Contrast safety in the cancer patient: preventing contrast-induced nephropathy

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Abstract
Cancer patients undergo frequent imaging examinations. Computed tomography (CT) examinations for tumor staging and assessment of treatment response generally require administration of intravascular contrast medium. Iodinated contrast agents for CT are associated with the risk of contrast-induced nephrotoxicity (CIN), particularly in patients with impaired renal function and diabetes. In many cancer patients the risk of complications from intravascular contrast medium administration is compounded by advanced age, dehydration and coadministration of nephrotoxic chemotherapeutic drugs. In this article I review the definition, clinical manifestations, possible mechanisms and risk factors for CIN, and provide recommendations for prevention of this potentially life-threatening complication.

Keywords: Contrast media; complications; kidney (effects of drugs on).

Introduction
An increased incidence of malignancy has been reported in patients with renal insufficiency\(^{1-3}\). Conversely, recent studies have demonstrated a very high prevalence of renal impairment in patients with solid tumors\(^4,5\). Consequently, chemotherapy drug dose adjustments are often necessary for many cancer patients. Likewise, assessment of renal function is very important when making decisions about the use of intravascular contrast agents for computed tomography (CT) examinations of cancer patients. This review focuses on the risk of contrast-induced nephrotoxicity (CIN) in the cancer population.

Contrast-induced nephropathy
Contrast-induced nephropathy is an acute deterioration of renal function after intravascular administration of contrast medium in the absence of another likely cause. It has been variably defined as an increase from baseline serum creatinine values of 25–50% or as an absolute increase of 0.5–1.0 mg/dL above precontrast values\(^6-8\). Most commonly CIN manifests as a non-oliguric and transient decline in renal function, with the serum creatinine level rising within 24 h, peaking in 3–5 days, and returning to baseline within 10–14 days\(^9\). Oliguric acute renal failure requiring dialysis is much less common\(^10\) but is associated with a significantly higher morbidity and mortality rate\(^11\). In a study of patients undergoing coronary angiographic intervention, the in-hospital mortality rates for patients without CIN, with CIN not requiring dialysis and with CIN requiring dialysis were 1.1%, 7.1% and 35.7% respectively\(^12\). The pathophysiologic mechanism of CIN is not fully understood but likely involves multiple factors including renal vasoconstriction which leads to renal medullary ischemia, and direct toxicity to the tubular epithelial cells\(^9,13\).

The risk factors for CIN are listed in Table 1\(^13,14,15\). Pre-existing renal insufficiency is the most important risk factor for CIN\(^16\). The poorer the renal function (i.e., the lower the glomerular filtration rate), the higher the risk of CIN\(^17\). The patients at highest risk of CIN, however, are those with both pre-existing renal insufficiency and
diabetes\textsuperscript{[18]}. It is not difficult to understand why cancer patients are at somewhat higher risk of CIN than the general population. The prevalence of renal insufficiency among cancer patients is high\textsuperscript{[4,5]}, and many of them are on concurrent nephrotoxic chemotherapeutic drugs (Table 2). In addition, a high percentage of cancer patients are elderly, and poor appetite, nausea and vomiting predispose them to dehydration.

Given that pre-existing renal insufficiency is the most important risk factor for CIN, it is important to note that the serum creatinine level has limitations as an accurate measure of renal function because it is influenced greatly by gender, muscle mass, nutritional status and age\textsuperscript{[14]}. Glomerular filtration rate (GFR) can be reduced by nearly 50% before an increase in serum creatinine occurs. Therefore, GFR is a more accurate measure of renal function. Although direct measurement of GFR is not practical, an estimated GFR (eGFR) can be obtained with formulas such as the Cockcroft–Gault formula or the Modification of Diet in Renal Disease (MDRD) formula, which take into account age, gender, weight and serum creatinine. Nephrologists recommend using the eGFR to identify individuals at risk for CIN\textsuperscript{[19]}.

The most recent classification system of chronic kidney disease\textsuperscript{[20]} is shown in Table 3. Patients with stage 3 disease have a moderately low GFR (30–59 mL/min per 1.73 m\textsuperscript{2}) and are considered to be at risk for CIN. Of note, however, nearly two-thirds of patients with an eGFR <60 mL/min per 1.73 m\textsuperscript{2} have a serum creatinine value within the normal range (\(\leq 1.4 \text{mg/dL}\))\textsuperscript{[21]}. Thus eGFR is a more sensitive method for identifying patients at risk for CIN.

| Table 1 | Risk factors for contrast-induced nephropathy |
|---------|---------------------------------------------|
| Pre-existing renal insufficiency |
| Diabetes mellitus |
| Dehydration |
| Advanced age (\(\geq 70\) years) |
| Hypertension |
| Multiple myeloma |
| Hyperuricemia |
| Concurrent nephrotoxic drugs |

| Table 2 | Potentially nephrotoxic anticancer drugs |
|---------|-----------------------------------------|
| Epirubicin |
| Gemcitabine |
| Carboplatin |
| Doxorubicin |
| Paclitaxel |
| Cisplatin |
| Oxaliplatin |
| Irinotecan |
| Trastuzumab |
| Zoledronate |
| Methotrexate |

Modified from Launay-Vacher et al\textsuperscript{[4]}.

The reported incidence of CIN has varied widely, ranging from 1% to 30%. This wide variation in incidence can be attributed to differences in the definition of CIN used, differing patient populations, variability of contrast doses, variations in timing of follow-up, and different routes of contrast medium administration (intra-arterial vs. intravenous)\textsuperscript{[18]}.

The route of administration is extremely important when assessing the risk of CIN. The rate of CIN is 2–4 times higher in patients who undergo intra-arterial contrast medium injection (e.g., cardiac catheterization) compared with those who receive intravenous injection (e.g., CT). The reasons for this difference are multiple. Patients undergoing cardiac catheterization are more likely to have diabetes and hypertension\textsuperscript{[14]}, and the volumes of contrast medium used for these procedures tend to be substantially higher than for CT examinations. In addition, the angiography procedure itself likely is an important factor, as studies have demonstrated high rates of cholesterol emboli in patients undergoing aortography\textsuperscript{[22,23]}.

Because of the differences in design of the published clinical trials, it is not possible to identify the true rate of CIN when contrast medium is administered intravenously as for CT. However, two recent multi-institutional studies of patients with chronic kidney disease have demonstrated CIN rates that are quite low, ranging from 1% to 4% depending on the definition of CIN used\textsuperscript{[24,25]}. Another multi-institutional trial demonstrated that even in patients with chronic renal disease and diabetes, the rate of CIN (based on an increase in serum creatinine of \(\geq 25\%\)) was only 5\%\textsuperscript{[26]}.

The osmolality of the contrast medium used has not proved to be strongly associated with the risk of CIN after intravenous administration\textsuperscript{[27–29]}. Of particular note is that in studies comparing an iso-osmolar dimer (iodixanol) and non-ionic monomers the rates of CIN have been comparable\textsuperscript{[24,26,30]}. Thus for intravenous contrast medium administration, iodixanol does
not appear to provide an advantage over low osmolar contrast agents in preventing CIN.

One final confounding variable that limits our understanding of CIN is that very few studies have included control subjects who did not receive intravascular contrast medium[31]. In one of the two published studies in which control subjects were included, an acute increase in serum creatinine was observed in 10% of patients with pre-existing renal insufficiency who received contrast medium and in 7% of patients with pre-existing renal insufficiency who did not[132]. Furthermore, a recent study has documented substantial acute variations in serum creatinine measurements among hospitalized patients[33]. In this study, patients with serum creatinine determinations on five consecutive days who had not received intravascular contrast medium during the prior 10 days were identified. Among patients with baseline creatinine levels of 0.6–1.2 mg/dL, increases of at least 25%, 33%, and 50% occurred in 27%, 19%, and 11% of patients, respectively. Among patients with baseline creatinine levels > 2.0 mg/dL, increases of at least 25%, 33%, and 50% occurred in 16%, 12%, and 7% of patients, respectively. Thus it is possible that in any group of ill patients, some will develop an acute decline in renal function as a coincident event or secondary to an adverse reaction to medication or some other nephrotoxic insult[8]. It is also possible that there are random daily variations in serum creatinine levels or in our measurement techniques.

Many prophylactic regimens to prevent or ameliorate the development of CIN in at risk patients have been tested, with variable results. The one intervention that has been shown to be helpful in preventing CIN is saline hydration, but no one regimen has demonstrated clear superiority[131]. Hydration regimens that have been shown to be useful include: (1) intravenous hypotonic (0.45%) saline administered at 1 mL/kg per h starting 12 h before and continuing for 12 h after contrast medium administration; (2) intravenous isotonic (0.9%) saline (1 mL/kg per h starting 4 h before and continuing for 12 h after contrast medium administration); or (3) oral hydration (1000 mL over 10 h) followed by intravenous hypotonic saline for 6 h[341]. Intravenous hydration with sodium bicarbonate may be more effective than with 0.9% saline, but the data are limited[135]. Other pharmacologic interventions such as forced diuresis with mannitol or furosemide in conjunction with intravenous saline hydration do not appear to work[36–38]. Studies on the oral or intravascular administration of the antioxidant N-acetylcysteine to prevent CIN have had variable results, particularly when used in conjunction with intravenous contrast medium administration.

When a cancer patient who is at risk for CIN requires an imaging study, the first determination that should be made is whether the desired clinical information can be obtained with a test that does not require the use of intravascular contrast medium. If contrast medium administration is required, a low osmolar or iso-osmolar contrast agent should be used in conjunction with an intravenous saline hydration regimen. The lowest dose of contrast medium that will provide the necessary imaging information should be used. Administration of nephrotoxic drugs should be stopped for at least 24 h prior to the imaging examination. N-Acetylcysteine can be administered prior to the examination if desired, but the data regarding its usefulness in preventing CIN are conflicting, especially for patients undergoing intravenous contrast medium administration.

**Conclusion**

Iodinated contrast agents are associated with the risk of CIN, primarily when administered to patients with impaired kidney function and diabetes. The risk of CIN in cancer patients may be compounded by advanced age, dehydration and coadministration of nephrotoxic chemotherapeutic drugs. Thus identification of patients who are at risk for CIN is important in order to avoid potentially serious complications related to acute deterioration of kidney function. Estimated GFR is a more accurate determinant of kidney function than serum creatinine level and can better identify patients who are at risk for CIN. Potential options for patients at risk for CIN include consideration of an alternative test that does not require intravascular contrast medium administration, hydration prior to and after the imaging procedure, and reduction of the contrast medium dose if feasible. Administration of nephrotoxic drugs should be stopped for at least 24 h prior to the imaging examination. It is important to keep in mind, however, that administration of intravascular iodinated contrast medium is not contraindicated in patients who are at risk for CIN (eGFR <60 mL/min per 1.73 m²), especially if the route of administration is intravenous (as for CT). Intravenous contrast medium administration is associated with a substantially lower risk of CIN than intra-arterial administration. Patients at risk for CIN should not be denied a contrast-enhanced CT examination if the benefit of the clinical information derived from the examination is considered to outweigh the risk of CIN. Nevertheless, screening of patients who are likely to be at risk for CIN and institution of precautionary measures when warranted are important components of optimal oncologic imaging practice.

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