Angioedema of the tongue in a patient with breast carcinoma treated with exemestane-everolimus in combination with an angiotensin-converting enzyme inhibitor

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This report describes the case of a patient with metastatic breast cancer that was treated with exemestane-everolimus and who developed unilateral angioedema of the tongue as an adverse effect due to the combination of everolimus and an angiotensin-converting enzyme inhibitor. Since high doses of everolimus are used in the treatment of more common malignancies such as advanced renal cell and breast cancer, an increase in the occurrence of this potentially severe adverse effect can be expected. We recommend carefully looking into the current medication list of the patient before starting everolimus and when an angiotensin-converting enzyme inhibitor is present, it should be replaced by an alternative antihypertensive drug until more data become available. That way treatment discontinuation or dose reduction of anti-cancer treatment can be avoided.

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Introduction

Everolimus has been approved for the treatment of several types of tumours, including advanced renal cell cancer, neuroendocrine tumours of pancreatic origin, subependymal giant-cell astrocytoma associated with tuberous sclerosis and more recently for the treatment of more common malignancies such as metastatic breast cancer.[1] The BOLERO-2 study showed that oral everolimus in addition to exemestane prolongs the progression free survival in patients with hormone receptor-positive, human epidermal growth factor receptor (HER) 2-negative advanced breast cancer, resistant to a non-steroidal aromatase inhibitor.[1,2] Everolimus is a selective inhibitor of mammalian target of rapamycin (mTOR), a serine/threonine protein kinase in the PI3K/Akt/mTOR pathway.[3] This pathway is abnormally activated in many types of cancer and plays an important role in breast cancer cell proliferation and anticancer drug resistance. Everolimus inhibits the downstream signalling events of the mTOR pathway. Adverse effects and toxicity of everolimus are a common problem and often lead to treatment discontinuation and dose reduction. Here we describe a patient that presented with an adverse effect due to everolimus in combination with an angiotensin-converting enzyme inhibitor.

Case report

We report the case of an 89-year old Caucasian male, with a history of ischemic heart disease, transient ischemic attack and metastatic breast cancer, who was admitted to the emergency department with complaints

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of a unilateral swollen tongue on the right side. The symptoms started suddenly, a few hours before he presented himself. There were associated complaints of weakness and fatigue, but no urticaria, bronchospasm, pruritus or throat tightness. Blood pressure at time of admission was 157/78 mmHg with a pulse of 80 bpm, a temperature of 36.4°C and an oxygen saturation of 95%. Physical examination showed him to be in moderately good condition. His tongue was swollen on the right side only. There were some bilateral crackles on lung auscultation but no further abnormalities except for the status after breast surgery. The current medication list contained the following medications: acetylsalicylic acid 80 mg OD, atenolol 25 mg OD, metformin 850 mg OD, gliclazide 60 mg OD, lisinopril 10 mg OD and two recently started antihormonal drugs (exemestane 25 mg OD and everolimus 5 mg OD). The patient was diagnosed with moderately-differentiated invasive ductal adenocarcinoma of the right breast in May 2011. He underwent a right-sided mastectomy and axillary node dissection (pT1pN1a, ER = 8, PR = 5, c-erbB-2 score 1+, Ki-67 proliferation index 7%). Adjuvant radiation therapy to the chest wall was performed (25 x 2 Gy). The treating physician at that time judged that the patient was not fit enough to be treated with adjuvant hormonal therapy.

Re-evaluation in October 2012 showed an elevated tumour marker CA 15.3 and the presence of lung, pleural, and liver metastases for which first line antihormonal therapy with tamoxifen 20 mg OD (Nolvadex-D®) was started. After six months there was further disease progression and second line hormonal therapy with an aromatase inhibitor was started (letrozole 2.5 mg OD, Femara®). This therapy was switched to third line hormonal therapy with exemestane 25 mg OD (Aromasin®) in September 2013 because of growth of the liver metastases. In December 2013 everolimus 10 mg OD (Afinitor®) was added to this therapy because of further disease progression. After three weeks the dosage of everolimus was reduced to 5 mg OD, after interrupting treatment for seven days, because of complaints of dizziness and weakness. Eleven days after this dose reduction the patient was admitted to the emergency department and was diagnosed with unilateral angioedema of the tongue. He was treated with a single dose of intravenous corticosteroids (methylprednisolone 80 mg) and H1 and H2 antihistamines were started. ACE inhibitor and everolimus were discontinued. The ACE inhibitor was replaced by an angiotensin II receptor antagonist. Further therapeutic options were discussed with the patient. He preferred best supportive care over further anti-tumoral treatment.

Conclusion

Everolimus may enhance the adverse effects of ACE inhibitors. Specifically, the risk of angioedema may be increased. Angioedema is a possible adverse effect of both mTOR inhibitors and ACE inhibitors. Increased incidence of angioedema is seen in patients who concomitant use an mTOR inhibitor and an ACE inhibitor compared to treatment with one of the two drugs alone.[4,5]

Angioedema is an asymmetric, non-pitting swelling of the subcutaneous or submucosal tissues. ACE inhibitors are the leading cause of drug-induced angioedema with an overall incidence estimated between 0.1 - 0.7%.[6] The clinical features include tissue swelling (tongue, face, lips and upper airways are most affected). Urticaria, pruritus, flushing and bronchospasm are typically absent. Symptoms may appear within a week of starting the medication, but can also arise after years of use.[6,7]

In general two types of angioedema can be distinguished: mast cell-mediated angioedema and bradykinin-mediated angioedema. The latter is the proposed mechanism of action in angioedema from ACE inhibitors. Bradykinin is an inflammatory vasoactive peptide which leads to vasodilatation and increased vascular permeability. Inhibition of ACE leads to impaired degradation of bradykinin and thus to elevated bradykinin levels.[7,8]

The mechanism for angioedema from mTOR inhibitors is not well understood. In renal transplant recipients using mTOR inhibitors (sirolimus or everolimus), a decrease in the metabolism of bradykinin has been shown. In combination with ACE inhibitors predisposal to the development of angioedema has been seen.[4] Also in cardiac transplant patients taking everolimus and ACE inhibitors, increased rates of angioedema have been reported.[5] The dosages of mTOR inhibitors used in transplant rejection prophylaxis are significantly lower than the dosages used in anti-cancer treatment. A dose-dependent effect on the development of angioedema has also been suggested in transplant patients taking mTOR inhibitors in combination with ACE inhibitors.[5]

Treatment is the discontinuation of the involved drugs.[6] Corticosteroids and antihistamines are commonly used but these medications are not known to alter levels of bradykinin and are therefore at most minimally effective in the treatment of bradykinin-induced

Key messages for clinical practice

1. Since high doses of everolimus are used in the treatment of more common malignancies, an increase in the occurrence of adverse effects can be expected.
2. Everolimus is associated with the development of angioedema and may enhance the adverse effects of ACE inhibitors when used together.
3. Before starting everolimus we recommend to carefully examine the current medication list of the patient.
4. When an ACE inhibitor is present, consider replacement by an alternative antihypertensive drug.
5. Potentially severe adverse effects and treatment discontinuation/dose reduction can be avoided.

angioedema. There are no clear literature data on re-starting mTOR inhibitors at a reduced dose after an episode of angioedema. Since an ACE inhibitor can easily be replaced by a product of another class of antihypertensive drugs, it is almost always permanently discontinued. In most reported cases, mTOR inhibitor was reintroduced after resolving of angioedema. Most often a reduced dose was started. When angioedema reappears mTOR inhibitor should be stopped definitively.[9]

Since the use of everolimus and other mTOR-inhibitors is indicated in the treatment of more common malignancies like metastatic breast cancer, we can expect a higher number of patients taking these medications. In the anti-cancer indication the dosage of everolimus is much higher than when used as rejection prophylaxis in transplant patients. Adverse effects and toxicity are a major limiting factor in the usage of everolimus and often lead to treatment discontinuation and dose reduction. We would like to highlight the occurrence of a possibly severe, and avoidable, adverse effect when everolimus is used in combination with ACE-inhibitors. We propose to carefully examine the medication list of the patient before everolimus is initiated. When patients are receiving an ACE inhibitor we suggest to cease and to choose an alternative antihypertensive drug. In this way we can prevent the development of angioedema from the combination of ACE inhibitors and everolimus. Also discontinuation of anti-cancer treatment or dose reduction can be avoided.

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