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Hyponatremia in cancer patients: Time for a new approach

Rossana Berardi[a,*], Silvia Rinaldi[a], Miriam Caramanti[a], Christian Grohè[b], Matteo Santoni[a], Francesca Morgese[a], Mariangela Torniai[a], Agnese Savini[a], Ilaria Fiordoliva[a], Stefano Cascinu[a,1]

[a] Medical Oncology, Università Politecnica delle Marche, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, GM Lancisi, G Salesi, Ancona, Italy
[b] Dept. of Respiratory Diseases, Ev. Lungenklinik Berlin, Lindenberger Weg 27, 13125 Berlin, Germany, Germany

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ABSTRACT

Hyponatremia is a common electrolyte disorder in cancer patients. It may be related to cancer, to anti-cancer therapy or to other concomitant treatments. In this setting hyponatremia is often caused by the syndrome of inappropriate anti-diuretic hormone secretion, which is due to the ectopic production of antidiuretic hormone (vasopressin), to extracellular fluid depletion, to renal toxicity caused by chemotherapy or to other underlying conditions.

Recent studies suggested that hyponatremia might be considered a negative prognostic factor for cancer patients therefore its early detection, monitoring and management might improve the patient's outcome.

Treatment of hyponatremia depends on patient's symptoms severity, onset timing and extracellular volume status.

In this review we summarize the main causes of hyponatremia in cancer patients and its management, including the available treatment options.

* Corresponding author at: Medical Oncology Unit, Università Politecnica delle Marche – Azienda Ospedaliero-Universitaria, Ospedali Riuniti Umberto I, GM Lancisi, G Salesi di Ancona, Via Conca 71, Ancona 60126 Italy.
E-mail address: r.berardi@univpm.it (R. Berardi).
[1] Present address: Oncologia Medica, Università degli Studi di Modena e Reggio Emilia.

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1. Introduction

Hyponatremia is defined as serum sodium lower than 135 mmol/l (Palmer et al., 2003). It can be classified into three levels of severity: mild (130/134 mmol/l), moderate (125/129 mmol/l) and severe (<125 mmol/l) (Ghali, 2008). According to its development, strictly linked to the volume status and serum osmolality of the patient, it can also be distinguish acute (if serum sodium decreases within 48 h) and chronic hyponatremia (if sodium depletion develops in more than 48 h) (Sjoblom et al., 1997).

Hyponatremia is reported as the most common electrolyte disorder linked to tumor-related conditions; however its incidence in this setting is unclear because of differences in cancer type, clinical setting, and serum sodium cut-off points (Sørensen et al., 1995).

Hyponatremia usually accompanies, but can also precede tumor diagnosis with an incidence ranging between 1% and more than 40% (Sørensen et al., 1995; Berghmans et al., 2000).

Cancer patients may present several risk factors for hyponatremia including chemotherapy itself or its toxicities. Furthermore fluids, that are frequently administered together with chemotherapy as well as in the palliative setting, cancer pain and opioids may increase the risk of hyponatremia or can worsen it. Moreover nausea promotes the release of arginine vasopressin (AVP) and vomiting also brings to gastrointestinal loss of sodium.

Lung, prostate, pancreatic, liver and renal cancers seem to be associated to the highest frequency of moderate-severe hyponatremia, whilst breast cancer to the lowest (Abu Zeinah et al., 2015). In particular small cell lung cancer (SCLC) is the most common cancer type related to this electrolyte disorder which occurs at diagnosis in approximately 15% of patients in retrospective studies (Sørensen et al., 1995; Hansen et al., 2010; Gross et al., 1993).

Hyponatremia in cancer patients mainly depends to the inappropriate antidiuretic hormone syndrome (SIADH). SIADH may be due to chemotherapy, especially platinum-based, opioids and non-steroidal anti-inflammatory drugs, but it can be also related to lung and central nervous system (CNS) diseases. Finally SIADH may arise as a paraneoplastic syndrome in different tumor types, with an ectopic production of antidiuretic hormone. Literature data suggest that hyponatremia can be considered an unfavourable prognostic factor in this setting (Berghmans et al., 2000; Abu Zeinah et al., 2015; Hansen et al., 2010; Gross et al., 1993; Castillo et al., 2012). Cancer-related hyponatremia has been also hypothesized to adversely affect the response to anticancer treatment (Schutz et al., 2014; Jeppesen et al., 2010). Furthermore there is a growing body of evidences that effective and timely acting on the normalization of sodium levels could lead to a positive effect on prognosis (Hansen et al., 2010; Gross et al., 1993; Castillo et al., 2012; Schutz et al., 2014; Jeppesen et al., 2010; Petereit et al., 2013).

In this review we analyse the role of hyponatremia in cancer patients focusing on its main causes, its diagnosis and its management.

2. Methods

The available scientific literature regarding hyponatremia was extensively reviewed. We used the MEDLINE and CancerLit databases searching studies on hyponatremia published between 1982 to February 2015 and the search was restricted to English-language publications. The search terms included “chemotherapy, survival, outcome, SIADH, tolvaptan, urea, saline, hypertonic saline, demeclocycline, lithium” in association with hyponatremia and cancer. Full articles were obtained, and we checked for additional appropriate references. Where results were reported or updated in more than one publication, only the most recent was used.

3. Importance of hyponatremia in cancer patients

Currently there is a growing interest on the prognostic and predictive role of hyponatremia, since it was found to be associated with poor survival in different medical conditions as well as in several solid tumors (Berghmans et al., 2000; Castillo et al., 2012; Jeppesen et al., 2010).

A large body of literature is available for hyponatremia in patients with non-cancer conditions, conversely little is known about hyponatremia in cancer patients.

Several studies evaluated the prognostic role of hyponatremia in this setting. Most of these studies evaluated the negative impact of hyponatremia on SCLC patients’ survival. In fact, hyponatremia along with lactate dehydrogenase (LDH), stage of disease, performance status and albumin resulted as negative prognostic factors in SCLC patients. (Cerny et al., 1987; Souhami et al., 1985).

Recently, in a retrospective study on 453 SCLC patients, Hansen at al. showed that 44% presented hyponatremia at diagnosis and significant lower values were observed in extensive disease compared with limited disease. In particular patients presenting with liver and pleural metastasis had a higher risk to develop hyponatremia. This study showed that survival in patients with hyponatremia was poorer than in patients with normal serum sodium (7.7 vs. 11.2 months $p = 0.0001$) (Hansen et al., 2010). Furthermore the authors observed that patients who did not fully normalize serum sodium within the first two studies, had a worse prognosis than hyponatremic patients who did.

A more recent study on 564 SCLC patients confirmed the negative prognostic role of hyponatremia for patients treated with Topotecan as second-line chemotherapy ($p = 0.0024$). However a trend of correlation between hyponatremia and response rate (RR) and progression free survival (PFS) was observed, although it was not statistically significant (Tiseo et al., 2014).

Hyponatremia was also confirmed as a negative prognostic factor in other types of cancer such as non-small cell lung cancer (NSCLC) (Ray et al., 1998), pleural mesothelioma (Berardi et al., 2015a), renal cell carcinoma (Jeppesen et al., 2010), gastrointestinal cancer (Kim et al., 2007) and lymphoma (Dhaliwal et al., 1993).

Petereit and coll., evaluating 2100 patients with lung cancer, confirmed the negative prognostic role of hyponatremia. In fact the median overall survival (OS) was lower in hyponatremic compared with eunatremic patients (10.08 vs. 12.2 months respectively) and the 2-years OS rate was 24,4% vs. 30,8%, respectively ($p = 0.08$). Moreover the authors suggested that an early and effective normalization of this electrolyte disorder might improve patients’ prognosis (Petereit et al., 2011).

Furthermore low serum sodium values have been reported to negatively correlate with performance status, which is considered a prognostic factor in several malignancies (Sengupta et al., 2013).

Several studies investigated the prognostic role of hyponatremia in hospitalized cancer patients. Doshi et al., analysing 3357 hospitalized cancer patients, found that those with hyponatremia had a longer length of hospitalization (10.2 vs. 5.6 days) and a higher risk of mortality (Doshi et al., 2012). Other authors confirmed these data and also showed that in patients with moderate-severe hyponatremia the risk of death increased 4.28 times compared to those with normal-mild hyponatremia (Abu Zeinah et al., 2015). In a recent retrospective study on 295 patients who underwent inpatient cancer rehabilitation Nelson et al. found that hyponatremic patients had a prolonged rehabilitation length of stay compared to eunatremic patients (Nelson et al., 2014). We have also recently shown an increase in length of stay for hospitalized hyponatremic patients with a significant increase of costs (Berardi et al., 2015b). According to these data, a timely and effective correction of this electrolyte disorder is important to improve patient outcomes.