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HER2-Amplified Salivary Duct Carcinoma: Regression with Dual HER2 Inhibition and Anti-VEGF Combination Treatment

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Abstract

Background—Salivary ductal carcinoma is a rare cancer with poor prognosis and limited treatment options. HER2-directed treatment has been attempted in HER2-amplified or overexpressed salivary gland malignancies with limited success.

Methods—We report resolution of measurable disease and minimal residual disease in a patient with salivary duct cancer treated with trastuzumab, lapatinib, and bevacizumab, with treatment ongoing for more than two years.

Results—This treatment has been tolerated well except for grade 2 diarrhea and mucositis, which required a dose reduction of lapatinib to 1000 mg daily. The response observed was achieved in spite of receiving extensive prior therapy, including trastuzumab and/or chemotherapy for 20 months on which his tumors progressed.

Conclusions—The combination of trastuzumab, lapatinib, and bevacizumab may warrant investigation as a non-cytotoxic alternative for treatment of HER2-amplified or overexpressed salivary duct carcinoma and other HER2-amplified or overexpressed salivary gland tumors, particularly those not responsive to trastuzumab monotherapy.

Keywords

salivary duct carcinoma; trastuzumab; lapatinib; HER2; bevacizumab

INTRODUCTION

Salivary duct carcinoma is a rare histological subtype representing 9% of malignant salivary gland tumors[1] and has a poor prognosis with three years mean survival after diagnosis and limited treatment options.[2-4] Of interest, salivary duct tumors have several similarities to breast ductal tumors including histological features,[5-7] HER2/neu overexpression and gene amplification (61-100%),[8, 9] estrogen receptor beta overexpression (73%),[10] and androgen receptor overexpression (67%).[10]

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HER2-directed treatment has been attempted in HER2-amplified or overexpressed salivary gland malignancies with limited success. A phase II trial of trastuzumab in 14 patients with HER2-overexpressing salivary gland cancers demonstrated only one partial response in a patient with mucoepidermoid carcinoma.[11] In contrast, two case reports suggest antitumor activity with trastuzumab in combination with chemotherapy in such patients. A patient with HER2-positive ex pleomorphic adenoma achieved a complete response for over two years with trastuzumab in combination with capecitabine;[12] similarly, a patient with salivary duct carcinoma receiving combination trastuzumab, paclitaxel, and carboplatin achieved complete response for 14 months.[13]

Clinical trials in HER2-amplified breast cancer have demonstrated promising clinical outcomes with the various doublet combinations of trastuzumab, lapatinib, and bevacizumab.[14-17] A regimen using all three of these agents together has also shown promising results in heavily pretreated metastatic breast invasive ductal carcinoma and several other malignancies,[18] and therefore may be promising for HER2-amplified salivary duct carcinoma.

Here, we report resolution of measurable disease and minimal residual non-measurable disease, in a patient with salivary duct cancer treated with trastuzumab, lapatinib, and bevacizumab, with treatment ongoing for more than two years.

CASE REPORT

A 55 year-old man presented with a growing mass in the right cheek and upper neck. Fine needle aspiration revealed high grade salivary duct carcinoma, with 3+ expression of HER2 by immunohistochemistry and gene amplification of *HER2/neu*. Computed tomography (CT) revealed extensive tumor in the right neck measuring 13 cm and multiple small lung nodules.

Treatment with cisplatin and docetaxel for one cycle, followed by carboplatin, docetaxel, and trastuzumab for six cycles, resulted in resolution of the lung nodules and near-complete response in the right neck and parotid gland. Residual tumor was treated with intensity-modulated radiation therapy, concurrently with trastuzumab, resulting in complete response of the neck and parotid gland tumor but new hypermetabolism in the ninth thoracic vertebral body and left fourth rib, as well as tiny pulmonary nodules. The patient was treated with zolendronic acid and trastuzumab for seven months after radiation, until a restaging positron emission tomography – CT (PET-CT) demonstrated progression in the bone metastases.

Weekly paclitaxel was then added for two months, resulting in improvement in the bone and pulmonary metastases. Maintenance trastuzumab and zolendronic acid were continued for an additional five months until scans demonstrated progression in the bone and pulmonary metastases, as well as a 2.1 cm lesion in the left medial temporal lobe. Trastuzumab was discontinued, and the brain metastasis was treated with gamma knife radiosurgery.

The patient was treated on a phase I trial of combination trastuzumab (8 mg/kg loading, 6 mg/kg maintenance, intravenously every 3 weeks), lapatinib (1250 mg orally daily), and bevacizumab (15 mg/kg intravenously every 3 weeks).[18] Restaging scans after six weeks revealed complete resolution of all measurable pulmonary lesions, with residual tiny pulmonary nodules and stable small osseous metastases (Figure 1). After 18 months of treatment, an asymptomatic but enlarging 3.2 cm lytic bone metastasis involving the right posterior ilium was treated with radiation. Because of absence of progressive disease in the lung, brain, or in the other osseous metastases on restaging scans, treatment with

trastuzumab, lapatinib, and bevacizumab was continued. Restaging scans included brain magnetic resonance imaging and CT chest, abdomen, and pelvis.

The patient remains on this treatment without any further evidence of tumor progression at 25+ months. This treatment has been tolerated well except for grade 2 diarrhea and mucositis, which required a dose reduction of lapatinib to 1000 mg daily. The dose reduction occurred at month nine and he has done well since.

DISCUSSION

We report sustained antitumor activity in a patient with HER2-amplified salivary duct carcinoma, who achieved resolution of all measurable disease in the lungs, with residual tiny pulmonary nodules and stable small bone metastases during treatment with combination trastuzumab, lapatinib, and bevacizumab. He has tolerated treatment well except for diarrhea requiring a dose reduction of lapatinib. Treatment is ongoing at 25+ months.

HER2-amplified or overexpressed salivary gland malignancies are associated with poor prognosis, compared to other subtypes.[19-21] HER2 oncoprotein is associated with increased vessel permeability, endothelial cell growth, proliferation, migration, and differentiation.[19]

Trastuzumab-based therapies for HER2-amplified or overexpressed salivary gland malignancies have yielded limited success, although two case reports of combinations with cytotoxic agents have been more successful.[11-13] In addition to trastuzumab-based therapies, lapatinib has demonstrated preliminary antitumor activity in a phase II study in which three out of the five patients with HER2-positive salivary gland malignancies achieved stable disease of at least 6 months, although no objective responses were observed.[22]

The patient in this report was previously treated with trastuzumab and/or chemotherapy for 20 months after which his tumor progressed. However, using a combination of dual HER2 inhibition along with VEGF inhibition resulted in renewed antitumor activity. Several factors may have contributed to the success in overcoming resistance with this three-drug combination regimen. Trastuzumab and lapatinib have complementary mechanisms of action and synergistic anti-tumor activity in models of HER2-overexpressing breast cancer.[23-25] In fact, in *HER2*-amplified breast cancer patients, this combination has demonstrated improved progression free survival and increased rate of pathological complete response compared to anti-HER2 monotherapy.[14, 15] By targeting both kinase-dependent and -independent tumor activity, it is possible that resistance to trastuzumab monotherapy has been overcome. Indeed, it has been noted that it is possible for cancer cells to survive treatment due to kinase-independent activity.[26] It has recently been demonstrated that EGFR has both kinase dependent and independent pathways, suggesting that a combination of kinase inhibitor and antibody may be more potent than either one alone; it is plausible that this is true for other kinase receptors such as HER2/neu.[26] The contribution of bevacizumab also must be considered, because in breast cancer xenografts that overexpress HER2, combination anti-VEGF and anti-HER2 treatment produced significantly greater inhibition of tumor growth than either individual agent.[27]

Another factor that may have contributed to disease control in this patient was our decision to treat the isolated enlarging lytic metastasis in the posterior iliac bone with radiation and to continue systemic trastuzumab, lapatinib, and bevacizumab, which maintained disease control elsewhere. A growing body of literature suggests that providing local therapy to an isolated area of progression while continuing targeted agents can be an efficacious treatment strategy.[28-31]

Bevacizumab, a VEGF monoclonal antibody, has also shown promising antitumor activity in salivary duct carcinoma when used in combination with temsirolimus, an mTOR inhibitor.[32] Further, the combination of trastuzumab, lapatinib, and bevacizumab has demonstrated promising activity in HER2-amplified breast cancer and other malignancies.[18] The combination of trastuzumab, lapatinib, and bevacizumab may warrant investigation as a non-cytotoxic alternative for treatment of HER2-amplified or overexpressed salivary duct carcinoma, other HER2-positive salivary gland tumors, and possibly in other HER2-positive tumors, particularly those not responsive to trastuzumab monotherapy.

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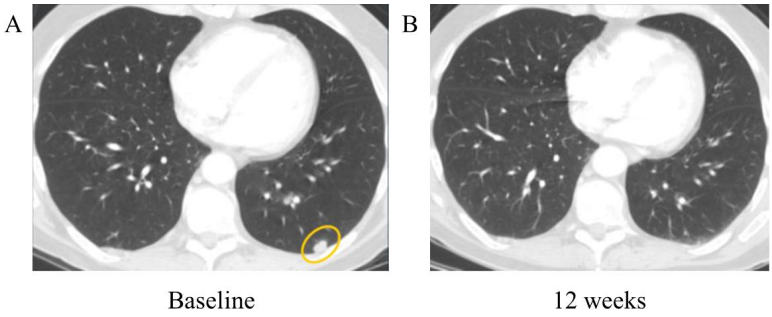

Figure 1.
Tumor regression of 100% of measurable disease observed in lung tumors on CT scan at baseline (A) and after 12 weeks of treatment with trastuzumab, lapatinib, and bevacizumab (B).