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The Impact of the Syndrome of Inappropriate Antidiuresis and Hyponatremia in Cancer Patients

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Abstract

Hyponatremia, which is associated with a number of pathological conditions, is a rather common finding also in cancer patients. The Syndrome of Inappropriate Antidiuresis is the cause of hyponatremia in more than 30% of these patients. There is a growing body of evidence that this electrolyte disorder is associated with a reduced progression-free survival and overall survival in different types of cancer. It is not completely clear whether hyponatremia *per se* is the cause of a worse prognosis in cancer patients or it is merely a marker of disease severity. However, some studies showed that the correction of hyponatremia is associated with an increased survival in cancer patients.

Admittedly, further confirmatory data from both basic and clinical research are needed, in order to validate the hypothesis that cancer patients may die for hyponatremia. Nevertheless, because published data also indicate that the normalization of natremia is associated with an improved quality of life, reduced length of stay in the hospital and reduced probability of re-admission, it is conceivable to recommend that hyponatremia is appropriately corrected.

Keywords: Hyponatremia; SIAD; Cancer; Mortality

Introduction

Etiopathogenesis of hyponatremia in cancer patients

Hyponatremia, which is associated with a number of pathological conditions, is rather frequently encountered also in cancer patients, with a prevalence ranging from 4 to 47% of cases [1]. In these patients hyponatremia may be secondary to the Syndrome of Inappropriate Antidiuresis (SIAD). The likelihood that SIAD is the cause of hyponatremia in cancer patients is >30% and may be due to ectopic vasopressin secretion by tumoral cells [2]. This is commonly reported in small-cell lung cancer, in which at least one episode of hyponatremia has been reported in up to 75% of patients [3]. However, hyponatremia has been also observed in other tumors, such as head and neck, gastrointestinal, genitourinary, breast, prostate or hematological malignancies [4].

SIAD may be also induced or worsened in cancer patients by pharmacological treatments, because a number of chemotherapeutic agents, opioid analgesics, antidepressants, including tricyclics and selective Serotonin Reuptake Inhibitors (SSRI), as well as phenothiazines used as antiemetic agents may stimulate the release of vasopressin or increase receptor sensitivity to this hormone. A list of drugs that may be used in cancer patient's and that may induce hyponatrenia is detailed in Table 1 [5]. Of notice, among chemotherapeutic agents, also newer pharmacological approaches, such as targeted therapies or immunotherapy, have been associated with hyponatremia [6].

It has to be kept in mind that hyponatremia in cancer patients may be also secondary to other cancer-related conditions, such as hydration, nausea, vomiting, pain, physical and emotional stress [7].

Prognostic role of hyponatremia in cancer patients

Several studies have demonstrated that hyponatremia is a negative prognostic factor in different clinical scenarios, including heart failure, acute myocardial infarction, pneumonia, cirrhosis, renal failure, pulmonary embolism, intracerebral haemorrhage [8-13]. Interestingly, similar findings have been reported also for cancer patients in the last ten years.

In 2009 a prospective cohort study showed that metastatic cancer patients with hyponatremia had higher in-hospital mortality rates at 1 year and at 5 years, compared to normonatremic patients [Hazard Ratio (HR) 2.05, 95% Confidence Interval (CI): 1.67-2.53] [14]. A subsequent study indicated hyponatremia as one of the predictors of in-hospital mortality (HR 3.02, 95%CI: 1.76-5.17) in patients admitted in an acute palliative care unit at the M.D. Anderson Cancer Center of the University of Texas. Another retrospective study from the same Center showed that the risk of 90-day mortality in patients with hyponatremia was significantly higher than in normonatremic patients, even in those with mild hyponatremia (serum [Na^+] 130-134 mmol/L) [15].

Similar data were confirmed by an Italian study, in which 105 consecutive cancer patients hospitalized during a period of 6 months were analyzed, in order to find whether hyponatremia could predict a reduced Overall Survival (OS). Hyponatremic patients had a significantly reduced OS *vs* normonatremic patients (P=0.0255). In addition, in patients with metastases OS was further reduced (P=0.0418). Castillo et al. also obtained similar results in patients with different cancers and the highest reduction of OS was found in patients with lymphoma and breast cancer, with an HR between 3 and 4 [3].

Hyponatremia was found to reduce survival also in patients

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Table 1: Drugs that may be used in cancer patients and that may induce hyponatremia [4].

DRUGS	INDICATION FOR USE
Vinca alkaloids	Chemotherapy
Platinum compounds	
Alkylating agents	
Anthracyclines	
TK inhibitors and monoclonal antibodies	
Methotrexate	
IFN α-γ	
Pentostatina	
IL2	
Immune checkpoint inhibitors	
Opioid	Pain control
Acetaminophen	
Non-steroidal anti-inflammatory drugs	
Tricyclic antidepressant	Depression
Amitriptyline	
Protriptyline	
Desipramine	
SSRI	
MAO inhibitors	
Duloxetine, venlafaxine, mirtazapine	
Carbamazepine, oxcarbazepine	Epilepsy
Sodium valproate	
Lamotrigine	
Phenothiazine	Vomiting
First antidiabetic generation (tolbutamide, chlorpropamide)	Diabetes mellitus
Antibiotics (ciprofloxacin, trimethoprim/ sulfamethoxazole linezolid, cefoperazone, sulbactam)	Infections
Proton pump inhibitors	Prevention of gastric ulceration
Hypotensive drugs (thiazides, angiotensin converting enzyme inhibitors)	Hypertension
Hypotonic solutions	Hydratation

with terminal cancer. In fact, a retrospective observational study, conducted in a palliative care unit, which included more than 500 patients, reported that serum [Na^+] ≤ 125 mmol/L was associated with a reduced survival time (HR = 1.91; $P < 0.001$) [16].

Hyponatremia has been associated also to the progression of radiation-induced brain necrosis, as demonstrated by a study that addressed patients affected by nasopharyngeal carcinoma, glioma or oral cancer, which had developed radiation-induced brain necrosis. In patients with hyponatremia the risk of progression (e.g. increase of brain edema) was three-fold higher than in patients with normonatremia [17].

Some studies that have been published have addressed specific cancer types. In particular, some studies focused on Renal Cell Carcinoma (RCC). Multivariate analyses performed in a series of more than 200 patients with this cancer showed that a preoperative serum [Na^+] cut-off of 139 mmol/L was an independent predictor of OS at 5 years. The median OS for patients with serum [Na^+] >139 mmol/L was 67.6%, whereas it was 44.3% for patients with serum [Na^+] <139 mmol/L [18]. A Danish study addressed patients with metastatic RCC and reported that hyponatremia was an independent prognostic factor (median OS 5.5 months in hyponatremic patients *vs.* 18.6 months in normonatremic patients) [19]. Similar results were reported by a Japanese study, in which both Progression-Free Survival (PFS) (median 10.0 *vs.* 20.9 months) and OS (median 28.4 *vs.* 38.5 months) were significantly reduced in patients with hyponatremia compared to those with normonatremia [20].

Reduced serum [Na^+] was found to be a negative prognostic factor also in patients with gastric cancer and with hepatocellular carcinoma [21,22].

Interestingly, a retrospective cohort study performed in Denmark, showed that hyponatremia may also have a predictive role in cancer development. In particular, the risk to develop cancer at 12 months was significantly increased even in patients with mild hyponatremia (serum [Na^+] 130-135 mmol/L), compared to normonatremic subjects [23].

Although it is not completely clear whether hyponatremia *per* se is the cause of a worse prognosis in cancer patients or it is merely a marker of disease severity, some studies appear to suggest that the former hypothesis is likely to be true.

For instance, a recent study showed that serum [Na^+] normalization is an independent prognostic factor for PFS and OS in patients affected by non-small cell lung cancer [24]. Similar findings were confirmed in patients with metastatic RCC treated with everolimus [25]. These results are in keeping with previous data from a meta-analysis, which showed that in patients with either tumoral or non tumoral diseases (e.g. heart failure, acute pulmonary embolism, myocardial infarction) serum [Na^+] improvement was associated with a reduced risk of mortality (HR 0.57, 95%CI: 0.40-0.81) [26].

A few basic research studies on cancer cell growth and invasiveness in low [Na^+] have been published, so far. However, currently available results suggest that a microenvironment with a low [Na^+] may stimulate cancer cell proliferation. It has been demonstrated for instance that the growth rate of prostate cancer cells in a culture medium with reduced [Na^+] markedly increased [27]. In another study the invasive ability of neuroblastoma cells increased when cells were cultured in low [Na^+] [28]. Interstingly, this was associated with dramatically increased expression levels of the Heme-Oxigenase-1 gene (HMOX-1), a marker of oxidative stress. Of notice, inhibition of HMOX-1 has been viewed as a possible target for antitumoral strategies [29].

Conclusion

A growing body of evidence indicates that hyponatremia is associated with a worse prognosis in cancer patients. Recent studies demonstrated that serum [Na^+] correction is able to counteract the negative prognostic role of hyponatremia, thus suggesting that this electrolyte alteration may promote disease progression. Admittedly, further studies, from the "bench-to-bedside", are needed in order to confirm this hypothesis.

Anyway, the published data and the demonstration that the normalization of hyponatremia is associated with an improved quality of life, reduced length of stay in the hospital and reduced probability of re-admission [30-32], strongly suggest that hyponatremia should be taken into account and appropriately treated [4,33,34].

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