Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Prior Injectable Somatostatin Receptor Ligand Dose Does Not Predict Oral Octreotide Response In The Treatment Of Acromegaly: Results From The Phase 3 OPTIMAL Study

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MON-LB53

Background: Injectable somatostatin receptor ligands (SRLs) are the most widely used therapy to control acromegaly. Oral octreotide capsules have been formulated as a potential therapy for this disorder and the efficacy and safety was evaluated in the CHIASMA OPTIMAL prospective phase 3 study in patients with acromegaly who were controlled on injectable SRL treatment of varying doses (Samson et al. ENDO 2020). **Methods:** Patients with confirmed acromegaly, who had been receiving a stable dose of injectable SRL (≥3 months) up until study entry, were randomized to receive octreotide capsules (40 mg/day) or placebo for 36 weeks. Patients were dose titrated to 60 or 80 mg of oral octreotide or equivalent placebo through week 24 at the investigator's discretion based on increase of IGF-I levels or worsening of acromegaly signs and symptoms. The primary efficacy endpoint was the proportion of patients who maintained their biochemical response at the end of 36 weeks, defined as average IGF-I ≤1 x ULN between Weeks 34 and 36. An analysis evaluated maintenance of response based on prior dose of injectable SRL. Prior doses of injectable SRL were categorized based on the following classifications: octreotide 10 mg every 4 weeks or lanreotide 60 mg every 4 weeks or 120 mg every 8 weeks were stratified as low; octreotide 20 mg every 4 weeks or lanreotide 90 mg every 4 weeks or 120 mg every 6 weeks were stratified as medium; octreotide 30 mg or 40 mg or lanreotide 120 mg every 4 weeks were stratified as high. Randomization was stratified based on low dose vs med/high dose and efficacy results compared for these strata. The response rates reported for the primary end point are slightly adjusted for stratification differences as prespecified in the statistical analysis plan. **Results:** Six patients (21.4%) in the octreotide capsule group had received prior treatment with low doses of injectable SRLs while 22 (78.6%) had received prior treatment with medium-high doses of injectable SRLs. Maintenance of response was observed in 16 patients receiving oral octreotide. This included 66.7% of patients (n=4) previously receiving low doses of injected SRLs and 54.5% of patients (n=12) on medium-high injected doses. The treatment effect was consistent irrespective of prior dose of injectable SRL (odds ratio: 5.4 in low dose and 5.9 in medium-high dose). **Conclusion:** The CHIASMA OPTIMAL study recruited a population receiving predominantly medium-high doses of injectable SRLs and demonstrated maintenance of response in 58% of patients. Oral octreotide treatment effect was consistent irrespective of prior dose of injectable SRL.

Tumor Biology

ENDOCRINE NEOPLASIA CASE REPORTS III

Amphotericin B Induced Hypocalcemia in a Patient With Severe Hypercalcemia Due to Acute T-Cell Leukemia/Lymphoma

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SAT-LB309

Abstract: Adult T-cell Leukemia/lymphoma (ATL) is a rare and aggressive type of non-Hodgkin's lymphoma. Patients with ATL commonly develop severe hypercalcemia leading to life-threatening complications like acute kidney injury, cardiac arrhythmias, altered mental status, and coma. The treatment of hypercalcemia of malignancy is often challenging. Here we present a case of ATL with severe hypercalcemia who was treated prophylactically with amphotericin B, leading to a significant and rapid drop in the calcium levels into the hypocalcemia range. We discussed the possible mechanism that leads to the rapid decline in the calcium levels in this patient. **Introduction:**Adult T-cell Leukemia/lymphoma (ATL) is a malignancy that develops from mature T-lymphocytes. It is a rare and highly aggressive type of non-Hodgkin's lymphoma. The incidence of ATL is reported to be high in endemic areas like Japan, south and Central America, Caribbean islands, and Florida state of the United States. Fortunately, the incidence of ATL is about 0.05 cases per hundred thousand people in the United States, which is very low [1]. There is a strong association between human T-lymphotropic virus type 1 (HTLV-1) and ATL, with HTLV-1 genome detectable in 100 percent of tumor clones of ATL [2]. However, the percentage of HTLV-1 carriers that develop ATL is minuscule. ATL is clinically divided into four clinical subtypes (acute, lymphomatous, chronic and smoldering types) with acute and lymphomatous subtypes having a very poor prognosis, median survival despite aggressive regimens being just 7.7 months [3]. Immunodeficiency, hypercalcemia (≥10.8 milligrams per deciliter) and tumor lysis syndrome are common complications of ATL as with many other malignancies. Along with aggressive chemotherapy regimens, the primary malignancy itself causes severe immunodeficiency and puts the patient at a very high risk of developing opportunistic infections [4]. Hence these patients will be needing antibiotic prophylaxis and antifungal prophylaxis during the chemo regimen and are often treated with multiple antibiotics and antifungals during the course of the disease. One such anti-fungal agent is amphotericin B, primarily used to treat aggressive and systemic fungal infections.Amphotericin B targets the fungal cell wall by binding to the ergosterol molecule in it and forms pores that

lead to fungal cell death. Amphotericin B is used to treat a wide range of invasive systemic fungal infections and some protozoan infections (visceral leishmaniasis). Amphotericin B is not the first line of choice in most fungal infections due to its well-known severe side effects. Most commonly it causes a universal febrile response with fever, chills, hypotension, tachypnea, nausea, vomiting and headache soon after the infusion probably due to histamine release. Other common side effects of amphotericin B are renal toxicities, hepatic toxicities and electrolyte imbalances, mainly Hypokalemia and Hypomagnesemia. Lipid-based liposomal formulation of amphotericin B has demonstrated fewer side effects compared to the conventional amphotericin B deoxycholate [5,6]. This is a case of ATL with severe hypercalcemia that was treated prophylactically with amphotericin B. Within two days of initiation of amphotericin B, the serum calcium levels fell sharply into the hypocalcemia range (to 6.5 milligrams per deciliter). To the best of our knowledge, no such case has been published in the past. Here we discussed what could be the possible mechanism that lead to such a drastic change in calcium levels. **Case presentation:**A 63-year-old male presents to our emergency department with altered mental status and high serum calcium. Present medical history was negative for fever, chills or shortness of breath but positive for constipation, reduced oral intake, urinary urgency, and excessive somnolence. His past medical history includes a recent hospitalization, a month ago, because of constipation, high calcium, and poor appetite. On evaluation at that time, he was diagnosed with having an acute subtype of Adult T-cell leukemia/lymphoma (ATL) in stage IV with cutaneous involvement and was reactive for human T- cell leukemia virus, type 1 (HTLV1). He was treated with zidovudine and interferon-alpha as first-line therapy, and intrathecal methotrexate, for suspected intrathecal involvement. His hospital stay was complicated by tumor lysis syndrome (TLS) and acute kidney injury (AKI). He was treated with pamidronate and calcitonin for hypercalcemia after which his AKI has resolved. He was discharged a week prior to his readmission, with a calcium level of 11.8 milligrams per deciliter (mg/dL), and asymptomatic. Apart from being a former smoker (quit 10 years ago), he has no other significant medical history.On physical examination, he was ill-appearing, febrile (100.1°F), confused, and minimally responsive. His abdomen was mildly distended, has an occasional cough and mild crackles on the left side of the chest. Chest X-ray showed left lower lobe consolidation with moderate pleural effusion consistent with pneumonia. CBC revealed 66% lymphocytes (with 8% reactive and 5 percent other lymphocytes), and thrombocytopenia (platelets 83,000 per microliter of blood). His Uric acid, phosphate, and potassium were normal, but had high Lactate dehydrogenase (LDH, 359 units per liter) and calcium (17 mg/dL). Computed tomography (CT) scan of head showed no mass effect but had diffuse mucosal thickening involving frontal, ethmoid and maxillary sinuses (probably from intrathecal chemotherapy from last admission). He was treated with piperacillin/tazobactam for pneumonia. Calcitonin was given for hypercalcemia. He was started prophylactically on liposomal amphotericin B. He developed low potassium and magnesium. Two days later his serum calcium levels (and ionized calcium levels) started dropping steeply to hypocalcemia range. His vitamin D was low at 9.6 nanograms per milliliter (ng/mL). He received supplemental magnesium, calcium, phosphate and vitamin D. Efforts were made to keep his potassium over 4 milliequivalents per liter (mEq/L), magnesium over 2 mEq/L and phosphate over 2.5 mg/dL. However, his calcium levels did not show any improvement. He developed severe electrolyte imbalances and suffered from two episodes of supraventricular tachycardia with hypotension that were stabilized. Further his stay in the hospital was complicated by urinary tract infection with vancomycin-resistant enterococcus which was treated with linezolid. Later the patient died shortly due to progression of his primary malignancy. Legend: units = milligrams per deciliter for total serum calcium and magnesium, Units = millimole per liter for ionized calcium, Units = milliequivalents per liter for potassium, Day 1 is start of amphotericin B**Discussion:** Adult T-cell Leukemia/lymphoma (ATL) is a very aggressive T-cell malignancy with poor prognosis. The most common presentation of ATL is immunodeficiency and hypercalcemia. Hypercalcemia in ATL is often very severe with calcium levels more than 16 mg/dL and presents with altered mental status, severe dehydration due to hypercalcemia induced renal insufficiency, and an increased risk for cardiac arrhythmias [7,8]. Hypercalcemia is seen up to 20 to 30 percent of malignancies during their entire course [9], and malignancy is the most common cause of hypercalcemia in inpatients. The three main mechanisms through which hypercalcemia of malignancy occurs are bone metastasis causing localized cytokine-mediated osteolysis, secretion of the parathyroid related peptide by the neoplastic cells, and increased vitamin D production or activation by the malignant cells. Hypercalcemia is often challenging to treat in patients with cancers, and it often relapses. Amphotericin B is known to cause hypomagnesemia, hypokalemia and hyperchloremic acidosis due to increased distal tubular permeability, often needing large supplementations of potassium and magnesium. In our case, it was observed that two days after the initiation of amphotericin B, there was a sharp decline in the serum calcium level along with the expected fall in potassium and magnesium levels. Moreover, that low level of calcium was continuously present throughout the course of amphotericin B even after stopping calcium reducing medication (calcitonin) and providing calcium supplementation. The possible mechanisms by which this phenomenon occurred are 1. Low magnesium (caused by amphotericin B) causing impaired Parathyroid hormone (PTH) secretion and increased PTH resistance in the bone [10]. 2. Low levels of Vitamin D (1,25-dihydroxy vitamin D) relatively common in patients with hypomagnesemia contributing to hypocalcemia, but the reason has not been identified. In a study, it has been observed that even after supplementation of magnesium and normalization of calcium and PTH levels, the vitamin D levels remained low [11]. However, our patient's magnesium levels were always above the severe hypomagnesemia (less than 1.2 mg/dL) that usually leads to the mechanisms mentioned above to hypocalcemia. Hence, we postulated that there must be an unknown mechanism that leads to hypocalcemia. Maybe amphotericin B has a potentiating effect on the calcium reducing agents like calcitonin, or perhaps it has a direct calcium reducing effect that is usually not seen but is seen here due to other unknown contributing factors. More studies have to be done to know what could be the possible cause of the above-observed phenomenon, so that, this effect can be potentially used in the future to treat treatment-resistant hypercalcemia. **Conclusion:**Hypercalcemia is commonly seen in patients

with HTLV-1 associated ATL. It could often be the presenting lab abnormality that leads to the diagnosis of an ATL. Patients who are being treated for hypercalcemia of malignancy with calcitonin (or pamidronate) should be managed cautiously as starting amphotericin B can lead to hypocalcemia that is difficult to treat.

Neuroendocrinology and Pituitary

PITUITARY TUMORS II

Biochemical Control of Most Patients Reverting to Injectable Long-Acting Somatostatin Receptor Ligands Is Achieved After One Dose: Results From the Phase 3, Randomized, Double Blind, Placebo-Controlled Optimal Study

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MON-LB55

Background: Injectable somatostatin receptor ligands (SRLs) are currently the most widely used medical therapy for acromegaly worldwide. Oral octreotide capsules (OOC) have been formulated as a potential therapy for this disorder and the safety and efficacy were evaluated in the CHIASMA OPTIMAL pivotal study (Samson et al. ENDO 2020). As reported, mean IGF-I levels of the OOC treatment group were maintained within normal range at the end of treatment in all patients. However, some patients may not respond to OOC treatment (25% of OOC group and 68% of placebo groups required rescue, P=0.003). This analysis describes the degree and rapidity with which patients achieve biochemical control (IGF-I ≤1.0 x ULN) when reverted to their prior injectable SRL treatment. **Methods:** Patients with confirmed acromegaly and receiving a stable dose of injectable SRL (≥3 months) were randomized to OOC (40mg/day; N=28) or placebo (N=28) for 36 weeks. Patients were dose titrated to 60 or 80mg of OOC (or placebo) through week 24 at investigator discretion based on increased IGF-I levels and/or worsening acromegaly signs/symptoms. Patients could be rescued via reversion to prior injectable SRL therapy if they met the predefined withdrawal criteria (i.e., IGF-I ≥1.3 x upper limit of normal [ULN] for 2 consecutive visits on the highest dose, and exacerbation of clinical signs/symptoms) or discontinued treatment early for any other reason. In the study, 7 patients in the OOC group and 19 in the placebo group required rescue. The change in IGF-I from Baseline was compared to the end of the Double-blind Placebo Controlled period. **Results:** In patients rescued up to week 32 and in whom there were at least 4 weeks of follow up, baseline IGF-I levels (mean of Screening Visit 2 and Baseline) were 0.80 and 0.87 x ULN in the OOC and placebo groups, respectively. In patients receiving rescue therapy, the end of study IGF-I levels (mean of week 34 and 36) were 0.80 and 0.89 x ULN in the OOC and placebo groups, respectively, virtually unchanged. The median time to return to normal baseline IGF-I values following loss of response was 4.0 weeks after discontinuing OOC and 4.0 weeks after discontinuing placebo treatment. Therefore, most patients who required rescue following a short trial of therapy with OOC returned to their baseline values following a single SRL injection. **Conclusion:** Most treatment failures in the CHIASMA OPTIMAL trial (on either OOC or placebo) rescued with injectable SRL re-established their baseline response levels after a single injectable SRL administration (at pre-study dose). Based on this data, patients may potentially be treated with OOC and for those not responding, either not biochemically controlled or who have adverse effects, they may be able to return to injectable SRLs with immediate IGF-I control after one SRL injection.

Thyroid

THYROID NEOPLASIA AND CANCER

The Sensitivity and Specificity of Various Thyroid Nodule Ultrasound Characteristics and the Diagnostic Accuracy of the ATA Guidelines and ACR TI-RADS for Predicting Thyroid Cancer at an Urban Endocrinology Clinic

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MON-LB86

Introduction: Several current guidelines assess sonographic features to guide management of thyroid nodules. The ACR uses an additive point system to assign the level of risk to various sonographic features, whereas the ATA groups sonographic features together to determine the level of risk. The purpose of this study is to compare the performance of the ATA guidelines and ACR TI-RADS at an urban endocrinology clinic in risk stratifying thyroid nodules by their specific sonographic features.

Methods: This retrospective, chart-review study includes adult patients who met sonographic criteria for fine needle aspiration (FNA) biopsy based on ATA or ACR TI-RADS at an outpatient endocrinology practice in San Francisco, CA between December 2011 and August 2019. Patients with a prior history of thyroid malignancy (anaplastic and medullary thyroid carcinoma or thyroid lymphoma) were excluded. The reference standard for the diagnosis of malignancy was surgical pathology or FNA cytology Bethesda category V or VI when surgical pathology was unavailable. Analysis of guideline performances and specific sonographic features included: sensitivities (Sn), specificities (Sp), positive predictive values (PPV), negative predictive values (NPV), and area-under-the-curve (AUC) using Fisher's exact test.