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CLINICAL VIGNETTE

A Case of Hypercalcemia of Malignancy: Evolving Treatments Targeting Osteoclast Mediated Bone Resorption

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Case Presentation

A 58-year-old female had been in excellent health with well controlled Type 2 diabetes mellitus on oral medication. As part of routine health maintenance, she had regular mammograms. She and her husband noted a left breast lump but did not pursue evaluation for about 5 months. She ultimately saw her primary care doctor who ordered diagnostic mammogram and ultrasound leading to a core biopsy demonstrating an infiltrating ductal adenocarcinoma. The biopsy was strongly estrogen receptor (ER) positive, progesterone receptor (PR) negative and Her2 negative for gene amplification by fluorescence in situ hybridization (FISH). A breast surgeon performed breast MRI which showed 2 left breast masses over 4 cm and a suspicious axillary lymph node and a possible right pleural effusion. The patient began developing progressive leg weakness without incontinence. PET-CT scan showed fluorodeoxyglucose (FDG) avid left breast mass and axillary and subpectoral lymph nodes and bone metastases involving the T3,4 & 5 vertebral bodies with a T5 compression fracture with extension into the spinal canal and compressing the spinal cord which was confirmed as cord compression on T spine MRI.

She was referred to neurosurgery who felt she was not a good neurosurgery candidate and underwent radiation therapy with dexamethasone 4 mg four times daily which was tapered off over several weeks. Given her ER + and Her 2 – metastatic breast cancer without extensive visceral metastases, she was started on anti-estrogen therapy with an aromatase inhibitor anastrozole 1 mg daily and the CDK 4 & 6 inhibitor ribociclib 600 mg daily days 1-21 every 28 days. Given her bone metastases she was also started on denosumab 120 mcg subcutaneously once every 4 weeks. She had an excellent clinical response and follow up PET scan response with improvement from being wheelchair bound due to leg weakness to virtually normal ambulation and reduction in the breast mass and regional lymph nodes and resolution of FDG PET activity in her vertebral metastases after 3 months of treatment. After 10 months of a sustained response she underwent a left modified radical mastectomy and axillary lymph node dissection which showed a 2.6 cm residual breast cancer and one involved axillary lymph node with 1.2 cm of breast cancer.

After 17 months on her initial therapy she had evidence of progression with small lung metastases and a few new lymph nodes and a new slightly FDG positive T3 vertebral metastasis on PET scan. Anastrozole was stopped and fulvestrant, an estrogen receptor downregulator was started, 500 mg intramuscularly every 4 weeks. She also underwent a repeat tissue sampling of a left axillary lymph node which confirmed ER positive and Her 2 negative breast cancer. After 5 months she had evidence of lung metastases response but hilar and mediastinal lymph node progression on PET and so was switched off anti estrogen therapy to single agent chemotherapy with nab paclitaxel iv weekly. She had good overall tolerance of nab paclitaxel with fatigue and mild non-progressive peripheral neuropathy. After 10 months she developed progressive fatigue and nausea and was found to have a calcium of 11.8 mg/ dL. Her PET showed dramatic progression with many new liver metastases and bilateral pleural carcinomatosis and 2 new bone metastases at T1 and T2. SS was switched from nab paclitaxel to eribulin as systemic therapy. She was also switched from denosumab to zolendronic acid 4 mg iv every 3 weeks and normal saline hydration on every chemotherapy visit for her new hypercalcemia which occurred despite monthly denosumab. Her hypercalcemia with associated fatigue, nausea, anorexia and somnolence progressed despite increasing zolendronic acid to days 1 & 8 every 21 days to correspond to the eribulin schedule and denosumab sc every 6 weeks on day 15 of every other chemotherapy cycle and intermittent nasal calcitonin. She was admitted several times for inpatient multi day hydration and iv zolendronic acid or denosumab with admission calcium levels of 14-16 mg/ dL which would transiently correct by time of discharge. Evaluation of the humoral component of hypercalcemia demonstrated a low parathyroid hormone (PTH) level of 2 pg/ mL (normal 11-51) and moderately elevated 1, 25 activated cholecalciferol level of 197 pg/ mL (normal 19.9 to 79.3) and markedly elevated PTH related peptide (PTHrP) of 82.1 pmol/ L (0.0 to 3.4).

Her 3-month follow up PET showed stable liver metastases and limited bone metastases but progression of lung metastases and some lymphangitic spread. Given her severely compromised performance status despite maximal supportive care she stopped therapy and started on home hospice and expired 4 weeks later.

Discussion

Hypercalcemia occurs in 20-30% of malignancies and confers a poor prognosis, with a median survival of 25-50 days from onset.[1] Hypercalcemia from bone metastases, representing

about 20 % of cases, generally occurs in the setting of extensive bone metastases from either breast cancer or multiple myeloma.[1] Humoral hypercalcemia involves most commonly PTHrP but occasionally overproduction of activated vitamin D and rarely overproduction of PTH. PTHrP production is most commonly associated with non-small cell lung cancer, squamous cell cancers, urothelial cancer and breast cancer[1] whereas activated vitamin D production is most commonly seen in lymphomas.[1,2] The patient had limited bone metastases throughout her disease course even when her cancer began progressing dramatically with associated severe symptomatic hypercalcemia requiring multiple hospital admissions. Evaluation in the hospital revealed a markedly elevated PTHrP and, surprisingly since she did not have lymphoma, a substantially elevated activated vitamin D, confirming humoral hypercalcemia of malignancy. Despite aggressive treatment with the latest anti-hypercalcemia agents she had only transient control and died with both extensive visceral metastases and refractory hypercalcemia.

Hypercalcemia of malignancy occurs almost entirely through activation of osteoclasts, the cells involved in breakdown or resorption of cortical bone.[1] PTHrP stimulates osteoblasts to produce receptor activator of nuclear factor kappa B ligand (RANK-L), the primary signal for osteoclast proliferation, differentiation and activation, which causes increased osteoclast mediated bone resorption and calcium release into the blood.[1,3] Osteoprotegerin, also released from osteoblasts, binds to RANK L and inhibits osteoclast activation and plays an important role in the balance between osteoblast and osteoclast function in normal bone remodeling.[3] For SS the dominant stimulus was ectopic expression of PTHrP with a secondary contribution from excess production of 1,25 dihydroxyvitamin D likely through upregulated expression of 1-alpha-hydroxylase.[1]

Treatment of hypercalcemia virtually always involves intravenous crystalloid hydration to correct virtually universal volume depletion with an added loop diuretic, like furosemide, when euvolemic to increase urinary calcium excretion.[1] This was part of the supportive treatment for SS in both as an outpatient and more effectively given the ability for multi-day continuous hydration as an inpatient.

Medications to treat hypercalcemia of malignancy have involved agents that inhibit the function of or are cytotoxic to osteoclasts. Early treatments included a chemotherapy agent for testicular cancer, used in the 1970s mithramycin,[4] and then iv gallium nitrate, which was effective and superior to an oral bisphosphonate, etidronate.[5] Since 2000, parenteral bisphosphonates, pamidronate and zolendronic acid, and most recently subcutaneous denosumab have been the mainstays of treatment.[1] Bisphosphonates, with the most potent being zolendronic acid, directly inhibit osteoclasts whereas denosumab is a monoclonal antibody which binds directly to RANK L and inhibits it's function, similar to the physiologic role of osteoprotegerin.[1] Our patient received both zolendronic acid and denosumab with only modest effect, perhaps due to the markedly elevated levels of PTHrP and secondarily activated vitamin D.

Her metastatic breast cancer demonstrated progressive resistance to therapy over time with a shift from anti estrogen therapy to chemotherapy. By the time humoral hypercalcemia had developed, her metastatic breast cancer had become refractory to treatment so treating the underlying cause, breast cancer, did not improve calcium control. Her declining performance status precluded other chemotherapy and she expired from both progressive cancer and refractory hypercalcemia.

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