

Alpelisib Combined with Low Dose Mifepristone for Treating Advanced Breast Cancer May Cause Hypokalemia Even When This Complication Does Not Occur from Single Use of The Anticancer Agents

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ABSTRACT

Alpelisib is a new targeted anticancer drug approved for the treatment of certain types of cancers, including advanced breast cancer. Mifepristone is a progesterone receptor antagonist that has generated renewed interest in its use as an anticancer agent. Some studies find the risk of hypokalemia to be 18% when treating with alpelisib. In higher dosages, mifepristone also blocks the glucocorticoid receptor but not the mineralocorticoid receptor. Thus, it has been approved for treatment of hyperglycemia related to Cushing's syndrome. However, the higher dosages needed for Cushing's syndrome can cause hypokalemia related to excessive mineralocorticoid effect. This case of advanced breast cancer did not exhibit hypokalemia when treated with single agent alpelisib. When mifepristone was added, hypokalemia ensued along with very high serum cortisol levels. Discontinuing the mifepristone and treating with single agent alpelisib, resulted in normal potassium levels. Furthermore, the elevated cortisol levels returned to normal. Stopping alpelisib and switching to single agent mifepristone also resulted in normokalaemia and normal cortisol levels. These data suggest that alpelisib interferes with metabolism or clearance of mifepristone. A treating physician must be cautious about using these two drugs together. If treatment with both is intended, a dose reduction should be considered.

Keywords

Advanced breast cancer, Alpelisib, Hyper-cortisolism, Hypokalemia, Mifepristone.

Introduction

Alpelisib is an oral inhibitor of the phosphatidylinositol 3 kinase mutation (Plk3CA), an essential kinase needed for growth of certain cancers. In fact, this enzyme appears to be mutated at a rate of nearly 30% in human cancers, leading to hyperactivation [1]. In May 2019, alpelisib was the first approved PI3k inhibitor for the treatment of hormone receptor positive, human epidermal growth factor receptor (HER2), negative Plk3CA-mutated in advanced or metastatic breast cancer, in combination with fulvestrant for postmenopausal women and male patients [2].

Alpelisib is marketed with the brand name Piqray by Novartis Pharmaceutical Corporation. According to product information, provided by Novartis, the risk of hypokalemia from taking alpelisib is 14% [3].

Mifepristone is an oral type II progesterone receptor modulator which promotes DNA binding and promotes progesterone receptor phosphorylation [4]. The interaction of progesterone with its receptor is needed for induction of many molecular events to sustain a pregnancy including its role in the production of a key immunomodulator protein known as the progesterone induced blocking factor (PIBF) [4]. Originally the 200mg tablet was approved for the purpose of performing therapeutic abortions. In higher dosages it can also block the glucocorticoid receptor.

Based on the assumption that the presence of hormone nuclear receptors in cancer cells may be needed for the cancer cells to thrive, competitive inhibitors, e.g., tamoxifen, were developed to block estrogen effect. Thus, it was thought that progesterone receptor antagonist may similarly inhibit cancer growth, e.g., breast cancer, that were positive for the nuclear P receptor. Mifepristone has been used to treat estrogen receptor positive breast cancer, especially advanced breast cancer, that was positive for the estrogen and progesterone receptors that became tamoxifen resistant [5,6].

There has not been a great continued interest in using mifepristone for breast cancer, however, because there was a lack of a high objective response rate [5,6]. Nevertheless, the drug did show a high percentage of stable disease [5,6].

There has been renewed interest in using oral mifepristone at the 200mg daily dosage for palliation of a variety of advanced or metastatic cancers [7-12]. This benefit from mifepristone was demonstrated even in cancers not known to be associated with the classic nuclear progesterone receptor [7-12]. Its beneficial mechanism of action has been hypothesized to be by blocking the production of the immunomodulatory protein, PIBF, by its antagonism of membrane progesterone receptors [4,13].

For all of these aforementioned cases of advanced cancer that improved with mifepristone, the dosage used was 200mg per day [5-11]. A 300mg tablet of mifepristone has been approved for its antagonism of the glucocorticoid receptor, and thus to be used for the treatment of hyperglycemia from Cushing's syndrome [14]. There is a much greater dosage of mifepristone needed to suppress the glucocorticoid receptor as opposed to the progesterone receptor. Thus, dosages of >600mg to 1200mg/day have been required to produce clinical improvement from Cushing's syndrome [14,15].

By blocking the glucocorticoid receptor on both the hypothalamus and pituitary when using higher dosages of mifepristone, the negative feedback effect of cortisol on ACTH secretion is precluded leading to excessive cortisol production, but the peripheral action of cortisol is also blocked. However, mifepristone has no inhibitory effect on mineralocorticoid receptors. Thus, high dosage mifepristone may cause symptoms of mineralocorticoid excess especially hypertension and hypokalemia (which can be life threatening) [16]. There have been a couple anecdotal reports in which the 300mg dosage of mifepristone was used to effectively treat metastatic lung cancer [10,17]. Thus, if studies eventually find that the dosages higher than 200mg daily mifepristone is more effective in treating some cancers, the possible risk of hypokalemia must be considered.

In a large double-blind phase III randomized trial of mifepristone for the treatment of unresectable meningiomas, it was found that the 200mg dosage of mifepristone is very well tolerated, and hypokalemia was not found to be a side effect [18]. This would be expected since the 200mg dosage, under normal conditions, would not block the glucocorticoid receptor.

In today's treatment of cancer, it is very common to use a combination of anti-neoplastic drugs simultaneously. Mifepristone has been found to increase the serum levels of alpelisib. Thus, it is possible that if one would add mifepristone therapy to the combination of alpelisib and fulvestrant, for treating estrogen and progesterone receptor positive advanced breast cancer, mifepristone could possibly potentiate side effects of alpelisib including, but not limited to, hypokalemia [19].

Case Report

We first met this patient in utero, since we had treated her mother for infertility related to anovulation from polycystic ovarian syndrome (PCOS). As frequently seen in PCOS, it is sometimes difficult to make a woman ovulate with only one follicle, even taking care to use the lowest dosage of gonadotropins to induce single ovulation. Thus, this young woman was one of the quadruplets born.

In 2012, at the age of 31, this woman was diagnosed with stage III T₂N₂aMO, grade 2 multifocal invasive ductal and lobular cancer of the right breast. BRCA1 and 2 testing was negative. She had a bilateral mastectomy with right axillary lymph node dissection revealing a stage III T₂N₂aMO₂ estrogen and progesterone receptor positive (90/60), human epithelial receptor 2 negative (FISH only), tumor with 5 separate foci of invasion measuring 0.8, 0.7, 1.3, 2.5, and 3.0 cm with 5 of 18 lymph nodes being positive.

In November 2012, when her breast cancer was diagnosed, and before chemotherapy, the patient age 31 came to our infertility center to freeze oocytes. There were 16 oocytes retrieved and frozen.

Five months later she completed adjuvant chemotherapy with dose-dense (dd) doxorubicin cyclophosphamide. In May 2013, she completed radiotherapy. She then began adjuvant tamoxifen. One month later, she began palbociclib/letrozole for 21 months. With evidence of disease progression, the therapy was stopped in favor of everolimus/fulvestrant which continued for one year.

After one year of everolimus/fulvestrant therapy, her cancer progressed with biopsy proven new liver metastases, followed by multiple episodes of small bowel obstruction. In September 2018 until February 2019 she began intravenous cyclophosphamide, methotrexate and 5 fluorouracil for 8 cycles. In February 2019 she started capecitabine (Xeloda®).

Her breast cancer progressed primarily in her liver, but the rest of the metastatic disease was stable. Thus, she was given yttrium 90 radioembolization.

Her bone marrow biopsy revealed that the breast cancer cells were now 40% ER+ and PR-. However, because of cytopenia, related to bone marrow suppression, the capecitabine was stopped because the marrow replacement with breast cancer cells was deemed insufficient (10-15%) to cause cytopenia.

She did demonstrate the PIK3 mutation, so the decision was made to use alpelisib with fulvestrant as her next treatment regimen. Unfortunately, the disease had progressed, i.e., metastatic peritoneal, bone and liver metastases.

In 2018 she decided to fertilize the oocytes with her husband's sperm and transfer the embryos that were formed from the frozen oocytes to her fraternal twin sister (who also had previous consultations for infertility in our practice and had a successful birth). This was against the advice of her oncologist who felt obligated to inform the patient that she should realize that she will probably not live long enough for her child to remember his/her mother. Her healthy son was born in March 2019 following frozen embryo transfer (two embryos had been transferred). However, she told us that having this baby would give her a reason to fight to stay alive.

Related to cancer progression and rising cancer markers, the patient decided to add mifepristone 200mg per day November 1, 2020 to her alpelisib therapy. A compassionate use IND was obtained from the Food and Drug Administration. Within 2 weeks she developed a generalized maculopapular rash. Her serum potassium had been normal during the 5 months of taking just the alpelisib and fulvestrant. However, after adding mifepristone, within two weeks her serum cortisol level was markedly increased at 52.4 mcg/dL and her serum potassium was low at 2.9 mmol/L. Thus, we advised her to stop the mifepristone and stay on the alpelisib/fulvestrant.

Six weeks later her cancer markers continued to rise (CA 27.29 was 143 U/mL with normal <38 U/mL, her CA15-3 was 46 U/mL with normal <32 U/mL and CEA was also rising at 8.6 ng/mL with normal 0.-3.0 ng/mL) With side effects from alpelisib (though the rash quickly disappeared after stopping mifepristone), she decided to stop the alpelisib, and restart the mifepristone. Within 3 days the serum potassium increased to 3.3 mmol/L and her serum a.m. cortisol dropped to 28 mcg/dL. Eleven days after restarting mifepristone, her serum potassium was normal at 3.7 mmol/L and the serum cortisol was 20 mcg/dL.

After 1 month on single agent mifepristone she stated that she felt better than she had in many years. However, her cancer markers continued to rise. Her oncologist advised her to stop the mifepristone and restart the alpelisib. Her cancer progressed despite the alpelisib. However, instead of restarting mifepristone, she chose hospice and died a few weeks later in August 2020 at the age of 39, nine years after her initial diagnosis of breast cancer.

Discussion

The 200mg dosage of mifepristone does not block the glucocorticoid receptor, and thus is not associated with hypokalemia. The fact that the serum cortisol increased to over the normal range in this patient, it seems likely that alpelisib interferes with the metabolism or clearance of mifepristone [19]. Thus, one strong possible explanation for the hypokalemia by the combination of drugs, but not each drug individually, is that the alpelisib, by

markedly increasing mifepristone concentration, caused blockage of negative feedback of cortisol to the hypothalamic-pituitary axis, causing a marked increase in ACTH leading to excessive stimulation of glucocorticoid hormones, leading to a marked mineralocorticoid effect, since the mineralocorticoid effect of cortisol was not blocked.

There had been previous evidence that mifepristone interferes with the degradation and/or excretion of alpelisib. Since 18% of patients treated with the normal dosage of alpelisib have hypokalemia, it is also possible that higher concentrations of alpelisib also contributed to the hypokalemia.

Neither drug alone caused a rash in this individual, but both together did. It is not clear as to which drug in higher concentration was responsible for the rash. Thus, if the 200mg/day dosage of mifepristone becomes a drug approved for advanced breast cancer, there should be consideration for a black box warning that it could lead to hypokalemia and cutaneous rash, when combined with alpelisib. This could influence clinical trials when considering a multiple drug regimen for advanced cancer, whether it be breast, or some other type of cancer, since both drugs have shown improvement in other types of cancers [2,3,7-12]. If this combination of drugs proves to be effective in treating breast, or other cancers, than either drug alone, or a research evaluation is proposed, one should probably reduce the dosage of both drugs.

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