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Prevention of contrast-associated acute kidney injury in cancer patients undergoing radiologic investigation using contrast media; a short-review to current knowledge

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ABSTRACT

Contrast agents are non-biologically active substances required for various diagnostic imaging procedures. Exposure to contrast materials, predispose some patients to renal disturbances entitled as contrast-associated acute kidney injury. Nephropathy of contrast medium is a deterioration of renal function which happens within 24 to 72 hours after iodinated contrast medium injection. Cancer individuals have several risk factors for contrast-associated acute renal failure, consisting of administration of chemotherapy regimen, which are mainly nephrotoxic, presence of diabetes or chronic renal failure, hypertension, taking of non-steroidal anti-inflammatory drugs, simultaneous use of nephrotoxic drugs, aminoglycosides, cisplatin, cyclosporine A or amphotericin B, increases the risk of contrast-associated acute renal failure. Similarly, age more than 65 years old and anemia is an independent risk factor for contrast-associated acute kidney injury and also timing of CT within 45 days after last chemotherapy and low fluid intake, as the common risk factors in cancer individuals.

Implication for health policy/practice/research/medical education:

Chemotherapy regimen dose adjustment is indispensable for cancer individuals. Accordingly, evaluation of kidney function is crucial when Administering intravascular contrast agents for computed tomography examinations of cancer individuals. Therefore, it is important to keep in mind that why individuals with malignancy are at somewhat higher risk of contrast nephropathy than the general population.

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Introduction

Contrast agents are non-biologically active substances required for various diagnostic imaging procedures. Exposure to contrast materials, predispose some patients to renal disturbances entitled as contrast-associated acute kidney injury (1-3). Nephropathy of contrast medium is a deterioration of renal function which happens within 24 to 72 hours after iodinated contrast medium injection. Imaging is frequently used in hospitals and outpatient settings detection and for therapeutic interventions (4-6). Contrast-induced acute kidney injury is associated with poor clinical outcomes and increased short-term and long-term mortality, the need for renal replacement therapy and prolonged hospital admission, and also an increase in cardiovascular disease (7,8). This complication

is one of the most known forms of acute renal damage due to its possibility for prevention. However, the risk of acute renal failure following contrast medium injection is overemphasized, since such investigations are critical in cancer patients. This condition causes decreases prescription of the imaging studies in these patients, presumably due to the concern on prompting acute renal failure, leading to delay in detection of malignancy or its development. Hence, the administration of contrast agents should be balanced to risk/benefit calculation, in cancer patients (9-12).

Materials and Methods

For this short-review, we applied for some of sources including PubMed, Web of Science Embase, EBSCO,

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Scopus and directory of open access journals (DOAJ). The search was directed toward using combinations of the following key words and/or their equivalents; contrast-associated acute kidney injury, malignancy, contrast medium, vasoconstriction, renal medulla, acute kidney injury, oxidative stress, vacuolization, mitochondria, contrast agents, contrast-induced acute kidney injury, cancer and post-contrast acute kidney injury.

Pathophysiology of contrast-associated acute kidney injury

Pathophysiological viewpoint, iodinated contrast material stimulates vasoconstriction and also inflammation in this vulnerable vascular bed of renal medullary region leading to the creation of reactive oxygen species. Additionally, the exposure to contrast medium, decreases oxygen pressure in the deep renal medulla and simultaneously induces an increase in ion transport and oxygen utilization at the TAL (thick ascending limb) (13-16). Accordingly, an increase in tubular pressure causes tubular obstruction which results in an enhanced oxygen consumption and worsening of ischemic damage (12-17). On the other hand, vasoconstriction imposes the oxidative damage which further intensifies the hypoxia in renal medullae, since the combined effects of low oxygen delivery due to vasoconstriction and high oxygen consumption in the proximal tubules render the renal medullae mainly vulnerable to hypoxic damage. Therefore, two main mechanisms are interacted, direct tubular cytotoxicity and kidney ischemia (18-20). Contrast materials provoke kidney vasoconstriction through intensifying the release of adenosine and endothelin from kidney cells. These substances also strengthen the creation and release of reactive oxygen species, which may result in direct cytotoxic consequences on kidney tubular cells. Additionally, hemodynamic instability, have been suggested (12-19).

The direct toxicity of contrast agents to renal tubular epithelial cells, leading to apoptosis and necrosis and resultant loss of function. Accordingly, indirect mechanisms are associated with ischemic injury due to renal vasomotor alteration implicated by vasoactive agents like nitric oxide, prostaglandins and endothelin, since following a diminution in nitric oxide creation, the ischemia will increase and will lead to nephrotoxicity (20-23). Numerous studies showed the value of endothelin, which has been detected to increase after contrast media exposure (24). The attentions are also toward the role of adenosine in inducing contrast-associated acute kidney injury, while intra-renal injected adenosine makes hemodynamic disturbances similar to contrast nephropathy (25,26).

Likewise, the direct cytotoxicity is conducted by vacuolization or osmotic necrosis which promotes

apoptosis in renal tubular cells when they resorb/adsorb iodinated contrast medium (27).

In summary iodinated radiocontrast material perturbs proximal renal tubule epithelium by alteration of cellular morphology (vacuolization), increasing the oxidative stress (enhanced creation of reactive oxygen species), decreased efficacy of the electron transport chain and ATP production due to mitochondrial dysfunction, cut activity of cell survival kinases (28-31).

Acute kidney insufficiency in individuals with malignancy

The incidence of acute kidney injury fluctuates in cancer patients. Several factors are responsible for acute renal failure including stage and type of underlying of malignancy, presence of metastasis, critical illness, infections and fluid intake (32). Most of chemotherapeutic drugs are excreted by the kidney. Conversely acute renal failure, by altering the pharmacokinetic of these drugs might lead to toxic concentration (32). Accordingly, when acute kidney injury requiring dialysis, chemotherapeutic drug level may fluctuate and result in sub-therapeutic levels and potentially could lead to unsuccessful cancer treatment. In addition, simultaneous antibiotic administration or narcotics, may aggravate acute kidney injury of cancer patients (33-35).

Post-contrast acute kidney injury in cancer individuals

Unfortunately, contrast-related acute renal failure is the third most common cause of hospital-acquired kidney damage, assuming for 12% of cases (17,36). Conventionally, contrast nephropathy is defined as an increase in the plasma creatinine concentration of at least 0.5 mg per deciliter or as a minimum of 25% increase from the baseline value within two to five days following administration of contrast agent (37). The intensity of this dysfunction can differ from a mild increase in plasma creatinine to long-lasting kidney injury requiring dialysis (38,39). In general, the incidence of contrast-associated acute kidney injury is low, less than two percent, in individuals with normal to slightly diminished kidney function (GFR more than 60 ml/min per 1.73 m²) (40,41). In contrast, in individuals with moderate to severe renal failure the frequency is high and is around 55% (42). Cancer patients have various risk factors for contrast-associated acute kidney injury like age more than 65 years and anemia are the independent risk factors (43-47). Additionally, timing of CT within 45 days after last chemotherapy and low-fluid intake, are other risk factors. Of predisposing factors mentioned above, however pre-existing kidney failure is the utmost important risk factor for contrast-associated acute kidney injury. Accordingly, the highest risk of contrast-induced nephropathy is in

patients with both diabetes and pre-existing kidney failure (48,49). Similarly, the type of chemotherapy and the timing of treatment and CT scanning are other risk factors for acute reactions to iodinated contrast material. Irrespective of the cause of acute kidney injury by contrast agents, cancer individuals who are complicated by contrast nephropathy may have worse survival and prognosis (50). In a study on 2,240 patients with malignancy, glomerular filtration rate below 45 mL/min/1.73 m² who underwent contrast-enhanced computed tomography with contrast-induced nephropathy preventive modalities Jeon et al, found, the global incidence of contrast nephropathy was 2.5%. They found that diabetes mellitus, glomerular filtration rate and plasma albumin value were independent predictors of contrast nephropathy (51,52).

Recently, Hong et al conducted a retrospective study on 820 cancer individuals to assess the frequency and possible predictors of contrast-associated acute kidney injury in cancer patients without chronic renal failure who underwent contrast-enhanced computed tomography. They detected, the incidence of contrast-associated acute kidney injury was 8.0%. Additionally, they found BUN/creatinine more than 20, serial CT examination, liver cirrhosis and hypotension, are associated with post-contrast acute kidney injury as the predisposing parameters. They concluded, baseline plasma creatinine below 1.5 mg/dL, is a risk for contrast-induced nephropathy (51).

Notably, cancer patients experience repeated imaging examinations. Malignancy staging and estimation of treatment response commonly necessitate injection of intravascular contrast medium to conduct computed tomography examinations. Some of these patients require multiple contrast-enhanced materials during the treatment schedule (53,54), thereby increases the risk of contrast-induced nephrotoxicity, predominantly in individuals with previous disturbed kidney function or diabetes (48). Some investigations have determined the presence of kidney insufficiency in individuals with solid tumors. Conversely, an increased incidence of cancer has been described in individuals with chronic kidney failure (55,56).

Therefore, chemotherapy regimen dose adjustments are indispensable for cancer individuals. Accordingly, evaluation of kidney function is crucial when there is a necessity to administration of intravascular contrast agents for computed tomography examinations of cancer individuals (48).

Overall, patients with cancer are at risk of acute kidney injury by sepsis, primary thrombotic microangiopathies, direct involvement of the kidney by hematological malignancies or tumor infiltration or propagation and various metabolic disturbances and also antineoplastic treatments (57). Acute kidney injury is a significant cause

of mortality and morbidity in patients with malignancy. Moreover, the presence of acute kidney injury may have an extremely negative influence on oncological regimen.

Conclusion

A life-threatening side effect of exposure to contrast media is post-contrast acute renal failure, which is detected as a deterioration of kidney function arising 48 to 72 hours after injection. The frequency of kidney failure amongst patients with cancer is high since a majority of them are on simultaneous nephrotoxic chemotherapeutic regimen. Similarly, most of cancer patients are old with poor appetite, nausea and vomiting which predispose them to dehydration and aggravation of acute kidney injury more. Therefore, it is not hard to identify why individuals with malignancy are at slightly higher risk of contrast nephropathy than the general population.

Authors' contribution

MAD and AM searched the data. MAD prepared the primary draft. AM edited the paper. MAD edited and finalized the paper. All authors read and signed the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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