Hyponatraemia and the syndrome of inappropriate antidiuresis (SIAD) in cancer

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Abstract

Hyponatraemia is a common electrolyte abnormality seen in a wide range of oncological and haematological malignancies and confers poor performance status, prolonged hospital admission and reduced overall survival, in patients with cancer. Syndrome of inappropriate antidiuresis (SIAD) is the commonest cause of hyponatraemia in malignancy and is characterised by clinical euvolaemia, low plasma osmolality and concentrated urine, with normal renal, adrenal and thyroid function. Causes of SIAD include ectopic production of vasopressin (AVP) from an underlying tumour, cancer treatments, nausea and pain. Cortisol deficiency is an important differential in the assessment of hyponatraemia, as it has an identical biochemical pattern to SIAD and is easily treatable. This is particularly relevant with the increasing use of immune checkpoint inhibitors, which can cause hypophysitis and adrenalitis, leading to cortisol deficiency. Guidelines on the management of acute, symptomatic hyponatraemia recommend 100 mL bolus of 3% saline with careful monitoring of the serum sodium to prevent overcorrection. In cases of chronic hyponatraemia, fluid restriction is recommended as first-line treatment; however, this is frequently not feasible in patients with cancer and has been shown to have limited efficacy. Vasopressin-2 receptor antagonists (vaptans) may be preferable, as they effectively increase sodium levels in SIAD and do not require fluid restriction. Active management of hyponatraemia is increasingly recognised as an important component of oncological management; correction of hyponatraemia is associated with shorter hospital stay and prolonged survival. The awareness of the impact of hyponatraemia and the positive benefits of active restoration of normonatraemia remain challenging in oncology.

Introduction

Hyponatraemia is an extremely common complication of malignancy, which may arise as a complication of the tumour or as a side effect of therapy. Although the management of hyponatraemia has not traditionally been regarded as an important aspect of oncological treatment, there is a growing awareness of the detrimental effects of hyponatraemia in cancer patients. Numerous studies have demonstrated that hyponatraemia confers poorer prognosis in patients with malignancy, and as survival in cancer improves, the negative effects of hyponatraemia on quality of life are also assumed importance.

The role of ectopic secretion of the antidiuretic hormone, arginine vasopressin (AVP), in causing hyponatraemia due to the syndrome of inappropriate antidiuresis (SIAD), is well established, as has hyponatraemia in association with cytotoxic therapy. New treatments, such as stem cell transplant, are also now recognised to be responsible for the development of SIAD.
of hyponatraemia, and the widespread use of immune checkpoint inhibitors has revealed hyponatraemia either from the development of SIAD or from hypophysitis and ACTH deficiency, which may present with a SIAD-like syndrome and primary adrenal failure secondary to an adrenalinitis. Hyponatraemia has well-described and widely accepted effects on cognitive function and quality of life in patients with cancer. Hyponatraemia is clearly also a predictor of poorer outcome and shortened survival in a wide spectrum of cancers; however, it is not clear whether the shortened survival is due directly to the electrolyte imbalance or whether hyponatraemia is a manifestation of more widespread or aggressive disease.

In this review, we will summarise the data on SIAD in malignant disease and discuss the emerging evidence that treatment of hyponatraemia due to SIAD can improve quality of life and positively influence survival outcome.

Hyponatraemia in malignancy

Background

The original description of syndrome of inappropriate antidiuretic hormone secretion (SIADH), in 1957, arose from a series of careful and sophisticated studies of water balance conducted in two hyponatraemic patients with bronchogenic carcinoma (Schwartz et al. 1957). Although both patients had post-mortem evidence of adrenal metastases, corticosteroid secretion was considered normal prior to death. The patients had clear evidence of antidiuresis, with concentrated urine despite serum hypoosmolality, and in elegant, carefully supervised in-patient studies, the authors were able to demonstrate that water restriction led to a rise in plasma sodium concentration, and liberalisation of fluid intake led to hyponatraemia worsening. The authors concluded that the presence of an antidiuretic hormone, which they termed ADH, was causing water retention, and dilutional hyponatraemia (Schwartz et al. 1957). The authors hypothesised that direct pressure from the mediastinal tumour masses had exerted compressive effects on a neural structure such as the vagus nerve and stimulated non-osmotic secretion from the brain or that cerebral secondaries had mediated secretion; ectopic hormone secretion from the tumour was not considered (Schwartz et al. 1957). The syndrome of SIADH, characterised by euvoalamaic hyponatraemia in the presence of inappropriate urine concentration and natriuresis, was developed from this classical description. Since then, the term ‘syndrome of inappropriate antidiuresis’ (SIAD) has superseded SIADH as the preferred terminology (Verbalis et al. 2013).

Since this classic index description, hyponatraemia became well recognised as a complication of malignancy and, in particular, small cell cancer of the lung. Early demonstration of elevated plasma AVP concentrations in the plasma of lung cancer patients (Vorherr et al. 1968) implicated the role of the hormone in the pathogenesis of SIAD. In their classical paper, George et al. showed that AVP could be detected by RIA in the tissue of a bronchogenic tumour removed surgically from a patient with hyponatraemia (George et al. 1972). This description raised the likelihood of ectopic AVP secretion from tumour tissue as the basis for SIAD in some cancer patients. The development of sensitive RIAs allowed for further characterisation of the control of AVP secretion in patients with lung cancer and hyponatraemia (Robertson et al. 1982, Maurer et al. 1983, Smith et al. 2004) and molecular biology techniques were able to demonstrate AVP gene expression in tissues derived from small cell lung cancers (Friedmann et al. 1994). A compelling case had therefore emerged for ectopic synthesis of AVP in lung tumour tissue, leading to elevated plasma hormone levels, and the development of hyponatraemia as a result of the antidiuretic effects of AVP.

Since then, hyponatraemia has been described in a wide variety of malignant processes. The association has been documented most often and most comprehensively in bronchogenic carcinoma (Alamoudi 2010, Hansen et al. 2010, Castillo et al. 2012, Sengupta et al. 2013, Tiseo et al. 2014, Fiordoliva et al. 2017, Chan et al. 2020, Bartalis et al. 2021, Sandfield-Paulsen et al. 2021). A meta-analysis published in 2021, of 31 articles, showed the mean prevalence of hyponatraemia in lung cancer was 25%; however, the findings were highly discordant, ranging from 3 to 95% due to heterogeneity in patient characteristics, evaluation of hyponatraemia and the cut-off points used (Bartalis et al. 2021). Although no study has compared the incidence of SIAD in lung cancer by histological type, it is widely accepted that SIAD due to ectopic production of vasopressin is significantly more common in small cell lung cancer than non-small cell (Cuesta & Thompson 2016). Hyponatraemia has been reported in association with almost all forms of cancer; one review, of over 2000 patients treated in Dubai, reported that hyponatraemia occurred in 57% of cases of prostate cancer, 57% of pancreatic cancer, 49% of liver cancer and 24% of liver cancer, compared with 40% of lung cancer (Abu Zeinah et al. 2014); 4% of patients with head and neck cancer develop hyponatraemia in one large series (Talmi 2012).
et al. 1992). Hyponatraemia has therefore been implicated in a wide range of solid organ and also haematological malignancies (Koumpis et al. 2020) and is associated with significant morbidity and mortality (Castillo et al. 2016, Workeneh et al. 2020).

It is important to recognise that most publications do not distinguish between the various pathophysiological mechanisms which lead to hyponatraemia. Hyponatraemia is not synonymous with SIAD, which is the focus of this review and which is characterised by euvolaemic hyponatraemia. SIAD is caused by different pathologies, requires different diagnostic criteria and has an entirely different therapeutic approach (Martin-Grace et al. 2022 in press) to hypovolaemic or hypervolaemic hyponatraemia. SIAD also has lower associated mortality than other forms of hyponatraemia (Cuesta et al. 2017, Kutz et al. 2020). Although hyponatraemia has been attributed to SIAD in lung cancer in 60% of cases (Grohé et al. 2015), and in 30% of all-cause cancers (Berghmans et al. 2000, Cuesta et al. 2017), the criteria used to diagnose SIAD in many studies are incomplete (Burst et al. 2017). In this review, we will distinguish as far as possible between the data related to SIAD in cancer and that related to all-cause hyponatraemia.

Pathogenesis of hyponatraemia in malignancy

It is recommended that the diagnostic approach to hyponatraemia should incorporate an assessment of blood volume status (Verbalis et al. 2013), partly because the management of hyponatraemia differs widely depending upon whether the patient is hypovolaemic, euvolaemic or hypervolaemic (Verbalis et al. 2013) and partly because mortality varies significantly between the groups, being higher in hypovolaemic and euvolaemic hyponatraemia than in SIAD (Cuesta et al. 2017, Kutz et al. 2020). Although it has been claimed that SIAD is the commonest cause of hyponatraemia in oncology patients (Berardi et al. 2019), the spectrum of hyponatraemia pathogenesis in malignancy is wide (Table 1).

In the diagnosis of SIAD in malignant disease, it is therefore important to exclude hypovolaemic and hypervolaemic causes (Thompson et al. 2012). It can be difficult clinically to distinguish between mild hypovolaemia and SIAD, where clinical signs may be subtle. However, the distinction is important as the first-line treatment recommended by guidelines is so different (Verbalis et al. 2013, Spasovski et al. 2014). In cases where the urine sodium is low, or where there is a history of vomiting, it would be usual to assume a diagnosis of hypovolaemic hyponatraemia, even in the absence of typical clinical signs and to treat empirically with i.v. sodium chloride solution.

In our clinical practice, we administered 1 L of sodium chloride intravenously over 8–12 h, while monitoring the serum sodium, typically every 2–4 h. Further treatment is dependent on the initial response to i.v. fluids.

**SIAD in malignancy**

SIAD has been reported in association with a wide variety of malignancies (Verbalis et al. 2013), which have been summarised in Table 2. In many instances, AVP is synthesised in tumour tissue (George et al. 1972), causing ectopic hormone secretion. Primary intracerebral tumours and brain metastases induce SIAD by physically interfering with the osmoregulatory pathways within the hypothalamus and neurohypophysis, causing the non-osmotic release of vasopressin (Esposito et al. 2011). Postoperative SIAD can also occur following neurosurgical resection of intracranial tumours (Sherlock et al. 2009) and is particularly common with suprasellar, thalamic and hypothalamic lesions (Madden et al. 2010). In addition, a number of treatments, particularly chemotherapy, can cause SIAD. Vinca alkaloids such as vincristine and vinblastine, platinum compounds such as cisplatin and carboplatin and alkylating agents, particularly cyclophosphamide and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Causes of hyponatraemia in malignancy.</th>
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<tbody>
<tr>
<td><strong>Clinical signs</strong></td>
<td><strong>Urine sodium &lt; 20 mmol/L</strong></td>
</tr>
<tr>
<td>Hypovolaemia</td>
<td>Dry mouth, skin</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
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<tr>
<td></td>
<td>Low BP/CVP</td>
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<tr>
<td>Euvolaemia</td>
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<td></td>
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</tr>
<tr>
<td>Hypervolaemia</td>
<td>Ankle/sacral oedema</td>
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<tr>
<td></td>
<td>Raised JVP</td>
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<td></td>
<td>Ascites</td>
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| BP, blood pressure; CVP, central venous pressure; JVP, jugular venous pressure; SIAD, syndrome of inappropriate anti-diuretics.
melphalan, all potentiate the secretion of AVP from the hypothalamus, while cyclophosphamide also augments the antidiuretic actions of AVP on the collecting ducts of the kidney (Castillo et al. 2012). Cisplatin is particularly liable to cause hyponatremia, which occurs in 40–60% of patients prescribed the drug during clinical trials (Verzicco et al. 2020), whereas if high-dose cyclophosphamide is included in the regimen, up to 90% of patients develop hyponatraemia (Lee et al. 2010). It should be emphasised that these figures are for all-cause hyponatraemia, rather than SIAD. They will therefore include a substantial number of patients who develop hyponatraemia due to vomiting, for instance, and have hypovolaemia, or secondary to i.v. fluids, and have increased blood volume.

Immune checkpoint inhibitors such as nivolumab, pembrolizumab and ipilimumab have transformed the outlook of many cancers but carry a substantial collateral burden of hyponatraemia. A recent large retrospective study of over 2000 patients reported that 62% developed hyponatraemia in the first year of therapy (Seethapathy et al. 2021). Hyponatraemia reported with immune checkpoint inhibitors may arise from a number of different mechanisms. Low plasma sodium concentrations may reflect SIAD due to drug treatment, the underlying malignant process, cortisol deficiency secondary to hypophysitis or adrenalitis, or it may be due to nausea; in some cases, it may be multifactorial. Published data suggest that most cases are due to SIAD (Verzicco et al. 2020). Although immune checkpoint inhibitors are associated with significant endocrinopathies, including hypophysitis, hypothyroidism and adrenalitis (Chang et al. 2019), they account for less than 0.3% of cases of hyponatraemia (Seethapathy et al. 2021). Targeted therapies such as cetuximab, an EGF receptor inhibitor, are associated with high rates of severe hyponatraemia (up to 35%), with even higher rates seen when used in combination with other therapies (Berardi et al. 2016). Bortezomib, a proteosome inhibitor, used in the treatment of multiple myeloma can induce SIAD. Hyponatraemia in multiple myeloma has been successfully reversed with the AVP-receptor antagonist tolvaptan, indicating an AVP-dependent mechanism (O’Connor-Byrne et al. 2019).

Stem cell therapy has been documented to cause SIAD, though in practice, it is difficult to tease out the effects of stem cell therapy itself, and the contribution of associated chemotherapy, such as cyclophosphamide and melphalan. Although there are multiple causes of SIAD in cancer patients, it is important to consider that hyponatraemia is often multifactorial. A patient with small cell lung cancer may have ectopic AVP synthesis and secretion but may also be on chemotherapy, anti-epileptics and diuretics and have a superimposed pneumonia. The full diagnosis of the cause of hyponatraemia may therefore be more nuanced and multifactorial than suggested by algorithms. Expert endocrine or renal opinion is often needed to tease out the precise causation.

### Diagnosis of SIAD

The basic criteria for the diagnosis of SIAD (Verbalis et al. 2013) have changed little from those originally proposed after the initial physiological studies were published (Schwartz et al. 1957) and are summarised in Table 3. It is essential that the patient is demonstrated to be clinically euvoalaemic and to have inappropriate urine concentration, reflecting AVP action on the kidney, and manifested by urine osmolality in excess of 100 mOsm/kg. Elevated urine sodium must be present and a crucial diagnostic step is to exclude glucocorticoid deficiency. Studies have shown poor documentation of the basic diagnostic criteria for SIAD in clinical practice (Tzoulis & Bouloux 2015, Berkman et al. 2018) and even in international registries (Greenberg et al. 2018).

### Table 2 Causes of SIAD in malignancy.

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Lung – small cell, non-small cell, mesothelioma, secondaries</td>
<td>Cytotoxics – vincristine, vinblastine, cisplatin, melphalan, levamisole, cyclophosphamide methotrexate, interferon (increased hypothalamic AVP secretion) and cyclophosphamide (potentiation of AVP action)</td>
</tr>
<tr>
<td>GI – oesophagus, stomach, colon, pancreas, duodenum</td>
<td>Immune checkpoint inhibitors – nivolumab, pembrolizumab, ipilimumab</td>
</tr>
<tr>
<td>Haematological – lymphoma, myeloma, leukaemia</td>
<td>Adjunctive therapy – opiates, anti-emetics, antidepressants, carbamazepine, haloperidol, phenothiazines</td>
</tr>
<tr>
<td>Brain – glioma, meningioma, medulloblastoma, pinealoma, neurofibroma, secondaries</td>
<td>Stem cell transplantation</td>
</tr>
<tr>
<td>Miscellaneous – renal, prostate, breast, urological, melanoma</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td>Associated infections – pneumonia, sepsis, covid-19</td>
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</tbody>
</table>
of cortisol (glucocorticoid) deficiency is particularly important. The electrolyte abnormalities in glucocorticoid deficiency are indistinguishable from those of SIAD (Thompson et al. 2012) and are principally related to the requirement for cortisol in order to excrete water from the kidneys. In a prospective study of over 500 patients admitted to hospital with euvolaemic hyponatraemia, with a presumptive diagnosis of SIAD, 4% had evidence of undiagnosed cortisol deficiency on formal testing (Cuesta & Thompson 2016). Despite this, the possibility of cortisol deficiency is often ignored, with testing performed in only 33–45% of hyponatraemic patients in routine clinical practice (Tzoulis & Bouloux 2015, Berkman et al. 2018) and in 33% of euvolaemic patients entered into the international hyponatraemia registry (Greenberg et al. 2015). Clearly, basic diagnostic standards are not routinely fulfilled in clinical practice, and equally clearly, cases of treatable cortisol deficiency are being missed.

The wide range of malignant complications can impair cortisol secretion and make it crucial to test the integrity of glucocorticoid secretion in patients with malignancy. Missing a diagnosis of cortisol deficiency can impair quality of life and render the cancer patient vulnerable to adrenal crisis during intercurrent illness or infection. The causes of cortisol deficiency in malignancy are summarised in Table 4. It has recently become apparent that 20–40% of patients treated with immune checkpoint inhibitors develop hypophysitis – higher rates are seen with combination therapy – most of whom require steroid replacement therapy (Chang et al. 2019, Garon-Czmil et al. 2019). These patients may all present with biochemical features indistinguishable from SIAD.

A largely unexplored field of oncology is the potential for high-dose corticosteroid therapy, used to supplement chemotherapy, to cause adrenal suppression. Immunosuppressive steroids have been reported to cause adrenal suppression in a spectrum of clinical conditions (Dineen et al. 2019, Tomkins et al. 2022), which is often unrecognised. Patients prescribed immunosuppressive steroids for inflammatory conditions are also much less likely than endocrine patients to be made aware of sick day rules or to carry steroid warning cards (Salehmohamed et al. 2018), so the potential vulnerability to adrenal crisis in this situation is considerable (Dineen et al. 2019). Although synacthen testing is the gold standard to establish the presence of adrenal insufficiency, data in euvolaemic hyponatraemia have shown that a 09:00 h plasma cortisol of >300 nmol/L (>10.9 ng/mL) is sufficient to exclude glucocorticoid deficiency in SIAD (Cuesta & Thompson 2016).

### Table 3  Diagnostic criteria for the diagnosis of SIAD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Explanatory notes</th>
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<tbody>
<tr>
<td>Hyponatraemia</td>
<td>pNa &lt; 132 mmol/L or pOsm &lt; 275 mOsm/kg</td>
</tr>
<tr>
<td>Euvolaemia</td>
<td>No evidence of dehydration or fluid overload</td>
</tr>
<tr>
<td>Inappropriate urine concentration</td>
<td>Urine osmolality &gt;100 mOsm/kg indicates inappropriate presence of AVP in a hyponatraemic patient</td>
</tr>
<tr>
<td>Elevated urine sodium</td>
<td>uNa &gt; 20–30 mmol/L, with a normal salt intake</td>
</tr>
<tr>
<td>Exclusion of confounding conditions</td>
<td>Glucocorticoid deficiency, most important confounder</td>
</tr>
<tr>
<td></td>
<td>Severe hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Normal renal function and absence of diuretic therapy</td>
</tr>
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</table>

pNa, plasma sodium concentration; pOsm, plasma osmolality; uNa, urine sodium concentration.

Of the various diagnostic criteria, the exclusion of cortisol (glucocorticoid) deficiency is particularly important. The electrolyte abnormalities in glucocorticoid deficiency are indistinguishable from those of SIAD (Thompson et al. 2012) and are principally related to the requirement for cortisol in order to excrete water from the kidneys. In a prospective study of over 500 patients admitted to hospital with euvolaemic hyponatraemia, with a presumptive diagnosis of SIAD, 4% had evidence of undiagnosed cortisol deficiency on formal testing (Cuesta & Thompson 2016). Despite this, the possibility of cortisol deficiency is often ignored, with testing performed in only 33–45% of hyponatraemic patients in routine clinical practice (Tzoulis & Bouloux 2015, Berkman et al. 2018) and in 33% of euvolaemic patients entered into the international hyponatraemia registry (Greenberg et al. 2015). Clearly, basic diagnostic standards are not routinely fulfilled in clinical practice, and equally clearly, cases of treatable cortisol deficiency are being missed.

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Effects of SAID in malignancy

Hyponatraemia has numerous detrimental effects in patients with cancer. It can interfere with the conduct of anti-tumour therapy, and it leads to impaired quality of life and an excess of hospital admissions (Burst et al. 2017). There is a considerable accumulation of evidence to show that in hospitalised patients with cancer, all-cause hyponatraemia is associated with increased mortality, prolonged duration of in-patient stay and amplification of health care costs (Hansen et al. 2010, Jeppesen et al. 2010, Peteriet et al. 2011, Doshi et al. 2012, Abu Zeinah et al. 2014, Schutz et al. 2014, Berardi et al. 2015a,b). Hyponatraemia has been associated with lower performance status using the Eastern Cooperative Group Performance Status (ECOG-PS) in patients with non-small cell lung cancer (Chan et al. 2020) and has been associated in two meta-analyses, with shorter overall survival in non-small cell lung cancer (Sandfeld-Paulsen et al. 2021) and all-cause lung cancer (Bartalis et al. 2021). It is important to emphasise that these are associations with hyponatraemia. The figures have been extrapolated in past publications to be readily translatable to SIAD, on the basis of a largely unproven assumption that hyponatraemia in cancer is nearly always due to SIAD (Burst et al. 2017), but confirmatory data are lacking. One of the few papers which analysed SIAD separately had no non-hyponatraemic control group for comparison (Burst et al. 2017). At present, therefore, we can comment on the effect of hyponatraemia on outcomes in cancer but not SIAD per se.

Treatment of SAID in malignancy

Acute hyponatraemia

Acute hyponatraemia is a medical emergency that requires immediate treatment, irrespective of the underlying condition, to prevent neurological damage and to reduce mortality (Sterns 2018b).Conventionally, acute hyponatraemia is defined as occurring in less than 48 h (Verbalis et al. 2013). When hyponatraemia develops as quickly as this, there is no time for cerebral adaptation to occur, and water moves osmotically across the blood-brain–barrier into the brain, which expands, causing cerebral oedema (Sterns & Silver 2016, Verbalis 2019). If intracerebral pressure rises sufficiently, seizures and brain herniation may occur.

The treatment of choice is i.v. infusion of 3% NaCl solution, as this offers the opportunity to reverse hyponatraemia promptly and reliably (Verbalis et al. 2013). Traditionally, a continuous infusion of i.v. 3% NaCl has been used, though recent expert consensus guidelines have recommended 100 ml i.v. boluses of 3% NaCl, aimed at elevating plasma sodium concentration by 4–6 mmol/L over 4–6 h (Verbalis et al. 2013). A subsequent observational study reported that changing from i.v. infusion of 3% NaCl to bolus correction was associated with a more rapid early rise in plasma sodium concentration, over the first 6 h, but similarly, plasma sodium rises at 24 h; crucially, the bolus treatment was associated with a quicker return of neurological disability, as measured by the Glasgow Coma Scale, in the first 6 h, with no recorded instance of osmotic demyelination (Garrahy et al. 2019). However, the need for intervention to address overcorrection of hyponatraemia was higher in the bolus group. In contrast, the SALSA trial, a large prospective randomised comparison of intermittent bolus therapy with continuous infusion, showed no difference in the rates of overcorrection, which were significant in both groups (17% of bolus-treated vs 24% of infusion-treated), though the data also showed a treatment advantage for bolus therapy in terms of achieving early plasma sodium targets (Baek et al. 2021). The authors concluded with their recommendation that bolus therapy could become the treatment of choice for acute severe symptomatic hyponatraemia. Some authors have recommended a further sophistication of ‘clamping’ renal-free water clearance with dDAVP (Achinger & Ayus 2017), in order to avoid the occasional, very rapid overcorrection seen when a sudden aquaresis accompanies the hypertonic infusate; the authors contend that this diminishes the need to treat for overcorrection of hyponatraemia and will further reduce the risk of osmotic demyelination.

In malignant disease, acute symptomatic hyponatraemia is seen most often in association with the administration of i.v. fluids, administered at the same time as chemotherapeutic agents which stimulate drug-induced SIAD. If a patient on chemotherapy and i.v. fluids develops disorientation, or neurological symptoms, urgent electrolytes should be ordered, and if hyponatraemia has developed, emergency endocrine consultation to supervise hypertonic saline is advisable.

Chronic hyponatreaemia

Evidence has accumulated that active management of hyponatraemia is associated with improved patient outcomes (Garrahy et al. 2021). There are data to show that this is true in the oncology population. Patients with neurocognitive symptoms due to symptomatic SIAD in small cell lung cancer have been shown to...
have improved symptom scores on the restoration of normonatraemia (Peteriet et al. 2013, Ren & Yang 2021), though a recent meta-analysis reported that this was not a consistent finding across all studies in non-small cell lung cancer (Sandfeld-Paulsen et al. 2021). Chronic, mild hyponatraemia can exacerbate common cancer-related symptoms including anorexia, nausea and lethargy; active treatment can reduce these symptoms and potentially improve overall quality of life. In addition, treatment of hyponatraemia has been shown to improve gait stability in the non-oncology population, which can reduce falls and the risk of pathological fractures (Renneboog et al. 2006). As long-term survivorship from cancer continues to improve, the deleterious effects of untreated chronic hyponatraemia on bone mineral density should also be considered (Upala & Sanguankeo 2016). Treatment of SIAD to improve hyponatraemia in lung cancer has also been shown to improve overall survival at 10 but not 20 months, in a meta-analysis, though it should be acknowledged that longer follow-up will document diminishing returns on survival with a malignant process (Bartalis et al. 2021). The reason for the positive effect of active treatment of SIAD is not known. Hyponatraemia treatment may improve cancer survival, improving patient well-being and performance status, thus allowing early and more intensive cancer treatment regimens. Several studies have found that hyponatraemia is associated with poorer chemotherapy responses; correction of hyponatraemia could therefore potentially improve treatment outcomes (Schutz et al. 2014, Svaton et al. 2014, Berardi et al. 2015).

The decision to treat hyponatraemia will remain individualised. A composite analysis of severity of hyponatraemia symptoms, likely overall survival, and appropriateness of treatment options available should inform the decision to treat in any clinical circumstance. There are a number of options available for the treatment of chronic SIAD, many of which have been used in patients with cancer. This was reflected in an analysis of treatments used in the hyponatraemia registry. In SIAD associated with malignancy, 12% of patients received no active treatment, while the most frequently used therapies – fluid restriction and isotonic saline – had very modest effects on plasma sodium concentration (Burst et al. 2017). Tolvaptan was the most effective therapy and the only treatment for SIAD that was as effective in cancer patients, as in non-cancer SIAD.

**Fluid restriction**

Both the US and European guidelines recommend fluid restriction (FR) as first-line treatment for chronic SIAD (Verbalis et al. 2013, Spasovski et al. 2014). The data to support this recommendation are limited. A randomised prospective trial of FR vs no therapy showed a modest rise in plasma sodium concentration of 3 vs 1 mmol/L after 3 days of FR, with minimal further rise in plasma sodium concentration at 30 days (Garrahy et al. 2020). Results from the hyponatraemia registry showed that FR produced an even less impressive rise in plasma sodium in a mixed aetiology group of patients with SIAD, with no statistical difference in the rise in plasma osmolality, when compared with no therapy at all (Greenberg et al. 2015). The SIAD cohorts in both of these studies were of mixed aetiology, but each contained patients with malignant causes of SIAD. If a presumption is made that patients with malignant SIAD respond in a similar way to SIAD from other causes, FR may not be effective for long-term treatment of SIAD.

There are also significant reasons why FR would not be an ideal choice for malignant SIAD. For FR to be effective, intake must usually be restricted to 800 mL daily, which includes fluids contained in fruit, yoghurt, etc. This is rarely compatible with long-term care, especially if there is a requirement to take fluids with medications, or to maintain fluid intake when on chemotherapy. In addition, when a balanced diet is required to replace weight or muscle loss, it is difficult to restrict fluid intake. Most importantly, hospitalised patients may be on i.v. antibiotics or antiemetics, as well as i.v. fluids associated with administration of chemotherapy. For this reason, FR is rarely of practical value in SIAD associated with malignancy.

**Vaptans**

Vaptans are vasopressin receptor antagonists with specificity for the renal V2 receptors. The SALT studies showed the effectiveness of tolvaptan in elevating plasma sodium concentration in a mixed cohort of patients with either SIAD or hypervolaemic hyponatraemia (Schrier et al. 2006). The rise in plasma sodium was accompanied by an improvement in gait stability and the risk of pathological fractures. Side effects, such as thirst and dry mouth, were mild and predictable given the mechanism of action of tolvaptan. The results were strongly suggestive of treatment benefit. However, in common with all post hoc analyses, the conclusions require confirmatory prospective evaluation. A comparison of tolvaptan treatment with
supportive care in SIAD in oncology patients showed that
tolvaptan therapy was associated with quicker reversal of
hyponatraemia, decreased hospital stay and decreased
symptoms and complications (Bilgetekin et al. 2021)
and also showed that if plasma sodium concentration
was normalised, overall survival improved. A small
retrospective review, of 23 patients with small cell lung
cancer treated with tolvaptan, confirmed that improved
performance status resulted from elevation in plasma
sodium concentration (Ren & Yang 2021). Interestingly,
this study showed that smaller doses of tolvaptan than
those utilised in the SALT studies (Schrier et al. 2006)
were equally efficacious in reversing hyponatraemia. This
reflects a sense that the doses of tolvaptan used in the
early SALT studies may have been higher than needed for
clinical effects and that better dosing studies are needed
in SIAD (Sterns 2018a). Although tolvaptan may be
efficacious in reversing hyponatraemia associated with the
SIAD of cancer, a loss of effect has been reported, associated
with rising plasma AVP concentrations, as small cell lung
cancer tumour mass progresses and cancer becomes more
active (Garrahy et al. 2018). In the patients reported,
escalating doses of tolvaptan were needed to maintain
normonatraemia as plasma AVP concentrations increased,
with eventual loss of drug effect.

Tolvaptan is an effective treatment for SIAD but is an
expensive therapy for long-term use. A recent Italian study
did suggest however that the use of tolvaptan was associated
with reduced length of hospital stay in patients with
cancer; it was argued that savings from reduced in-patient
bed days could offset the cost of therapy (Berardi et al.
2019). Vaptans can be useful for short-term interventions
which allow i.v. fluid replacement during chemotherapy
(O’Connor-Byrne et al. 2019) or for longer-term therapy to
reverse hyponatraemic symptoms (Bilgetekin et al. 2021).
Side effects are reflective of the aquaretic effects of the drug
and include polyuria and thirst. Overcorrection has been
reported (Schrier et al. 2006), particularly when the starting
plasma sodium is very low, but osmotic demyelination
has not been a significant issue. Although tolvaptan is
marketed at doses of 15–30 mg, in practice, many clinicians
initiate therapy with lower doses, to diminish the risk of
overcorrection of sodium. A reversible transaminitis
has been reported with tolvaptan therapy in autosomal
dominant polycystic kidney disease (Torres et al. 2012)
but not in hyponatraemia, where lower doses of tolvaptan
are typically used (Schrier et al. 2006). It is recommended
that liver function tests be monitored at baseline, 2 and 4
weeks and monthly thereafter. Tolvaptan should be held if
aspartate aminotransferase (AST) or alanine transaminase
(ALT) increases to two times the upper limit of normal
(ULN) and permanently discontinued if the increase
exceeds three times the ULN (Chebib et al. 2018).

Urea

Urea acts as an osmotic diuretic, which increases renal
water loss, resulting in elevation in plasma sodium
concentration. The European guidelines recommend it
as an effective and inexpensive second-line treatment
(Spasovski et al. 2014). Urea has been reported to be effective
in a number of small non-randomised, retrospective
European studies (Decaux & Genette 1981, Soupart et al.
2012) and in the data available suggest that it is safe and
well-tolerated (Rondon-Berrios et al. 2018). A retrospective
review of 36 non-randomised oncology patients, who were
reated with urea for SIAD, concluded that it was safe and
well-tolerated, although with the caveat that there was no
control group or comparison with other treatments (Nervo
et al. 2019). A significant advantage in the treatment
of patients with cancer is that fluid restriction is not
required with urea therapy. As with tolvaptan, the risk of
overcorrection mandates the regular monitoring of plasma
sodium concentrations after initiating therapy.

Demeclocycline

Demeclocycline is a tetracycline antibiotic which induces
nephrogenic diabetes insipidus (Padfield et al. 1978) and
causes a rise in plasma sodium concentration consequent
upon an aquaresis. The onset of action is unpredictable
and as a result of this, and side effects such as renal
failure and photosensitivity rash, European guidelines
have recommended against the use of demeclocycline in
SIAD (Spasovski et al. 2014). A systemic literature review
discovered no evidence based on the use of demeclocycline
in SIAD (Miell et al. 2015), though two of the three authors
were employed by Otsuka pharmaceuticals, which
produces tolvaptan. There seems little to justify the side
effects of demeclocycline given the toxicity, the lack of
evidence and the availability of better agents.

Frusemide

Frusemide monotherapy for SIAD is not recommended,
as the natriuresis leads to volume contraction, with the
secondary stimulation of AVP secretion (Dineen et al.
2017). However, frusemide in combination with oral
sodium chloride tablets, which are administered to replace
urine sodium losses, has been endorsed by the European
guidelines as second-line therapy (Spasovski et al. 2014) and is used extensively in the treatment of SIAD. There are little prospective data to support the use of frusemide/sodium chloride replacement, however. The available data have shown no advantage of frusemide/sodium chloride over fluid restriction alone with the disadvantage of higher rates of adverse events including hyponatraemia and acute kidney injury (Krisanapan et al. 2020). The hyponatraemia registry recorded that 4% of SIAD patients were treated with this form of therapy (Greenberg et al. 2015), with slightly higher usage, at 6.5%, in patients with cancer (Burst et al. 2017). Prospective randomised data are needed to support the recommendation for the use of this therapy in oncology with cancer.

Are patients with malignancy treated for hyponatraemia?

The evidence is compelling that hyponatraemia is common in malignancy and has negative effects on performance, survival and duration of hospital stay. There are little data from randomised, prospective trials that treatment of hyponatraemia improves outcomes, but there is enough evidence from the data available to strongly suggest symptomatic (Petereil et al. 2013, Bilgetekin et al. 2021, Ren & Yang 2021) and survival benefit (Tiseo et al. 2014, Yang et al. 2017, Wu et al. 2020, Bartalis et al. 2021, Sandfield-Paulsen et al. 2021). Unpublished data from our own hospital (Murphy B., unpublished audit) suggest that other than renal medicine, where hyponatraemia is actively within-house, the lowest rate of endocrine referral is from patients who develop hyponatraemia on oncology/haematology services. As a consequence, the rate of active management of hyponatraemia is also lowest in oncology services. There is good evidence from the literature that active management of hyponatraemia reduces mortality (Garrahy et al. 2021), and the recommendations of a British expert panel have emphasised early referral to endocrinologists or renal physicians for symptomatic hyponatraemia (Grant et al. 2015). It has been recommended that SIAD is managed by specialised endocrinologists (Garrahy & Thompson 2017), though it is probably important that each hospital has a designated hyponatraemia specialist, irrespective of speciality, who can set protocols, audit standards and manage the most difficult cases. However, even after this system was introduced in our own hospital, referrals of oncology patients with hyponatraemia remained low and active management correspondingly remained low. It remains a challenge for endocrinologists to build partnerships with local oncology and haematology services, to ensure that patients with malignancy are properly assessed for causation of hyponatraemia and that management of SIAD is appropriate. Symptomatic outcomes, and perhaps even survival, of patients with malignancy and SIAD, may depend upon it.

Conclusion

Hyponatraemia confers significant morbidity to individuals with cancer, it is associated with impaired performance status, prolonged hospital admission, reduced treatment efficacy and overall survival. Thorough evaluation of the aetiology of hyponatraemia, in particular, differentiating between SIAD and cortisol deficiency is essential to ensure appropriate treatment. Active treatment of hyponatraemia, with specialist endocrinology input, is increasingly recognised as an important component of oncological management. Restoration of eunatraemia has been shown to improve hyponatraemia symptoms, reduce hospital stays and may improve overall survival. Tolvaptan is a safe and effective treatment of SIAD in the oncology setting.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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