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Hyponatraemia and cancer

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Hyponatraemia is the most common electrolyte alteration in cancer patients and the main cause is the syndrome of inappropriate antidiuresis. In this context, arginine vasopressin secretion can be due to ectopic secretion by tumoral cells or to drugs, including chemotherapeutics. It is known that hyponatraemia is associated with a worse prognosis in cancer. Conversely, the correction of serum [Na^+] is associated with a favourable effect on the disease's outcome. Basic research provided evidence that reduced [Na^+] activates several intracellular pathways in cancer cells, which lead to an increased growth and invasiveness. Interestingly, vasopressin receptor antagonists, mainly used for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuresis and in polycystic kidney disease, effectively reduced cancer cell proliferation in *in vitro* and *in vivo* experiments. Although this needs to be confirmed on clinical grounds, it is tempting to hypothesize that vasopressin receptor antagonists might have a possible role in future anti-cancer strategies.

Introduction

It is well known that hyponatraemia is the most common electrolyte alteration in hospitalised patients, with a prevalence of about 30 % [1,2]. As mentioned in previous chapters of this special issue, hyponatraemia can be due to a number of different aetiologies. However, the syndrome of inappropriate antidiuresis (SIAD), which accounts for up to 50 % of cases, is the most frequent cause [3]. There is evidence that hyponatraemia is the most frequent electrolyte disorder also in cancer patients and it has been reported in up to 40 % of patients at hospital admission [4,5]. In addition, around half of patients experience one or more episodes of hyponatraemia at follow up. In patients with lung cancer, either small cell (SCLC) or non-small cell lung cancer (NSCLC), the proportion of patients in which hyponatraemia is detected at some point of their clinical history raises to 75 % [6]. SIAD remains the most frequent cause of hyponatraemia also in cancer patients [7], although other conditions may cause hyponatraemia in these subjects. Interestingly, it has been well demonstrated that reduced serum [Na^+] is associated with a significantly decreased progression-free (PFS) and overall survival (OS) in cancer [4]. Consequently, it has been hypothesized that low serum [Na^+] might be viewed as a possible biomarker of

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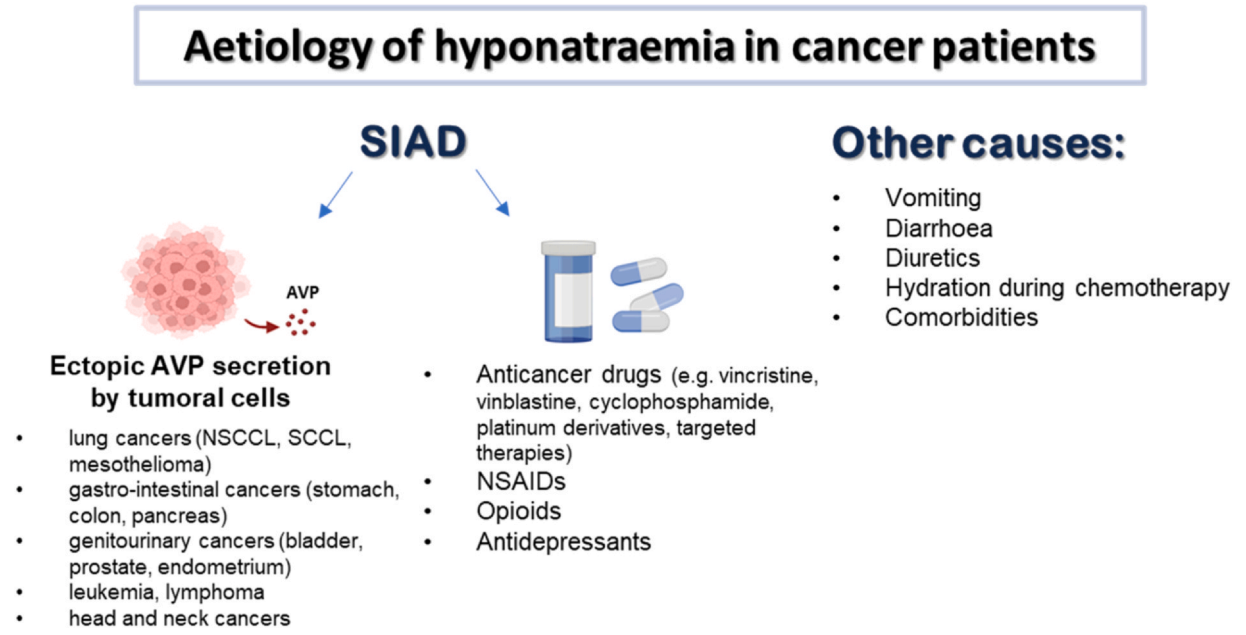

Fig. 1. Aetiology of hyponatraemia in cancer patients. AVP, arginine vasopressin. NSAIDs, non steroidal anti inflammatory drugs.

disease severity [8]. This review will describe several aspects related to hyponatraemia and cancer, from the aetiology to the impact on patients' outcome and to treatment strategies. Part of the review will cover the main basic research findings related to this topic, which have been of crucial help in understanding the impact of hyponatraemia on cancer progression.

Hyponatraemia and cancer: The clinical perspective

Aetiology of hyponatraemia in cancer

As already mentioned, the aetiology of hyponatraemia in cancer is multifaceted (Figure 1). SIAD due to ectopic arginine vasopressin (AVP) secretion is the cause of hyponatraemia in many types of cancer, particularly in lung cancer. However, tumoral AVP secretion has been observed in tumours affecting nasopharynx, oropharynx, stomach, duodenum, colon, pancreas, prostate, uterus, ureter, bladder, breast and also in lymphomas, leukemias, sarcomas, brain tumours, mesotheliomas and thymomas [9–11]. Overall, in $>$ 30 % of cases hyponatraemia is secondary to ectopic AVP secretion [9].

Drug-related hyponatraemia is also observed in cancer patients, because several drugs that are used in this setting can stimulate the release of AVP or amplify the response of the type 2 AVP receptor (AVPR) [11,12]. Noteworthy, commonly used chemotherapeutic agents can induce SIAD-related hyponatraemia, such as vincristine, vinblastine, cyclophosphamide, cisplatin (it can also cause hyponatraemia through a salt loosing nephropathy), melphalan. In addition, other drugs that are used in cancer patients may cause hyponatraemia with the above mentioned mechanisms. The list includes morphine and other narcotic painkillers, immunomodulators (immunoglobulins, interferon, interleukin-2, levamisole), antiepileptic drugs (in particular carbamazepine and oxcarbazepine, but also eslicarbazepine, lamotrigine, sodium valproate, levetiracetam and gabapentin), antidepressants (e.g. tricyclics, selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors), phenothiazines (used as antiemetic agents), and non steroidal anti inflammatory drugs [11–14]. It has to be said that also more recent pharmacological anti-cancer strategies, such as targeted therapies and immune-check points inhibitors, should be considered among drugs that can induce hyponatraemia. In fact, these molecules can cause corticotropin deficiency and therefore hypocortisolism and consequent serum [Na^+] reduction [15,16].

Finally, other conditions may have an effect on serum [Na^+], possibly contributing to the onset of hyponatraemia. Among these, diarrhoea, nausea, vomiting, pain, physical and emotional stress, hydration in patients subjected to chemotherapy, and heart or kidney failure are the most prevalent [13].

Does hyponatraemia affect cancer patients' outcome?

It is well known that hyponatraemia is associated with increased health care costs, mainly because it can require a prolonged hospitalisation compared to normonatraemic cancer patients [17]. Furthermore, low serum [Na^+] may negatively affect the quality of life [18] and is associated with a worse prognosis in different pathological conditions, such as myocardial infarction, heart failure, cirrhosis and pulmonary infections [19]. Whether hyponatraemia may affect cancer patients' outcome has been a matter of debate.

The literature suggests that this condition is indeed an independent, negative prognostic factor in many different tumours, including SCLC [20,21] and NSCLC [6], gastrointestinal cancer [22], lymphoma [23], hepatocellular carcinoma [24,25], renal cell carcinoma [26,27], prostatic and pancreatic carcinoma [28,29], biliary tract cancer [30], mesothelioma [30], multiregional upper tract urothelial carcinoma [31], and epithelial ovarian cancer [32].

Other studies indicated that low serum [Na^+] is associated with a reduced survival at all cancer stages [21,33], and that among cancer patients the risk of death in those with hyponatraemia is almost three fold higher than in those with normonatraemia [4]. A prospective cohort study of 98,411 adults hospitalised for different clinical conditions between 2000 and 2003 at two teaching hospitals in Boston, MA, showed that one of the highest rates of in-hospital mortality (OR = 2.05, 95 % CI 1.67–2.53) was observed in metastatic patients with hyponatraemia [34].

The question also came up whether low serum [Na^+] may also affect the response to cancer therapy. A study performed in NSCLC patients treated with pemetrexed-platinum doublet chemotherapy demonstrated a significantly reduced progression-free survival in hyponatraemic patients compared to normonatraemic ones (6 months *vs*. 7 months, respectively; $p < 0.05$) [35]. Other studies, which included patients with metastatic renal cell carcinoma treated with sunitibib, sorafenib, or everolimus [36,37], or with neuroendocrine tumours treated with peptide receptor radionuclide therapy [38], or with hepatocellular carcinoma treated with sorafenib [39], obtained similar results. Furthermore, a multivariate analysis indicated that low serum [Na^+] was an independent predictive factor of non-response to therapy in NSCLC patients treated with the EGFR inhibitor erlotinib, similarly to the negative predictive role of a poor performance status and the absence of EGFR mutations in the tumour [40].

Interestingly, there is growing evidence that metal ions play a role in modulating immunity [41]. For instance, manganese, potassium, calcium and zinc have shown their efficacy in stimulating the immune response, thus counteracting tumour growth [42–45]. On the other hand, ion deficiencies might be associated with a reduced efficacy of immunotherapy against cancer. It has been reported that PFS and OS were reduced in hyponatraemic patients treated with immune check point inhibitors for gastric cancer and cholangiocarcinoma, compared to normonatraemic patients [46,47].

Whether hyponatraemia might be viewed also as a risk factor to develop cancer has been the topic of two large retrospective studies performed in Denmark. These studies confirmed that low serum [Na^+] affects all-cause mortality, but also indicated that this condition is associated with a higher risk to develop a tumour [48,49]. Should these results be confirmed by future studies, it would be reasonable to suggest that serum [Na^+] is assessed on a routine basis in the general population.

Overall, these data do not provide a direct evidence that the correction of hyponatraemia might have a favourable role on cancer prognosis. However, other studies suggested that this might be the case. One study assessed the role of the normalisation of serum [Na^+] in patients with SCLC undergoing treatment with carboplatinum/etoposide. In patients with normalised serum [Na^+] an increased OS and PFS was observed, compared to uncorrected patients [50]. Similar findings were obtained in patients with NSCLC. Here, a longer OS and PFS were observed in patients with normalised serum [Na^+] (11.6 vs. 4.7 months and 6.7 vs 3.3 months, respectively) [51]. In view of these results, it has been suggested that hyponatraemia might be considered as a biomarker targeting high-risk patients affected by lung cancer [8]. These results were also confirmed in different tumours. For instance, in a cohort of patients with terminal cancer (gastrointestinal, lung, breast, head and neck, haematological, urological, gynaecological) the normalisation of serum [Na^+] was associated with a median OS of 13.6 months compared with 16 days in patients that remained hyponatraemic [52]. More recently, the analysis of medical records of 1100 patients with solid cancers indicated that an increase of serum [Na^+] from admission to discharge was associated with an increased OS in metastatic patients [HR 0.96 (95 % CI 0.94–0.99), $p = .0041$] [53]. It has to be said that that all these findings were obtained by non-randomised studies and therefore it cannot be concluded that the better outcome reported in patients with corrected hyponatraemia is effectively due to serum [Na^+] normalisation.

Treatment of hyponatraemia in cancer patients

In principle, the treatment of hyponatraemia in cancer patients does not differ from the recommendations followed for other conditions and that are described elsewhere in this special issue. One specific comment deserves fluid restriction, which is included in the main guidelines [11,54] for the correction of mild non-hypovolemic hyponatraemia, although usually it is not very effective nor well tolerated by patients [55]. An additional issue against the use of fluid restriction for the correction of serum [Na^+] in cancer is represented by the fact that patients receiving chemotherapy need appropriate hydration. Urea, which is considered as a possible strategy for the correction of non-hypovolaemic hyponatraemia, has been successfully used in cancer patients [56–59].

AVPR antagonists, also known as vaptans, were designed in order to inhibit the binding of AVP to its receptors [60]. Of particular interest is the effect on type 2 AVPR, which is localised in the basolateral membrane of renal collecting duct cells. Upon binding this receptor, vaptans inhibit the synthesis and activation of aquaporin-2 into the apical membrane of duct cells [11,61]. Therefore, type 2 AVPR antagonists induce aquaresis and ultimately an increase of serum [Na^+]. Several studies indicated that vaptans effectively and safely correct hyponatraemia [11,61]. Conivaptan, a mixed type 1–2 AVPR antagonist, was approved in the U.S. in 2005 for the “treatment of euvolemic and hypervolemic hyponatraemia in hospitalised patients”. Another molecule, tolvaptan, which is a selective type 2 AVPR antagonist, was approved in the U.S. in 2009 for the “treatment of clinically significant hypervolemic and euvolemic hyponatraemia” and in Europe in the same year, with the limitation to the “treatment of adult patients with hyponatraemia secondary to SIAD”. The use of vaptans, as well as other interventions for the treatment of hyponatraemia in clinical practice, are discussed elsewhere in this special issue and therefore will not be commented in detail here. In general, the instructions that are followed for a proper use of these drugs for patients with other morbidities also apply to cancer patients [11,54].

With regard to vaptans treatment, this option can be recommended in cancer patients with hyponatraemia that are scheduled for surgery or chemotherapy. The aim is to achieve a prompt correction of serum [Na^+] and to proceed with the prescribed treatment strategy. Interestingly, there is evidence that cancer patients with uncorrected pre-treatment hyponatraemia have a reduced survival [62]. Because many anticancer drugs can induce or worsen hyponatraemia, as discussed previously, patients undergoing chemotherapy deserve great attention and regular serum [Na^+] monitoring should be scheduled. A final comment about the use of vaptans in treating SIAD-related hyponatraemia in cancer deserves mozavaptan, which was approved in Japan as early as 2006 for the specific use in "patients with paraneoplastic SIAD" [63].

Vasopressin receptor antagonists in cancer: More than serum [Na^+] correction?

There is another aspect about vaptans that is worth mentioning in the context of hyponatraemia in cancer. Two type 2 AVPR antagonists, OPC-31260 and tolvaptan, effectively counteracted cystogenesis in polycystic kidney disease (PKD) models. The mechanism underlying this effect was based on the binding of vaptans to type 2 AVPR that are expressed on the cell membrane of renal cysts. Hence, cAMP production is inhibited and cAMP-dependent proliferative pathways are blunted [64–66]. Subsequently, clinical studies [Tolvaptan Efficacy and Safety in Management of ADPKD and Outcomes (TEMPO) program] have evaluated the effect of tolvaptan in autosomal dominant PKD (ADPKD). Relevant results were obtained by a phase 3, multicenter, double-blind, placebo-controlled, 3-year trial in 2012 [67]. This study reported that high doses of tolvaptan (up to 120 mg/d) effectively counteracted the growth of kidneys and the progression to end-stage kidney failure, compared to placebo. Additional studies confirmed the effectiveness of tolvaptan in ADPKD [68] and currently this molecule is used by nephrologists against the progression of ADPKD. In view of these findings on the effect of tolvaptan in counteracting the growth of renal cysts in ADPKD, it is tempting to speculate that AVP receptor antagonists might have a role as antiproliferative agents also in other clinical scenarios. The next chapters will describe what we have learned so far about the relationship between hyponatraemia and cancer and about the possible role of vaptans in anticancer strategies, so far.

Hyponatraemia and cancer: The laboratory perspective

Effects of low extracellular [Na^+] on cancer cells

In an experimental rat model hyponatraemia was obtained by infusing the type 2 AVPR agonist desmopressin via subcutaneously implanted osmotic minipumps and by administering a liquid diet to rats [69]. Thus, following this procedure, an *in vivo* model of SIAD was obtained. Interestingly, several alterations were observed after a few weeks of hyponatraemia, e.g. increased bone resorption, hypogonadism with decreased testicular weight and abnormal histology, decreased body fat, skeletal muscle sarcopenia and cardiomyopathy with perivascular and interstitial fibrosis. The authors claimed that these findings were consistent with previous results indicating that low extracellular [Na^+] was associated with increased oxidative stress, which, in turn, might induce manifestations of senescence. Interestingly, our group also observed that oxidative stress was elicited in the presence of low extracellular [Na^+] *in vitro*. Specifically, using a micro-array approach, we found that in neuroblastoma cells cultured in low [Na^+] there was a marked induction of the expression of the hemeoxygenase-1 (HMOX-1) gene, which is an indirect marker of oxidative stress [70]. In addition, an Ingenuity Pathway Analysis, a software application that allows to identify alterations in signaling, biological mechanisms and functions, and metabolic pathways, indicated that the most dysregulated pathway in low [Na^+] involved genes that were grouped under the tags "cell death and survival" and "cell migration". In a subsequent study, we directly demonstrated the presence of a marked increase in the production of reactive oxygen species in neuroblastoma cells maintained in low extracellular [Na^+] [71].

HMOX-1 is known to be a stress protein, which has a function in heme turnover [72], but also has anti-apoptotic activity [73]. Oxidative stress is known to promote local invasiveness and metastatization by different mechanisms, which include the activation of pro-survival and pro-metastatic pathways [74].

We also developed an animal model of chronic SIAD in mice, using the same experimental protocol described by the group of Joseph Verbalis [69]. Hypogonadism and a significantly reduced testis volume, with a marked reduction of the size of seminiferous tubules, were observed in these animals, according to the previously published data. In addition, we observed the presence of liver steatosis at histological assessment. Accordingly, in the liver of hyponatraemic mice the expression of SREBP-1, PPARα and PPARγ, which are proteins involved in the metabolism of lipids, as well as the expression of α-SMA and CTGF, which are involved in myofibroblast formation, were significantly increased. Again, HMOX-1 overexpression was detected in Kupffer and stellate cells in the liver of hyponatraemic mice [75]. This original finding appears of interest, considering the topic of this manuscript, if we consider that non-alcoholic fatty liver disease represents the initial condition that can result in steatohepatitis, fibrosis, and then cirrhosis and hepatocarcinoma [76].

In studies that were specifically designed to address the relationship between hyponatraemia and cancer, we found that in different human cancer cell lines (from pancreatic adenocarcinoma, neuroblastoma, colorectal adenocarcinoma, chronic myeloid leukemia, SCLC and renal cell carcinoma) maintained in low [Na^+], HMOX-1 overexpression was associated with a markedly increased cell proliferation [77–80]. Based on this body of evidence, we hypothesized that oxidative stress elicited by low [Na^+] might represent a possible molecular explanation of the worse outcome observed in cancer patients with hyponatraemia. In the above mentioned studies we also demonstrated that cancer cells cultured in low [Na^+] change their morphology and acquire the ability to grow without a solid substrate and to degrade the extracellular matrix. Overall, these changes increase cell invasiveness. Accordingly, we observed the activation of molecular pathways (e.g. RhoA, ROCK-1, ROCK-2) that are associated with cell proliferation and invasiveness. Furthermore, alterations in the proteins that are associated with the cytoskeleton were found, ultimately leading to

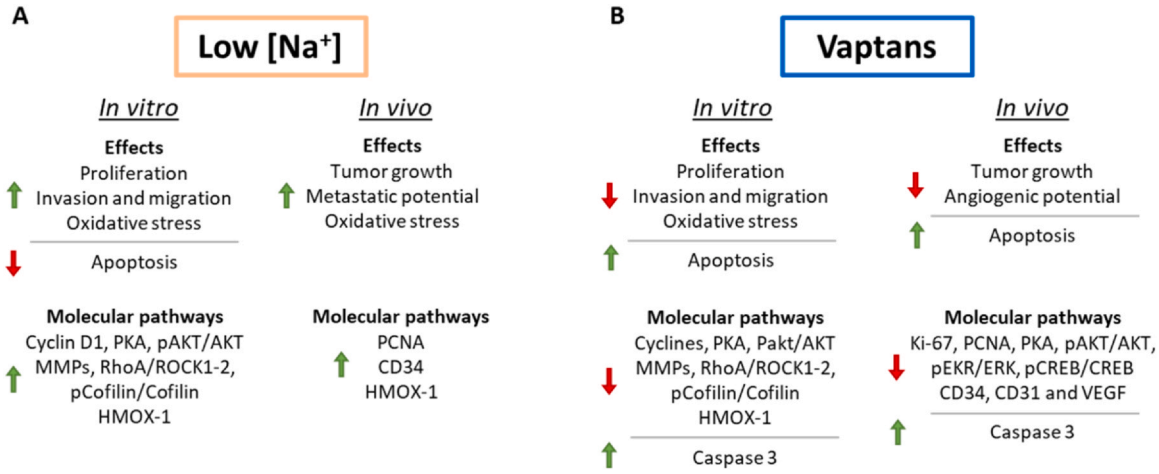

Fig. 2. Effects of low [Na^+] (A) and vaptans treatment (B) in cancer and molecular pathways involved.

actin cytoskeletal remodelling and to increased invasiveness. It is worth mentioning that the RhoA/ROCK1–2 pathway has been hypothesized as a molecular target in cancer treatment [80–83], in view of its interaction with the actin cytoskeleton. An *in vivo* study performed in our lab confirmed these results. We found that hyponatraemia was associated with a significantly increased tumour growth and with an increased angiogenetic potential in a murine xenograft model of neuroblastoma. The expression of proteins involved in cell proliferation and in angiogenesis, such as PCNA and CD34, was increased, as well as the expression of HMOX-1, in tumours of hyponatraemic mice compared to the control group [84]. A summary of the effects of low [Na^+] in cancer is represented in Fig. 2A.

Effects of vaptans on cancer cells

As already mentioned, vaptans inhibit the cAMP-dependent intracellular signaling by binding the type 2 AVPR. This effect represented the basis that promoted the development of tolvaptan as a new pharmacological strategy in the treatment of ADPKD. The pre-clinical studies, which suggested a previously unpredicted antiproliferative effect of tolvaptan, were performed in a rat model of PKD and demonstrated that the inhibition of serum AVP, obtained by an increased water intake, caused reduced renal cAMP and ERK activation, thus counteracting cell proliferation and slowing the progression of the disease [85]. Similar results were obtained by the introduction of a non-sense mutation of the AVP gene in PKD rats [66]. On the contrary, the administration of the AVP analogue desmopressin was associated with a relapse of cysts growth in AVP-deficient PKD rats. Furthermore, tolvaptan inhibited AVP-induced growth of ADPKD renal cells by inhibiting the B-Raf/MEK/ERK pathway [86]. More recently, it has been shown in HeLa cells that tolvaptan has an anti-mitotic activity by binding and inhibiting Eg5, which is a motor protein essential for forming a bipolar mitotic spindle that allows for correct cell division [87]. In view of these findings, it was hypothesized by researchers that vaptans might have a role also in anti-cancer strategies. Hence, several studies were designed, in order to test this hypothesis. It is known that overexpression of the type 1 and type 2 AVPR is observed in tumours of different organs and tissues, such as breast, bladder, colon, kidney, liver, lung, ovary, prostate, pancreas, skin, thymus, thyroid, head and neck cancer, sarcoma, and diffuse large B-cell lymphoma, as reported by The Cancer Genome Atlas and The Human Protein Atlas databases. The first study that addressed a possible antiproliferative effect of vaptans in cancer cells was performed in human hepatocarcinoma cells [88]. In this study it was shown that tolvaptan inhibited cell growth, reduced the rate of cell cycle progression, and induced apoptosis. Similar results were obtained by our group in different cancer cell lines from SCLC, neuroblastoma and colon adenocarcinoma, that express the type 2 AVPR [78,80,89]. In particular, we observed that tolvaptan significantly reduced the expression of cAMP, PKA and AKT, and inhibited cell proliferation. Cell motility was also reduced, likely by the activation of type IV collagenases, and the inhibition of the RhoA/ROCK1–2 pathway. *In vivo*, tolvaptan treatment for 60 days was able to significantly reduce tumor growth and increase apoptosis in a murine xenograft model of SCLC compared to untreated mice. Furthermore, a prolonged survival was observed in the tolvaptan group [90].

Another study was performed by Sinha and colleagues on clear cell Renal Carcinoma Cells (ccRCC). The authors demonstrated *in vitro* and *in vivo* that the type 2 AVPR plays an important role in stimulating tumor growth. In contrast, two type 2 AVPR antagonists, tolvaptan and OPC31260 (e.g. mozavaptan), decreased ccRCC proliferation and angiogenesis, whereas they triggered apoptosis. In the same study, type 2 AVPR antagonists effectively inhibited tumour growth in a xenograft model of ccRCC [91]. The authors suggested these molecules as possible treatments for ccRCC. Noticeably, ccRCC, which is the most frequent form of kidney cancer, can be very aggressive and many patients experience a high recurrence rate after surgery. Usually, chemotherapy or radiation therapy are not effective in metastatic patients [92,93].

Other studies have addressed the type 1 AVPR as a possible target for anti-cancer strategies. An example is represented by relcovaptan, which is a type 1a AVPR antagonist [94–96]. This molecule is known in clinical scenarios for its beneficial effects in

Raynaud's disease and dysmenorrhea [97,98], although it is not officially approved for clinical use. Castration-resistant prostate cancer (CRPC) is a very aggressive form of prostate cancer that relapses after androgen deprivation therapy. Elevated expression levels of type 1a AVPR were detected in CRPC and relcovaptan was suggested as a possible strategy [99]. With regard to this point, some *in vitro* studies have shown that relcovaptan counteracted cell proliferation in CRPC, by downregulating the cell cycle-related protein cyclin A. Opposite effects were observed when CRPC cells were treated with AVP, which elicited cancer growth [99]. The inhibitory role of relcovaptan on CRPC growth was also confirmed *in vivo* in mice. [99]. Here, relcovaptan was also able to prevent the formation of bone metastases in CRPC [99]. Furthermore, a strong correlation between the co-expression of type 1a and type 2 AVPR and prostate cancer progression was demonstrated. Accordingly, in CRPC xenografts tolvaptan and relcovaptan had a synergistic effect in inducing cell apoptosis and in reducing tumour growth [100]. A summary of the effects of vaptans in cancer is represented in Fig. 2B.

Overall, these findings open the field for hypothesizing a possible new role of AVPR antagonists as pharmacological anti-cancer strategies. However, additional studies and especially human clinical data will be needed in order to confirm this hypothesis.

Summary

Basic research and clinical data provided evidence that low [Na^+] have an unfavourable effect on cancer outcome, similarly to what has been demonstrated in other diseases [19]. Experimental evidence and observational data indicated that normalisation of serum [Na^+] has a positive effect on prognosis, however, randomized controlled trials to prove causality are lacking. AVPR antagonists might play a dual role, by effectively correcting serum [Na^+] and, based on experimental data, by possibly counteracting tumour growth and spread. Clinical trials, specifically designed to test this possibility, might tell us whether this hypothesis is correct.

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] Adrogué HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342(21):1581–9.
[2] Rondon-Berrios H, Agaba EI, Tzamaloukas AH. Hyponatremia: pathophysiology, classification, manifestations and management. Int Urol Nephrol 2014;46(11):2153–65.
[3] Cuesta M, Thompson CJ. The syndrome of inappropriate antidiuresis (SIAD). Best Pract Res Clin Endocrinol Metab 2016;30(2):175–87.
*[4] Doshi SM, Shah P, Lei X, et al. Hyponatremia in hospitalized cancer patients and its impact on clinical outcomes. Am J Kidney Dis J Natl Kidney Found 2012;59(2):222–8.
[5] Berardi R, Rinaldi S, Caramanti M, et al. Hyponatremia in cancer patients: Time for a new approach. Crit Rev Oncol Hematol 2016;102:15–25.
[6] Castillo JJ, Glezerman IG, Boklage SH, et al. The occurrence of hyponatremia and its importance as a prognostic factor in a cross-section of cancer patients. BMC Cancer 2016;16:564.
[7] Grohé C. Hyponatremia in oncology patients. Front Horm Res 2019;52:161–6.
[8] Kasi PM. Proposing the use of hyponatremia as a marker to help identify high risk individuals for lung cancer. Med Hypotheses 2012;79(3):327–8.
[9] Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer J Multinatl Assoc Support Care Cancer 2000;8(3):192–7.
[10] Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. N Engl J Med 2007;356(20):2064–72.
*[11] Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med 2013;126(10 1):S1–42.
[12] Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. Am J Kidney Dis J Natl Kidney Found 2008;52(1):144–53.
[13] Raftopoulos H. Diagnosis and management of hyponatremia in cancer patients. Support Care Cancer J Multinatl Assoc Support Care Cancer 2007;15(12):1341–7.
[14] Norello D, Defazio G, Corona G, et al. Treatment with antidepressant drugs and hyponatremia: a network meta-analysis. J Endocrinol Invest 2025;48(8):1707–15.
[15] Berardi R, Santoni M, Rinaldi S, et al. Risk of hyponatraemia in cancer patients treated with targeted therapies: a systematic review and meta-analysis of clinical trials. PLoS One 2016;11(5):e0152079.
[16] Terashita M, Yazawa M, Murakami N, et al. Water and electrolyte abnormalities in novel pharmacological agents for kidney disease and cancer. Clin Exp Nephrol 2025;29(5):521–33.
[17] Boscoe A, Paramore C, Verbalis JG. Cost of illness of hyponatremia in the United States. Cost Eff Resour Alloc 2006;4:10.
[18] Berardi R, Caramanti M, Fiordoliva I, et al. Hyponatraemia is a predictor of clinical outcome for malignant pleural mesothelioma. Support Care Cancer J Multinatl Assoc Support Care Cancer 2015;23(3):621–6.
[19] Corona G, Giuliani C, Parenti G, et al. Moderate hyponatremia is associated with increased risk of mortality: evidence from a meta-analysis. PLoS One 2013;8(12):e80451.
[20] Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. J Natl Compr Canc Netw 2006;4(6):631–8.
*[21] Rawson NS, Peto J. An overview of prognostic factors in small cell lung cancer. A report from the subcommittee for the management of lung cancer of the United Kingdom Coordinating Committee on Cancer Research. Br J Cancer 1990;61(4):597–604.
[22] Choi JS, Bae EH, Ma SK, et al. Prognostic impact of hyponatraemia in patients with colorectal cancer. Color Dis J Assoc Coloproctol Gt Br Irel 2015;17(5):409–16.
[23] Dhaliwal HS, Rohatiner AZ, Gregory W, et al. Combination chemotherapy for intermediate and high grade non-Hodgkin's lymphoma. Br J Cancer 1993;68(4):767–74.
[24] Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. Hepatology 2008;48(3):1002–10.
[25] Cescon M, Cucchetti A, Grazi GL, et al. Indication of the extent of hepatectomy for hepatocellular carcinoma on cirrhosis by a simple algorithm based on preoperative variables. Arch Surg 2009;144(1):57–63.
[26] Vasudev NS, Brown JE, Brown SR, et al. Prognostic factors in renal cell carcinoma: association of preoperative sodium concentration with survival. Clin Cancer Res J Am Assoc Cancer Res 2008;14(6):1775–81.
[27] Schutz FAB, Xie W, Donskov F, et al. The impact of low serum sodium on treatment outcome of targeted therapy in metastatic renal cell carcinoma: results from the International Metastatic Renal Cell Cancer Database Consortium. Eur Urol 2014;65(4):723–30.
[28] Abu Zeinah GF, Al-Kindi SG, Hassan AA, et al. Hyponatraemia in cancer: association with type of cancer and mortality. Eur. J. Cancer Care 2015;24(2):224–31.
[29] Berardi R, Rinaldi S, Belfiori G, et al. The role of hyponatraemia before surgery in patients with radical resected pancreatic cancer. Clin Med Insights Oncol 2020;14:1179554920936605.

[30] Berardi R, Mocchegiani F, Rinaldi S, et al. Hyponatremia is a predictor of clinical outcome for resected biliary tract cancers: a retrospective single-center study. Oncol Ther 2020;8(1):115–24.
[31] Yeh H-C, Li C-C, Wen S-C, et al. Validation of hyponatremia as a prognostic predictor in multiregional upper tract urothelial carcinoma. J Clin Med 2020;9(4). https://doi.org/10.3390/jcm9041218.
[32] Guo J-Y, Gong T-T, Yang Z, et al. Prognostic value of preoperative hyponatremia in patients with epithelial ovarian cancer. J Cancer 2019;10(4):836–42.
[33] Osterlind K, Andersen PK. Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Res 1986;46(8):4189–94.
[34] Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med 2009;122(9):857–65.
[35] Doshi KH, Shriyan B, Nookala MK, et al. Prognostic significance of pretreatment sodium levels in patients of nonsmall cell lung cancer treated with pemetrexed-platinum doublet chemotherapy. J Cancer Res Ther 2018;14(5):1049–53.
[36] Kawashima A, Tsujimura A, Takayama H, et al. Impact of hyponatremia on survival of patients with metastatic renal cell carcinoma treated with molecular targeted therapy. Int J Urol J Jpn Urol Assoc 2012;19(12):1050–7.
[37] Penttilä P, Bono P, Peltola K, et al. Hyponatremia associates with poor outcome in metastatic renal cell carcinoma patients treated with everolimus: prognostic impact. Acta Oncol 2018;57(11):1580–5.
[38] Refardt J, Brabander T, Minczeles NS, et al. Prognostic value of dysnatremia for survival in neuroendocrine neoplasm patients. Eur J Endocrinol 2022;187(1):209–17.
[39] Kegasawa T, Sakamori R, Maesaka K, et al. Lower serum sodium levels are associated with the therapeutic effect of sorafenib on hepatocellular carcinoma. Dig Dis Sci 2021;66(5):1720–9.
[40] Svaton M, Fiala O, Pesek M, et al. Predictive and prognostic significance of sodium levels in patients with NSCLC treated by erlotinib. Anticancer Res 2014;34(12):7461–5.
[41] Roach KA, Stefaniak AB, Roberts JR. Metal nanomaterials: Immune effects and implications of physicochemical properties on sensitization, elicitation, and exacerbation of allergic disease. J Immunotoxicol 2019;16(1):87–124.
[42] Lv M, Chen M, Zhang R, et al. Manganese is critical for antitumor immune responses via cGAS-STING and improves the efficacy of clinical immunotherapy. Cell Res 2020;30(11):966–79.
[43] Feske S, Wulff H, Skolnik EY. Ion channels in innate and adaptive immunity. Annu Rev Immunol 2015;33:291–353.
[44] Wang C, Zhang R, Wei X, et al. Metalloimmunology: the metal ion-controlled immunity. Adv Immunol 2020;145:187–241.
[45] Zhang Y-Y, Ren K-D, Luo X-J, et al. COVID-19-induced neurological symptoms: focus on the role of metal ions. Inflammopharmacology 2023;31(2):611–31.
[46] Pan Y, Ma Y, Guan H, et al. Pre-treatment of hyponatremia as a biomarker for poor immune prognosis in advanced or metastatic gastric cancer: a retrospective case analysis. Hum Vaccin Immunother 2024;20(1):2414546.
*[47] Wang T, Lv Z, Fan R, et al. Hyponatremia predicts immunotherapy resistance in biliary tract cancer. Hum Vaccin Immunother 2025;21(1):2535168.
*[48] Selmer C, Madsen JC, Torp-Pedersen C, et al. Hyponatremia, all-cause mortality, and risk of cancer diagnoses in the primary care setting: a large population study. Eur J Intern Med 2016;36:36–43.
[49] Holland-Bill L, Christiansen CF, Heide-Jørgensen U, et al. Hyponatremia and mortality risk: a Danish cohort study of 279 508 acutely hospitalized patients. Eur J Endocrinol 2015;173(1):71–81.
[50] Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Cancer 2010;68(1):111–4.
[51] Berardi R, Santoni M, Newsom-Davis T, et al. Hyponatremia normalization as an independent prognostic factor in patients with advanced non-small cell lung cancer treated with first-line therapy. Oncotarget 2017;8(14):23871–9.
[52] Balachandran K, Okines A, Gunapala R, et al. Resolution of severe hyponatraemia is associated with improved survival in patients with cancer. BMC Cancer 2015;15:163.
[53] Ward K, Page VD, Song J, et al. Correcting hyponatraemia is associated with improved survival in hyponatraemic metastatic cancer patients. Clin Kidney J 2025;18(3):sfaf023.
[54] Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Eur J Endocrinol 2014;170(3):G1–47.
[55] Verbalis JGHE. The use of an algorithm to aid diagnosis and treatment of patients with hyponatraemia secondary to SIADH. 12th Eur Congr Endocrinol 2010.
[56] Nervo A, D'Angelo V, Rosso D, et al. Urea in cancer patients with chronic SIAD-induced hyponatremia: old drug, new evidence. Clin Endocrinol 2019;90(6):842–8.
[57] Woudstra J, de Boer MP, Hempenius L, et al. Urea for hyponatraemia due to the syndrome of inappropriate antidiuretic hormone secretion. Neth J Med 2020;78(3):125–31.
[58] Perelló-Camacho E, Pomares-Gómez FJ, López-Penabad L, et al. Clinical efficacy of urea treatment in syndrome of inappropriate antidiuretic hormone secretion. Sci Rep 2022;12(1):10266.
[59] Sousa C, Ferreira R, Santos SB, et al. Advances on diagnosis of Helicobacter pylori infections. Crit Rev Microbiol 2022:1–22.
[60] Peri A. Clinical review: the use of vaptans in clinical endocrinology. J Clin Endocrinol Metab 2013;98(4):1321–32.
[61] deGoma EM, Vagelos RH, Fowler MB, et al. Emerging therapies for the management of decompensated heart failure: from bench to bedside. J Am Coll Cardiol 2006;48(12):2397–409.
[62] Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist 2012;17(6):756–65.
[63] Yamaguchi K, Shijubo N, Kodama T, et al. Clinical implication of the antidiuretic hormone (ADH) receptor antagonist mozavaptan hydrochloride in patients with ectopic ADH syndrome. Jpn J Clin Oncol 2011;41(1):148–52.
[64] Gattone 2nd VH, Wang X, Harris PC, et al. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. Nat Med 2003;9(10):1323–6.
[65] Torres VE, Wang X, Qian Q, et al. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. Nat Med 2004;10(4):363–4.
[66] Wang X, Wu Y, Ward CJ, et al. Vasopressin directly regulates cyst growth in polycystic kidney disease. J Am Soc Nephrol 2008;19(1):102–8.
*[67] Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med 2012;367(25):2407–18.
[68] Gittus M, Haley H, Harris T, et al. Commentary: tolvaptan for autosomal dominant polycystic kidney disease (ADPKD) - an update. BMC Nephrol 2025;26(1):79.
[69] Barsony J, Manigrasso MB, Xu Q, et al. Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. Age 2013;35(2):271–88.
[70] Benvenuti S, Deledda C, Luciani P, et al. Low extracellular sodium causes neuronal distress independently of reduced osmolality in an experimental model of chronic hyponatremia. Neuromol Med 2013;15(3):493–503.
[71] Benvenuti S, Deledda C, Luciani P, et al. Neuronal distress induced by low extracellular sodium in vitro is partially reverted by the return to normal sodium. J Endocrinol Invest 2016;39(2):177–84.
[72] Mancuso C. Heme oxygenase and its products in the nervous system. Antioxid Redox Signal 2004;6(5):878–87.
[73] Chen K, Gunter K, Maines MD. Neurons overexpressing heme oxygenase-1 resist oxidative stress-mediated cell death. J Neurochem 2000;75(1):304–13.
[74] Zelenka J, Koncošová M, Ruml T. Targeting of stress response pathways in the prevention and treatment of cancer. Biotechnol Adv 2018;36(3):583–602.
[75] Marroncini G, Anceschi C, Naldi L, et al. Hyponatremia-related liver steatofibrosis and impaired spermatogenesis: evidence from a mouse model of the syndrome of inappropriate antidiuresis. J Endocrinol Invest 2022. https://doi.org/10.1007/s40618-022-01962-9.
[76] Anstee QM, Reeves HL, Kotsiliti E, et al. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol 2019;16(7):411–28.
*[77] Marroncini G, Fibbi B, Errico A, et al. Effects of low extracellular sodium on proliferation and invasive activity of cancer cells in vitro. Endocrine 2020;67(2):473–84.
[78] Marroncini G, Anceschi C, Naldi L, et al. Low sodium and tolvaptan have opposite effects in human small cell lung cancer cells. Mol Cell Endocrinol 2021;537:111419.
[79] Naldi L, Catalano M, Melica ME, et al. Effects of reduced extracellular sodium on proliferation and invasive activity of renal cell carcinoma cell lines. Sci Rep 2025;15(1):8067.

*[80] Fibbi B, Marroncini G, Naldi L, et al. Hyponatremia and cancer: from bedside to benchside. Cancers 2023;15(4). https://doi.org/10.3390/cancers15041197.
[81] Dyberg C, Fransson S, Andonova T, et al. Rho-associated kinase is a therapeutic target in neuroblastoma. Proc Natl Acad Sci USA 2017;114(32):E6603–12.
[82] Xia Y, Cai X, Fan J, et al. RhoA/ROCK pathway inhibition by fasudil suppresses the vasculogenic mimicry of U2OS osteosarcoma cells in vitro. Anticancer Drugs 2017;28(5):514–21.
[83] Xia Y, Cai X-Y, Fan J-Q, et al. Rho kinase inhibitor fasudil suppresses the vasculogenic mimicry of B16 mouse melanoma cells both in vitro and in vivo. Mol Cancer Ther 2015;14(7):1582–90.
*[84] Marroncini G, Naldi L, Fibbi B, et al. Hyponatremia promotes cancer growth in a murine xenograft model of neuroblastoma. Int J Mol Sci 2023;24(23). https://doi.org/10.3390/ijms242316680.
[85] Nagao S, Nishii K, Katsuyama M, et al. Increased water intake decreases progression of polycystic kidney disease in the PCK rat. J Am Soc Nephrol 2006;17(8):2220–7.
[86] Reif GA, Yamaguchi T, Nivens E, et al. Tolvaptan inhibits ERK-dependent cell proliferation, Cl^- secretion, and in vitro cyst growth of human ADPKD cells stimulated by vasopressin. Am J Physiol Ren Physiol 2011;301(5):F1005–13.
[87] Sebastian J, Raghav D, Rathinasamy K. MD simulation-based screening approach identified tolvaptan as a potential inhibitor of Eg5. Mol Divers 2023;27(3):1203–21.
[88] Wu Y, Beland FA, Chen S, et al. Mechanisms of tolvaptan-induced toxicity in HepG2 cells. Biochem Pharm 2015;95(4):324–36.
[89] Marroncini G, Anceschi C, Naldi L, et al. The V(2) receptor antagonist tolvaptan counteracts proliferation and invasivity in human cancer cells. J Endocrinol Invest 2022;45(9):1693–708.
*[90] Naldi L, Fibbi B, Polvani S, et al. The vasopressin receptor antagonist tolvaptan counteracts tumor growth in a murine xenograft model of small cell lung cancer. Int J Mol Sci 2024;25(15). https://doi.org/10.3390/ijms25158402.
[91] Sinha S, Dwivedi N, Tao S, et al. Targeting the vasopressin type-2 receptor for renal cell carcinoma therapy. Oncogene 2020;39(6):1231–45.
[92] Jones TM, Carew JS, Nawrocki ST. Therapeutic targeting of autophagy for renal cell carcinoma therapy. Cancers 2020;12(5). https://doi.org/10.3390/cancers12051185.
[93] Hsieh JJ, Purdue MP, Signoretti S, et al. Renal cell carcinoma. Nat Rev Dis Prim 2017;3:17009.
[94] Serradeil-Le Gal C, Raufaste D, Marty E, et al. Binding of [3H] SR 49059, a potent nonpeptide vasopressin V1a antagonist, to rat and human liver membranes. Biochem Biophys Res Commun 1994;199(1):353–60.
[95] Greenberg A, Verbalis JG. Vasopressin receptor antagonists. Kidney Int 2006;69(12):2124–30.
[96] Lemmens-Gruber R, Kamyar M. Vasopressin antagonists. Cell Mol Life Sci 2006;63(15):1766–79.
[97] Brouard R, Bossmar T, Fournié-Lloret D, et al. Effect of SR49059, an orally active V1a vasopressin receptor antagonist, in the prevention of dysmenorrhoea. BJOG 2000;107(5):614–9.
[98] Decaux G, Soupart A, Vassart G. Non-peptide arginine-vasopressin antagonists: the vaptans. Lancet 2008;371(9624):1624–32.
[99] Zhao N, Peacock SO, Lo CH, et al. Arginine vasopressin receptor 1a is a therapeutic target for castration-resistant prostate cancer. Sci Transl Med 2019;11(498). https://doi.org/10.1126/scitranslmed.aaw4636.
[100] Heidman LM, Peinetti N, Copello VA, et al. Exploiting dependence of castration-resistant prostate cancer on the arginine vasopressin signaling axis by repurposing vaptans. Mol Cancer Res 2022;20(8):1295–304.