

Electrolyte Disturbances and Acute Kidney Injury in Patients With Cancer

Norbert Lameire, MD, PhD, Wim Van Biesen, MD, PhD, and Raymond Vanholder, MD, PhD

Summary: The interrelation between kidney disease and cancer is complex and reciprocal. Among the most frequent cancer-associated kidney diseases are the electrolyte and acid-base disturbances, which occur frequently and often are associated with an ominous prognosis, and acute kidney injury. Tumor lysis syndrome is a potentially life-threatening condition that frequently occurs in patients with a high tumor burden and high cellular turnover after cytotoxic therapy (including steroids in steroid-sensitive hematologic malignancies). Electrolyte and acid-base disturbances are the consequence of neoplastic spread, anticancer treatment, or, more rarely, paraneoplastic phenomena of all types of tumors. This article reviews hyponatremia and hypernatremia, hypokalemia and hyperkalemia, hypomagnesemia, hypercalcemia and hypocalcemia, hypophosphatemia, and the most important disturbances in acid-base balance in cancer patients. Acute kidney injury (AKI) is a frequent occurrence in cancer patients and has the potential to substantially alter the outcome of patients with cancer and jeopardize their chances of receiving optimal cancer treatment and a potential cure. As in many other circumstances, the etiology of AKI in cancer patients is multifactorial. Initiation and/or continuation of dialysis in the AKI cancer patient should be based on the general clinical condition and overall life expectancy and the personal patient expectations on quality of life after eventual recovery.

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In most industrialized countries, more than 40% of all incident cancer patients are older than age 70, and accordingly may suffer from other comorbid diseases, mostly cardiovascular disease, hypertension, and/or diabetes. Besides affecting their life expectancy, these comorbid conditions may complicate their clinical management.¹

The interrelation between kidney disease and cancer is complex and reciprocal. Because cancers may affect glomerular and tubular functions, kidney diseases sometimes may become central to their clinical presentation but their presence also may preclude aggressive cancer

therapy. Alternatively, therapies for cancer might induce direct or indirect nephrotoxicity.

The differential diagnosis of acute kidney injury (AKI) remains the same as in the noncancer population (ie, severe glomerular disorders, and acute vasculitis and interstitial nephritis syndromes). By far the most frequent causes of AKI are acute prerenal azotemia and acute ischemic and/or toxic tubular necrosis. The underlying mechanisms/causes of these diseases are often cancer-specific or cancer-related.

Electrolyte and acid-base disturbances occur frequently in cancer patients and often are associated with an ominous prognosis.

This article focuses on the most frequent acid-base and electrolyte disturbances in the cancer patient and on specific cancer-related mechanisms of AKI. Nephrotoxicity induced by the many chemotherapeutic agents to which cancer patients can be exposed is discussed in

Renal Division, University Hospital, Gent, Belgium.

Address reprint requests to Norbert Lameire, Renal Division, University Hospital, 185, De Pintelaan, 9000 Gent, Belgium. E-mail: norbert.lameire@ugent.be

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the article by Perazella and Moeckel (p. 570) in this issue of *Seminars in Nephrology*.

ELECTROLYTE AND ACID-BASE ABNORMALITIES IN CANCER PATIENTS

Electrolyte and acid-base disturbances are prevalent in cancer patients, can be life-threatening, and are the consequence of neoplastic spread, anticancer treatment, or, more rarely, paraneoplastic phenomena of all types of tumors. Correct diagnosis is key because it has direct impact on treatment decisions.

Hyponatremia

Serum sodium concentration (SNa) is the main determinant of plasma osmolality and usually reflects hypo-osmolality, resulting in a water shift from the extracellular to the intracellular fluid compartment. The overhydration of brain cells is primarily responsible for the neurologic symptoms associated with hyponatremia. In myeloma patients, pseudohyponatremia can occur when the load of circulating monoclonal proteins is very high. SNa is represented by the ratio of the sum of exchangeable sodium and exchangeable potassium to the total body water. Any modification of any of these parameters will affect SNa.² Hyponatremia thus can be caused by a relative surplus of body water, or a relative lack of body sodium.

The work-up of hyponatremia in a cancer patient is similar to that in patients without malignancy, and has been detailed in one of the recent issues of *Seminars in Nephrology*.³ The greatest diagnostic challenge in clinical practice is to discern hypovolemic patients with sodium depletion from euvolemic patients with inappropriate secretion of antidiuretic hormone (SIADH).

Epidemiology of hyponatremia

The general epidemiology of hyponatremia was recently reviewed,⁴ but there are scant data on the frequency of hyponatremia in cancer patients. A prospective study in medical cancer patients found a 3.7% incidence of hyponatremia.⁵ Sodium depletion and SIADH each accounted for almost one third of cases. The percentage of deaths observed in the hy-

ponatremic group (19.5%) was higher than in the whole cancer population (6.3%). In a recent prospective cohort of 12,562 patients with a SNa level of less than 135 mmol/L, 10.8%, suffered from metastatic cancer disease.⁶ Hyponatremia was strongly related to mortality, especially when it did not resolve during hospitalization. A different picture emerges from the longitudinal data from a large managed-care claims database.⁷ Of 167,299 patients, hyponatremia was present in 1,274 patients, of which only 32 (2.5%) suffered from metastatic malignancy. SIADH was diagnosed in only 7 of the hyponatremic patients. Finally, of 6,766 intensive care unit (ICU) patients with hematologic malignancy in the United Kingdom,⁸ 4.21% presented with hyponatremia (<130 mmol/L), and this was associated with an adjusted odds ratio for mortality of 2.47 (95% confidence interval, 1.70-3.60). The correct diagnosis of the pathophysiological basis for each patient with hyponatremia is important because it significantly alters the treatment approach: water restriction or salt loading (for review see Onitilo et al,⁹ Raftopoulos,¹⁰ and Sterns et al¹¹).

Etiology of hyponatremia

In clinical practice, the causes of hyponatremia can be conveniently grouped into three categories, depending on the patient's volume status: hypovolemia, hypervolemia, and euvolemia. In all these conditions, there might be increased ADH secretion, be it appropriate or inappropriate. The clinical history may give some clue to the underlying cause of hyponatremia: recent chemotherapy, nausea and vomiting, overhydration, pain, administration of narcotic drugs, and physical and emotional stress.

When dehydration and salt losing have been excluded, the most common cause of hyponatremia in (euvolemic) cancer patients is SIADH, sometimes resulting from ectopic production of arginine vasopressin (AVP) by the tumor tissue. Unfortunately, plasma AVP cannot be measured routinely because of significant pre-analytical and analytical problems. As a consequence, SIADH remains an exclusion diagnosis. Copeptin, a 39-amino acid glycopeptide of unknown function, is derived from the same precursor peptide as AVP; it is released in equimo-

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