Assessment of Kidney Function in Patients With Cancer

Verônica Torres da Costa e Silva, Elerson C. Costalonga, Fernanda O. Coelho, Renato A. Caires, and Emmanuel A. Burdmann

Cancer patients are living longer. The sequelae of cancer treatment and the role of comorbid conditions present before the diagnosis, such as CKD, have been increasingly recognized. The interface between CKD and cancer is multifaceted. CKD is frequently observed in patients with cancer, and cancer treatment contributes to CKD development and progression. In addition, CKD has been recognized as an important risk factor for cancer development and reduced specific cancer survival. In this context, an accurate evaluation of the glomerular filtration rate (GFR) during oncologic treatment is pivotal and is used to define surgery strategies, program prophylactic management of contrasted examinations, make decisions on cisplatin eligibility, and adjust drug prescriptions, particularly chemotherapy agents. Although the most commonly used equations to estimate GFR based on serum creatinine levels in clinical practice (Cockcroft-Gault, Modification of Diet in Renal Disease Study, and CKD Epidemiology Collaboration equations) have not been validated in patients with cancer in large prospective studies, there is increasingly evidence supporting the use of CKD Epidemiology Collaboration equation to assess the GFR in patients with cancer, including for the use of chemotherapy prescriptions. Many patients with cancer may have changes in nutrition status and clearance measurements such as exogenous filtration markers might be extremely useful when clinical decisions differ depending on the GFR level. Future perspectives include the advent of new serum GFR biomarkers such as cystatin C, beta-trace protein, and beta-2 microglobulin as well as the GFR assessment by measuring total kidney parenchymal volume through image examinations.

Key words: CKD, Cancer, Glomerular filtration rate, Chemotherapy dose, Biomarkers

INTRODUCTION

The number of new cases of cancer is growing worldwide and is expected to increase to 15.5 million in 2030 from 14.1 million in 2012.[1,2] Conversely, the global 5-year relative cancer survival has increased from 50% in 1975 to approximately 70% in 2008.[3] Herein, the number of patients with cancer undergoing treatment has increased in several countries. In the United States, the projected number of cancer survivors will be 18.1 million in 2020 with associated costs of cancer care of 157 billion yearly.[4] In this scenario, some features of anticancer treatment are becoming increasingly relevant such as kidney disease, a scenario that stimulated the development of a new and quickly expanding subspecialty, Onconephrology, devoted to the care of kidney diseases in patients with cancer (Tables 1 and 2).[5-12]

There are several interfaces between cancer and CKD, leading to important therapeutic and prognostic implications for affected patients. This article will review data on the burden (prevalence and progression) of CKD in patients with cancer and the increased risk of cancer and augmented mortality in patients with CKD. We will assess the crucial role of estimating the glomerular filtration rate (GFR) and its clinical implications for cancer care, with particular emphasis on chemotherapy prescriptions. In addition, data on the use of new serum GFR biomarkers and emerging information on image techniques will be addressed. We will focus discussion on solid tumors affecting adult individuals. Patients with hematologic malignancies are usually more frail, present a more precarious nutrition status, and may demonstrate a diverse biological behavior, and have been usually studied as a separate group. There are special considerations of the GFR assessment in pediatric patients with cancer that are also beyond the scope of this article.

THE INTERFACE BETWEEN CKD AND CANCER

CKD Prevalence and Progression in Patients With Cancer

Patients with cancer tend to be older than the general population and tend to exhibit a higher prevalence of comorbidities (diabetes, hypertension, heart failure, and liver disease). On the basis of these factors, it is believed that the prevalence of CKD is high among cancer patients. Launay-Vacher and colleagues performed a retrospective assessment of 4684 patients with solid tumors from 15 centers in France (Insuffisance Rénale et Médicaments Anticancereuxstudies) and found that the prevalence of CKD Stage 3 or higher,[13] on the basis of the Modification of Diet in Renal Disease (MDRD) Study equation[14] was 12% in the overall population and increased to 23% among patients older than 75 years.[15]

CKD prevalence is higher in certain cancer subtypes. A retrospective survey assessing 4299 patients before nephrectomy for kidney cancer, using the CKD Epidemiology Collaboration (CKD-EPI) equation[16] reported that 28.7% of them had CKD.[17] Eisenberg and colleagues[18]

From the Nephrology Division, Sao Paulo State Cancer Institute, University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil and LIM 12, Division of Nephrology, University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil.

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Address correspondence to Verônica Torres da Costa e Silva, Instituto do Câncer do Estado de São Paulo, Av. Dr. Arnaldo, 251, 2° Andar, Hemodiálise, São Paulo, CEP 01246-903, SP, Brazil. E-mail: veronica.silva@hc.fm.up.br

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retrospectively studied 1631 patients with bladder cancer, demonstrating that CKD was observed in 46% of them before surgery.

There is also evidence that patients with cancer exhibit a significant loss of kidney function during anticancer treatment. Launay-Vacher and associates[19] retrospectively assessed kidney function in 4945 patients with solid tumors and found a reduction in the estimated GFR (eGFR) from 91 to 84 mL/min/1.73 m^2 after 2 years, and 17.7% of patients changed from CKD Stage 2 to 3 or 4 at the end of the follow-up. Christiansen and associates prospectively followed 37,267 patients with cancer and found that the risk of acute kidney injury (50% increase in the baseline estimated GFR) was 17.5% in the first year after cancer diagnosis and 27% over 5 years.[20] Considering that cancer treatment frequently extends through months or even years, repeated acute kidney injury episodes are likely to contribute significantly to the development and progression of CKD in patients with cancer.

CLINICAL SUMMARY

- There are several interfaces between cancer and CKD: CKD is frequent in patients with cancer and oncology treatment contributes to the loss of kidney function over time; CKD is related to increased cancer incidence and mortality.
- Evaluation of the glomerular filtration rate (GFR) is pivotal for cancer care and has been used to guide surgical decisions, management of contrasted examinations, drug prescriptions, and particularly adjustment of chemotherapy agents.
- The most commonly studied equations based on serum creatinine levels to estimate the GFR are Cockcroft-Gault, Modification of Diet in Renal Disease Study, and CKD Epidemiology Collaboration equations. Cockcroft-Gault equation is less accurate, especially in the obese, elderly, and with creatinine assays traceable to reference materials. Although not validated in large prospective studies, there is emerging evidence to endorse the use of CKD Epidemiology Collaboration equation to assess the GFR in patients with cancer.
- Measured GFR using exogenous markers can be useful in circumstances where GFR estimates are not thought to be valid and where accurate levels of the GFR will effect treatment decisions.

Cancer Risk in Patients With CKD

Increased risk of cancer is a well-established phenomenon in individuals after transplantation and on regular dialysis, according to large prospective population-based surveys published in the last 20 years.[21-26] In the most recent large survey, Butler and colleagues[27] retrospectively assessed the cancer incidence rate in 482,510 adult patients with hemodialysis from the US Medicare's End Stage Renal Disease (ESRD) program between 1996 and 2009. The 5-year cumulative incidence of any cancer accounting for death as a competing risk was 9.48 (95% confidence interval [CI] 9.39%-9.57%) and a total of 35,767 cancer cases were detected compared with 25,194 observed rates in the US general population at the same period (standardized incidence ratio [SIR], 1.42; 95% CI, 1.41-1.43 for all cancer sites). Risk was higher for cancer of the kidney (kidney cell and urothelial cell of the renal pelvis) (SIR, 4.03; 95% CI, 3.88-4.19) and bladder (SIR, 1.57; 95% CI, 1.51-1.64).

A similar increased risk of cancer was reported in individuals with CKD not on dialysis. Wong and colleagues[28] prospectively assessed 3654 older adults in Australia for more than a 10-year period and found an increased risk of urinary tract and lung cancer among males with CKD beginning at the threshold of eGFR (calculated by the MDRD Study equation) <55 mL/min/1.73 m^2 (hazard ratio [HR], 1.29; 95% CI, 1.10-1.53, for every 10 mL/min/1.73 m^2 decrease in eGFR, adjusted for age, blood pressure, smoking, and sun-related skin damage). The greatest risk was observed at eGFR <40 mL/min/1.73 m^2 (HR, 3.01; 95% CI, 1.72-5.27). In another survey, Lowrance and colleagues[29] retrospectively assessed 1,190,538 adult patients from Northern California between 2000 and 2008. They reported an increased risk of kidney cancer after adjustment for time-updated confounders (age, sex, race, comorbidities, smoking, and socioeconomic status among others), ranging from a 39% increased rate for eGFR (calculated by the CKD-EPI equation) of 45-59 mL/min/1.73 m^2 to a more than 2-fold increased rate for eGFR <30 mL/min/1.73 m^2, compared with patients with eGFR of 60-89 mL/min/1.73 m^2.

The increased risk of kidney and bladder cancer in patients with CKD could be partly explained because these patients are more likely to undergo imaging of the urinary tract as part of routine clinical practice. Nevertheless, nephrologists should be aware of this risk, particularly in patients who are at high risk for these forms of cancers such as those with significant smoking or family history.

Prognosis of Patients with Both Cancer and CKD

There is an increasing amount of evidence indicating that CKD may worsen the prognosis of cancer patients. Na and colleagues[30] retrospectively assessed 8233 patients with cancer in South Korea and demonstrated that tumor-related mortality was higher after 5 years of follow-up for all but lung and breast cancer sites in patients with CKD after adjustment for age, gender, diabetes, hypertension, proteinuria, and serum hemoglobin and albumin. A prospective cohort including 123,717 general patients recruited from screening centers in Taiwan was followed for 7 years. This study demonstrated that CKD was associated with increased mortality from liver (HR, 1.74; 95% CI, 1.24-2.44), kidney (HR, 3.30; 95% CI, 1.24-8.81), and urinary tract cancer (HR, 7.30; 95% CI, 2.48-21.46).[31] In a recent study conducted in Australia, 4077 older individuals (mean age, 71 years) were prospectively followed over an average of 12.8 (8.6-15.8) years. It was observed, an 18% increase in cancer-specific mortality for every 10 mL/min/1.73 m^2 reduction in eGFR, calculated using the CKD-EPI equation, following adjustment for confounding variables (age, gender, smoking status, blood pressure, fibrinogen, and fasting blood glucose levels) ($P < .0001$). Compared with patients with eGFR ≥60 mL/