the authors:

Bruno Nogueira César[1], literature review, drafting of the paper. Marcelino de Souza Durão Júnior[1,2], literature review, drafting, and review of the article.

RESUMO

A crescente prevalência de neoplasias se associa a novos desafios clínicos, sendo a lesão renal aguda (LRA) um deles. Além de ser possível emergência clínica, a insuficiência renal interfere significativamente na escolha e continuação da terapia antineoplásica, tendo implicações prognósticas no paciente com câncer. Alguns tipos de neoplasias são mais suscetíveis a LRA, como o mieloma múltiplo e o carcinoma renal. Nos pacientes oncológicos, a LRA pode ser dividida em pré-renal, renal (intrínseca) e pós-renal. A quimioterapia convencional com platinas e os novos agentes de terapia-alvo contra o câncer são exemplos de drogas que causam lesão renal intrínseca nesse grupo de pacientes. Este tema é de grande importância atual para a prática diária do nefrologista, tornando-se inclusive subespecialidade na área, a onconefrologia.

PALAVRAS-CHAVE: *Lesão renal aguda. Neoplasia. Tumor maligno. Quimioterapia.*

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