nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Editorial

Post-contrast acute kidney injury in cancer patients☆

Lesión renal aguda poscontraste en pacientes con cáncer

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ARTICLE INFO

Article history:
Received 10 December 2018
Accepted 19 February 2019

According to data of the Spanish Society of Medical Oncology,[1] cancer continues to be one of the main causes of morbidity world in continuous growth. Studies in Population indicate that the number of new cases is likely to increase by 70% in the upcoming decades, reaching approximately 24 million cases in 2035. Also in Spain, cancer is one of the main causes of morbidity, with 228,482 estimated cases for the year 2017 and it is predicted 315,413 cases for the year 2035.

In the evaluation of the cancer patient, the information obtained through radiological procedures using contrast media (CM) is of great importance for the diagnosis and evolution of the disease, and the CMs are increasingly used to obtain better images in a broad spectrum of techniques such as computed tomography (CT) and magnetic resonance imaging.

Cancer and kidney

The relationships between cancer er and kidney are being analyzed with more precision. Presently there multiple etiologies that are well known : acute or chronic renal failure (ARF, CKD), hydroelectrolytic disorders, glomerular nephropathies, toxic effects of different chemotherapies, etc. Of all these renal complications, post-contrast acute renal injury (AKI) (PC-AKI) has been widely discussed, especially strategies for prevention. In the case of the cancer patient, the possibility of AKI is accentuated for several reasons, underlining: the coincidence with other nephrotoxic factors, situations of inadequate renal perfusion, the frequent administration of iodinated contrast (CT

DOI of original article:
https://doi.org/10.1016/j.nefro.2019.02.001.
☆ Please cite this article as: de Francisco ALM, Guillén MA, Pérez-Valderrama B, Sebastia C. Lesión renal aguda poscontraste en pacientes con cáncer. Nefrologia. 2019;39:563–567.
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and PET-CT with contrast) which is essential for the correct assessment of the neoplastic disease and in many cases the existence of previous renal insufficiency (glomerular filtration rate (GFR < 60 ml/min/1,73 m^2). There are recent studies that consider that PC-AKI is a transitory state with elevations in serum creatinine values with no clinical expression.[2] There are, however, studies that have shown that short and long-term mortality rates are significantly higher in patients with PC-AKI as compared to patients without PC-AKI.[3] In addition, the history of PC-AKI may be associated with the development of chronic kidney disease (CKD) and long term progression to end-stage renal disease.[4,5]

Risk factors for post-contrast acute kidney injury

One of the several modifications of the recommendations recently published in the new guides of the European Society of Urogenital Radiology (ESUR 10),[6,7] is the change of the denomination of AKF induced by iodinated contrast is changed to AKI associated to contrasts (AKI-PC); since in most cases, the kidney injury is coincidental and not necessarily caused by the contrast.

One of the most important changes in these new recommendations has to do with the risk factors related to the patient and specifically with cancer patients. Renal insufficiency continues to be considered as the most important risk factor for AKI-PC. However, other risk factors previously included have been excluded. According to the authors of the latest ESUR version 10, many meta-analyzes and systematic reviews of uncontrolled studies have identified a large number of possible clinical risk factors for AKI in general, such as advanced age, female gender, low body mass index, classic cardiovascular and metabolic risk factors, malignancy, inflammation, bleeding, anemia and hyperuricemia.[6] However, an objection is that in uncontrolled studies the baseline clinical risk factors cannot be reliably differentiated from the specific effects of the contrast. And based on this, the authors consider only as risk factors, in addition to renal failure, dehydration and the critical state or multiorgan failure of the patient. Age, the presence of a single kidney and the history of transplantation (renal, pancreatic or hepatic) are no longer considered risk factors. Stage 3 or 4 heart failure (according to the NYHA classification) is not a risk factor in itself, but it is the fact that it prevents proper hydration of the patient due to the restriction of fluids involved. The last ESUR 10 recommendations excluded the cancer patient as a risk factor for AKI-PC, however for the reasons explain below we do not share this decision.

Why does the cancer patient is at high risk for acute renal injury after contrast?

The cancer patient has a higher risk of acute kidney injury

There are many studies showing an increased risk of AKI for any cause in the cancer patient. In a Danish study that includes 37,267 cancer patients, the risk of AKI (defined as > 50% increase in serum creatinine values) was 17.5% after one year of diagnosis and 27% at 5 years.[8] In hospitalized patients without cancer, the incidence of AKI was 5%, while it reached 12% in cancer patients.[9]

In a cancer reference center with 3558 patients, the possibility (OR) to develop AKI was significantly greater in the presence of a number of risk factors, highlighting the use of CM: diabetes (OR 1.89; 95%, confidence interval [CI] 1.51–2.36), chemotherapy (OR 1.61; 95% CI, 1.26–2.05), intravenous contrast (OR 4.55; 95% CI, 3.51–5.89), hyponatremia (OR 1.97; 95% CI, 1.57–2.47) and antibiotics (OR 1.52; 95% CI, 1.15–2.02).[9] And this higher risk of developing an ARI (including cancer patients) has its consequences: an increase in hospital stay, mortality and costs.[10]

Age and renal failure

In the cancer patient, the increased age is associated frequent renal alterations. The average age of patients at the time of cancer diagnosis is 65 years. Of the 47% of cancer survivors, almost half are 70 years of age or older and only 5% are under 40 years.[11] The aging of the population increases the number of patients whose cancer is complicated by other chronic diseases. In the EPIRCE study, by the Spanish Society of Nephrology, on the general Spanish population,[12] 22% of adult patients over 65 years of age had a GFR < 60 ml / min / 1.73 m^2.

The data reporting renal failure (GFR < 60 ml / min / 1.73 m^2) in cancer patients at all ages are variable: from 18% in the BIRMA[13] study to 22% in the US. UU.[14] or 25% in Japan.[15] In a study conducted by us in hospitalized oncology patients in Spain, 18. 2% had GFR < 60 ml / min / 1.73 m^2).[16]

Therefore, a second reason for AKI-PC is the high percentage of kidney failure in cancer patients especially those in which the cancer is more common with age >65 years.

Nephrotoxic treatments

A 50% of anticancer drugs are predominantly excreted in the urine and 80% of patients receive potentially nephrotoxic drugs and / or for whom the dose should be adjusted.[13] The presence of pre-existing renal failure may limit the use of otherwise active regimes that may be curative. This combination of cancer, kidney disease and mortality has led to the recognition that Nephrology and Oncology are closely linked and the birth of the subspecialty, Onco-Nephrology.[17]

Many cancers affect kidney function. Some directly, such as myeloma, others by infiltration of the renal parenchyma in leukemia and lymphomas, cast nephropathy, obstruction or secondary glomerulopathies. Others indirectly, through volume depletion (vomiting, diarrhea, ascites, etc.), sepsis, heart failure or metabolic disorders such as hypercalcemia. It is important to consider, especially in the cancer patient, that the combined effect with other potentially nephrotoxic drugs, such as iodinated contrast, increases the risk of kidney damage.[18] Sendur et al. found that in patients with exposure to CM a week before the administration of cisplatin, the risk of AKI-PC was significantly higher than in patients without such exposure.[19]

Frequency of studies with contrast media

The recommendations for staging and monitoring cancer treatments require evaluations that includes frequent imaging tests with iodinated contrast. In most tumors, thoracoabdominal CT with contrast is recommended every 3 or 6 months for the first 2 or 3 years and even more frequently if the patient is included in a clinical trial, and annually until the 5th or even the first 10 years.[20,21]

It is not clear if the repetition of radiological studies with administration of iodinated contrasts, as in the case of some cancer patients, increases the risk of AKI-PC. The studies are often observational retrospective, with many differences among patients in relation to hydration, dose and type of contrast, route of administration, comorbidities, association of nephrotoxic drugs, etc. Even studies using Propensity Machted Score (PMS) adjusting certain variables are not exempt from bias by indication. However, Hsieh et al.[22] studied with PMS 7100 patients with non-advanced CKD receiving contrast CT and using PMS they adjusted another population of 7100 patients undergoing by CT but without contrast. They found a much higher risk of developing ESRD in the 2 groups exposed to >1 and <2 contrast per year and a mean of ≥2 exposures per year (adjusted HR = 8.13, 95%, CI, 5.57–11.87 and adjusted HR = 12.08, CI 95%, 7,39–19.75, respectively) as compared with patients who underwent CT without using contrast medium. It seems that what represents a clear risk of kidney damage is the repeated exposure to contrast at 36−72 h or performing urgent radiological studies. Similarly, in the series by Chan et al. in cancer patients, the absolute risk after contrast CT increases from 0.3 to 2.3%, depending on the type of cancer.[23]

Loss of renal functional reserve or hidden renal damage

The renal functional reserve (RFR) represents the ability ofthe kidney to increase the GFR in response to certain stimuli that can be physiological (high protein intake, amino acid infusion) or pathologic (first stage of diabetes). The difference between the the maximum FGR and the basal GFR represents the RFR. There may be a damaged kidney in which the loss of FG is compensated by intact nephrons that function as the RFR, an d the increase in serum creatinine does not occur. The RFR may be is lost after the repetition of renal injuries (decompensation of failure heart, ischemia / reperfusion, repeated use of iodinated contrasts or nephrotoxic drugs). And this may happen especially in cancer patients. Therefore, in the absence of an elevation of the serum creatinine, AKI may not be ruled and the possibility subclinical kidney damage after repeated injuries not can be ruled out.[24] Some studies that must be confirmed point to the value of serum NGAL and FGF23 determinations in the early diagnosis of AKI-PC.[25]

Prevention of post-acute acute renal injury in the cancer patient

For all the above reasons, preventive specific measures must be implemented in the cancer patient. In the series by Chan Ng et al.[23] a patient hospitalized with cancer receiving contrast CT has a 2.4% baseline risk of developing AKI-PC. This risk increases progressively in patients with CKD stage 1 (4.9%), 2 (7.0%), 3 (9.6%) and 4–5 (10.5%), so in the cancer patient it is very important to consider the degree of CKD.

It is advisable as a preventive measure (in addition to adjustment of the contrast dose to the GFR) the correct hydration, without differences between saline and bicarbonate. There are also no differences between oral N-acetylcysteine and placebo.[26] The use of oral (rather than intravenous) hydration is not recommended in patients at risk of AKI, as is the case in cancer patients, with some exceptions.[27] Recently, it has been shown that prolonged fasting for liquids and solids is in itself a risk factor for developing AKI-PC due to the dehydration that may cause to the patient. Currently, it is recommended to advise the patient correct and profuse self-hydration, and in many hospitals, fasting of solids is not performed, increasing the well-being of the cancer patient.[28]

Recommendations of different guides on the type of contrast medium for prevention of acute post-contrast renal injury

ESUR 10 does not refer to differences between low osmolarity contrast injection (577–823 mOsm / kg H_2O) and isoosmolar (290 mOsm / kg H_2O).[6] However, the isoosmolar iodixanol CM induces less cytotoxic effects in cultured tubular cells and the production oxididated radicals is less than lowösmolarity iohexol and iopamidol.[29] In addition, in high-risk patients, the iodixanol isoosmolar dimer is associated with less nephrotoxic effects than the lowösmolarity.[30]

The incidence of AKI-PC, dialysis or mortality in patients at high risk adjusted for PMS was similar in CT with isoosmolar (iodixanol) than in patients who did not receive contrast. This may not be applied to low osmolarity contrasts in high-risk patients.[31]

The use of isoosmolar CM is contemplated in different guidelines on the prevention of AKI-PC:

- ACCF / AHA / ACP / AATS / PCNA / SCAI / STS: state: to avoid the worsening of the underlying disease "use a renal protection strategy that includes the use of isoosmolar MC during angiography".[32]
- American Society of Nephrology: Geriatric nephrology curriculum 2009: older patients are more frequently subjected to invasive procedures, nephrotoxic medications and CM that increase the risk of AKI. Renal protection strategies include, among others, intravenous hydration and isosmolar CMs.[33]
- KDIGOGuides 2012[27] : recommend that all persons with GFR < 60 ml / min / 1.73 m^2 (GFR stages G3a-G5) undergo elective evaluation involving intravascular administration of radioiodinated media according to the K DIGO Clinical Practice Guide for AKI, which includes, among others:
- Identify risk factors such as diabetes, dehydration, nephrotoxic agents, heart failure, cancer patients, etc.
- Avoid high osmolarity agents (1B). Isoosmolar agents, in comparison with low osmolarity agents, are associated with lower rates of AKI in some, but not in all studies. Wherever possible, the isoosmolar agents should be used in individ-

uals with CKD with high risk of AKI (GFR <30 ml / min / 1.73 m^2).
- The American Society of Nephrology in its 2016 educational program in Onco-Nephrology, recognizes that the cancer patient needs a special approach (by multiple tests, association of nephrotoxic drugs, complex hemodynamic situations, etc.) to prevent AKI- PC they establishes a set of preventive measures in patients with GFR < 60 ml / min, including limiting the volume of contrast, using iso — osmolar contrast, prior hydration with normal saline and discontinue concurrent nephrotoxic agents.[34]
- Guidelines for Medicines Optimization in Patients with Acute Kidney Injury July 2016 NHS England with UK Renal registry: contrast induced nephropathy (CIN) is increased with high or low osmolarity contrast as compared with with isoosmolar contrast.[35]
- Low contrast volumes can reduce AKI -PC rates and it is recommended to use the lowest possible dose of contrast medium to reduce the risk.[36]

In conclusion

We believe that the oncological patients should be included as a high-risk group in view of the possibility of AKI-PC. Taking into account that a eGFR value of < 30 ml / min / 1.73 m^2 is too limited and inaccurate, since 20–30% of the estimated FG have an error from the measured eGFR value,[37] our position for cancer patients with FG < 45 ml / min / 1.73 m^2 (pending prospective randomized studies)would be:

- Adjustment of the dose of contrast to the GFR.
- Prophylaxis with intravenous hydration.
- Suspend nephrotoxic medication and adapt the examination according to cancer treatment (cisplatin).
- Use isoosmolar contrast if:
- eGFR < 30 ml / min / 1.73 m^2 (or creatinine > 2 mg / dl).
- it is intraarterial administration.

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