

# Onconeurology: An Evolving Field

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## INTRODUCTION

Cancer therapeutics have evolved over the last two decades, from traditional chemotherapies to novel therapies that target genetic mutations and immunotherapies that harness the body's own immune system to fight cancer cells. Together, these treatments have led to improved survival in cancer patients, yet all are also associated with renal toxicity. Because kidney function is a major determinant of a patient's eligibility for newer drugs and clinical trials, it is important to consider how the presence of chronic kidney disease, acute kidney injury, and other kidney disorders may affect treatment options, and how certain treatments may increase the risk of kidney toxicity.

## ACUTE KIDNEY INJURY

Acute kidney injury (AKI) in the setting of cancer is mostly related to pre-, direct, or post-renal toxicity. A study of 1.2 million people in Denmark followed from 1999 to 2006, with 37,267 patients developing incident cancer, determined that the 1-year risk of AKI was 17.5% as defined by the RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification.<sup>1</sup> The 5-year risk for the Risk, Injury, and Failure RIFLE categories was even higher at 27%, 14.6%, and 7.6%, respectively. In these patients, AKI incidence was highest in those with renal cell cancer, liver cancer, multiple myeloma, and leukemia. Among 9,613 cancer patients at any AKI stage, 5.1% required renal replacement therapy within 1 year of AKI onset.

### *Prerenal AKI*

It is estimated that 30% of cancer patients admitted with AKI have prerenal AKI, in which sudden renal hypoperfusion results in reduced kidney function. Prerenal AKI is associated with chemotherapy-induced nausea, vomiting, and diarrhea. There are also prerenal states related to tumor burden, leading to a hepatorenal-like physiology.

### *Intrinsic Renal Injury*

Several chemotherapeutic agents, as well as antibiotics and other medications, can lead to a toxic tubular injury known as acute tubular necrosis, the most common cause of intrinsic renal injury. Severe immunosuppression ensues after chemotherapy, leading to sepsis and, therefore, acute tubular necrosis.<sup>2,3</sup> Another common intrinsic-associated injury is acute interstitial nephritis, which is related to drug use such as antibiotics. However, with exposure to new immunotherapies and targeted therapies, the number of patients with acute interstitial nephritis is increasing.<sup>4-6</sup>

### *Postrenal AKI*

Urinary tract obstruction, the most common cause of postrenal AKI, is typically associated with rectal, bladder, prostate, or gynecologic tumors. In the setting of bladder cancer, for example, obstruction intrinsic to the kidney, such as transitional cell carcinoma, blood clots, deposition of crystals (uric acid, acyclovir, and methotrexate), or tubular casts (multiple myeloma) can block urine flow.

## PROGRESSION TO CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) and cancer have a bidirectional relationship: cancer and/or its treatments can lead to CKD, and CKD is a risk factor for cancer. Chronic kidney disease can affect the bioavailability of the cancer treatment, leading to underdosing and, in turn, less desirable cancer outcomes.<sup>7</sup> As mentioned earlier, acute tubular necrosis from direct toxicity, thrombotic microangiopathy, and glomerulonephropathies can lead to glomerulosclerosis and tubulointerstitial fibrosis, thereby causing further renal injury.

Chronic kidney disease is more evident in patients with renal cell cancer. A study by Cho et al. demonstrated that 22% of patients with renal cell cancer had CKD stage 3 or higher

before they received nephrectomy surgery. This percentage increased to 40% for patients older than 70 years.<sup>8</sup> Cancer-associated CKD is also found in patients who undergo allogeneic or autologous hematopoietic stem cell transplantation (HSCT). Although HSCT improves survival in a significant number of patients, it is associated with an increased risk of secondary cancers, infections, and organ dysfunction.<sup>9</sup> A retrospective review of 2,477 allogeneic HSCT recipients at MD Anderson Cancer Center showed that roughly 943 of them (38.1%) had a 25% decrease in glomerular filtration rate from baseline (median 101 days), and 61% of those 943 had an estimated glomerular filtration rate < 60 mL/min/1.73 m<sup>2</sup>.<sup>10</sup> The impact of renal impairment in the allogeneic HSCT population negatively compounds their survival, and a BK virus infection was an independent predictor of both CKD and overall poor survival.<sup>10</sup>

Chronic kidney disease is strongly associated with poor outcomes in myeloma and occurs in about 50% of myeloma patients, 20% of whom have serum creatinine > 2 mg/dL and 9% of whom require hemodialysis. In a group of 756 patients, median survival in those with CKD was 19.5 months compared to 40.4 months for those without CKD.<sup>11</sup>

## METABOLIC COMPLICATIONS

### *Tumor Lysis Syndrome*

One of the more pronounced oncological emergencies is tumor lysis syndrome (TLS). It is usually associated with aggressive to highly aggressive lymphomas (particularly the Burkitt subtype), T-cell acute lymphoblastic leukemia, and tumors with a high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy. Tumor lysis syndrome can lead to hyperuricemia, hyperkalemia, hyperphosphatemia, and acidosis; in turn, the resulting buildup of urate crystals in the tubules can lead to AKI. Patients with clinical TLS have an increased risk of mortality, morbidity, associated complications, and associated costs.<sup>12</sup> Preventing TLS in high-risk patients involves hydration to maintain a high urine output (> 100 mL/hr) and the use of allopurinol or rasburicase to reduce hyperuricemia. Rasburicase, which degrades uric acid to water-soluble allantoin, lowers uric acid levels more effectively than allopurinol.<sup>13</sup> Patients with a high tumor burden and renal dysfunction have a low threshold for early dialysis due to their limited ability to handle the excessive electrolyte load, which precipitates further renal injury.

### *Common Electrolyte Disorders*

Hyponatremia is the most common electrolyte abnormality, affecting nearly 50% of hospitalized cancer patients.<sup>14</sup> Hyponatremia is frequently caused by the syndrome of

inappropriate antidiuretic hormone (SIADH), which was originally described in small cell lung cancer but may occur with non-small cell lung cancer, head and neck cancers, and a number of hematological cancers.<sup>15</sup> Nausea, pain, analgesics such as morphine and its derivatives, antidepressants, and several chemotherapeutic agents may also cause hyponatremia by increasing arginine vasopressin secretion. Oral sodium chloride and loop diuretics are modestly effective, whereas V2-receptor antagonists effectively correct hyponatremia.<sup>16</sup>

Hypernatremia is much less frequent in hospitalized cancer patients compared to hyponatremia (3% vs 47%), but it is associated with higher mortality and longer hospital stays.<sup>17</sup> Most cases of hypernatremia occur in the hospital and are observed primarily in critically ill patients with leukemia and HSCT who are receiving loop diuretics.

Other electrolyte abnormalities associated with cancer treatments include hypokalemia, hypomagnesemia, and hypophosphatemia. Nausea/vomiting, diarrhea, and poor nutrition from chemotherapy account for many of these abnormalities. Ifosfamide and cisplatin are among the more common drugs that induce tubular injury and can cause Fanconi syndrome, leading to malabsorption of electrolytes. Cetuximab is an epidermal growth factor receptor antibody that inhibits normal reabsorption of luminal magnesium and causes renal wasting.

Hypercalcemia is common in patients who have advanced cancer with bone metastasis and is a poor prognostic indicator. Multiple myeloma is one of the more common cancer diagnoses

## KEY POINTS

- Acute kidney injury (AKI) and chronic kidney disease (CKD) are common conditions in cancer patients and are associated with higher cost, longer length of hospital stay, limited cancer treatment, and increased morbidity and mortality.
- The kidneys are a major excretion pathway for many antineoplastic agents and thus require dose adjustment when administered in the setting of AKI or CKD.
- Several conventional chemotherapeutics and novel immunotherapies can lead to electrolyte disorders, tubular injury, glomerular lesions, tubulointerstitial nephritis, and the development of thrombotic microangiopathy.
- Cancer- or treatment-related electrolyte disturbances in cancer patients are a continual challenge with an overall impact on survival.

associated with hypercalcemia. Hypercalcemia can result from local osteolytic bone resorption, humoral hypercalcemia of malignancy (high calcium levels due to increased parathyroid-related peptide excretion by the tumor), or increased production of 1,25-dihydroxyvitamin D (calcitriol). Intravenous saline is the mainstay treatment for hypercalcemia, although corticosteroids and calcitonin have been added for more effective reduction. Bisphosphonate therapy for long-term control is often used but may be less effective in patients with renal insufficiency since zoledronate and pamidronate have been associated with collapsing focal segmental glomerulosclerosis.<sup>18</sup>

Interestingly, a recent meta-analysis by Manohar et al. of 11,482 patients treated with programmed cell death protein 1 (PD-1) inhibitors found that PD-1 treatment confers a higher risk of AKI, hypocalcemia, and electrolyte abnormalities such as hyponatremia, hypokalemia, and hypophosphatemia.<sup>19</sup>

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