The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Electrolyte disturbances in cancer patients

Farahnaz Dadras, M.D
Firoozgar Hospital
Iran University of Medical Sciences

TEHRAN 2023

Introduction

✓Electrolyte disorders in cancer patients are a very common complication

✓In most cases, these alterations are asymptomatic and therefore not always

✓taken into consideration in clinical practice.

✓Associated with Worsening outcome

✓Influencing the quality of life

✓ possibility to receive anticancer drugs

✓ Conditioning survival

✓

Berardi et al. J Cancer Metastasis Treat 2019;5:79

Original Research

A study of 1088 consecutive cases of electrolyte abnormalities in oncology phase I trials

Alvaro H. Ingles Garces [a,b], Joo Ern Ang [a,b,1], Malaka Ameratunga [a,b,1], Maxime Chénard-Poirier [a,b], David Dolling [b], Nikolaos Diamantis [a,b], Satyanarayana Seeramreddi [a,b], Raghav Sundar [a,b], Johann de Bono [a,b], Juanita Lopez [a,b], Udai Banerji [a,b,*]

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Received 23 July 2018; accepted 28 August 2018
Available online 10 October 2018

- ✓ A review of phase I trials performed between 2011 and 2015. n=1088
- ✓ patients who had electrolyte disturbances during follow-up had **a poorer median** overall survival (26 weeks vs. 37 weeks, hazard ratio = 1.61; P < 0.001).

European Journal of Cancer 104 (2018) 32e38

✓ These alterations usually involve sodium, potassium, calcium, and magnesium serum levels.

✓

Berardi et al. J Cancer Metastasis Treat 2019;5:79

Causes of electrolyte disorders in cancer patients

- ✓**cancer effects**, such as paraneoplastic SIADH
- ✓**Anti-cancer therapies**
- ✓**Tumor lysis syndrome**
- ✓ **Concomitant clinical conditions or treatments**

- ✓The origin of the electrolyte disorder is **often multifactorial**.
- ✓A prompt correction of electrolyte disorders is commonly associated with a better prognosis.

✓ Berardi et al. J Cancer Metastasis Treat 2019;5:79. DOI: 10.20517/2394-4722.2019.008

HYPONATREMIA

- ✓The most common tumor-related electrolyte disorder.
- ✓Its accurate incidence is still unknown.
- ✓it occurs more frequently in patients with small-cell lung cancer, with a median estimated rate of 15%.

Berardi et al. J Cancer Metastasis Treat 2019;5:79

Hyponatremia in Cancer Patients Hospitalized in a Palliative Care Department: A Cross-Sectional Analysis

Hiponatremia em Doentes com Cancro Internados num Serviço de Cuidados Paliativos: Uma Análise Transversal

José FERRAZ GONÇALVES✉[1,2], Mariana BRANDÃO[3,4], Ana AREDE[5], Bárbara PRUCHA[6], Inês GRILO[7], Susete FREITAS[8], Isabel COSTA[1], Olímpia MARTINS[9], Vânia ARAÚJO[1]
Acta Med Port 2022 Feb;35(2):105-110 ▪ https://doi.org/10.20344/amp.15810

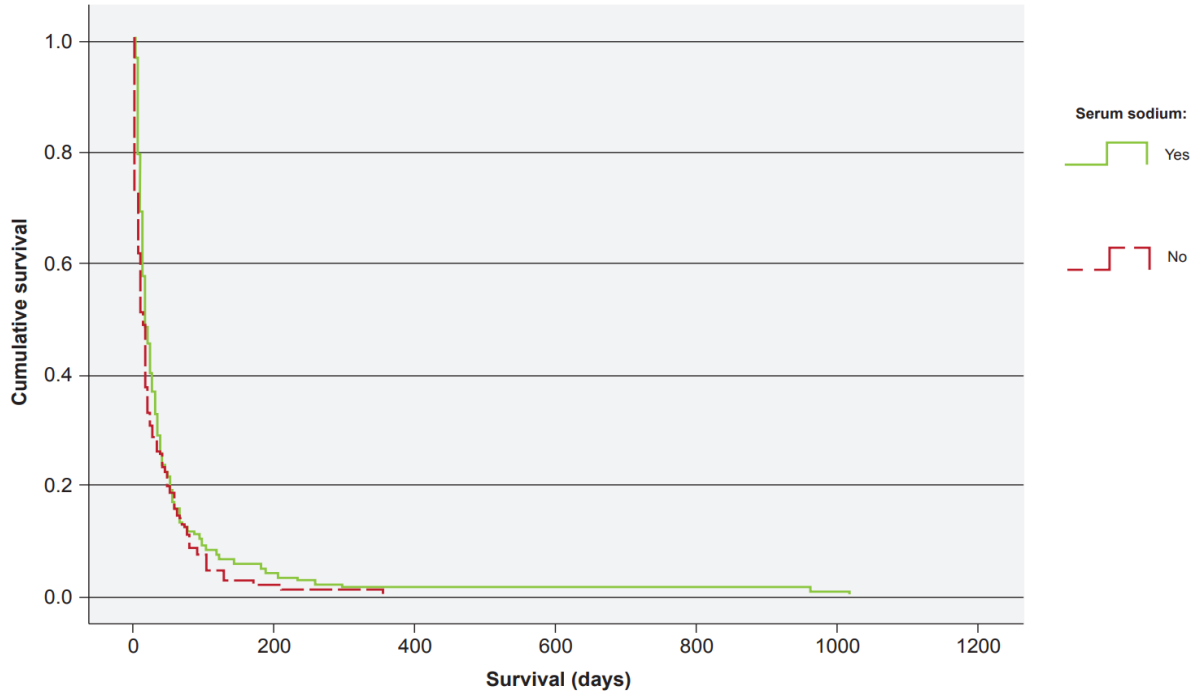

Figure 2 – Survival comparison between patients tested and not tested

49% of the cancer patients hospitalized in the **palliative care** department had hyponatremia.

However, in this end-of-life setting, hyponatremia was not associated with a poorer prognosis.

cancers

MDPI

Review

Hyponatremia and Cancer: From Bedside to Benchside

Benedetta Fibbi [1,2,†], Giada Marroncini [2,3,†], Laura Naldi [2,3], Cecilia Anceschi [2,3], Alice Errico [2,3], Dario Norello [1,2] and Alessandro Peri [1,2,3,*]

Cancers 2023, 15, 1197. https://doi.org/10.3390/cancers15041197

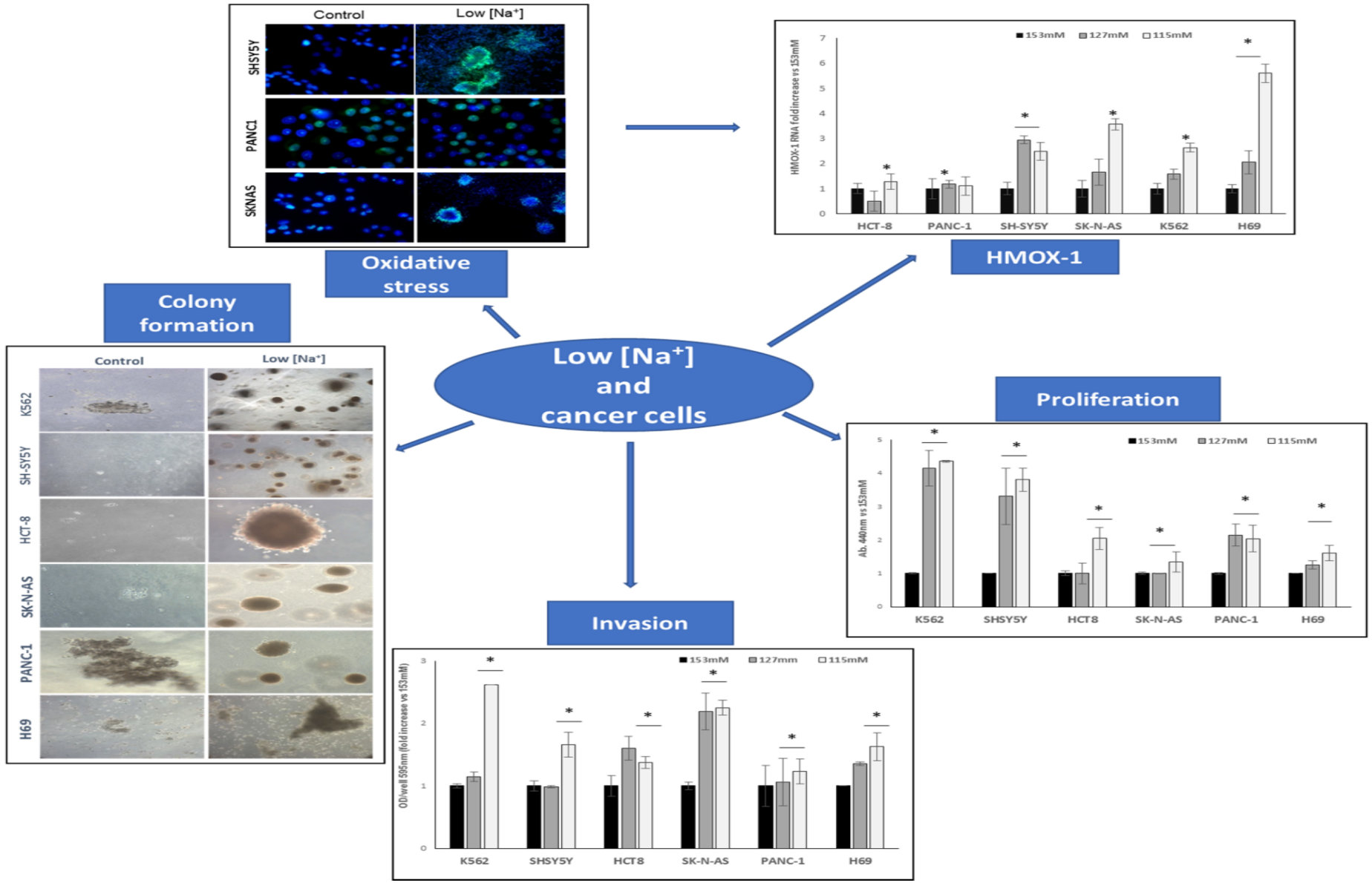

Figure 1. Different features of cancer cell lines cultured in normal extracellular [Na^+] vs. low [Na^+]. *: $p \leq 0.05$.

Cancers 2023, 15, 1197. https://doi.org/10.3390/cancers15041197

Etiolgy

- ✓Cancer:

- ✓ Paraneoplastic syndromes such as SIADH,
- ✓ Brain metastasis
- ✓ Adrenal metastasis
- ✓ Kidney metastasis

- ✓

Berardi *et al*. *J Cancer Metastasis Treat* 2019;5:79

Bioelectricity. March 2020; 2(1): 14–20.
Published online 2020 Mar 18. doi: 10.1089/bioe.2019.0035
PMCID:
PM

Hyponatremia and Cancer Progression: Possible Association with Sodium-Transporting Proteins

Mustafa B.A. Djamgoz, PhD [1, , 2]

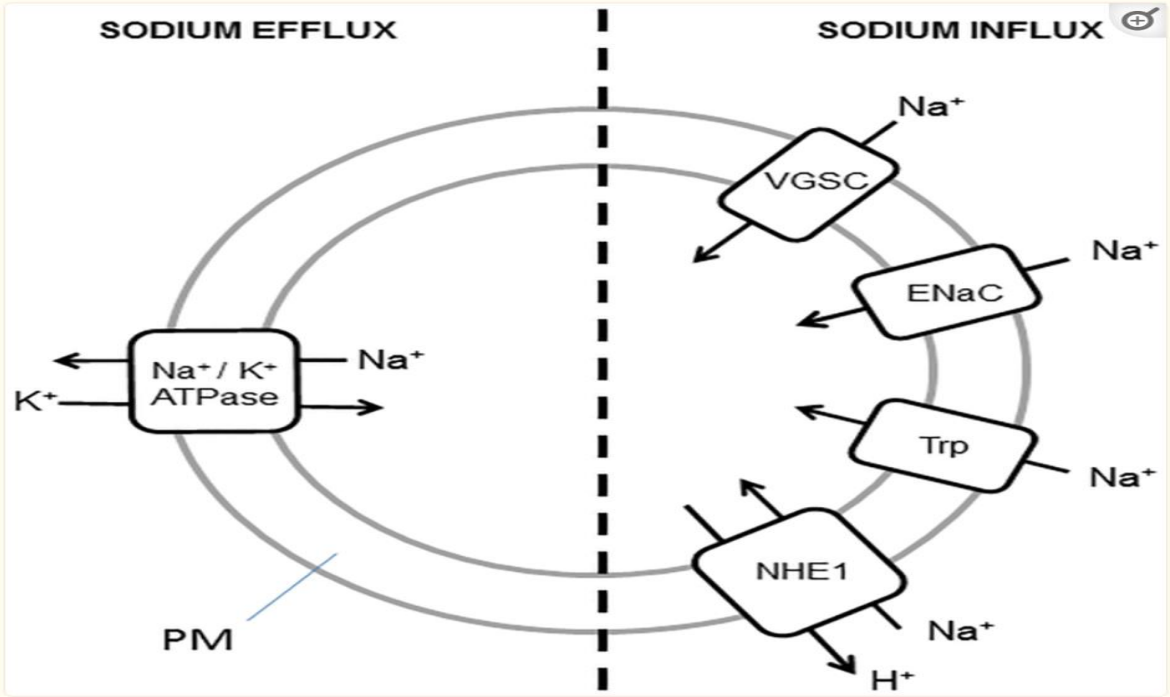

FIG. 2.

A schematic cell showing sodium-transporting proteins in the PM. Various sodium-transporting proteins are responsible for influx of Na^+ into cells. These are exemplified by VGSC, ENaC, and Trp channels. The other set of sodium-transporting proteins are exchangers, exemplified in the scheme by the NHE1. ENaC, epithelial sodium channel; NHE1, Na^+-H^+ exchanger; PM, plasma membrane; Trp, transient receptor potential; VGSC, voltage-gated sodium channel.

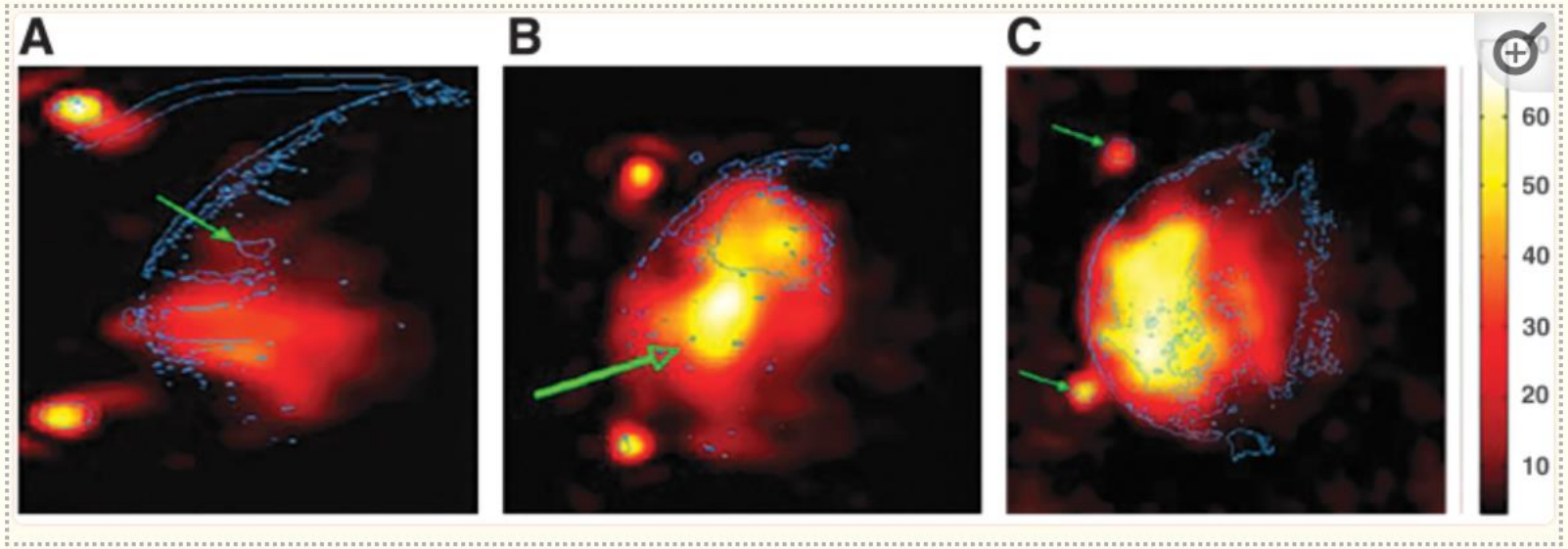

FIG. 4.

Accumulation of sodium in breast tissue during cancer initiation and progression, measured with [23]Na-magnetic resonance imagining. Images from three different breast cancer patients are shown. **(A)** A benign lesion (proliferative fibrocystosis), indicated by the arrow, aligned from gadolinium-enhanced image. **(B)** Infiltrating poorly differentiated ductal carcinoma (outlined in blue). Below (indicated by the green arrow) is a region with edema. **(C)** A large locally advanced breast cancer (outline in middle blue). The arrows indicate positioning landmarks. The intensity scale on the far right indicates approximate sodium concentrations (relative). Modified from Ouwerkerk et al.[42]

✓Cancer-treatment:

- ✓As a result of side effects such as gastrointestinal losses (vomiting and diarrhea caused by most of the chemotherapeutic agents, target therapies, and immunotherapy)
- ✓ Direct effect of their mechanism of action (vinca alkaloids, platinum derivates; and target therapies, in particular anti-angiogenetic agents.)
- ✓kidney loss
- ✓Heart failure (**cardiotoxic drugs** such as anthracyclines and **target therapies** such as anti-HER-2, anti-ALK, and anti-MEK.)
- ✓Immunotherapeutic agents might cause **direct damage to adrenal or pituitary** gland,Thyroidiyis,SIADH

Berardi *et al*. *J Cancer Metastasis Treat* 2019;5:79

✓Concomitant drugs:

✓diuretics, antibiotics, (NSAIDs), opioids, antidepressants, and neuroleptics

✓Concomitant diseases:

✓ heart failure, kidney failure, thyroiditis, hypocortisolism, liver cirrhosis, pneumonia, and inflammatory lung or brain diseases

Journal of Pharmaceutical Research International

34(40A): 6-13, 2022; Article no.JPRI.87968
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Causes of Dysnatremia in Cancer Patients: A Review

Daniela Rădulescu [a,b*], Ileana Adela Văcăroiu [a,b], Flavia Liliana Turcu [a,b] and Carmen Bogeanu [a,b]

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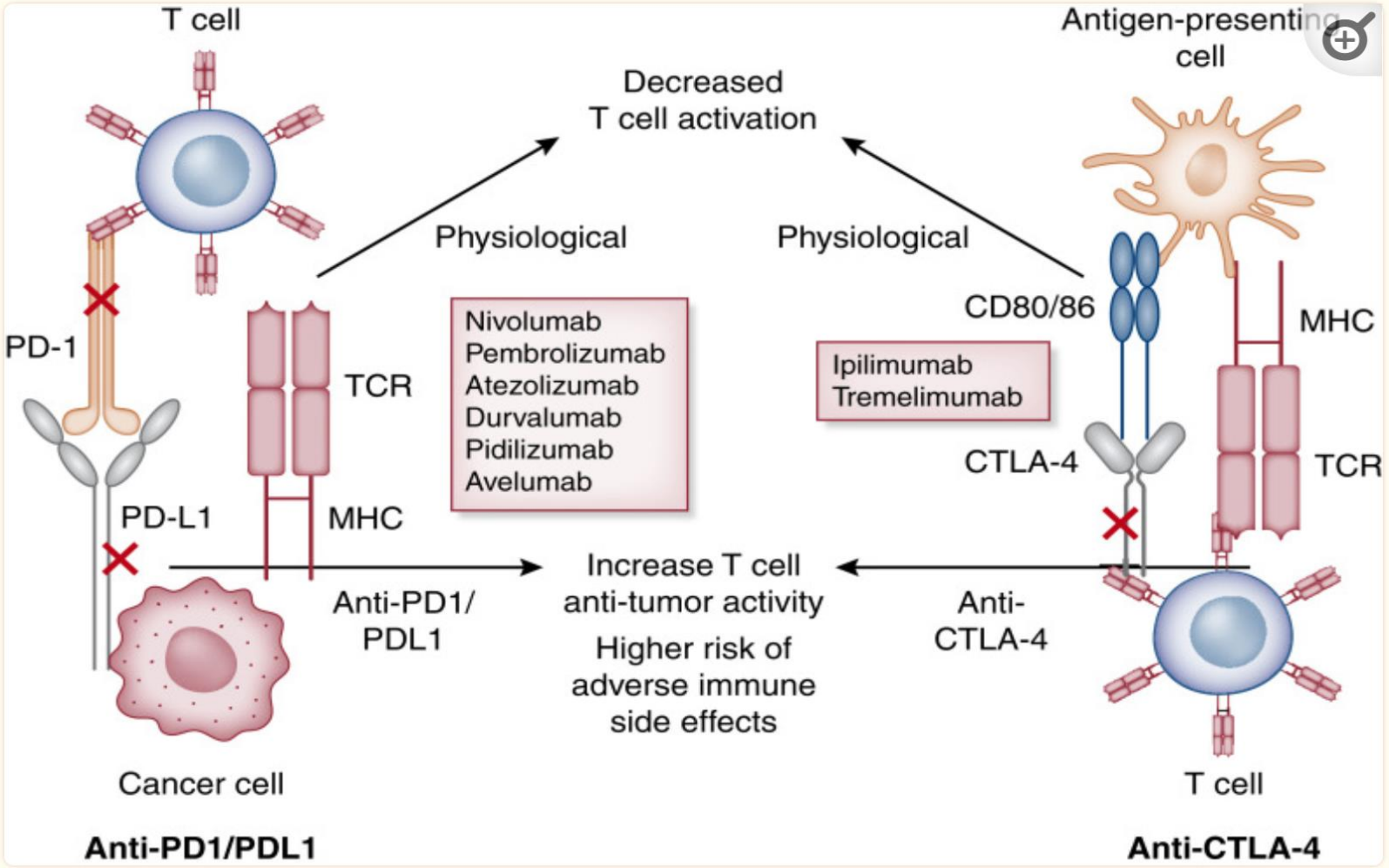

T cell
Antigen-presenting cell
Decreased T cell activation
Physiological
Physiological
PD-1
TCR
Nivolumab
Pembrolizumab
Atezolizumab
Durvalumab
Pidilizumab
Avelumab
CD80/86
MHC
Ipilimumab
Tremelimumab
CTLA-4
TCR
PD-L1
MHC
Increase T cell anti-tumor activity
Higher risk of adverse immune side effects
Anti-PD1/ PDL1
Anti-CTLA-4
Cancer cell
T cell
Anti-PD1/PDL1
Anti-CTLA-4

Immune check point inhibitors

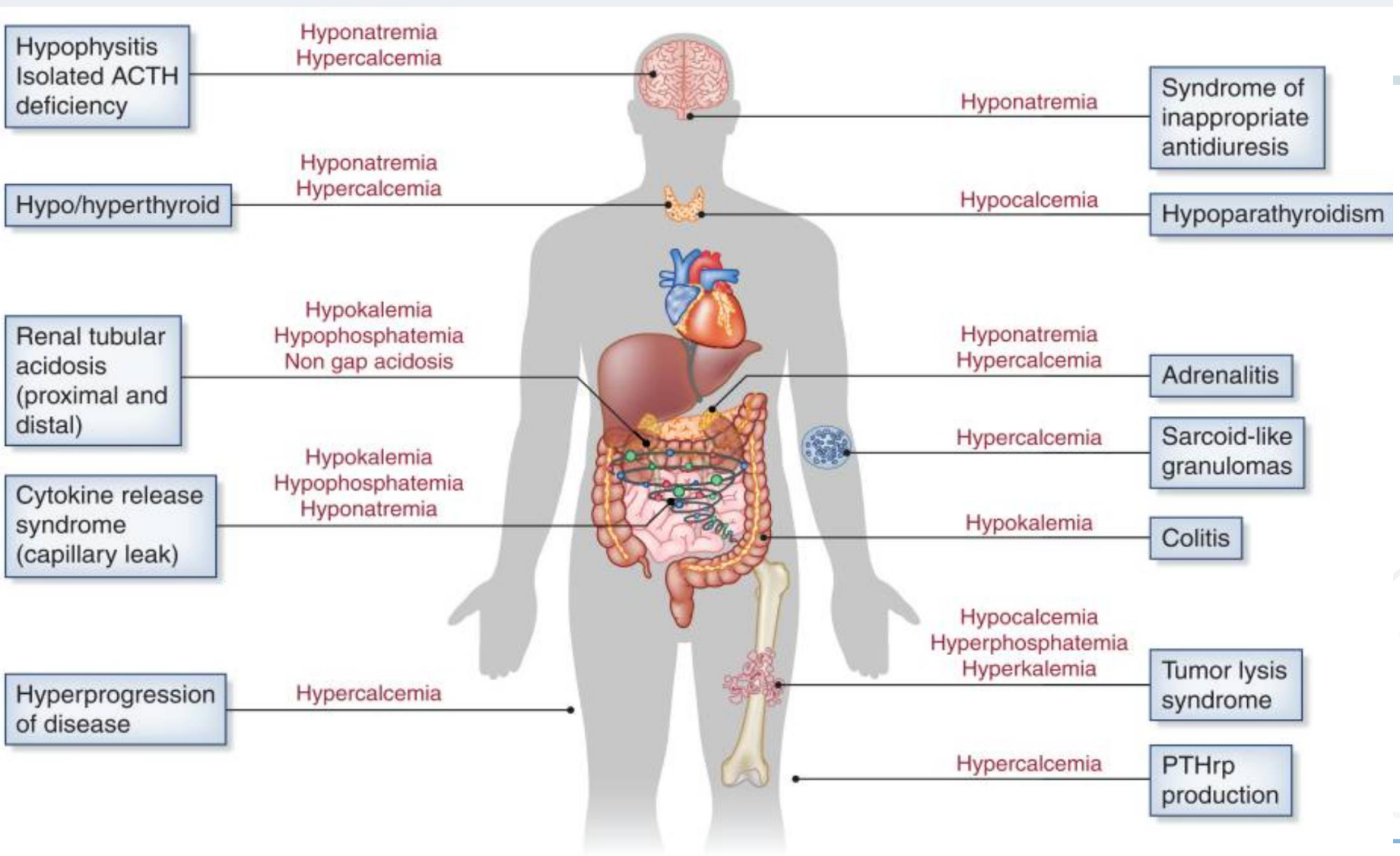


Table 2. Cancer immunotherapy–associated electrolyte disorders

Electrolyte	Disorder	Cancer Immunotherapy	Mechanism
Sodium	Hyponatremia	Immune checkpoint inhibitors	Hypophysitis Adrenalitis Thyroiditis SIADH
		CAR-T cell therapy	CRS Hypovolemia
Potassium	Hypokalemia	Immune checkpoint inhibitors	GI losses (Gastritis, Colitis) Distal and proximal RTA
		CAR-T cell therapy	Renal tubular defect
Calcium	Hypocalcemia	Immune checkpoint inhibitors	Autoimmune hypoparathyroidism TLS
		CAR-T cell therapy	TLS
	Hypercalcemia	Immune checkpoint inhibitors	Hypophysitis Thyroid disorders ICI-related PTHrP Hyperprogression of disease Sarcoid-like granulomas
Phosphorous	Hypophosphatemia	Immune checkpoint inhibitors	Proximal tubulopathy GI losses
		CAR-T cell therapy	Unknown (hypotheses GI or kidney losses)
	Hyperphosphatemia	Immune checkpoint inhibitors	TLS
		CAR-T cell therapy	TLS
Magnesium	Hypomagnesemia	Immune checkpoint inhibitors	GI losses, inflammatory diarrhea.

SIADH, syndrome of inappropriate antidiuretic hormone; CAR-T, chimeric antigen receptor T cells; CRS, cytokine release syndrome; GI, gastrointestinal; RTA, renal tubular acidosis; TLS, tumor lysis syndrome; ICI, immune checkpoint inhibitor; PTHrP, parathyroid-related peptide.

- ✓Diagnosis of hyponatremia requires routine laboratory tests.
- ✓For a correct therapeutic approach, it is crucial to identify the underlying causes,
- ✓thus assessment should also include
- ✓ ECV status evaluation
- ✓ plasma and urine osmolality
- ✓urinary sodium concentration

Tolvaptan

- ✓In the case of hyponatremia secondary to SIAD, the use of Tolvaptan, should be considered.
- ✓It has shown an important efficacy to correct and stabilize serum sodium concentration.
- ✓ Tolvaptan schedule requires starting dose of 15 mg once daily and it should be administrated first in a hospital department.
- ✓ It could be increased at 24-h interval, to a maximum of 60 mg once a day.

Effects of tolvaptan in cancer cell lines

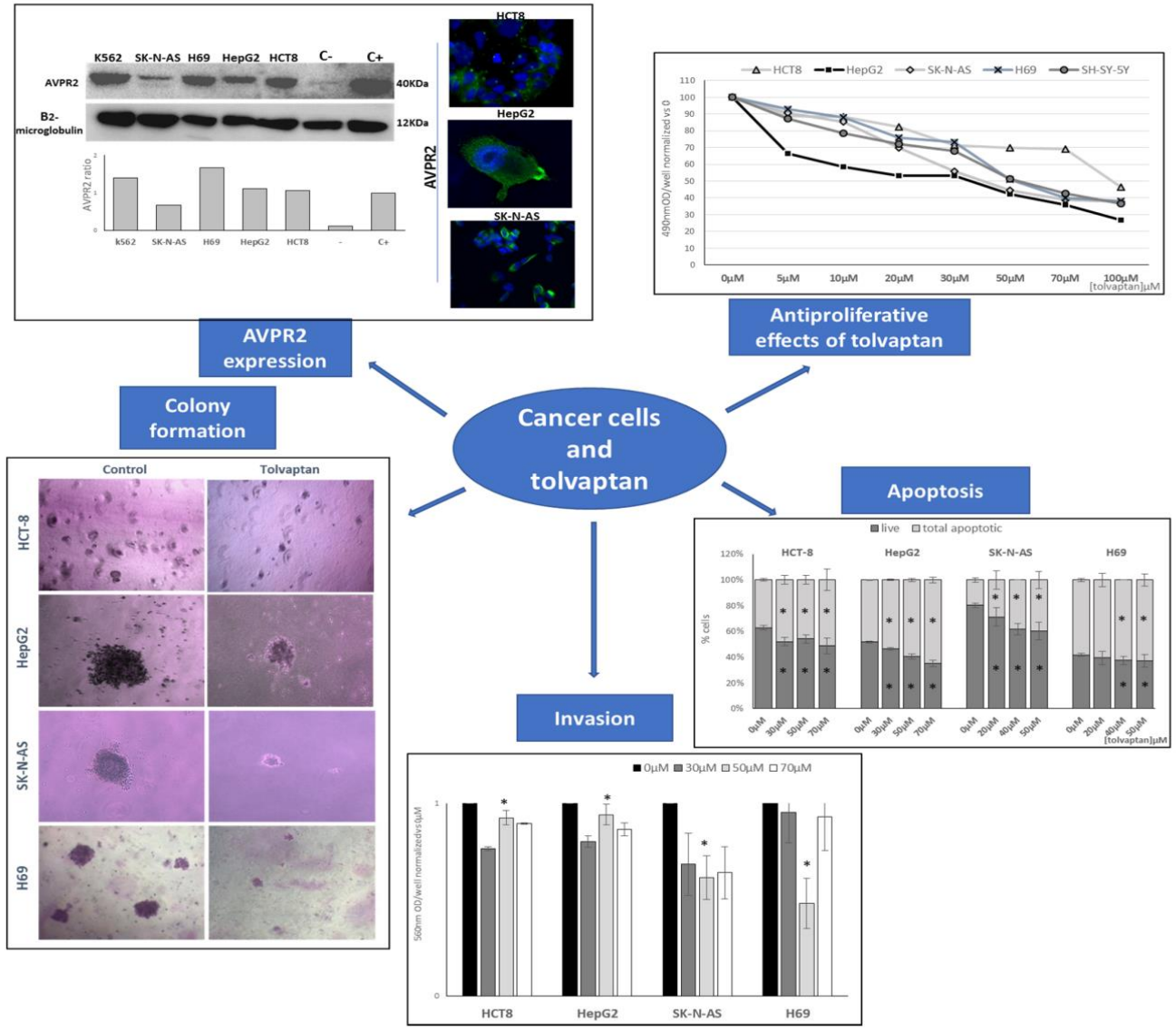


Figure 2. Effects of tolvaptan in cancer cell lines. *: $p \leq 0.05$.

- ✓The normalization of serum [Na+] has an independent beneficial effect on the prognosis of cancer patients.
- ✓In this scenario, the **encouraging effects of AVPR antagonists** in **counteracting cell proliferation** and **invasivity** in experimental models could be considered

Cancers 2023, 15, 1197

Clin Endocrinol (Oxf). 2019 Jun;90(6):842-848. doi: 10.1111/cen.13966. Epub 2019 Mar 29.

Urea in cancer patients with chronic SIAD–induced hyponatremia: Old drug, new evidence

Alice Nervo [1], Valentina D'Angelo [1], Daniela Rosso [1], Eleonora Castellana [2], Francesco Cattel [2], Emanuela Arvat [1], Emidio Grossi [1]

- ✓Retrospectively analysed **36** cancer patients, affected by moderate or profound **SIADH-induced** chronic hyponatremia, who started oral urea (initial daily dose 15 g or 30 g) without fluid restriction between July 2013 and July 2018.
- ✓Almost **all patients** reached eunatremia **within the first month** of therapy, and urea was globally well tolerated.

Hypernatremia

- ✓ True hypernatremia is rare in cancer patients, reported in less than 3% of patients
- ✓ It is associated with higher mortality and hospitalization length.

- ✓The presence of hypernatremia denotes reduced water intake, free water loss, or increased sodium intake.

Current Oncology

MDPI

Article

Outcome of Hospitalized Cancer Patients with Hypernatremia: A Retrospective Case-Control Study

Jessica del Rio [1] and Martin Buess [2,*]

Hypernatremia was found in 93 (**3.16%**) of **2945 inpatients** bearing cancer or lymphoma. From 991 eligible normonatremic control patients, 93 were matched according to diagnosis, age, and sex. The **median overall survival time** (OS) of patients with hypernatremia was **1.5 months** compared to **11.7 months** of the normonatremic controls (HR 2.69, 95% CI 1.85–3.90, $p < 0.0001$).

Curr. Oncol. **2022**, *29*(11), 8814-8824

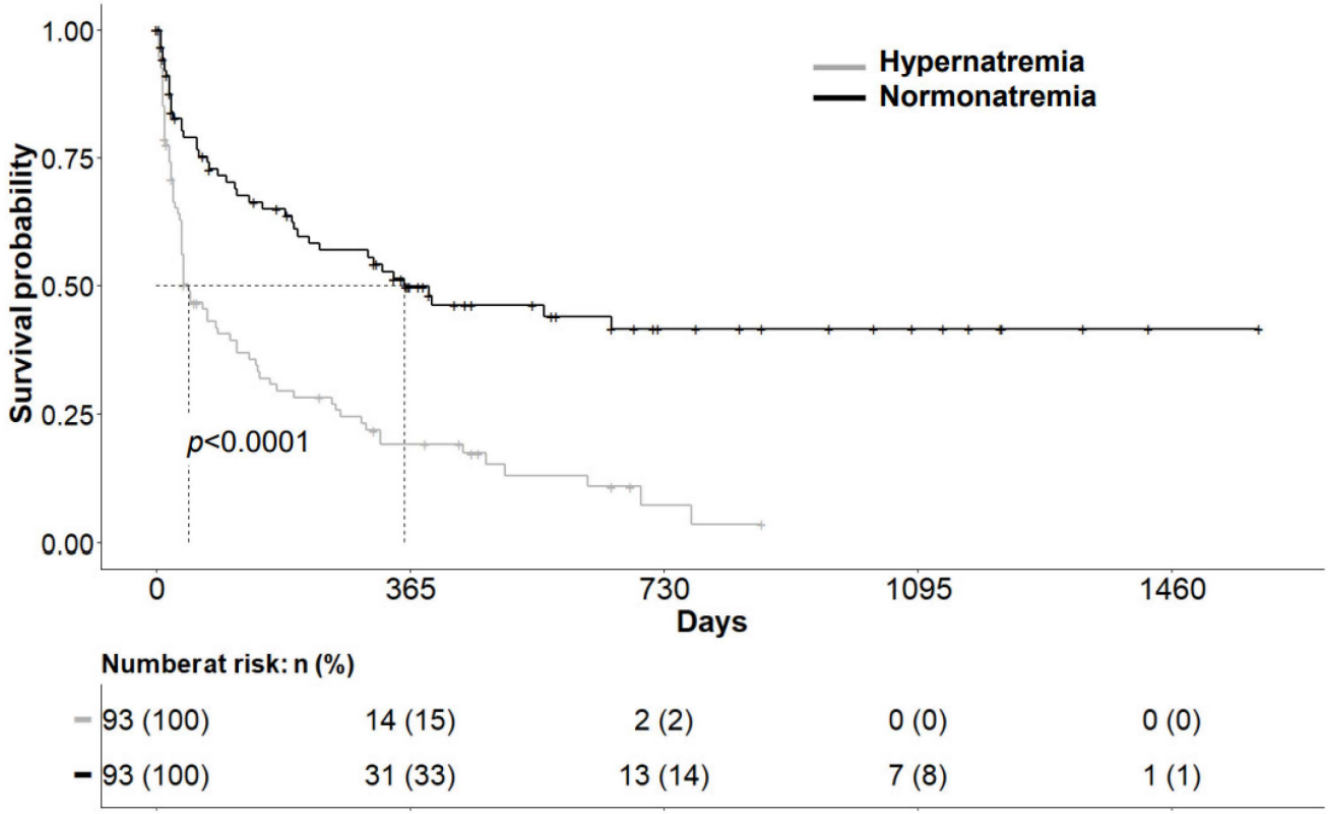


Figure 2. Kaplan–Meier analysis of Overall Survival: Log rank test was performed to compare the survival curves, which showed a significantly different survival ($p < 0.0001$). Median survival time of the hypernatremic group was 1.5 months compared to 11.7 months for the normonatremic group.

Hypernatremia

- ✓ Cancer:
- ✓ **anorexia and cancer cachexia**,
- ✓ kidney damage,
- ✓ **brain metastasis** inducing diabetes insipidus
- ✓ **gastrointestinal disorders** due to cancer infiltration (e.g., fistulae and nasogastric drainage due to bowel obstruction)

- ✓ Cancer treatment:
- ✓ adverse events such as **vomiting and diarrhea** common to most anti-cancer agents
- ✓ (**Chemotherapy, TKIs, and immunotherapies**) associated with **reduced thirst stimulation**.

- ✓ **Direct bowel damage due to antiangiogenetic agents or immunotherapy.**
- ✓ some chemotherapeutic agents such as **ifosfamide** might induce an iatrogenicDI.

Hypernatremia

✓ Concomitant drugs:

osmotic diuretics, corticosteroids, enteral or parenteral nutrition, hypertonic saline infusion can induce hypernatremia.

✓ Concomitant diseases:

Cushing syndrome might induce hypernatremia.

- ✓ **BrainTumors** or secondary to **whole brain radiation** in patients with central nervous system lymphomas or brain tumors.(**DI**)

- ✓ lesions involving **hypothalamic osmoreceptors** may lead to **reduced thirst**, a dangerous and rare syndrome called **adipsic diabetes insipidus.**

- ✓ Some chemotherapeutics may induce **nephrogenic diabetes insipidus**; the most commonly involved are **amphotericin B, ifosfamide, platinum derivatives,Pemetrexed**

Review Article

Kidney360®

Onconephrology 2022: An Update

Marco Bonilla,[1] Prakash Gudsoorkar,[2] Rimda Wanchoo,[3] Sandra M. Herrmann,[4] and Kenar D. Jhaveri[3]

Table 1. Summarized kidney adverse effects from anticancer therapies

Drug Class	Drug Name	Mechanism of Injury	Kidney Effect
Conventional chemotherapy			
Platinum-based	Cisplatin, carboplatin, oxaliplatin.	Platinum-DNA adducts mediate arrest of cell cycle, initiate apoptosis. ATP depletion.	ATI, renal magnesium wasting, proximal tubulopathy, NDI
Antimetabolite	Methotrexate	Intratubular crystal formation. Afferent arteriolar constriction	Crystal nephropathy, ATI
	Gemcitabine	Endothelial injury	TMA, HTN
	Pemetrexed	Unknown	ATI, chronic interstitial fibrosis, proximal tubulopathy, NDI
Alkylating agent	Cyclophosphamide	Toxic metabolite, acrolein	Hemorrhagic cystitis
	Ifosfamide	Toxic metabolite, chloroacetaldehyde	ATI, proximal tubulopathy, NDI
	Melphalan	Increase ADH release	SIADH
	Nitrosoureas	Alkylation of tubular cell proteins	Chronic interstitial nephritis
Antitumor antibiotics	Mitomycin C	Endothelial injury	TMA, HTN

Hypercalcemia

- ✓ It is a common electrolyte disorder in patients with advanced malignancies and it correlates with poor prognosis.

- ✓ It was described as occurring in 20%-30% of cancer patients, especially those hospitalized, and it represents one of the **most common life-threatening metabolic disorders.**

Cancer-related hypercalcemia and potential treatments

Elvina Almuradova[1] and Irfan Cicin[2*]

[1]Tınaztepe Galen Hospital, Medical Oncology Center, Izmir, Türkiye, [2]Medical Oncology Department, Faculty of Medicine, Trakya University, Trakya, Türkiye

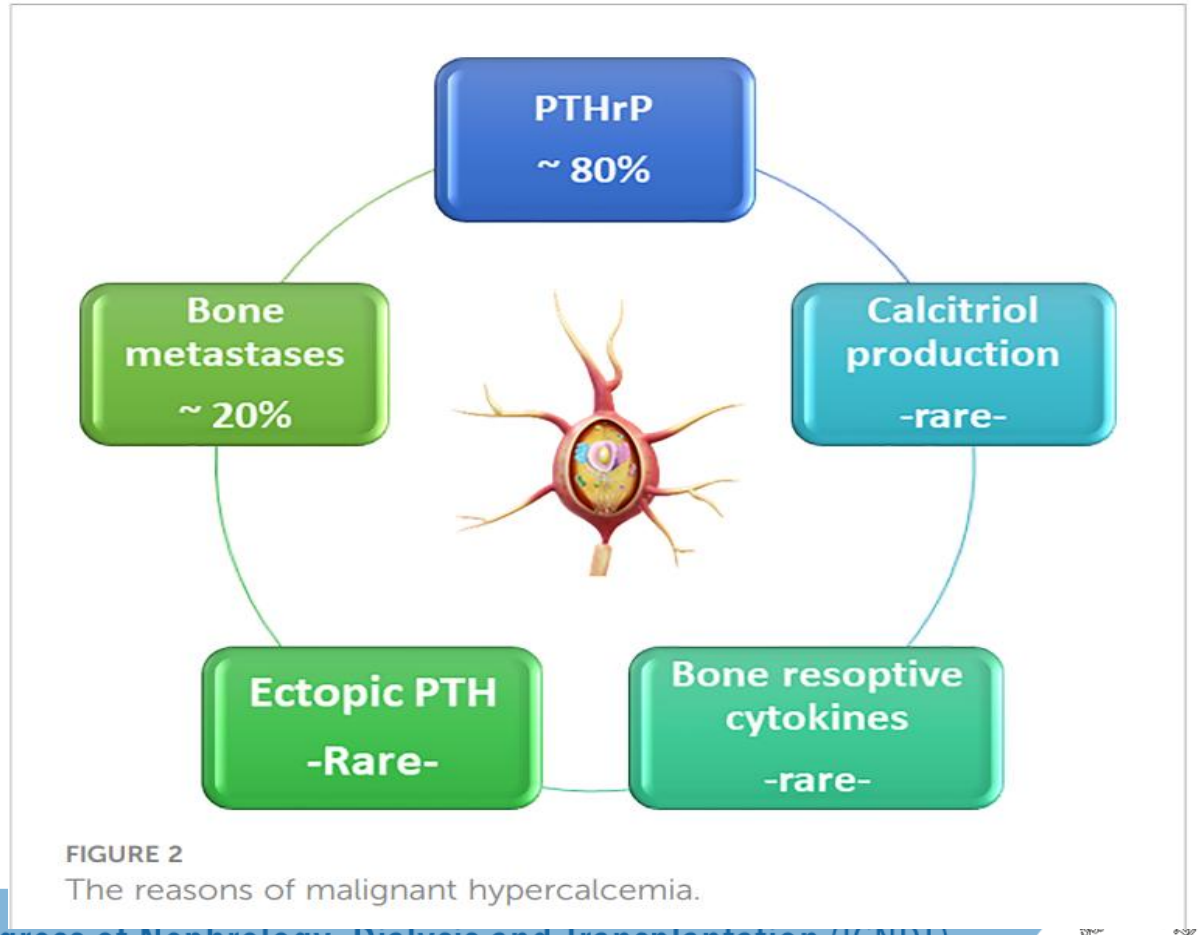


FIGURE 2
The reasons of malignant hypercalcemia.

Front. Endocrinol. 14:1039

- ✓ Bone metastasis, in particular **osteolytic ones**, is often associated with hypercalcemia due to calcium release from bone.

- ✓ It represents a common cause of hypercalcemia, occurring in approximately 20% of patients.

- ✓ Bone metastasis releases several local factors, e.g., TGF β, RANKL, lymphotoxin, interleukin-1, interleukin-6, hepatocyte growth factor, and macrophage inflammatory protein (MIP-1alfa).

- ✓Rarely, hypercalcemia might be due to **ectopic activity of 1-alpha-hydroxylase** resulting in calcitriol production.
- ✓This mechanism is described in some kinds of tumors such as **lymphomas** and **ovarian germ cell tumors**.
- ✓Finally, **immobilization** due to bedridden patients, a common condition of advanced cancer, can favor an **acceleration of bone resorption** resulting in hypercalcemia.

Review

Thieme

Diagnosis, Pathophysiology and Management of Hypercalcemia in Malignancy: A Review of the Literature

Authors
Nikolaos Asonitis[1], Anna Angelousi[1], Christos Zafeiris[2], George I. Lambrou[3], Ismene Dontas[2], Eva Kassi[1,4]

Horm Metab Res 2019; 51(12): 770-778

► **Table 1** Clinical features of hypercalcemia of malignancy.

Signs and symptoms of hypercalcemia of malignancy	
Neurologic	Muscle weakness, fatigue, hyporeflexia, apathy, disturbances of perception and behavior, lethargy, stupor, and coma
Renal	Polyuria, polydipsia, volume depletion, progressive renal insufficiency, nephrocalcinosis, and nephrolithiasis
Gastrointestinal	Nausea, anorexia, vomiting, constipation, ileus, peptic ulcer disease, pancreatitis
Cardiovascular	Shortened ST segments and QT intervals, widened T waves, and bundle branch Block depressed ST segments, second-degree block, bradydysrhythmias, complete heart block, cardiac arrest, and hypertension
Dermatologic	Pruritus

Hypercalcemia

✓Cancer treatment:

✓antineoplastic drugs can indirectly cause hypercalcemia.

✓ Concomitant drugs:

✓several drugs might cause hypercalcemia. Thiazide diuretics, vitamin D intoxication, and parenteral nutrition are the most common agents involved in this electrolyte disorder in cancer patients.

✓ Concomitant diseases:

✓ primary hyperparathyroidism due to parathyroid adenoma, familial hypocalciuric hypercalcemia, isolated familial hyperparathyroidism, or most commonly secondary hyperparathyroidism, due to renal failure or drugs such as lithium).

✓ Mechanisms independent of PTH (chronic granulomatous disorders, hyperthyroidism, acromegaly, pheochromocytoma, and adrenal insufficiency

✓

TABLE 1 Treatment options for hypercalcemia of malignancy.

Agent	Regimen	Mechanism of action	Onset	Duration	Side Effects
0.9% saline	2-4 l/day or 200-500 ml/h	Enhance renal excretion of Ca^{2+}	Immediate	1-3 days (depends on cardiovascular and renal status)	Volume overload
Zoledronic acid or Pamidronate	4 mg IV over 15 to 30 minutes in a solution of 50-100 ml NS or D5W 60 to 90 mg IV over 4 to 24 hours	Inhibits osteoclastic bone resorption	48 hours	Every 3-4 weeks May be additional	Renal toxicity, acute-phase reactions, gastrointestinal toxicity, hypocalcemia and osteonecrosis of the jaw
Denosumab	120 mg SQ	İnhibits the binding of RANKL with its receptor RANK and decreases OC activity	7-10 days	Every 4 weeks and additional on days 8 and 15 for first month	Allergic reactions, hypocalcemia, osteonecrosis
Calcitonin	4 units/kg SQ repeated every 6-12 hours	Increases renal calcium excretion reduce bone resorption by interfering with OC function	4-6 hours	24 to 48 hours	Pain at the injection site and cutaneous flushing, anaphylactic reactions
Glucocorticoids	200-400 mg/day of hydrocortisone 10-20 mg/day of prednisone	Inhibit $1,25(OH)_2$ D synthesis and thus calcium absorption from the intestine	7 days	3-10 days (unclear)	Myopathy, immunosuppression, elevated blood glucose
Gallium Nitrate	100 to 200 mg/m2 IV over 24 hours for 5 days	inhibits osteoclast activity	4 days	2 weeks	Nephrotoxicity, bone marrow supression

Ca^{2+} calcium ions; SQ subcutaneously; D5W 5% dextrose in water; NS normal saline; OC osteoclastic; RANK receptor activator of nuclear factor kappa-B ligand.

Parathyroid carcinoma is the only malignancy for which cinacalcet is approved

Glucocorticoid	Inhibits 1-alpha-hydroxylase and lowers 1,25-dihydroxyvitamin D levels	Oral administration of 60 mg of prednisone per day for 10 days†	Has variable effects. Normalization of calcium levels possible if 1,25-dihydroxyvitamin D levels are significantly reduced. Response typically transient unless tumors are treated.	Hyperglycemia, altered mental status, hypertension, increased risk of infection and thromboembolism	Most commonly used in patients with lymphoma. Consider adding to bisphosphonate or denosumab in patients with humoral hypercalcemia and elevated circulating levels of 1,25-dihydroxyvitamin D.
Cinacalcet	Binds calcium-sensing receptor and inhibits secretion of parathyroid hormone in patients with parathyroid carcinoma and may increase renal calcium absorption through renal calcium-sensing receptor in nonparathyroid hypercalcemia	Oral administration of 30 mg per day initially. Can increase to 90 mg four times daily as needed to control hypercalcemia	Reduced calcium by at least 1 mg/dl in approximately 60% of patients with inoperable parathyroid carcinoma. Case reports of normalization of calcium in some nonparathyroid cancers in combination with other treatments.	Nausea, vomiting, headache, fractures	Approved for treatment of hypercalcemia related to parathyroid cancer. Case reports indicate reduction of calcium levels in patients with refractory hypercalcemia related to non–small-cell lung, neuroendocrine, breast, or renal cancer.
Dialysis	Removes excess calcium directly	Administration of low-calcium or calcium-free dialysate through peritoneal dialysis or hemodialysis	Transient reduction of calcium during dialysis		Can be useful initially in patients with severe chronic kidney disease or acute, life-threatening hypercalcemia.

Editorial: Cancer-related hypercalcemia and potential treatments

Lorenzo Scappaticcio[1,2*], Arif Nur Muhammad Ansori[3,4] and Pierpaolo Trimboli[5,6]

Front. Endocrinol. September 2023,14:1281731

TABLE 1 Main findings of each paper included in this Research Topic.

Main findings	Reference
The mainstay of therapy is represented by IV saline hydration and antiresorptive agents	Almuradova and Cicin
In refractory/recurrent CrH on bisphosphonate therapy denosumab should be started. Other treatment options are oral phosphorus, corticosteroids, furosemide	Farooki et al.
In case of CrH due to PC, in moderate to severe hypercalcemia IV bisphosphonates or denosumab are the initial therapy; conversely, cinacalcet is started in mild hypercalcemia	Roukain et al.
Therapy of liver metastases by PC is palliative and primarily aims to improve symptoms of hypercalcemia through surgery and/or ablation therapies	Su et al.
When CrH is associated with NETs, SSAs can serve as a further therapy to reduce hypercalcemia	Herrera-Martínez et al., Sapuppo et al.

IV, intravenous; CrH, cancer-related hypercalcemia; PC, parathyroid carcinoma; NETs, neuroendocrine tumors; SSAs, somatostatin analogues.

Hypocalcemia

- ✓ Cancer:
- ✓ malnutrition due to anorexia, cancer cachexia or bowel obstruction, malabsorption related to bowel tumor infiltration or previous intestinal surgery, and abnormal liver function due to liver metastasis might promote the development of hypoalbuminemia and subsequent hypocalcemia.
- ✓ Malabsorption and malnutrition might frequently cause vitamin D deficiency and then hypocalcemia in cancer patients.
- ✓ PTH deficiency is a common condition in patients undergoing total thyroidectomy with subtotal or total parathyroidectomy for cancer.
- ✓ tumor lysis syndrome or hungry bone syndrome. The "hungry bone syndrome" is frequent in **metastatic parathyroid and prostate cancer** and it is characterized by **osteoblastic metastases**.

✓Cancer treatment:

✓receiving bisphosphonates or denosumab, an anti-RANKL monoclonal antibody, employed in cancer patients with **bone metastasis** .

✓ Ionized calcium: **hyperlipidemia, parenteral nutrition** enriched of free fatty acid Extravascular deposition: **osteoblastic metastases**, **pancreatitis,** Renal failure Iatrogenic, **post-renal obstruction**, compression and infiltration by malignancy, **tumor lysis syndrome**, **sepsis**, contrast agent nephropathy.

✓ Endocrine disorders Vitamin D deficiency or resistance: inadequate dietary intake, reduced absorption due to **hepatobiliary or intestinal malabsorption**, **liver disease, PTH deficiency or resistance**: **parathyroidectomy**, **autoimmune disorders**, hungry bone syndrome.

✓Concomitant electrolyte disorders **Hypomagnesemia, Hyperphosphatemia.**

✓ Drugs

✓**Antiepileptics**: phenytoin, phenobarbital

✓ **Anticancer agents**:

✓ **fluorouracil, leucovorin, nab-paclitaxel, estramustine, octreotide**, imatinib, axitinib, panitumumab, cetuximab, cisplatin

✓Others: **bisphosphonates, denosumab**, **rifampicin,** calcium chelators, radiographic contrast agent, furosemide, foscarnet, EDTA, cinacalcet.

✓ chemotherapeutic agents, **target therapies**, and **immunotherapies** can induce hypocalcemia in cancer patients, through different mechanisms: **kidney injuries**, iatrogenic **magnesium deficiency**, **gastrointestinal damage**, and **pancreatitis.**

✓In particular, monoclonal **anti-EGFR antibodies** can cause **hypomagnesemia** with consequent hypocalcemia.

Berardi *et al. J Cancer Metastasis Treat* 2019;5:79

- ✓ Concomitant drugs: **diuretics** and **parenteral nutrition** can induce hypocalcemia.

- ✓ Concomitant diseases: **kidney failure**, autoimmune disorders causing **PTH deficiency**, **sepsis**, and **pancreatitis** can induce hypocalcemia.

Hypokalemia

Cancer:

- ✓ **Inadequate intake** (**malnutrition, anorexia, and malabsorption** due to cancer bowel infiltration or bowel obstruction).
- ✓ Some **neuroendocrine tumors** might cause hypokalemia through **secretive diarrhea**, favoring potassium losses.
- ✓ The production of **hormones** such as **mineralocorticoids** (**ACTH), cortisol, and**, or through **kidney** damage, such as **multiple myeloma**,AML.
- ✓ Cancer treatment:
- ✓ chemotherapeutic agents target therapies, and immunotherapies might cause hypokalemia secondary to diarrhea or vomiting. **drug-related tubular toxicity**.
- ✓ Concomitant drugs: thiazide diuretics, insulin, **GSCF,** beta-2 agonists, and glucocorticoids
- ✓ Concomitant diseases: endocrine dysfunctions causing **excess glucocorticoids** or **mineralocorticoids, toxic epidermal necrolysis**, and inflammatory bowel diseases
- ✓ Berardi *et al*. *J Cancer Metastasis Treat* 2019;5:79

- ✓For example, Cushing syndrome can be due in rare cases to **ACTH-producing tumors**, especially in patients with **small-cell** lung cancer, **medullary thyroid** carcinoma, **islet cell adenoma** or carcinoma, **pheochromocytoma**, and **ganglioneuroma**.

- ✓.

Hyperkalemia

- ✓Causes Several causes might induce hypokalemia in cancer patients:
- ✓ Cancer:
- ✓ Tumors with **high proliferative index** such as leukemia and small-cell lung carcinomas can result in **lysis syndrome**.

- ✓ Cancer treatment:
- ✓chemotherapeutic agents, such as **platinum** derivatives, might cause **renal injury**, which can lead to hyperkalemia.

✓ Concomitant drugs:

✓diuretics, potassium-sparing diuretics, angiotensin-converting enzymes, inhibitors, and NSAIDs might induce hyperkalemia.

✓Concomitant diseases: **renal failure**, **diabetes mellitus**, **sepsis**, and **parenteral nutrition** might induce hyperkalemia

✓However, despite the high frequency of adrenal metastasis (**40%-60%** of patients), **adrenal insufficiency is rarely** described.

✓**Adrenal insufficiency** secondary to **metastasis involving both adrenal** glands might cause hyperkalemia in cancer patients, especially with advanced **lung** and **breast** cancer or **lymphomas**.

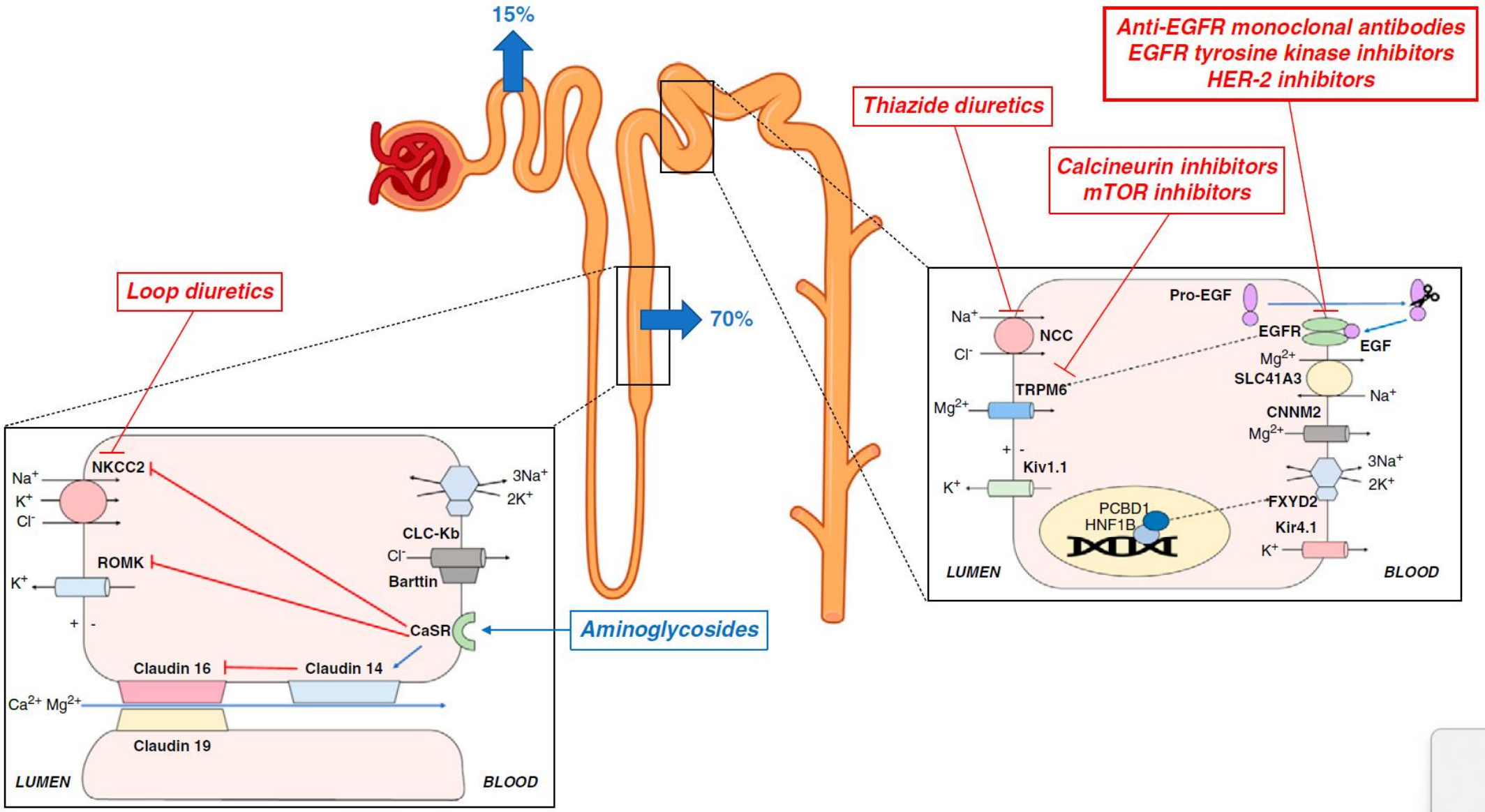
Finally, in the case of elevated leukocytosis or thrombocytosis, hyperkalemia should be distinguished from **pseudo-hyperkalemia**.

Hypomagnesemia

- ✓Hypomagnesemia is a **common** medical problem that contributes to the morbidity and mortality of patients with cancer.
- ✓ The causes of hypomagnesemia : decreased intake, transcellular shift, gastrointestinal losses, and kidney losses.
- ✓Patients with cancer are at risk for **opportunistic infections**, frequently experience **cardiovascular complications**, and often receive classes of medications that cause or exacerbate hypomagnesemia.
- ✓ Also, cancer-specific therapies : **platinum**-based chemotherapy, **anti-EGF receptor mAbs**, human EGF receptor-2 target inhibitors (**HER2**), and **calcineurin inhibitors.**
- ✓ We recommended checking serum magnesium at **the beginning** of treatment and as part of **routine monitoring**.
- ✓ Berardi et al. J Cancer Metastasis Treat 2019;5:79

✓Cetuximab-induced hypomagnesemia is also secondary to primary **renal magnesium wasting**, mechanistically from an **inhibition** of the **basolateral epidermal growth factor receptor**, which **prevents** the transcellular magnesium **reabsorption** through the **(TRPM6)** Mg channels.

KIDNEY360 4: 258–271, 2023


15%
70%
Loop diuretics
Thiazide diuretics
Anti-EGFR monoclonal antibodies
EGFR tyrosine kinase inhibitors
HER-2 inhibitors
Calcineurin inhibitors
mTOR inhibitors
Aminoglycosides
NKCC2
ROMK
CaSR
CLC-Kb
Barttin
Claudin 16
Claudin 14
Claudin 19
LUMEN
BLOOD
NCC
TRPM6
Kiv1.1
Pro-EGF
EGFR
EGF
SLC41A3
CNNM2
FXYD2
Kir4.1
PCBD1
HNF1B

Targeted therapy

VEGF inhibitors	Bevacizumab	Endothelial injury	TMA, HTN, ATI
Tyrosine kinase inhibitors	Sorafenib, sunitinib, axitinib, pazopanib, lenvatinib.	Endothelial injury, podocyte injury.	ATIN, ATI, TMA, FSGS
BCR-ABL tyrosine kinase inhibitor	Imatinib, dasatinib.	Tubular injury, endothelial injury	ATI, TMA
BRAF inhibitors	Vemurafenib, dabrafenib	Tubular injury, ERK activation	ATIN, ATI
BCL-2 inhibitors	Venetoclax	Tubular injury	AKI, TLS
ALK inhibitors	Crizotinib, lorlatinib, alectinib	Inhibition of creatinine secretion, renal arteriolar myocyte vacuolization	Pseudo-AKI, ATIN, ATI, kidney cyst, podocytopathies
CDK4/6 inhibitors	Palbociclib, ribociclib	Inhibit MATE1 and MATE2 transporters	Pseudo-AKI, ATI
PARP inhibitors	Olaparib, talazoparib	Inhibition of creatinine secretion	Pseudo-AKI
MET tyrosine kinase	Capmatinib, tepotinib	Inhibition of creatinine	Pseudo-AKI
EFGR monoclonal antibodies	Cetuximab, panitumumab	Inhibition of EGFR signaling at the DCT	Renal magnesium wasting
mTOR inhibitors	Everolimus	Decrease cubilin and megalin, VEGF inhibition	ATI, podocytopathies
Protease inhibitors	Bortezomib, carfilzomib	Endothelial injury, autoantibody formation	TMA, HTN
BTK inhibitors	Ibrutinib	Endothelial injury	ATI, HTN
XPO inhibitor	Selinexor	Volume depletion	Hemodynamic AKI, hyponatremia

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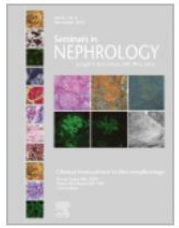

Hypomagnesemia in Patients With Cancer: The Forgotten Ion

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ADJUNCT AGENTS USED IN PATIENTS WITH CANCER

- ✓The link between **PPIs** and hypomagnesemia is well established.
- ✓ PPIs can lead to **intestinal losses** and malabsorption of magnesium, as well as **renal wasting** of the mineral.
- ✓Cancer patients commonly use **laxatives and diuretics**, both of which can cause hypomagnesemia.
- ✓Medications such as **pamidronate and denosumab**, used to treat hypercalcemia in cancer, also have been associated with hypomagnesemia.
- ✓Antimicrobial agents such as **aminoglycosides, amphotericin B**, and capreomycin, an

- ✓Sodium glucose transporter 2 inhibitors have been used in patients with refractory hypomagnesemia above and beyond the magnesium replenishment.
- ✓A meta-analysis showed increased serum Mg levels in patients by 0.15–0.24 mg/dl, but the exact mechanism of this effect is unknown.
- ✓ A plausible explanation of improvement in Mg levels is by increased Mg absorption in the intestine or reabsorption in the kidney, possibly by **enhancing TRPM6**-mediated transport in the **intestine** and/or the **kidney**.
- ✓ KIDNEY360 4: 258–271, 2023

Table 4. Drug-induced hypomagnesemia in a patient with cancer: antineoplastic agents

Drug Class	Drugs Reported to Cause Hypomagnesemia	Incidence	Mechanism	Reference
Anti-EGFR mAbs	Cetuximab, panitumumab, zalutumumab	34% for cetuximab; 4% for zalutumumab	Decrease stimulation of TRPM6 in DCT leading to renal Mg wasting (1), inhibition of TRPM6 channels in gut, causing decrease in Mg absorption from gut (2)	(31,54,59,60,69,121)
EGFR tyrosine kinase inhibitors	Afatinib, erlotinib, gefitinib	None reported	Postulated similar mechanism as EGFR antibodies	(60)
Platinum-based agents	Cisplatin, carboplatin, oxaliplatin	Cisplatin, 40%–90%;carboplatin and oxaliplatin, 10%	Downregulation of TRPM6/EGF pathway, may lead to persistent distal tubular dysfunction with a Gitelman-like syndrome, can also cause Mg loss from gut due to anorexia, vomiting, diarrhea	(63,122,123)
HER-2 inhibitors	Trastuzumab, pertuzumab	Patients on pertuzumab: 14% with HypoMg (≥G1), 9% with HypoMg (≥G1) in neoadjuvant setting	Inhibition of Mg reabsorption in DCT due to EGF blockade, secretory diarrhea	(71)
Calcineurin inhibitors	Cyclosporine, tacrolimus	Case series and reports	EGF production is downregulated, which in turn inhibits TRPM6 activation. Reduce mRNA expression of NCC, reduce transcript for TRPM6 in DCT	(124)
Immunotherapy	IL-2	Case reports	Unknown	(125)
mTOR inhibitors	Rapamycin	Case report	Reduction in mRNA expression of TRPM6 at the DCT *via* inhibition of EGF-induced increase in TRPM6 expression, likely by reducing the stability of TRPM6 mRNA	(126)
Topoisomerase inhibitors	Amsacrine	Case reports only	Unknown	(127)
Anthracyclines	Pegylated liposomal doxorubicin	Case reports only	Unknown	(128)
Alkylating agents	Ifosfamide	1%	Unknown	(129,130)

EGFR, EGF receptor; TRPM, transient receptor potential melastatin; DCT, distal convoluted tubule; Mg, magnesium; HER-2, human EGF receptor 2; HypoMg, hypomagnesemia; ≥G1, grade 1 or higher; NCC, renal sodium-chloride cotransporter; mTOR, mammalian target of rapamycin.

Hypermagnesemia

- ✓Hypermagnesemia is defined as a magnesium plasma level > 2.2 mEq/L.
- ✓
- ✓It is a rare electrolyte disorder and is usually iatrogenic (**intravenous** magnesium, **magnesium-containing laxatives, or anti-acids**).
- ✓ Patients with hypomagnesemia might complain of hypotension, respiratory depression, confusion, and ECG alterations such as **bradycardia and complete AV-block** until asystole.

Berardi et al. J Cancer Metastasis Treat 2019;5:79

Hypermagnesemia

- ✓ Treatment requires **discontinuation of magnesium intake.**
- ✓ In symptomatic patients presenting **cardiac arrhythmias, respiratory depression, and hypotension**, an intravenous infusion of **calcium gluconate** 10% is suggested.
- ✓ In **severe cases, hemodialysis** may be necessary.
- ✓ Berardi et al. J Cancer Metastasis Treat 2019;5:79