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REVIEW

Prevention of post-contrast kidney injury in patients with cancer

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Abstract

Post-contrast acute kidney injury is defined as a nephropathy with an increase in serum creatinine of >0.3 mg/dL (or >26.5 µmol/L) or >1.5-times the baseline within 48–72 h of intravascular administration of a contrast medium. Patients with cancer have an increased risk of post-contrast acute kidney injury not only related to the frequent use of contrast medium for computed tomography scans but also to other factors, including the type of tumour, age, oncological therapies, use of other nephrotoxic agents and dehydration. Preventive strategies were developed and may be applied to different risk profiles. Patients at risk may be detected by recently published risk scores.

Keywords: cancer, computed tomography, post-contrast acute kidney injury.

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Introduction

The administration of iodinated contrast media (CM) for imaging examinations is a frequent medical practice, especially for patients with cancer who, for example, undergo over 40% of the 8 million computed tomography (CT) scans performed in Europe in 1 year.[1] The intravascular administration of CM is rarely followed by an acute decrease in renal function — not necessarily caused by the CM — described as post-contrast acute kidney injury (PC-AKI).[2] PC-AKI is associated with increased morbidity and mortality.[3–5] Its incidence was higher In studies conducted in the 1970s and 1980s,[6] ranging from 5% to 17%, whereas the incidence is of ~5% in more recent reports.[3,7] The risk in patients with cancer is higher than in the general population and, in hospitalized patients with cancer, it has been estimated to be as high as 12%.[8,9] In a Danish study, the risk of acute kidney injury (AKI) (defined as >50% increase in serum creatinine levels) was about 17.5% in the first year after cancer diagnosis in a population of 37,267 patients with cancer and 27% after 5 years.[10]

The increased risk of PC-AKI in patients with cancer is not only related to the frequent intravenous administration of CM for CT scans for the diagnosis and monitoring of the disease but also to other, often concomitant, factors, including the type of tumour, age, oncological treatments, use of other nephrotoxic agents and dehydration.[10,11]

The mechanism of AKI is not fully understood, but it is known that the main pathological lesion is acute tubular necrosis. Intrarenal vasoconstriction likely induces tubuloglomerular feedback and increased hydrostatic pressure, resulting in tissue hypoxaemia and reduced glomerular filtration.[12] CM could induce nephropathy by direct toxicity on tubular cells or by promoting renal ischaemia.[12] Several clinical and experimental observations suggest that the characteristics of the CM, amongst which osmolarity seems to be the most relevant, may play a role in the pathogenesis of contrast-induced nephropathy.[12,13] Indeed, increased blood osmolarity after administration of the CM is likely responsible for endothelial cell and red blood cell changes, resulting in renal vasoconstriction and kidney hypoxaemia.[12]

Because contrast-enhanced CT scans are the more common setting for CM use in oncology, this article is focused on the risk of AKI following intravenous (IV) contrast-enhanced CT scans. This article aims to review

the literature on mechanisms of PC-AKI, risk factors and available strategies to control the risk in patients with cancer and to report the authors' experience with managing PC-AKI risk in oncology.

Methods

A review of the literature was conducted. MEDLINE/PubMed was searched for appropriate keywords: "post-contrast kidney injury", "contrast medium", "oncology", "guideline", "computed tomography" and "risk factor". Clinical studies, reviews, meta-analyses and guidelines were retrieved; articles in English or English abstracts were considered. All retrieved articles were read and examined by authors and were selected based on relevance. This selection was based on the authors' clinical and scientific expertise. A narrative review article was written, reporting published evidence and the expert opinion of the authors.

Review

Mechanisms of kidney injury

PC-AKI is defined by Kidney Disease: Improving Global Outcomes (KDIGO) as either a ≥0.3 mg/dL increase in serum creatinine from baseline to a value obtained within 48 hours after the scan, or a ≥1.5-fold increase in serum creatinine from baseline to the peak value obtained within 14 days after the scan.[14] The European Society of Urogenital Radiology (ESUR) defined PC-AKI as a nephropathy with an increase in serum creatinine of >0.3 mg/dL (or >26.5 µmol/L) or >1.5-times the baseline, within 48–72 hours of intravascular administration of a CM.[2]

Although the pathophysiology of PC-AKI is still not completely understood, animal and human studies suggest some possible mechanisms involved in acute renal impairment.[15,16] The main mechanisms involved in AKI are ischaemia of kidney tissues and direct cytotoxicity of tubular epithelial cells. After CM is injected, renal blood flow, after a transient increase, decreases over a long period, suggesting that renal ischaemia may be a major contributor to nephropathy.[17] This hypothesis is supported by pathological evidence of ischaemic changes, including necrosis of the medullary thick ascending limbs and tubular collapse involving primarily the outer medullary area of the kidney, as observed in experimental studies.[18] Physiologically, the kidney cortex and medulla have a low oxygen tension, which is easily reduced after the injection of CM.[19] This effect may be due to active transport across membranes being increased in response to osmotic diuresis induced by hyperosmolar agents, the release of vasoconstrictive compounds such as endothelin and adenosine, and reduced production of vasodilatory molecules such as nitrous oxide and prostaglandins.[17,18,20,21] Increased production of reactive oxygen species would be responsible for direct cytotoxicity on endothelial and epithelial tubular cells.[12]

The activation of these mechanisms is highly dependent on the osmolarity of the injected medium. High-osmolar (osmolarity was about 2,000 mOsm/L) or ionic CMs are no longer available because they lead to a high degree of intrarenal vasoconstriction, which activates tubuloglomerular feedback, or results in increased tubular hydrostatic pressure with decreased glomerular filtration and medullary hypoxaemia.[12] Low-osmolar CM, with osmolarity of about 600–900 mOsm/L, introduced after the 1980s, are non-ionic but risk inducing renal vasoconstriction, as osmolarity is nonetheless higher than that of plasma.[22] Clinical studies demonstrated that low-osmolar contrast agents were less nephrotoxic than high-osmolar agents.[12,23] Furthermore, in one study,[24] contrast-induced AKI incidence was lower with a plasma-iso-osmolar contrast agent (with an osmolarity of 290 mOsm/L) than with a low-osmolar agent, supporting the role of osmolarity in the pathophysiology of PC-AKI. These non-specific adverse effects are not fully understood; it has been suggested that hyperosmolality could activate tubuloglomerular feedback or increase tubular hydrostatic pressures; each of these events would result in decreased glomerular filtration. In addition, the osmotic diuresis produced by CM may induce increased active transport of sodium in the thick ascending limb and vasoconstriction; both events could worsen medullary hypoxaemia.[19,20,25]

Risk factors in patients with cancer

AKI is a common complication in patients with cancer, and many factors contribute to the increased risk.[9,10] The highest risk for AKI within a cohort of patients with new cancer in Denmark was observed in patients with kidney cancer (44.0%; 95% CI 40.5–47.5), liver cancer (33.0%; 95% CI 28.2–37.8%) or multiple myeloma (31.8%; 95% CI 27.3–36.3%).[10]

Additionally, comorbidities and concomitant treatments contribute to the increased risk. Compared with those without the characteristics, Salahudeen et al. found that the odds ratio (OR) for AKI is significantly higher for patients with cancer and diabetes (OR 1.89, 95% CI 1.51–2.36), hyponatraemia (OR 1.97, 95% CI 1.57–2.47), or receiving chemotherapy (OR 1.61, 95% CI 1.26–2.05) or antibiotics (OR 1.52, 95% CI 1.15–2.02); intravenous injection of any type of iodinated CM yielded an OR of 4.55 (95% CI 3.51–5.89).[26] Heart failure, a recent myocardial infarction, hypertension, pre-existing chronic kidney disease and age over 70 years were also correlated with AKI incidence.[27]

Anticancer therapy is an important risk factor for AKI. PC-AKI incidence after chemotherapy in hospitalized

patients with cancer was 20%.[28] Moreover, the injection of CM within 45 days of chemotherapy was demonstrated as an independent risk factor (p=0.017).[29] Cisplatin is associated with glomerular and tubular damage, especially with repeated cycles of therapy.[30] The risk of AKI was shown to be increased by 2.56-fold in patients with cancer receiving iodinated CM in the week previous to cisplatin administration.[31] Given that new anticancer agents, including immune-checkpoint inhibitors and targeted therapies, may damage the kidney at the level of glomerulus, tubule and interstitium, and that treated patients with cancer often repeatedly receive iodinated CM to monitor the efficacy of treatments, the risk of AKI must be carefully managed.[9]

Strategies to mitigate the risk

The awareness of PC-AKI risk in patients with cancer cannot limit the use of diagnostic procedures that help monitor and tailor treatments, limiting unnecessary medications and promoting early therapy changes. Conversely, such awareness suggests the importance of strategies to prevent PC-AKI risk, with the necessary cooperation of primary care and specialists in the follow-up of patients with cancer. International scientific societies in cardiology, nephrology and radiology issued clinical guidelines for preventing PC-AKI, and multidisciplinary groups recommended the interventions necessary in different settings.[32] All such recommendations include the screening of risk and the management of CM administration, the main issues being the assessment of serum creatinine before CM administration, saline pre-hydration and the choice of CM.[14,32–35] Nevertheless, it is not easy to draw a unitarian protocol for clinical practice that includes recommendations for all the specialists caring for patients with cancer.

Practices of unproven efficacy should be avoided. As an example, preventive haemodialysis, although considered by some clinicians, was never demonstrated to reduce the risk of PC-AKI and its use was discouraged by the consensus statements from the Italian College of Radiology (SIRM), Italian College of Nephrology (SIN) and Italian Association of Medical Oncology (AIOM).[36]

Selection of the iodinated contrast medium

Although current evidence does not support using a specific CM in patients with cancer, an iso-osmolar agent may be preferred, especially in frail patients at high risk. As mentioned above, the hyperosmolarity of the CM contributes to the pathophysiological mechanisms of kidney damage responsible for PC-AKI. Only one CM for intravenous administration is iso-osmolar to plasma, iodixanol.[37,38]

Iodixanol has been shown to have a good tolerability and safety profile, particularly for intra-arterial injection.[39–42] Similarly, studies comparing intravenous iso-osmolar *versus* low-osmolar CM found lower incidence of discomfort, better safety and greater enhancement of the hepatic, aorta and portal vein[43–45] in patients receiving the iso-osmolar CM. Some clinical studies investigated the possible benefit of iso-osmolar CM in terms of the risk of AKI, with inconsistent results.[46–55] Indeed, no consensus has been obtained in identifying patients with a homogeneous baseline risk of renal damage, resulting in an uncontrollable bias in clinical trials. Mentioning only intravenous administration, Nguyen et al. found less frequent PC-AKI in patients with decreased renal function treated with iodixanol (8.5%) than in those treated with iopromide (27.8%; p=0.012).[56] More recently, a clinical trial on patients with cancer evaluated the safety of iodixanol or iopromide.[57] All the patients had an estimated glomerular filtration rate (eGFR) of >60 mL/min/1.73 m^2 (without differences between groups) and underwent chest, abdomen and pelvis contrast-enhanced CT with iodinated CM. PC-AKI was significantly more frequent with iopromide than with iodixanol (15 *vs* 5; p=0.11).[57]

Several guidelines recommend that iodinated CM with the lowest osmolarity should be used in any patient and that iso-osmolar CM should be always used in patients with high risk of PC-AKI, including those with ischaemic heart disease, chronic kidney disease and advanced age.[14,33,35]

Risk assessment: clinical experiences

Although patients with cancer have an increased risk of PC-AKI and intravenous CM administration is necessary to diagnose and monitor the disease, the assessment of renal damage risk has not been standardized. Such risk stratification would facilitate the best management of patients at higher risk and the implementation of differentiated patient journeys, with the role of the involved professionals. The authors previously reported their experience setting up a protocol for PC-AKI risk assessment in patients with cancer in the Azienda Ospedaliera Universitaria P. Giaccone of Palermo, Italy.[1]

Based on the evaluation of risk factors for AKI published by Cosmai et al.,[9] which considered current guidelines,[14,33–35] an evidence-based checklist for PC-AKI risk identification was prepared. Three patient risk profiles were identified – high, medium and low risk – and differentiated care pathways were used for each risk profile.

The first version of the assessment checklist included nine items, with a score for each level of each item (Table 1). The assessed patient was considered to be at high risk when: (a) item 1 is scored as 3 independently of any other score; (b) at least one item is scored as 3 and one as 2; (c) at least three items are scored as ≥2; and (d) at least

Table 1. First tentative version of a checklist for post-contrast acute kidney injury assessment.

Item	Level	Score
Baseline kidney function	Chronic kidney disease	3
	eGFR <30 mL/min/1.73 m^2	3
	eGFR 30–40 mL/min/1.73 m^2	2
	eGFR 45–60 mL/min/1.73 m^2	1
Age	≥70 years	3
	≥60 years	2
	<60 years	1
EF/HF	EF <30% or HF NYHA class ≥III	3
	EF <35% or HF NYHA class <III	2
	EF <45% or HF NYHA class I	1
	EF >45% or no HF	0
Volume of CM to be administered	≥250 mL	3
	140–250 mL	2
	<140 mL	1
Diabetes	Uncontrolled	3
	Controlled with systemic comorbidity	2
	Controlled without systemic comorbidities	1
	No diabetes	0
Blood concentration of Hb	<9.5 g/dL	3
	<11 g/dL	2
	<14.5 g/dL	1
	>14.5 g/dL	0
Type of tumour	Kidney, renal pelvis, urothelial cancer	3
	Liver cancer	3
	Myeloma	3
	Other tumour on treatment	2
	Other tumour not on treatment	1
Recent use of nephrotoxic drugs and/or CM	Nephrotoxic drug in the last 7 days and/or CM in the last 48 hours	3
	Nephrotoxic drug in the last 7–45 days and/or CM in the last 3–7 days	2
	No nephrotoxic drug in the last 45 days nor CM in the last 8 days	1
Number of current nephrotoxic drugs	3	3
	2	2
	1	1
	0	0

CM, contrast medium; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure.

five items are scored as ≥1. The patient is considered at medium risk when item 1 and another item are scored as 2. The patient is considered at low risk in all other cases.

This checklist asseswsed 54 consecutive patients with cancer for a pilot usability evaluation. All outpatients with solid tumours were eligible for CT with CM. Thirty (55.6%) patients were males, 15 (27.8%) were aged >70 years, 5 (9.3%) had kidney cancer, and the others had cancers that do not affect kidney function. Seventeen (31.5%) patients were found to be at high risk, 13 (24.1%) at medium risk and 24 (44.4%) at low risk. Amongst patients at high risk, four factors were present in 3 (17.6%) individuals, three factors in 2 (11.8%), two factors in 9 (52.9%) and one factor in 3 (17.6%).

Based on these results, the incidence of high risk resulting from the checklist assessment was too high, according to data from the literature[9] and the clinical experience of a multidisciplinary team, including a radiologist, nephrologist and oncologist. Indeed, the team realized that anaemia was scored too high and too many patients were considered to be at high risk of PC-AKI only because of its presence. The checklist was amended, reducing the impact of anaemia (Table 2). Each item in the list should be assessed and risk scores for all items are summed up. A high risk for PC-AKI is here indicated by a total score of ≥5 points; a total score of 2–4 shows a medium risk, and a low risk is shown by total scores of 1–0.

The final checklist was applied to the same 54 patients already assessed with the first version. The risk profile found by the two versions of the checklist disagreed in 24 (44.4%) patients, with the risk always being lower with the final version. A high risk of PC-AKI was found in 5 (9.2%) patients; four had eGFR of 30–45 mL/min/1.73 m^2 with advanced age, diabetes, recent nephrotoxic drug administration and kidney cancer. A medium risk was found in 11 (20.3%) patients; amongst these, 4 had eGFR of >60 mL/min/1.73 m^2 and at least two risk factors

Table 2. Final checklist for post-contrast acute kidney injury assessment. Items to evaluate are listed with risk scores related to each item level.

Item	Level	Score
Baseline kidney function	eGFR ≥60 mL/min/1.73 m^2	0
	eGFR <30 mL/min/1.73 m^2	5
	eGFR 30–45 mL/min/1.73 m^2	4
	eGFR 45–60 mL/min/1.73 m^2	1
Age	≥70 years	1
	≥60 years	0
	<60 years	0
EF/HF	EF <30% or HF NYHA class ≥III	1
	EF ≥30% or HF NYHA class <III	0
Diabetes	Uncontrolled	1
	Controlled	0
Blood concentration of haemoglobin	<9.5 g/dL	1
	≥9.5 g/dL	0
Tumour type	Kidney, renal pelvis, liver, urothelial cancer	1
	Other tumours	0
Recent use of nephrotoxic drugs	Nephrotoxic drug in the last 7 days	1
	Nephrotoxic drug in the last 7–45 days and/or CM in the last 3–7 days	0
	No nephrotoxic drug in the last 7 days	0
Recent use of CM	CM in the last 48 hours	1
	No CM in the last 48 hours	0

CM, contrast medium; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure.

Box 1. Protocol for the management of CT with intravenous contrast medium in patients at medium–high risk.

- Intravenous injection of sodium bicarbonate 1.4% 3 mL/kg/h for 1 h before CT or saline solution 0.9% 1 mL/kg/h for 3–4 h before and 4–6 h after CT
- Baseline serum creatinine is measured at least 7 days before CT; it is also measured 48–72 after CT in patients at high risk
- Cisplatin is discontinued 5–7 days before CT
- Bisphosphonates are discontinued 14 days before CT
- Pre-hydration in the oncology department
- Post-hydration in the radiology department
- Use of iso-osmolar contrast medium (the CM volume to administer is calculated to obtain an iodine concentration (mg)/eGFR ratio = 0–1)

of advanced age, diabetes, recent nephrotoxic drug administration and kidney cancer; 5 had eGFR of 45–60 mL/min/1.73 m^2 with at least two other risk factors; and 1 had eGFR of <30 mL/min/1.73 m^2 with advanced age and kidney cancer. A low risk was assessed in 38 (70.3%) patients; 36 with eGFR of ≥60 mL/min/1.73 m^2 and 2 with eGFR of 45–60 mL/min/1.73 m^2 without other risk factors.

The checklist was included in the clinical practice of a multidisciplinary team. The risk profile was assessed by oncologists, with the nephrologist's advice, for patients at high risk and selected individuals at medium risk. All patients at low risk, medium risk without radiological evaluation and those at high–medium risk with a favourable nephrological evaluation undergo CT with CM according to a radiological protocol adequate to each patient's risk profile. The protocol for patients at medium–high risk is reported in Box 1.

Another risk model for predicting PC-AKI in patients with cancer has been developed by Gupta et al.[58] based on a retrospective study of 25,184 patients. A score was assigned to patients based on clinical variables, including haematological malignancy, diuretic use, angiotensin-converting inhibitor/angiotensin II receptor blocker use, chronic kidney disease stage IIIa or higher, serum albumin, platelet count, proteinuria, heart failure, diabetes and CM volume.

Conclusion

CT with intravenous injection of CM is an important investigation for diagnosis, stage identification and disease monitoring in patients with cancer. Nevertheless, these individuals have an increased risk of renal damage following the administration of CM due to the disease itself, treatments and comorbidities. Thus, the risk must be carefully managed to allow imaging tests to be used as necessary to manage cancer efficiently.

Patients may follow differentiated care pathways based on the assessment of risk profile. A multidisciplinary team is involved in the risk assessment and test management. Prevention of renal damage in individuals at medium–high risk is finally based on serum creatinine assessment at baseline and within 48–72 hours from CT, before and after hydration, and on the use of an iso-osmolar CM with adequate volume and concentration.

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