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LETTER TO THE EDITOR

Lingual angioedema associated with everolimus

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Targeted therapy is now the standard treatment for metastatic renal cell carcinoma (mRCC). A key pathway that has been targeted is the mTOR (mammalian target of rapamycin) pathway which is involved in regulating cell proliferation, growth, differentiation, migration, and survival. Drugs that target this pathway have been studied in phase III clinical trials which have led to the approval of both temsirolimus and everolimus for patients with mRCC in Europe and the United States [1,2].

Oncologists are now using these drugs on a daily basis and becoming familiar with the toxicities associated with them. However, a much longer and vast clinical experience with mTOR inhibitors exists in the transplant arena where drugs like sirolimus/rapamy-cin (Rapamune®) and everolimus (Certican®) have been used as immunosuppressants for a number of years. Temsirolimus and everolimus are derivatives of sirolimus.

A recent experience in a patient on everolimus for mRCC highlighted an important toxicity and one that appears to be known in the transplant literature but not the oncology literature. The toxicity was lingual angioedema and given it is potentially life threatening, we feel knowledge about this toxicity is critical to oncologists.

In this case, a 61-year-old man with mRCC was started on second line everolimus 10 mg a day. On cycle 1 day 21, he awoke with a swollen tongue and a feeling like he could not breathe. He presented to the emergency department six hours later with a grossly swollen and edematous tongue, a hoarse voice and difficulty speaking. He was diagnosed with lingual angioedema and given epinephrine 0.3 mg subcuta-neously, methylprednisolone 125 mg iv, and diphen-hydramine 50 mg iv. Thirty minutes later, there was no real improvement and he was having difficulty swallowing. He received a second dose of epinephr-ine and ranitidine 50 mg iv. Three and half hours later, there was no change in the size of his tongue and he was given a second dose of diphenhydramine 50 mg iv. Five hours later, the lingual angioedema was decreasing and he was discharged home with as needed oral diphenhydramine and prednisone of which he took one dose of each. Once at home, he ate a frozen yogurt bar, and found the cold temperature from this markedly helped his local symptoms. Eighteen hours after the onset, his signs and symptoms were completely resolved. His concurrent medications were: ramapril 10 mg a day, triamterene and hydrochlorothiazide 50/25 mg a day, and ome-prazole 20 mg a day. Everolimus was resumed one week later at 5 mg a day given this was a grade 3 toxicity. He now carries an epinephrine pen, diphen-hydramine and dexamethasone. More than 12 weeks after re-initiation, there has been no recurrence.

To review the occurrence, presentation, and management of lingual angioedema in association with mTOR inhibitors, Pubmed was searched using the terms angioedema and everolimus/RAD001/temsirolimus/sirolimus/rapamycin/Rapamune/Certi-can. No reports in oncology related journals were found. The reports from the transplant literature are summarized below.

The first report in 2004 is from an Italian renal transplant clinic [3]. Fifty-two renal transplant patients were followed over 10 months. Fifteen of these patients were on sirolimus as part of their

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immunosuppression and five of 15 developed isolated, moderately severe, bilateral lingual edema. Patients had normal eosinophil and IgE levels and mycotic, viral, and bacterial cultures from the oral surfaces were negative. Interestingly, all patients had been on the Angiotensin Converting Enzyme Inhibitor (ACEI) ramipril pre transplant and it was restarted two months post transplant. The lingual angioedema occurred one month after the reintroduction of ramapril in all patients which made the authors speculate on a drug interaction. The differences between the five patients in whom lingual edema occurred and the 10 patients in whom it did not occur, include higher trough levels of sirolimus (18.4 ng/ml compared to 14.2 ng/ml) and a higher dose of ramapril (5 mg compared to 2.5 mg a day). Mucosal angioedema can occur with ACEI, but all these patients were on ramapril pre transplant with no problems. In all patients, the ACEI was discontinued, the sirolimus was continued and the angioedema resolved. Three months later, the sirolimus doses were lowered as per standard of care and ramapril was reintroduced at 2.5 mg a day with no recurrence of this problem.

The largest series reports on 114 German cardiac transplant recipients who were on everolimus 1.5 mg perdayfor immunosuppression [4]. Sixof114 (5.3%) developed lingual angioedema after two to 41 days. All had associated petechial bleeding and lingual bullae on the lateral aspect of the tongue. All patients were hospitalized and treated with steroids and antihistamines. All six patients were re-challenged and five had no recurrence after 15 to 126 days. One patient had two recurrent episodes associated with dyspnea on day 42 and day 67 after which everolimus was discontinued. At the time, everolimus serum concentrations were within or below the therapeutic range. At the time, all affected patients were also treated concomitantly with acetyl-salicylic-acid (ASA) and an ACEI (ramipril 5 mg a day or enalapril 10 mg aday). The ASA and ACEI were stopped. The authors speculate that the ASA triggered the occurrence of the everolimus associated toxicity. In this publication, they do not associate the use of ACEI as being contributory.

Another report describes three cases of sirolimus induced angioedema but not isolated to the tongue [5]. Angioedema of the face, periorbital region, floor of mouth, and tongue occurred in African American renal transplant recipients. The timing of the angioedema ranged from three days to four weeks after initiating sirolimus and in two of these patients, the angioedema occurred following re-exposure to sirolimus. In the third patient, it occurred within two weeks of starting sirolimus. In this case, trough levels were elevated and the angioedema recurred after 2 further doses of sirolimus. All patients responded to parental steroids, oral diphenhydramine and ranitidine and the discontinuation of sirolimus. The first two patients had sirolimus trough levels at or below target. No patients were taking ACEI however the third patient was on ASA.

Another study from France reported on 80 renal transplant recipients on sirolimus. Twelve patients (15%) experienced angioedema involving different areas with 83% involving predominantly the face [6]. The angioedema occurred after two days to 48 months. Three patients had tongue involvement. This report does comment on other causes of angioedema including other drugs, food allergies, and physical activity and thus the incidence of angioedema truly due to sirolimus is much less clear in this report.

Two further cases were reported at the German-Austrian Everolimus Consensus Conference in 2006 where lingual angioedema occurred in patients on both everolimus and ACEI [7]. Both patients had high everolimus trough levels, recovered after a decrease in everolimus and the discontinuation of ACEI. If angioedema occurred, the 2006 Consensus Conference recommendations were to discontinue the ACEI and reduce the everolimus trough blood levels to 3-4 ng/ml (from 3-8 ng/ml).

No reports of temsirolimus associated with lingual angioedema were found. Of note, temsirolimus is not used in the transplant population and is a newer agent. The only reference to this possible side effect is found in the prescribing information from Wyeth which states that some patients who were "angio-neurotic edema-type reactions have been observed in some patients who received TORISEL (temsiroli-mus) and ACE inhibitors concomitantly" [8]. The prescribing information from Novartis states that "hypersensitivity reactions including angioedema, swelling of the airways or tongue with or without respiratory symptoms, have been noted with ever-olimus and other rapamycin derivatives" [9].

What the exact incidence of lingual angioedema is in our mRCC patient population is unknown. If the incidence is truly as high in our patient population as the 5% published in heart transplant population treated with everolimus, it is imperative we, as oncology specialists, along with our multidisciplinary team and more importantly our patients are aware. The possible interaction with ACEI is also essential to know as many of these patients are on full dose ACEI post VEGF targeted therapy due to hypertension and consideration may have to be taken to discontinuing the ACEI prior to mTOR inhibition.

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