An Overview of the Management of Electrolyte Emergencies and Imbalances in Cancer Patients

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Electrolyte imbalances are common in patients with cancer. They may arise from tumor- or treatment-related factors or other causes. These imbalances can lead to life-threatening oncologic emergencies, such as tumor lysis syndrome, syndrome of inappropriate antidiuretic hormone secretion, and hypercalcemia of malignancy. Early recognition and management are crucial to prevent serious complications and improve patient outcomes. Advanced practice providers must be aware of the symptoms in order to incorporate preventive measures and manage these abnormalities appropriately. This article will review the current evidence-based literature on electrolyte abnormalities and emergencies associated with electrolytes in the care of oncology patients.

Electrolyte imbalances are common in patients with cancer. They may arise from tumor- or treatment-related factors or other causes (Turcotte et al., 2022; Verzicco et al., 2020; Table 1). Early recognition and management are crucial to prevent serious complications and improve patient outcomes (Berardi et al., 2019). A systematic review showed these abnormalities were associated with adverse clinical outcomes such as higher mortality rates, increased hospitalization rates, and extended hospital stays (Berardi et al., 2019). These imbalances can lead to life-threatening emergencies if not effectively managed. Advanced practice providers (APPs) must be aware of the symptoms in order to incorporate preventive measures and manage these abnormalities appropriately.

CANCER-RELATED CAUSES OF ELECTROLYTE ABNORMALITIES

Tumor-Related Factors

There are several tumor-related factors that can contribute to electrolyte abnormalities in cancer patients (Table 1). For example, lung cancer has been associated with syndrome of inappropriate antidiuretic hormone secretion (SIADH), leading to hyponatremia (Turcotte et al., 2022;

Table 1. Cancer-Related Factors and Other Causes for Electrolyte Imbalances

Electrolyte imbalance	Tumor-related factors	Treatment-related factors	Other causes
Hyponatremia	AML, ALL, NHL, lung, colon, breast, head and neck, adrenal carcinoma, metastatic disease	• Chemotherapy: platinum compounds (e.g., cisplatin), alkylating agents (e.g., cyclophosphamide, chlorambucil, melphalan, busulfan, and ifosfamide), and vinca alkaloids (e.g., vincristine and vinblastine) • Medications: diuretics (e.g., thiazides), trimethoprim, anticonvulsants (e.g., lamotrigine, levetiracetam, gabapentin, calcitonin inhibitors, carbamazepine), antidepressants (e.g., selective serotonin reuptake inhibitors), antipsychotics, calcitonin inhibitors, ketoconazole, heparin, NSAIDs	• Water excess (antidiuretic hormone) • Syndrome of inappropriate antidiuretic hormone secretion • Fluid loss • Renal disease • Hypothyroidism • Adrenal insufficiency
Hypernatremia	AML, ALL, MDS	• Osmotic diuretics • Corticosteroids • Parenteral nutrition • Hypertonic saline infusions	• Excessive water loss or sodium intake • Diabetes insipidus • Dehydration secondary to chemotherapy or radiation • Diuresis • Heat stroke • Anorexia and/or cachexia • Brain metastasis or GI infiltration of disease
Hypokalemia	AML, ALL, renal cell, adrenal carcinomas, lymphoma, ACTH-secreting tumors: SCLC, medullary thyroid cancer	• Chemotherapy: platinum compounds (e.g., cisplatin), alkylating agents (e.g., cyclophosphamide, ifosfamide) • Antineoplastics: immunomodulators, tyrosine kinase inhibitors, mAbs • Antibiotics: amphotericin B, aminoglycosides • Diuretics	• Hyperaldosteronism • Treatment-related induced GI symptoms (i.e., nausea, vomiting, diarrhea) • Malnutrition • Alkalosis
Hyperkalemia	Lymphoproliferative disorders (e.g., ET), CLL, AML	• Calcineurin inhibitors • Ketoconazole • NSAIDs • Trimethoprim • Heparin	• Tumor lysis syndrome • Leukemic infiltration of kidneys • Severe leukocytosis and pseudohyperkalemia • Acidosis

Note. ACTH = adrenocorticotropic hormone; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; ET = essential thrombocythemia; GI = gastrointestinal; MM = multiple myeloma; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; NSAID = nonsteroidal anti-inflammatory drug; SCLC = small cell lung cancer; EGFR = epidermal growth factor receptor; mAbs = monoclonal antibodies. Information from Espinoza-Munoz et al. (2023); Kim (2022); Tenma et al. (2019); Workeneh et al. (2021); Berardi et al. (2019); Verzicco et al. (2020); Puri et al. (2020); Klemencic & Perkins (2019).

Table 1. Cancer-Related Factors and Other Causes for Electrolyte Imbalances (cont.)

Electrolyte imbalance	Tumor-related factors	Treatment-related factors	Other causes
Hypophosphatemia	AML, ALL, various mesenchymal tumors, MM	• Chemotherapy: platinum compounds (e.g., cisplatin) • Antacids	• Malnutrition • Poor intake of calcium and vitamin D • Rapid growth of cancer cells • Alcohol use disorder • Diabetic ketoacidosis
Hyperphosphatemia	NHL, AML, ALL	• High-dose liposomal amphotericin B	• Tumor lysis syndrome • Acute kidney injury due to tumor infiltration
Hypocalcemia	Parathyroid carcinoma, MM, metastatic bone disease	• Chemotherapy: platinum compounds (e.g., cisplatin) • Bisphosphonates • Antiepileptics • Aminoglycosides • Diuretics • Proton pump inhibitors	• Tumor lysis syndrome • Tumor infiltration of the parathyroid gland • Bone metastases • Renal involvement • Vitamin D deficiency • Hypoparathyroidism
Hypercalcemia	Bladder, breast, colorectal, leukemia, lymphoma, lung, MM, ovary, pancreatic, prostate, renal cell, rhabdomyosarcoma, squamous cell carcinomas (e.g., lung, head and neck), thyroid papillary	• Thiazide diuretics	• Release of parathyroid hormone-related protein • Bone metastasis • Tumor-produced calcitriol • Increased osteoclastic bone resorption • Impaired renal excretion of calcium • Increased calcium intake • Hypercalcemia of malignancy
Hypomagnesemia	AML, ALL	• Chemotherapy drugs: platinum compounds (e.g., cisplatin) • Antineoplastic agents (cetuximab), anti-EGFR mAbs, anti-HER2 agents • Calcineurin inhibitor • Antibiotics (e.g. aminoglycosides, amphotericin B) • Diuretics • Proton pump inhibitors	• Secondary to GI loss and poor dietary intake • Renal wasting from drug-related tubular dysfunction

Note. ACTH = adrenocorticotropic hormone; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; ET = essential thrombocythemia; GI = gastrointestinal; MM = multiple myeloma; MDS = myelodysplastic syndrome; NHL = non-Hodgkin lymphoma; NSAID = nonsteroidal anti-inflammatory drug; SCLC = small cell lung cancer; EGFR = epidermal growth factor receptor; mAbs = monoclonal antibodies. Information from Espinoza-Munoz et al. (2023); Kim (2022); Tenma et al. (2019); Workeneh et al. (2021); Berardi et al. (2019); Verzicco et al. (2020); Puri et al. (2020); Klemencic & Perkins (2019).

Tenma et al., 2019). Hypokalemia is commonly seen in acute leukemia. Hypercalcemia of malignancy (HCM) occurs frequently in solid tumors, particularly breast and lung cancer. Multiple myeloma can result in hypophosphatemia (Rosner & Dalkin, 2014). Tumor lysis syndrome (TLS) is most common in high-grade non-Hodgkin lymphoma (NHL) and acute leukemias but also occurs in the treatment of solid tumors that are highly chemosensitive, such as hepatocellular carcinoma and metastatic prostate cancer (Findakly et al., 2020).

Cancer Treatment-Related Factors

There are several cancer treatment-related factors that can contribute to electrolyte abnormalities (Table 1). Chemotherapy with agents such as platinum compounds is associated with sodium, potassium, and magnesium abnormalities, while alkylating agents and vinca alkaloids are associated with hyponatremia (Verzicco et al., 2020). Radiation therapy can cause electrolyte imbalances by damaging the kidneys or other organs responsible for electrolyte regulation. Surgical procedures, especially those involving the gastrointestinal tract, can lead to malabsorption. The use of targeted therapies, monoclonal antibodies, and immunomodulators can result in clinically significant magnesium and potassium losses (Verzicco et al., 2020).

SODIUM ABNORMALITIES ASSOCIATED WITH CANCER

Hyponatremia

Hyponatremia is defined as a serum sodium concentration of less than 135 mEq/L (Table 2). It is divided into three grades of severity: mild (130–134 mEq/L), moderate (125–129 mEq/L), and severe (less than 125 mEq/L; Berardi et al., 2019). Patients are usually asymptomatic with mild-to-moderate hyponatremia, while severe hyponatremia may manifest as nausea, confusion, lethargy, or headache (Rosner & Dalkin, 2014).

Hyponatremia is common in the oncology population and multifactorial (Berardi et al., 2019). Hyponatremia is commonly associated with malignancies such as small cell lung cancer (SCLC), NHL, renal cell carcinoma, and gastric cancer (Rosner & Dalkin, 2014). Chemotherapies commonly associated with hyponatremia are cisplatin, carboplatin, cyclophosphamide, and vinca alkaloids (Verzicco et al., 2020). In addition, many treatment regimens require excess hydration to avoid toxicities, which can lead to further sodium loss (Kim, 2022). Gastrointestinal fluid loss secondary to nausea, vomiting, and diarrhea is a frequent side effect of cytotoxic treatment and can result in hyponatremia if not managed. Noncytotoxic medication-related causes of hyponatremia include response to diuretics, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors (SSRIs), narcotics, and carbamazepine (Kim, 2022; Berardi et al., 2019). Other causes of hyponatremia include concomitant diseases such as heart failure, renal dysfunction, adrenal insufficiency, and thyroid dysfunction, as well as situational causes including fever, infection, and the administration of IV fluids (Berardi et al., 2019).

Treatment for hyponatremia is based on onset, duration, severity, and consideration of the patient's fluid volume status (Rosner & Dalkin, 2014). Assessing plasma osmolarity and evaluating extracellular volume (ECV) can help identify potential causes and interventions (Berardi et al., 2019). This assessment requires obtaining blood work and urine samples to evaluate plasma and urine osmolality along with urine sodium concentration. Further, ECV can be evaluated by assessing a patient's vital signs and skin turgor, and checking for the presence of peripheral edema, pulmonary crackles, or jugular vein distention (Kearney et al., 2022; Figure 1). In instances of reduced osmolarity and reduced ECV, hypovolemia secondary to GI losses, nephropathy, or diuretic use is suspected. Treatment includes administering isotonic (0.9% NaCl) or hypertonic (3% NaCl) intravenous saline bolus depending on the severity of the hyponatremia. If reduced plasma osmolarity with elevated ECV is present, then potential causes for this could be heart failure, cirrhosis, or nephrotic syndrome (Berardi et al., 2019).

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Syndrome of inappropriate antidiuretic hormone secretion is the most common cause of hyponatremia that is directly attributed to malignancy. The malignancy most commonly associated with

Table 2. Laboratory Ranges of Electrolytes

Electrolyte	Normal range	Hypo- ranges	Hyper- ranges
Sodium	135 to 145 mEq/L	Grades of severity • Mild: 130–134 mEq/L • Moderate: 125–129 mEq/L • Severe: < 125 mEq/L	> 145 mEq/L
Potassium	3.5–5.2 mmol/L	< 3.5 mmol/L • Severe: < 3.0 mmol/L	> 5.3 mmol/L
Phosphate	2.5–4.5 mg/dL	< 2.5 mg/dL	> 4.5 mg/dL
Calcium	8.5–10.5 mg/dL (ionized Ca+ 4.7–5.2 mg/dL)	< 8.5 mg/dL (ionized Ca+ < 1.0 mmol/L) • Severe: < 6 mg /dL	Levels of classification • Mild: 10.5–11.9 mg/dL • Moderate: 12–13.9 mg/dL • Crisis: 14.0–16.0 mg/dL
Magnesium	1.6–2.5 mg/dL	< 1.8 mg/dL	Critical: > 3 mg/dL

Note. Adapted from Espinoza-Munoz et al. (2023); Sadiq et al. (2023); Verzicco et al. (2020); Berardi et al. (2019).

SIADH is SCLC, with 70% of patients noted to have elevated arginine vasopressin levels and a subsequent 10% to 15% with hyponatremia at the time of presentation (Tenma et al., 2019). Head and neck tumors comprise a smaller population and are also associated with SIADH.

Antineoplastic therapies can contribute to the development of SIADH. Patients receiving platinum compounds (e.g., cisplatin), alkylating agents (e.g., cyclophosphamide, chlorambucil, melphalan, busulfan, and ifosfamide), and vinca alkaloids (e.g., vincristine and vinblastine) have been implicated as causing SIADH due to significant release of ADH (antidiuretic hormone) or ADH-like byproducts from damaged tumor cells as well as damaged healthy cells. Other drugs can also cause SIADH, such as SSRIs, antipsychotics, and antiepileptics (Verzicco et al., 2020). Syndrome of inappropriate antidiuretic hormone secretion is a diagnosis of exclusion (Table 3).

Hyponatremia secondary to SIADH related to malignancy is challenging to treat because it is less responsive to treatment (Rosner & Dalkin, 2014). In instances when the cancer itself or the antineoplastic medication needed to treat the disease results in SIADH, treatment options must be considered. In mild, asymptomatic cases, fluid restriction is a practical choice. However, it may be difficult given the hydration recommendations associated with many chemotherapy regimens (Berardi et al., 2019). In acutely severe or symptomatic hyponatremia, administration of hypertonic saline is needed to improve the patient's symptoms. A loop diuretic such as furosemide may also be considered to help keep proper volume status and prevent overload (Rosner & Dalkin, 2014).

Table 3. Criteria for Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

SIADH is a diagnosis of exclusion requiring several criteria to be met. The main criteria are:
- Na < 135 mEq/L
- Serum osmolality < 275 mOsm/kg
- Urine osmolality > 100 mOsm/kg
- Euvolemic/normal extracellular volume
- Absence of adrenal or thyroid dysfunction
- No diuretic use

Note. Information from Rosner & Dalkin (2014); Berardi et al. (2019).

Hypernatremia

Hypernatremia is classified as an elevated serum sodium level > 145 mEq/L. Hypernatremia is much less prevalent than hyponatremia, occurring in less than 5% of oncology patients (Berardi et al., 2019). Concerning clinical findings for APPs to be aware of include central nervous system effects and subsequent neurological symptoms (Verzicco et al., 2020).

Hypernatremia is most often associated with total body water loss secondary to impaired thirst stimulation or renal water loss. Several factors may contribute to this, including anorexia, cachexia, brain metastasis, kidney damage, malignant infiltration within the GI system, diabetes insipidus, or Cushing syndrome (Berardi et al., 2019). Medications known to be associated with

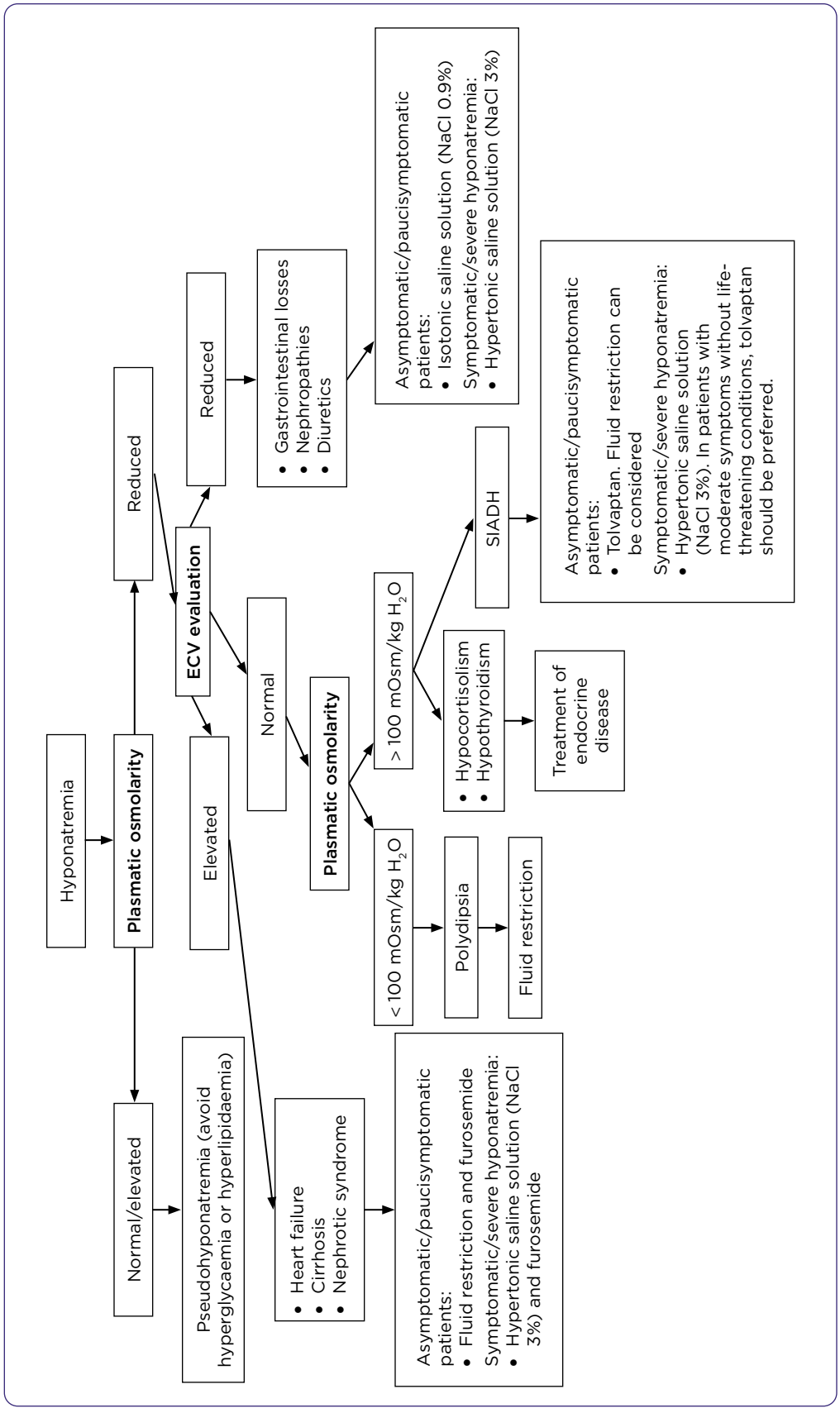

Figure 1. Hyponatremia management algorithm. ECV = extracellular volume; SIADH = syndrome of inappropriate antidiuretic hormone secretion. The correct management of hyponatremia and its treatment require the detection of its cause. Plasmatic osmolarity and ECV evaluation are necessary to recognize the origin of hyponatremia. Symptomatic hyponatremia should be treated with hypertonic saline solution. Tolvaptan should be considered in hyponatremia due to SIADH. Used with permission from Berardi et al. (2019).

hypernatremia include osmotic diuretics, corticosteroids, parenteral nutrition, and hypertonic saline infusions. Adverse gastrointestinal side effects as well as some direct bowel damage from cancer therapies may contribute to hypernatremia (Berardi et al., 2019).

Treatment of hypernatremia involves administration of isotonic or hypotonic saline solutions; however, identifying the underlying cause is essential (Berardi et al., 2019). Hypernatremia is a poor prognostic indicator correlated to an elevated mortality rate (Berardi et al., 2019).

POTASSIUM ABNORMALITIES ASSOCIATED WITH CANCER

Hypokalemia

Hypokalemia (K < 3.5 mmol/L) is the second most common electrolyte disorder. It occurs in 12% of oncology patients but can be seen in up to 43% to 64% of patients with acute leukemia (Espinoza-Munoz et al., 2023; Verzicco et al., 2020). In most cases, the etiology of hypokalemia is multifactorial and includes medications that can cause tubular damage (such as cisplatin, ifosfamide, amphotericin B, and aminoglycoside antibiotics), as well as potassium losses through the gastrointestinal tract or kidneys (Rosner & Dalkin, 2014).

In addition, hypokalemia is seen in conjunction with other electrolyte disorders such as hyponatremia and hypomagnesemia and reflects etiologies such as diuretic use. Patients with hypercalcemia may also develop hypokalemia due to increased secretion of potassium in the urine and use of diuretics in this population (Espinoza-Munoz et al., 2023).

Transcellular shifts can also occur post phlebotomy, leading to "false" hypokalemia. This phenomenon is usually seen in patients with marked leukocytosis (100,000/mL) and with blood kept at room temperature for prolonged periods. Rapid separation of the plasma and storage at 4°C limits this issue (Rosner & Dalkin, 2014).

Ectopic adrenocorticotropic hormone (ACTH) syndrome is a rare cause of severe hypokalemia, occurring when cortisol overloads cellular mechanisms that limit mineralocorticoid receptor access to glucocorticoids, thereby enhancing renal excretion of potassium. Numerous tumors can produce ectopic ACTH, with the most common etiologies including bronchial carcinoid tumors, SCLC, adenocarcinoma of the lung, thymic tumors, pancreatic tumors, and medullary thyroid cancer (Rosner & Dalkin, 2014).

There is a prominent association between hypokalemia and acute myelogenous leukemia (AML; specifically subtypes M4 and M5), with 40% to 60% of these patients developing significant hypokalemia (Naseer et al., 2023). Of importance to note is that hypokalemia in these patients is usually associated with other electrolyte and acid-base disorders (hyponatremia, hypocalcemia, hypophosphatemia, hypomagnesemia, and non-anion gap metabolic acidosis), suggesting a more global tubular defect.

When patients are asymptomatic with severe hypokalemia (K < 3.0 mmol/L), an oral potassium supplementation with potassium chloride 40 mEq every 3 to 4 hours should be considered (Berardi et al., 2019). In symptomatic patients with life-threatening complications or those unable to take oral drugs, intravenous potassium (10–20 mEq can increase the serum potassium level by an average of 0.25 mEq/hour) is recommended (Berardi et al., 2019). Patients with carcinoid syndrome should receive somatostatin analog to inhibit hormonal hypersecretion and improve symptoms (Berardi et al., 2019).

Hyperkalemia

Hyperkalemia (K > 5.3 mmol/L) is often related to TLS or acute and/or chronic oliguric kidney disease (Verzicco et al., 2020). Less common causes include adrenal insufficiency associated with metastatic disease or drugs such as ketoconazole, calcineurin inhibitors (used in stem cell transplant patients), nonsteroidal anti-inflammatory drugs, trimethoprim, or heparin (Berardi et al., 2019).

The presence of pseudohyperkalemia should be considered in patients with marked leukocytosis or thrombocytosis (e.g., patients with chronic lymphocytic leukemia, AML, or essential thrombocytosis), in which elevated potassium values are present in the absence of corresponding clinical symptoms or electrocardiogram (ECG) changes (Berardi et al., 2019). This is caused by a shift of potassium out of platelets or leukocytes after a blood draw and when a blood clot has formed. If the first sample was a serum, repeat measurements using simultaneously drawn plasma and

serum specimens should be performed to obtain disparate results (Berardi et al., 2019). A serum-to-plasma potassium gradient greater than 0.4 mEq/L is diagnostic of pseudohyperkalemia (Rosner & Dalkin, 2014). Pseudohyperkalemia must always be ruled out before implementing treatment for true hyperkalemia (Gujarathi et al., 2022).

The management of hyperkalemia requires an ECG to evaluate alterations or cardiac arrhythmia (Berardi et al., 2019). In cases of severe hyperkalemia and ECG abnormalities, immediate treatment should be provided to decrease the serum potassium in intracellular components. Treatment options to be considered are calcium gluconate or calcium chloride, insulin and glucose, sodium bicarbonate, diuretics, sodium polystyrene sulfonate, or hemodialysis (Berardi et al., 2019). Treating the underlying cause is important to prevent recurrence.

PHOSPHATE ABNORMALITIES ASSOCIATED WITH CANCER

Normal phosphate levels ranging between 2.5 and 4.5 mg/dL result from a balance between intestinal absorption, renal excretion, and release from the bone exchangeable fraction, which is regulated by parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and calcitriol (Verzicco et al., 2020). FGF23 and PTH decrease phosphate serum levels by inhibition of tubular reabsorption. Conversely, calcitriol increases the intestinal absorption of phosphate and inhibits PTH secretion (Verzicco et al., 2020).

Hypophosphatemia

Hypophosphatemia is common in the oncology population (Verzicco et al., 2020). Cachexia and malnutrition, including calcium and vitamin D deficiency, can result directly from malignancy or cancer treatment. These patients can present with hypocalcemia, hypophosphatemia, low vitamin D, and elevated PTH levels (Rosner & Dalkin, 2014). Chemotherapy, such as cisplatin, can damage renal tubules and result in phosphate wasting. Clinical manifestations include weakness, proximal myopathy, rhabdomyolysis, hemolytic anemia, and heart failure (Verzicco et al., 2020).

The first step in the evaluation of a patient with acquired hypophosphatemia is a thorough evaluation of medications, nutritional status, and medical history. In the presence of hypercalcemia, causes of hyperparathyroidism should be pursued (chemistry panel including calcium, albumin, kidney function, PTH, and PTHrP; Rosner & Dalkin, 2014). If there is coexistent hypocalcemia, vitamin D status must be evaluated. In patients with a normal calcium level and hypophosphatemia, the presence of kidney phosphate wasting should be pursued. Assessment of either the percentage tubular reabsorption of phosphate or tubular maximum for phosphate corrected for the glomerular filtration rate can be used. If phosphate wasting is confirmed, measurement of FGF23 levels can be performed (Rosner & Dalkin, 2014).

Phosphate supplements are given using either sodium phosphate or potassium phosphate preparations, with the usual dose of 1 to 3 g/day in divided dosing and limited by the development of loose stools (Rosner & Dalkin, 2014).

Hyperphosphatemia

Hyperphosphatemia (phosphate > 4.5 mg/dL) is related to TLS, particularly in hematologic malignancies, and occurs more often due to chemotherapy than in spontaneous TLS (Verzicco et al., 2020). Certain malignancies, such as lymphoma, may have the enzyme 1α-hydroxylase and lead to increased levels of active vitamin D metabolites causing hypercalcemia and, to a lesser degree, hyperphosphatemia (Rosner & Dalkin, 2014). Oral supplements with phosphate and vitamin D can exacerbate hyperphosphaturia, thus increasing the risk of developing calcium phosphate kidney stones. Thiazide diuretics may be needed to help reduce urine calcium excretion (Rosner & Dalkin, 2014).

CALCIUM ABNORMALITIES ASSOCIATED WITH CANCER

Normal serum calcium levels range between 8.5 and 10.5 mg/dL, with ionized Ca+ between 4.7 and 5.2 mg/dL.

Hypocalcemia

Although rare and described primarily in case reports, some malignancies are associated with hypocalcemia. The tumors are usually metastatic to the bone and have osteoblastic activity (Rosner & Dalkin, 2014). Symptomatic hypocalcemia presents as irritability, tetany, psychosis, and prolonged

QT interval. Calcium levels should be checked in cases of hypomagnesemia due to concomitant low PTH activity. Agents such as platinum compounds and anti-EGFR monoclonal antibodies can cause hypomagnesemia and may also induce hypocalcemia (Verzicco et al., 2020).

Diagnosis of hypocalcemia is based on symptoms and laboratory analysis that should include both a total calcium and ionized calcium level. If ionized calcium is unavailable, a corrected calcium value can be calculated using the formula: serum calcium (mg/dL) + 0.8 × (4 – patient's albumin) (Berardi et al., 2019; Klemencic & Perkins, 2019; Feldenzer & Sarno, 2018).

Treatment depends on the severity, clinical manifestations, and underlying causes. When possible, it is recommended to correct the cause. Symptomatic patients should receive intravenous calcium. Calcium gluconate should be administered slowly since rapid correction can cause cardiac arrhythmias. It should also be administered via a central line to prevent extravasation complications (Berardi et al., 2019). Patients receiving bisphosphonates or antiresorptive agents should be on oral calcium and vitamin D supplementation (Ganesan et al., 2023).

Hypercalcemia

Hypercalcemia is more common than hypocalcemia, found in 20% to 30% of patients with lung, breast, kidney, cervix, and hematologic malignancies (Verzicco et al., 2020; Klemencic & Perkins, 2019; Feldenzer & Sarno, 2018; Higdon et al., 2018). The severity of hypercalcemia in cancer patients varies and depends on the patient's overall health status and hydration. In the presence of mild hypercalcemia (10.5–11.9 mg/dL), symptoms are vague, such as fatigue, malaise, constipation, or anorexia (Sadiq et al., 2023; Klemencic & Perkins, 2019).

As the degree of hypercalcemia worsens, bone pain (either related directly to the presence of malignancy or secondary to increased bone remodeling), abdominal pain (peptic ulcer disease), polyuria (nephrogenic diabetes insipidus), and weakness is common. In severe hypercalcemia with levels above 14 mg/dL, neurologic changes including altered mental status, confusion, and coma may be present, calling for immediate intervention and hospitalization (Rosner & Dalkin, 2014).

There are three main classification types of cancer-associated hypercalcemia: humoral hypercalcemia, local osteolytic hypercalcemia, and vitamin D-mediated hypercalcemia (Table 4).

The humoral cause (sometimes referred as PTHrP-mediated disease) is the most common and accounts for approximately 80% of cases. Tumors can synthesize and secrete PTHrP, which increases bone resorption via osteoclast activity and enhances calcium reabsorption in the renal tubules (Sadiq et al., 2023; Klemencic & Perkins, 2019; Feldenzer & Sarno, 2018; Higdon et al., 2018). As with phosphate, PTH activates bone turnover and thereby favors the release of bone calcium stores, along with phosphate, into the circulation (Klemencic & Perkins, 2019). Association with lymphomas and cancers of the lung, cervix, esophagus, renal cell, breast, prostate, and ovary have been reported (Sadiq et al., 2023).

Local osteolytic hypercalcemia caused by bone invasion and local osteolysis by cytokines

Table 4. Types of Cancer-Associated Hypercalcemia and Their Laboratory Findings

	Humoral hypercalcemia	Local osteolytic hypercalcemia	Vitamin D 1,25–mediated hypercalcemia
Calcium	High	High	High
Phosphorus	Low	Variable	High
PTHrP	High	Low	Low
PTH	Low	Low	Low
1,25(OH)2D	Variable	Variable	High

Note. PTHrP = parathyroid hormone-related protein; PTH = parathyroid hormone.
Adapted from Sadiq et al. (2023); Guise & Wysolmerski (2022); Klemencic & Perkins, (2019); Feldenzer & Sarno (2018); Higdon et al. (2018).

accounts for approximately 20% of cases (Sadiq et al., 2023; Feldenzer & Sarno, 2018; Higdon et al., 2018). The degree to which bone metastases cause hypercalcemia correlates directly with the bone tumor burden. Each metastasis releases factors such as prostaglandins or PTHrP that stimulate local osteoclast activity and the release of calcium into the circulation (Sadiq et al., 2023). Immobility can increase this process. This is commonly seen in metastatic breast cancer, lung cancer, and multiple myeloma (Sadiq et al., 2023).

The third type, vitamin D 1,25-mediated hypercalcemia, is rare. It is caused by the increased conversion of inactive vitamin D to the active form of vitamin D, calcitriol, by the tumor itself causing an increase calcium level. This is seen in lymphoma, sarcoidosis, and other granulomatous diseases (Sadiq et al., 2023). In patients with tumors directly activating vitamin D, hypercalcemia with hypoparathyroidism is seen due to feedback inhibition of calcium on the normal parathyroid glands (Sadiq et al., 2023).

The evaluation of the cancer patient with hypercalcemia includes an investigation of these potential causes (Figure 2). After confirming true hypercalcemia, measurement of circulating PTH levels is the first and most crucial step. If the PTH levels are inappropriately normal or elevated, patients should undergo evaluation for a coexistent parathyroid adenoma (Feldenzer & Sarno, 2018). More likely, PTH levels will be suppressed, and other etiologies need to be sought. Other laboratory results may provide a clue to aid in the investigation (Feldenzer & Sarno, 2018).

A low phosphorus level, coupled with an elevated marker of bone turnover such as alkaline phosphatase, can indicate PTHrP-mediated disease (Rosner & Dalkin, 2014). Of note, alkaline phosphatase is derived from many sources, including the liver and bone, and hence is nonspecific (Rosner & Dalkin, 2014). Hyperphosphatemia in the presence of hypercalcemia, especially in the absence of coexisting kidney insufficiency, often shows vitamin D-mediated etiology. Thus, added testing should include measurement of phosphorus, 1,25(OH)2D, PTHrP, and alkaline phosphatase along with a serum and urine protein electrophoresis to evaluate for light-chain disease (Rosner & Dalkin, 2014).

Hypercalcemia of Malignancy

Hypercalcemia of malignancy has a poor prognosis, with a median survival of 35 days from diagnosis (Higdon et al., 2018). The first step, regardless of the cause, is the emergent reduction in circulating calcium concentration. The mainstay of therapy is aggressive intravenous hydration with the goal of increasing kidney clearance of calcium (Rosner & Dalkin, 2014). Most patients with significant hypercalcemia are volume depleted at presentation, and a reduced glomerular filtration rate can worsen the hypercalcemia with ongoing mobilization from bone. Aggressive hydration usually has a clinical response within a few hours, in which the serum calcium levels decrease by 2 mg/dL; however, the effect is transient, and further management or treatment of the underlying malignancy is important (Feldenzer & Sarno, 2018).

If hydration results in excessive fluid retention and potentially cardiac compromise, usually a congestive failure, the addition of a loop diuretic, such as furosemide, is suggested. However, the evidence does not support the routine use of diuresis (Feldenzer & Sarno, 2018).

The primary class of medications recommended is bisphosphonates. The high-potency bisphosphonates available for intravenous dosing include pamidronate, zoledronic acid, and ibandronate. Pamidronate and zoledronic acid are approved by the US Food and Drug Administration for the treatment of hypercalcemia (Klemencic & Perkins, 2019; Feldenzer & Sarno, 2018). Ibandronate has been shown to have efficacy in this setting, but hypercalcemia is not an approved indication. Each of these agents targets the osteoclast to reduce resorption. Tubular injury and glomerular damage have been reported. Therefore, each agent should be dose adjusted when used in patients with kidney insufficiency. Side effects associated with bisphosphonates are infusion-related fever and flu-like symptoms such as myalgia and bone pain (Feldenzer & Sarno, 2018). A rare but serious side effect of bisphosphonates is osteonecrosis of the jaw (Feldenzer & Sarno, 2018).

Alternative antiresorptive agents include denosumab, a monoclonal antibody directed against receptor activator of nuclear factor kappa-B ligand. Denosumab is not cleared by the kidney; therefore, kidney insufficiency does not alter

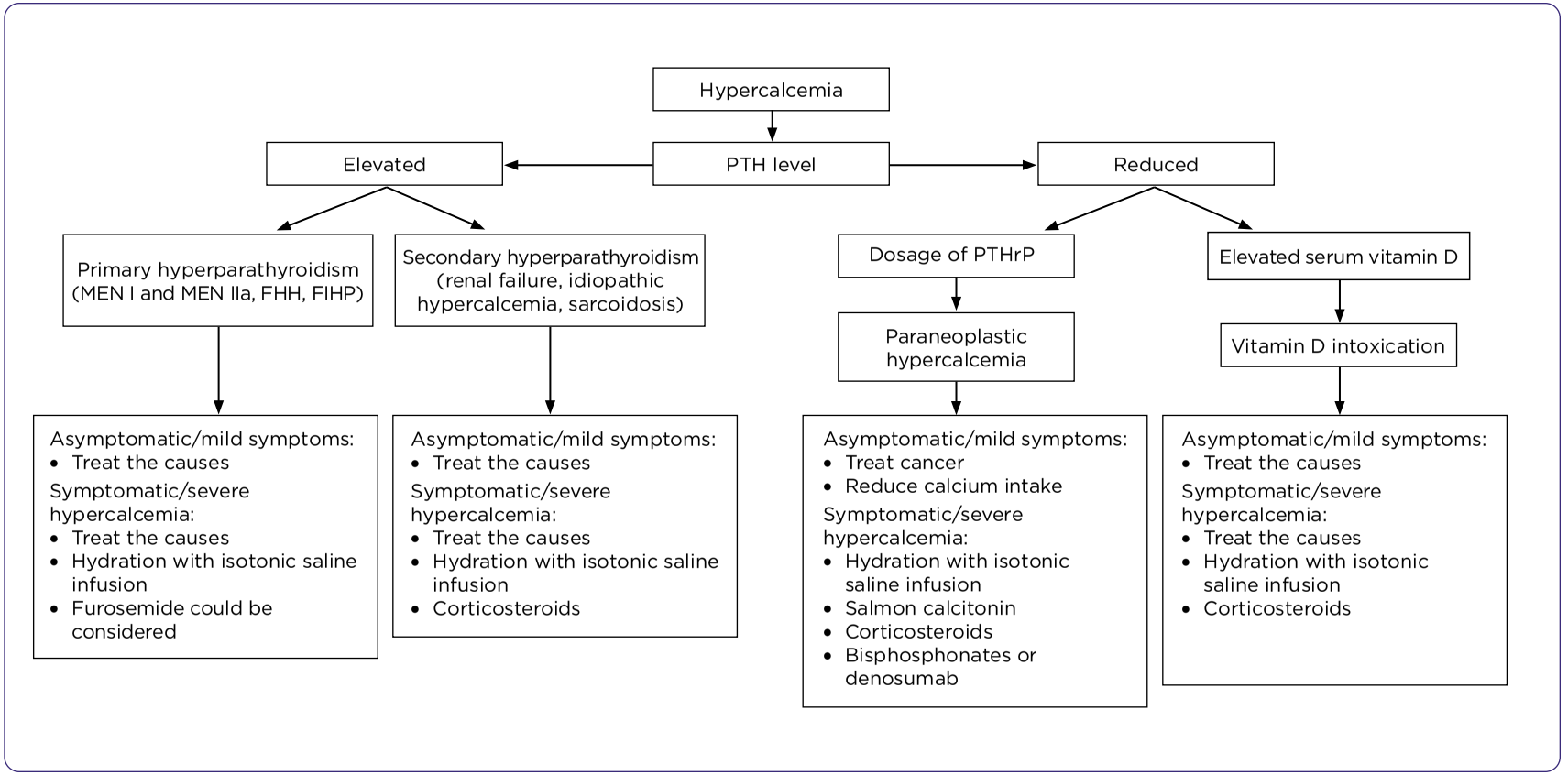

Figure 2. Hypercalcemia management algorithm. PTH = parathyroid hormone; PTHrP = parathyroid hormone-related protein; MEN = multiple endocrine neoplasia; FHH = familial hypocalciuric hypercalcemia; FIHP = familial isolated hyperparathyroidism. To treat hypercalcemia, a correct diagnostic framework is essential, which is based on the parathyroid dosage to distinguish between hyperparathyroidism and other causes. In the case of low blood PTH concentrations, the dosage of PTHrP is useful to exclude paraneoplastic hypercalcemia and vitamin D intoxication. Used with permission from Berardi et al. (2019).

dosing or efficacy. Denosumab has documented benefits in metastatic cancers and can reduce skeletal-related events. In addition, denosumab (along with the intravenous bisphosphonates) has antiresorptive actions that can extend for weeks to months, providing a longer-term effect (Klemencic & Perkins, 2019). Denosumab is well tolerated, with the most common side effects being arthralgia and mild dyspnea (Feldenzer & Sarno, 2018).

Another agent that can be used is calcitonin. Calcitonin inhibits all osteoclast activity and prevents the renal absorption of calcium. Calcitonin has a rapid transient hypocalcemia effect in which a decrease in serum calcium levels can be seen about 2 hours after administration; however, it should be noted that calcitonin must be administered every 6 to 8 hours to keep its effect (Berardi et al., 2019). It has a rebound effect on hypercalcemia that usually develops after 2 to 3 days of treatment; therefore, it should only be used in the acute phase of hypercalcemia while bridging to bisphosphonates (Berardi et al., 2019; Feldenzer & Sarno, 2018).

Corticosteroids (e.g., prednisone 20 to 40 mg daily) can be used in the management of HCM, particularly for patients with vitamin D-secreting tumors or lymphomas (Berardi et al., 2019; Feldenzer & Sarno, 2018). Although the response is not rapid, the limitation of dietary calcium may be helpful in speeding up the effect. High doses of corticosteroids can have a direct action on the underlying malignancy (for example, certain lymphomas). After 3 to 5 days of intravenous steroid administration, it is standard to transition patients to oral dosing, usually prednisone at 10 to 30 mg/day (Klemencic & Perkins, 2019).

MAGNESIUM ABNORMALITIES ASSOCIATED WITH CANCER

Magnesium is the second most common intracellular cation. Magnesium is an essential electrolyte that plays a significant role as a cofactor in biochemical pathways. Its deficiency can cause a wide range of clinical manifestations, such as lack of magnesium in association with other electrolyte abnormalities such as hypocalcemia and hypokalemia (Workeneh et al., 2021).

Hypomagnesemia

Hypomagnesemia is defined as a serum magnesium concentration of < 1.8 mg/dL, and its homeostasis depends on intestinal absorption and renal excretion (Workeneh et al., 2021; Verzicco et al., 2020). Hypomagnesemia is also associated with reduced release and activity of PTH and reduced synthesis of active vitamin D and its receptors. Both hepatic 25-hydroxylation and renal 1α-hydroxylation of vitamin D, leading to the active form of 1,25-dihydroxycholecalciferol, are magnesium-dependent processes. In addition, magnesium plays a significant role in innate and adaptive immunity by interacting with vitamin D metabolites (Verzicco et al., 2020). Treatment involves supplementation replacement (Verzicco et al., 2020).

Causes of hypomagnesemia in cancer are diverse and categorized according to their pathophysiologic mechanisms: decreased intake, intracellular shift, and gastrointestinal and kidney losses (Workeneh et al., 2021). Patients with cancer are at risk for opportunistic infections and can develop cardiovascular complications and receive classes of medications that can worsen hypomagnesemia. Cancer-specific therapies associated with hypomagnesemia include platinum-based chemotherapy, anti-EGF receptor mAbs, HER2 inhibitors, and calcineurin inhibitors (Workeneh et al., 2021).

The impact of hypomagnesemia on chemotherapy-induced peripheral neuropathy (PN) varies. A systematic review of magnesium infusions to prevent oxaliplatin-induced chronic PN found no benefit of supplemental magnesium (Workeneh et al., 2021; Jordan et al., 2016). Cetuximab-induced hypomagnesemia can be challenging to manage, as its causes are multifactorial. In colorectal cancer patients, poor oral tolerance to magnesium supplementation is often exacerbated by increased diarrhea (Workeneh et al., 2021).

Mild hypomagnesemia can be pauci-symptomatic, but it can also cause severe life-threatening conditions. Symptoms involve the cardiovascular system (electrocardiographic alterations and prolonged QT interval) and the neuromuscular system (tremors, paresthesia, tetany, spasms, and seizures; Verzicco et al., 2020). Data have shown that hypomagnesemia may contribute to

increasing atherosclerotic cardiovascular disease and heart failure in cancer survivors (Workeneh et al., 2021; Jordan et al., 2016).

Treatment of hypomagnesemia depends on clinical manifestation and severity. Patients are usually asymptomatic until their serum magnesium level falls below 1.2 mg/dL (Workeneh et al., 2021; Berardi et al., 2019). Asymptomatic patients can receive oral supplementation of magnesium salts (e.g., magnesium oxide); however, diarrhea can be a dose-limiting side effect. Symptomatic patients should receive intravenous magnesium sulfate 1 to 4 g administered slowly (1 g/hour; Workeneh et al., 2021; Berardi et al., 2019). Patients with severe hypomagnesemia should receive immediate replacement to prevent cardiac arrhythmia and death (Workeneh et al., 2021; Berardi et al., 2019).

ONCOLOGICAL EMERGENCIES

Electrolyte imbalances are caused by many factors but may also arise from factors such as dehydration due to poor oral intake, nausea, vomiting, or diarrhea. These can lead to more life-threatening electrolyte imbalances that are considered oncologic emergencies requiring immediate attention. There are three common oncologic emergencies: TLS, along with SIADH and HCM, previously discussed.

Tumor Lysis Syndrome

Tumor lysis syndrome is an oncologic emergency that often occurs due to a rapid release of intracellular components into the circulation following chemotherapy but can also be seen after radiation and biologic therapies. It can also be seen in highly chemosensitive solid tumors, such as hepatocellular carcinoma and metastatic prostate cancer. It is most common in hematologic malignancies, particularly acute leukemias and high-grade lymphomas (Findakly et al., 2020; Verzicco et al., 2020; Puri et al., 2020; Thandra et al., 2018; Higdon et al., 2018).

There are both clinical and laboratory criteria for the diagnosis of TLS quantified by the Cairo-Bishop definition (Cairo & Bishop, 2004). This can occur within 3 days prior to or 7 days after treatment (Verzicco et al., 2020; Puri et al., 2020; Thandra et al., 2018). Laboratory TLS criteria are two or more metabolic abnormalities, including hyperuricemia, hyperphosphatemia, hyperkalemia, or hypocalcemia. Hyperuricemia occurs due to the breakdown of nuclear proteins leading to increased blood levels of hypoxanthine and xanthine (Verzicco et al., 2020; Puri et al., 2020). These compounds are degraded into uric acid by the enzyme xanthine oxidase. Clinical TLS is defined by the presence of acute kidney injury (increase in creatinine 0.3 mg/dL from baseline or > 1.5 times the upper limit of normal in those without known baseline creatinine) or presentation of symptomatic hyperkalemia or hypocalcemia, including cardiac arrhythmias, tetany, paranesthesia, or seizure (Thandra et al., 2018; Cairo & Bishop, 2004).

The American Society of Clinical Oncology (ASCO) stratifies patients into high, intermediate, or low risk of developing TLS based on the type of cancer, leukocyte count, and rapidity of proliferation with the expected response risk to chemotherapy (Coiffier et al., 2008). A summary of the ASCO guidelines for each risk group and coexisting electrolyte abnormality is found in Table 5.

Key to the management of TLS is prevention with vigorous hydration and hypouricemic agents (Thandra et al., 2018). Allopurinol is effective in the prevention of uric acid production; however, it does not decrease uric acid already present and is less effective (Puri et al., 2020; Higdon, Atkinson, & Lawrence, 2018). Rasburicase, a recombinant urate oxidase that metabolizes insoluble uric acid to allantoin, may be considered if hyperuricemia develops despite allopurinol therapy or as initial treatment in pediatric patients. It is well tolerated and does not require dose adjustment due to renal impairment. The recommended dose is 0.2 mg/kg intravenously. Of note, rasburicase is contraindicated in patients with a history of glucose-6-phosphate dehydrogenase deficiency (Puri et al., 2020; Klemencic & Perkins, 2019; Higdon et al., 2018; Thandra et al., 2018).

The highest incidence of TLS occurs with dinaciclib and alvocidib, with a reported rate of 15% to 53% in acute leukemia trials. The incidence of TLS is 8% to 10% with venetoclax, CAR T-cell therapy, and obinutuzumab, and less than 5% with brentuximab, carfilzomib, lenalidomide, dasatinib, and oprozomib. Idelalisib and ofatumumab have no reported cases of TLS (McBride et al., 2017).

Table 5. Treatment Algorithm for the Prevention and Management of Tumor Lysis Syndrome

Acute TLS management: Clinical symptoms may include nausea and vomiting, diarrhea, seizures, shortness of breath, renal insufficiency, or cardiac arrhythmias

Low risk	Intermediate risk	High risk
• Clinical judgment and monitoring	• Allopurinol 100–300 mg po q8–12 hours. Start 3 days prior to or 7 days after treatment • Hydration: Normal saline 2.5–3 L/m2/day • Strict I/O: Target urine output: 80–100 mL/m2/hour • Monitor lab every 8–12 hours	• Consider pre-phase cytoreductive therapy prior to starting primary therapy • Rasburicase 3–6 mg IV over 30 minutes. Check uric acid level 4 hours after administration and repeat if clinically necessary • Hydration: Normal saline 3 L/m^2/day • Strict I/O: Target urine output: 80–100 mL/m^2/hour • Monitor lab every 6–8 hours

Hyperuricemia	Hyperkalemia	Hyperphosphatemia	Hypocalcemia
• Aggressive hydration for intermediate and high risk except in renal failure or oliguria • Monitor urine output • Allopurinol in intermediate risk • Rasburicase for allopurinol failure or allergy • Diuretics may be used for obstructive uropathy or hypovolemia • Alkalinization is not warranted except in metabolic acidosis	• Intervention required > 7 mEq/L (or EKG shows widening of QRS) • Asymptomatic: Sodium polystyrene sulfonate • Symptomatic: Treatment of life-threatening arrhythmias, calcium gluconate. Regular insulin with glucose	• Eliminate phosphate from IV solutions, adequate hydration, phosphate binders may be used • Hemodialysis, peritoneal dialysis, or continuous venovenous hemofiltration	• Calcium gluconate, administered slowly with EKG monitoring

Note. TLS = tumor lysis syndrome; I/O = intake/output; EKG = electrocardiogram. Adapted ASCO guidelines and Coiffier et al. (2008).

CONCLUSION

Electrolyte imbalances are common in oncology and can lead to life-threatening emergencies if not promptly managed. The causes, clinical manifestations, and management of electrolyte imbalances in oncology are complex and require a multidisciplinary approach. Advanced practice providers have a vital role in the care and prevention of these imbalances. They should also be proactive in identifying patients who are at increased risk so that prompt diagnosis and treatment can be implemented, ultimately improving patient outcomes.

Disclosures

The authors have no conflicts of interest to disclose.

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