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ARTICLE

Progesterone Receptor Antagonists – A Novel Treatment for Severe Hyponatremia from the Endocrine Paraneoplastic Syndrome

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ABSTRACT

Hyponatremia related to ectopic secretion of cancer cells of arginine vasopressin (AVP) or atrial natriuretic peptide (ANP) is most commonly caused by small cell lung cancer. The ideal treatment would be one that not only corrects the hyponatremia, especially if it is life threatening, but at the same time causes regression of the cancer, and thus improves both quality and length of life. As one is waiting for chemotherapy, surgery, or radiotherapy to decrease the cancer burden, tolvaptan has been used to correct the hyponatremia to improve symptoms or prevent death. Mifepristone, a progesterone receptor modulator/antagonist has been used to treat various cancers. The oral 200mg tablet was given to an 80-year-old woman who developed sudden extensive lung cancer with a serum sodium of 118 mmol/L. She refused chemotherapy but agreed to take mifepristone. The hyponatremia was completely corrected (145 mmol/L) within one month of treatment. She was in complete remission for 5 years and died not from lung cancer, but an acute myocardial infarction. Mifepristone may serve the purpose to not only quickly correct hyponatremia when it is related to an endocrine paraneoplastic syndrome, but also to provide improved quality and length of life.

1. Introduction

Lung cancer is one of the most common cancers to cause endocrine paraneoplastic syndromes [1]. When paraneoplastic syndrome occurs, the associated metabolic or endocrine disorder is related to the malignant tumor secreting hormones or peptides [2]. One of these paraneoplastic syndromes is hyponatremia related to inappropriate secretion of the anti-diuretic hormone (ADH), and thus the condition is called the syndrome of inappropriate anti-diuretic hormone (SIADH) [3-5].

The most common type of lung cancer associated with SIADH is small-cell lung cancer (SCLC) representing about 70% of the lung cancer cases (1). SIADH may be present in 7-16% of patients with SCLC [6,7]. Though non-SCLC (NSCLC) has also been associated with SIADH, it only accounts for 1% of the cases of SIADH resulting from a paraneoplastic syndrome [8,9].

Another paraneoplastic etiology for hyponatremia associated with lung cancer is the ectopic secretion of the atrial

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natriuretic peptide (ANP) [1,10]. Studies of SCLC cell lines have demonstrated that ectopic ADH, and ANP, are equally likely to be the cause of the hyponatremia, and not uncommonly both may be increased at the same time [10-12].

The prognosis for patients with lung cancer with hyponatremia is worse than those with normal serum sodium levels [13]. Serum sodium levels <125 mEq/L are associated with an extremely poor prognosis, with death generally within two weeks associated with severe brain edema that is associated with very low sodium levels with the resulting low plasma hypo-osmolarity leading to headache, memory impairment, generalized muscle weakness and associated fatigue, seizures, nausea, and psychiatric dysfunction progressing to coma and death [13,14].

Chemotherapy, possibly combined with surgery or radiotherapy, and supportive measures are the main treatment modality for hyponatremia associated with lung cancer [15]. If one achieves a remission following chemotherapy, there is a high success rate in correcting the hyponatremia. However, with tumor recurrence, the hyponatremia generally also returns [15]. In very rare circumstances, aggressive chemotherapy may be associated with marked hyponatremia related to sudden excessive release of stored ADH (otherwise known as arginine vasopressin AVP)) and ANP [16].

A case is reported of probable rapid onset very aggressive SCLC, with marked hyponatremia, who had quick resolution of the hyponatremia, not with chemotherapy, but with a progesterone modulator/antagonist.

2. Case Report

A 78-year-old woman was first diagnosed with chronic lymphocytic leukemia (CLL). Since she was asymptomatic, she was given no therapy but continued observation and evaluation by blood studies. With continued slow progression of leukocytosis (38,000) and mild thrombocytopenia, and with the development of some symptoms of dyspnea on exertion and weakness, her hematologist when she was age 80 decided to try treatment with oral chlorambucil.

Three days after starting the chlorambucil her clinical status significantly deteriorated with confusion, extreme weakness, and severe respiratory distress. Three months prior to her admission to the hospital for this acute decline in her health status, it was noted that she had mild hyponatremia of 130 mmol/L. On admission her serum sodium was life threatening at 118 mmol/L. By manipulating fluid intake and administration of electrolytes intravenously, her serum sodium increased to 122 mmol/L. Her serum PO2 on admission was 72 mmHg.

A chest x-ray revealed extensive pulmonary nodules with the radiologic diagnosis of metastatic lung cancer, or less likely, rapidly advancing lymphoma, as opposed to rapid progression of her CLL to a more acute leukemia process.

A biopsy of a pulmonary lesion with possible chemotherapy was recommended, but she refused this management. However, after a brief discussion, she agreed to be treated with oral mifepristone 200 mg/day as an outpatient. A compassionate use investigational drug approval (IND) was obtained from the United States Food and Drug Administration and her treatment was approved by the Western Institutional Review Board.

She clinically was much improved after two weeks of treatment. After one month of treatment her PO2 was 99-100 mmHg without supplemental oxygen. Her serum sodium level was normal at 145 mmol/L.

After 2 months of treatment her computerized axial tomography (CT-scan) showed mostly complete resolution of all of her lung nodules with those remaining much smaller.

Subsequent chest x-rays over the next 5 years continued to demonstrate no pulmonary nodules just a ground glass appearance to the lungs. Her PO2 and serum sodium were continually normal. Her CLL did seem to respond to the very short course of chlorambucil and the CLL just slowly progressed over these 5-year period requiring no additional therapy.

At age 85 while sleeping she had an acute myocardial infarction, and she was pronounced dead when she arrived by rescue squad to the hospital's emergency room.

3. Discussion

The radiologists and oncologist based on chest x-ray and CT scan were convinced that the woman was suffering from lung cancer, but rapidly advancing lymphoma was a much less likely possibility. However, without a pathological diagnosis, they could not determine if the woman was suffering from SCLC or NSCLC. However, based on the very rapid aggressive onset, and the fact that hyponatremia related to excessive secretion of AVP or ANP is much more common in SCLC vs. NSCLC (or lymphoma), her oncologist favored SCLC as her diagnosis.

It is not clear if the severe sudden drop in serum sodium was related to rapid advancing lung cancer, or did the chlorambucil treatment, which was given for CLL (and would not be a very effective treatment for lung cancer), caused cell lysis with acute release of AVP or ANP further exacerbating pre-existing SIADH from mild ectopic AVP or ANP release from lung cancer cells?

Mifepristone has been proven to be an effective treatment for advanced lung cancer providing significant improved quality and extension of life [17-19]. Mifepristone

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has provided similar benefits in patients with a variety of different advanced cancers [20-26]. The mechanism of action is thought to be secondary to its effect on blocking membrane progesterone receptors that are needed to make a protein called the progesterone induced blocking factor (PIBF) [27-31]. This PIBF protein is unique with no amino acid homology to any known protein, is needed by both the fetal-placental unit and cancer cells to proliferate, invade, tissue and escape immune surveillance, but is not essential for everyday life in people that are healthy [27-31].

Tolvaptan has been used to treat cancer patients with hyponatremia due to SIADH [32]. Tolvaptan is an oral selective V2-receptor antagonist [33]. AVP normally acts on V2 receptors in the renal collecting duct to promote free water absorption, thereby increasing extracellular fluid volume [34]. The continued upregulated expression of AVP in paraneoplastic SIADH leads to excessive dilution of free sodium which leads to the state of hyponatremia [34].

In the post-hoc analysis of the SALT-1 and SALT-2 trials, 7 of 8 taking tolvaptan normalized their serum sodium vs. 2 of 16 placebo controls [32]. A previous study found similar results [35]. Tolvaptan could be used concomitantly with mifepristone to try to get the hyponatremia corrected in case the mifepristone is not able to cause regression of that particular patient's cancer. In that case, the tolvaptan could be used with the drug of choice for treating that cancer.

Nevertheless, the best treatment for the hyponatremia is to correct the cause of ectopic production by cancer cells of AVP or ANP, since the obvious goal is to prolong and improve quality of life. Nevertheless, tolvaptan seems to be a reasonable short-term solution in case the person could die from the hyponatremia before regression of the cancer is obtained by mifepristone, chemotherapy, radiotherapy or immune therapy. Nevertheless, in the case reported here, rapid correction of the severe life-threatening hyponatremia related to SIADH was solely related to mifepristone therapy.

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