The Challenges of Treating Cancer Patients on Hemodialysis, or With Chronic Kidney Disease

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It is challenging to diagnose, manage, and treat patients who have kidney disease in addition to cancer. Second to cardiovascular disease, cancer represents a major cause of mortality and morbidity in the kidney disease population.

Epidemiologic studies have consistently shown an increase in the incidence of malignancy in dialysis patients with end-stage renal disease (ESRD). In a recent review of data from the United States Renal Data System, the 5-year cumulative incidence of any cancer among Medicare patients receiving hemodialysis was 9.48%. The risk of malignancy in this hemodialysis population, particularly for kidney and bladder cancers, was higher than that of the general population.[2] While there appears to be a similar tendency in patients with CKD who do not require dialysis, these findings vary across studies.[3]

Should We Screen Renal Patients More Aggressively for Malignant Disease?

Most cancer surveillance and treatment trials exclude the CKD population, and it is unclear whether changes in standard screening practices and early diagnosis would reduce mortality in these patients. Therefore, in the absence of specific guidelines, patients with CKD should be screened for malignancies according to guidelines applicable to the general population. However, in the ESRD population, the benefits and cost-effectiveness of age-appropriate cancer screening are limited, since these patients have reduced life expectancy due in part to dialysis-associated comorbid illness. It appears to be preferable to tailor screening protocols based on the individual patient’s risk factors and expected survival on dialysis.[4] An exception is patients being considered for renal transplantation; these patients should undergo routine cancer screening as part of their initial transplant evaluation, and as long as they are active waiting-list candidates for transplant.[5]

The Impact of Kidney Disease on Imaging and Laboratory Testing

Kidney disease has an impact on many of the imaging techniques and laboratory examinations used for the screening, diagnosis, or staging of cancer. For instance, the increase in vascular calcifications common in CKD may limit the interpretability of mammograms in women with ESRD.[6] When reading a positron emission tomography/computed tomography (CT) scan, one should keep in mind that hemodialysis patients show significantly higher physiologic $^{18}$F fluorodeoxyglucose uptake in the soft tissues, spleen, and blood pool.[7] Furthermore, certain tumor markers are cleared or metabolized by the kidney, and become unreliable in the setting of kidney disease. As a result, carcinoembryonic antigen levels are falsely elevated in ESRD patients. The usefulness of cancer-associated carbohydrate antigens (CA 19-9, CA 50, CA 125, CA 15.3) as biomarkers has also been questioned. CA 125 may increase in the setting of peritonitis in patients using peritoneal dialysis modalities. Increased levels of serum alpha-fetoprotein and total prostate-specific antigen (PSA) remain highly specific in ESRD patients. As free PSA accumulates due to the decreased glomerular filtration rate (GFR) inherent in kidney disease, it becomes a less reliable marker.[8]

Avoiding Contrast-Induced Nephropathy (CIN)
Because of the risk of CIN, the use of contrast agents for enhancement of CT and MRI studies may be limited in cancer patients with kidney disease or poor kidney function. CIN is associated with the iodinated agents used for CT scanning. The risk of CIN increases with age, the presence of diabetes, reduction of the GFR, and the hypovolemic or prerenal states that are common in many cancer patients. Accordingly, volume repletion is essential for preventing CIN. Generally, an infusion of isotonic sodium chloride is recommended at a rate of 1 mL/kg per hour for 12 hours before and 12 hours after radiocontrast administration in high-risk patients.[9] It is also preferable to measure creatinine levels not only at baseline but also 48 to 96 hours after the infusion procedure. There is no evidence that dialysis can prevent CIN. Gadolinium-based contrast media used for MRI hold minimal risk of kidney injury, but are not recommended for use in patients with an estimated GFR < 30 mL/min/1.73 m² due to an association with nephrogenic systemic fibrosis in some cases. If there are no alternatives to gadolinium, then use under nephrology and radiology supervision using lower-dose macrocyclic compounds is recommended. Hemodialysis should be considered for patients with an estimated GFR < 30 mL/min/1.73 m² who are exposed to gadolinium either intentionally or inadvertently.[10]

**The Impact of Kidney Disease on Cancer Treatment Efficacy and Toxicity**

The efficacy of antineoplastic drugs is closely tied to the administered dosage and therapeutic blood and tissue levels of the agent(s). To maintain the balance between treatment efficacy and side effects, clinicians need to adjust the dose of renally cleared anticancer drugs using a surrogate of renal function, the estimated GFR. The Chronic Kidney Disease Epidemiology Collaboration equation has been shown to be the best-performing tool for estimating the GFR, since it has been shown to provide more accurate GFR estimates in individuals with normal or only mildly reduced GFR, compared with other formulas.[11] While the Chronic Kidney Disease Epidemiology Collaboration, the 4-variable Modification of Diet in Renal Disease, and the Cockcroft-Gault formulas may differ slightly in their estimation of GFR, they appear to be concordant for the purpose of dosing renally excreted cancer drugs.[12] Consistent use of the same estimating formula to track renal function is preferable for following the progression of a patient’s renal function throughout the course of treatment. Notably, estimations of GFR, including the cumbersome 24-hour urine collection for assessment of creatinine clearance, are only valid when a patient is in a steady state. They should not be used for dose adjustments in patients with AKI.

It should also be borne in mind that other factors can influence the therapeutic index of cancer drugs. Hypoalbuminemia, which is common in ESRD, CKD, and patients with nephrotic syndrome, may worsen the toxicity of protein-bound drugs by increasing their free circulating fraction. Severe volume overload may alter the volume of distribution, and certain drugs, like methotrexate, can accumulate in effusions and other extravascular fluid compartments. Finally, CKD has also been shown to suppress various liver metabolic enzymes (CPT2C9, CYP2C19, and CYP3A4), thereby affecting the pharmacokinetics and pharmacodynamics of non–renally excreted drugs.[13] Given these factors, careful monitoring and pre-emptive measures to avoid side effects are essential when adjusting doses of antineoplastic drugs for patients with renal impairment.

AKI and electrolyte derangements are part of the side-effect profile of cytotoxic agents like cisplatin and methotrexate. With the introduction of more targeted therapies into clinical practice, directly or indirectly related nephrotoxicities are emerging. It has become increasingly challenging for clinicians to parse out these effects; in the Table, we report the more common nephrotoxicities encountered. AKI can accelerate the progression of CKD and is a risk factor for increased mortality among cancer patients, especially those who are critically ill.[14,15]

**Cancer as a Contributor to Renal Injury**

Malignancy itself can be a major cause of renal injury. This may occur as a direct consequence of the cancer—for example, in cases of malignant invasion of the kidney or urinary tract obstruction. Or it may occur indirectly, as in patients with thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, hypercalcemia, or tumor lysis syndrome. Most frequently, though, AKI is part of the multi-organ failure syndrome seen in septic shock, or it occurs secondary to other common AKI risk factors, like the use of contrast agents and antibiotics.

In a large Danish cohort, renal cell carcinoma, multiple myeloma, and liver cancer were associated with 1-year AKI risks of 44.0%, 33.0%, and 31.8%, respectively.[16] Multiple myeloma can lead to kidney injury via multiple mechanisms, including cast nephropathy, light-chain deposition disease, and light-chain amyloidosi. Hypercalcemia, which is frequently associated with multiple myeloma,
as well as other malignancies, can lead to a decreased GFR, mediated by direct renal vasoconstriction and natriuresis-induced volume contraction. Patients with acute leukemia and non-Hodgkin lymphoma are susceptible to AKI from tumor lysis syndrome, which can occur either spontaneously or upon initiation of therapy; the release of urate and calcium phosphate crystals results in tubular obstruction. Calcium phosphate can also deposit directly into the renal interstitium. The severity of tumor lysis syndrome has been significantly reduced with prophylactic hydration and the use of rasburicase.

**KEY POINTS**

- Cancer screening and diagnostic strategies may need to be tailored in patients with kidney disease.
- Various mechanisms related to the cancer, the therapeutics, or the clinical state of the patient may cause nephrotoxicity.
- Treating cancer patients who are undergoing hemodialysis, or who have chronic kidney disease, is a multidisciplinary effort by oncologists and nephrologists.

One study has shown that, when critically ill, between 13% and 42% of cancer patients develop AKI, and approximately 8% to 60% receive renal replacement therapy, depending on the underlying malignancy and the definition of AKI used.[14] Among patients receiving renal replacement therapy in the intensive care unit, overall mortality is higher in those with an underlying hematologic malignancy. This difference appears to be accounted for by the severity of illness and the duration of hospitalization before admission to the intensive care unit, rather than by the malignancy itself.[17] The long-term renal outcomes of cancer patients after an AKI episode have not been frequently studied. In one analysis, 82% had complete recovery of their renal function, 12% had partial recovery, and 6% needed chronic dialysis.[18] If clinically warranted, antineoplastic drugs can be continued for patients receiving renal replacement therapies on an acute or chronic basis. When the treatment drug is known to be dialyzable, it should be administered after dialysis to maintain its efficacy.[19]

**Considerations for the Use of Erythropoiesis-Stimulating Agents (ESAs)**

Nephrologists frequently use ESAs to maintain their CKD patients’ hemoglobin levels (at 10 g/dL to 11.5 g/dL), based on multiple studies and guideline recommendations.[20-22] The evidence for use of ESAs in this setting is not clear-cut; however, juxtaposition of the clinical trials of ESAs in dialysis and in cancer suggests that erythropoietin may worsen the outcome of the malignancy and increase the risk of thrombosis.[23] This is an added challenge to the management of patients with CKD and ESRD who have underlying malignant disease, and recommendations from guideline agencies are vague in this regard.[24,25] Discussion of ESA use with the treating oncologist is necessary when making treatment decisions for patients with CKD/ESRD and malignant disease. The approach may be different in patients with hematologic malignancies compared with those who have solid tumors, especially if the goal of treatment is cure.[23] In the case of severe anemia and with a transfusion requirement, low doses of ESAs, targeting a hemoglobin level less than 10 g/dL, may be reasonable to avoid allosensitization through transfusion.

**Management of Patients With Cancer and Kidney Dysfunction Requires a Multidisciplinary Approach**

Treating cancer patients who are undergoing hemodialysis, or who have CKD, is a multidisciplinary effort. Oncologists and nephrologists need to coordinate with each other and with various healthcare team members to manage the complexities of the patient’s medical problems. While population studies show that outcomes in this setting have improved over the years, dealing with the morbidities of two chronic diseases, such as cancer and renal disease, complicates patient management and can have a negative impact on these patients. When deciding whether to initiate or continue hemodialysis in patients with cancer, it is important to consider the status of the underlying malignancy, the patient’s age, his or her performance status, and the presence of other comorbidities or organ failures. Clinicians should periodically reassess the individual patient’s goals of care, and work with the patient to create a treatment plan based on consensus and shared decision making.

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References:


12. Dooley MJ, Poole SG, Rischin D. Dosing of cytotoxic chemotherapy: impact of renal function...


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