Title

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BRIEF CLINICAL UPDATE

T-DM1: Proof HER2 is a Target in Salivary Gland Cancers

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Salivary gland cancers are rare tumors that arise in the head and neck region. The majority of tumors arise in the parotid gland (70%) and, of these, approximately 25% are malignant.[1] Salivary gland cancers are managed primarily with surgical resection and, if indicated by aggressive features on pathology, adjuvant radiation is recommended. Systemic therapy is generally reserved for locoregional recurrence and/or metastatic disease.[1] Although chemotherapy such as doxorubicin, cisplatin, 5-fluorouracil, paclitaxel, and navelbine have some activity in this disease, response rates are generally in the range of 15–30%, and short in duration.[2-7]

Because of their strong histological resemblance to invasive breast cancer, salivary gland cancers were evaluated for the presence of human epidermoid receptor-2 (HER2) on their cell surface. Approximately one-third of salivary gland carcinomas overexpress HER2.[8-9] Like its counterpart in breast cancer, HER2 overexpressed salivary gland cancers are high grade cancers with poor prognoses. These cancers tend to recur distally, with most common sites being lung, liver and bone.[8-10] Management of these cancers is based primarily on retrospective reviews of clinical experience.

All breast cancers are now surveyed for the presence of HER2 amplification and such cases frequently benefit from treatment with the humanized antibody trastuzumab. Similarly, HER2 overexpressed salivary gland cancers have demonstrated benefit from trastuzumab. A phase II trial of weekly trastuzumab in 14 patients with metastatic disease was the first to demonstrate the potential benefit of trastuzumab in salivary gland cancers.[11] One patient in this study with metastatic cancer received 40 cycles with a documented partial response. Two patients with previously progressive cancer had disease stabilization for 26 and 40 weeks. Overall there was low single agent activity. Thus, there have subsequently been many case reports demonstrating durable responses to trastuzumab-containing chemotherapy regimens in patients with HER2 overexpressed salivary gland tumors. Sharon et al reported a complete response in a patient with carcinoma ex-pleomorphic adenoma with multiple bone metastases treated with trastuzumab, capecitabine, and zoledronic acid. Nashed et al also reported a durable complete remission of a metastatic salivary duct cancer treated with a combination of docetaxel and trastuzumab. Similar results have been seen with trastuzumab in combination with platinum containing regimens as well.[12-15]

The largest case series to date demonstrated the efficacy of targeting HER2 in 13 patients including treatment in both the metastatic and adjuvant setting. Eight patients received trastuzumab in the adjuvant setting while 5 received trastuzumab in the palliative/metastatic setting. Adjuvant treatment consisted of taxotere carboplatin trastuzumab (TCH) concurrent with radiation for 6 weeks followed by 12 weeks of TCH followed by trastuzumab alone to complete one year. Five of the 8 had no evidence of disease more than 2 years from completion of therapy, all patients in the adjuvant group had stage IVA disease, 6 out of 8 of them had N2b disease. In the palliative/metastatic setting TCH was given every 3 weeks for 6 cycles followed by trastuzumab for variable time periods. Second line therapy was also given upon progression for some patients. In the metastatic/palliative setting all 5 patients had distant metastatic disease at the time they initiated TCH. All 5 of them demonstrated objective responses to TCH. One patient achieved a complete response and had no evidence of disease 52 months from initiation of therapy. The mediation duration of response was 18 months, with a range of 8-52 months.[16]

Subsequently, additional drugs have been developed to target the HER2 receptor and currently five therapies are approved in breast cancer: two antibodies- trastuzumab and pertuzumab), two small molecule kinase - lapatinib and neratinib and the antibody-drug conjugate ado-trastuzumab emtansine, also known as T-DM1.

Trastuzumab-Emtansine, otherwise known as Kadcyla or T-DM1, is an antibody-drug conjugate in which the monoclonal antibody trastuzumab is linked covalently to a potent microtubular inhibitor, emtansine. Emtansine is derived from Maytansine which was discovered in the 1970's as an extremely cytotoxic microtubule inhibitor. It was more potent than vincristine/vinblastine, but abandoned due to profound toxicities. Antibody-drug conjugates such as T-DM1 selectively direct drugs to tumor cells and minimize systemic toxicity. This specificity occurs because the molecule binds to the HER2 receptor and is internalized into the cell via endocytosis. Inside the cell, emtansine only separates from the antibody when it combines with the lysosome which degrades the covalent linker. This ensures targeted delivery of potent chemotherapy while minimizing systemic toxicity. T-DM1 is presently approved to treat HER2-positive metastatic breast cancer that has recurred following treatment with Herceptin and a taxane.[17,18] Because of its promising results in HER2 positive metastatic breast cancer, and its relatively low side effect

profile, it is an attractive agent in other HER2-overexpressing cancers.

We report a 72 year-old Caucasian male with a history of malignant salivary gland cancer who received T-DM1 for metastatic salivary gland cancer who had a sustained response for over 11 months.

Our patient had a parotid mass for over 20 years that had been stable in size until he began having tingling sensation in his cheek. Examination revealed a 4 cm parotid mass on the left side without any enlarged lymphadenopathy in the neck. His facial nerve was neurologically intact. FNA results demonstrated malignant cells consistent with salivary duct carcinoma.

CT scan failed to demonstrate any evidence of metastatic disease. The patient underwent a left superficial and deep lobe parotidectomy with sternocleidomastoid rotation flap and left functional neck dissection. Pathology revealed high grade salivary duct adenocarcinoma measuring 2.2 cm in greatest dimension with focal extra parotid extension, extensive perineurial and lymphovascular invasion. One of 5 intra and peri-parotid lymph nodes were POSITIVE for metastatic salivary duct adenocarcinoma. No extra nodal extension was seen. In the left neck 5/29 lymph nodes were positive for metastatic salivary duct adenocarcinoma, again without extra nodal extension. The cancer was found to be HER2/neu 3+ by immunohistochemistry and FISH was positive with a copy number of 6.6 signals/cell.

Treatment

The patient received adjuvant radiotherapy with chemotherapy sensitization with Carboplatin (AUC 2) weekly along with trastuzumab. Radiotherapy was delivered to the parotid tumor bed and right neck to a dose 6840 cGy. He tolerated chemotherapy and radiation well. He was followed expectantly with serial imaging and continued to receive trastuzumab on a 3 weekly basis to complete 1 year.

Approximately 6 months later on surveillance imaging a new liver lesion was identified measuring 1.5 cm was seen on the lateral aspect of the right hepatic lobe. No other sites of metastatic disease was seen. A biopsy confirmed metastatic salivary gland cancer that was her2+. FISH was positive with average her2 copy number of 11.5 signals/cell.
He then received treatment with chemotherapy using taxotere, carboplatin and trastuzumab for 4/6 cycles and trastuzumab was continued. Chemotherapy was complicated by neutropenic fever and patient declined further chemotherapy. Follow-up imaging at 3 months showed the lesion had decreased in size. He then received RFA to the solitary lesion and follow up PET/CT months later showed complete resolution of the right hepatic metastasis. Six months following his imaging demonstrated new growth at the posterior superior margin of the ablation zone. This area received repeat radio frequency ablation. The area of ablation improved with again, growth on the margin of ablation defect. The patient was then referred to hepatobiliary surgery team for consideration of partial hepatectomy. He was considered a satisfactory candidate, as there remained no other focus of metastatic disease outside this right lobe liver lesion. Unfortunately, 6 months later surveillance imaging revealed resection of right lobe of the liver; however, diffuse hyper-metabolism at the area of resection was seen but additional two hyper-metabolic lesions within the lateral segment of the left lobe of the liver with metabolic activity. Lesions measured 2.3 and 2.7 cm in diameter, respectively. (See Figure 1) In addition, two adjacent hyper-metabolic lesions were present in the inferior aspect of the right lobe of the liver and measure 2.3 and 1.9 cm. In addition, a porta-caval node was hyper-metabolic and enlarged along with one other node. Because the surgery was complicated and the patient had deteriorated clinically, he was not an ideal candidate for cytotoxic chemotherapy. We requested authorization for T-DM1, which was approved by Medicare. Eight months following his liver surgery, he commenced treatment with TDM-1. He received a loading dose and then 3.6 mg/kg every 3 weeks for 20 cycles. The treatment was well tolerated with no thrombocytopenia. Repeat imaging after the 3rd cycle and demonstrated that the previous metabolic liver and peri-portal lesions virtually resolved. There was some slight activity in two out of the six hyper-metabolic areas. Repeat imaging every 3 months continued to show improvement in SUV activity in the resection cavity and resolution of the liver lesions. (See Figure 2) He maintained this response for over 1 year. Most recent imaging unfortunately has revealed progression.

Figure 1.

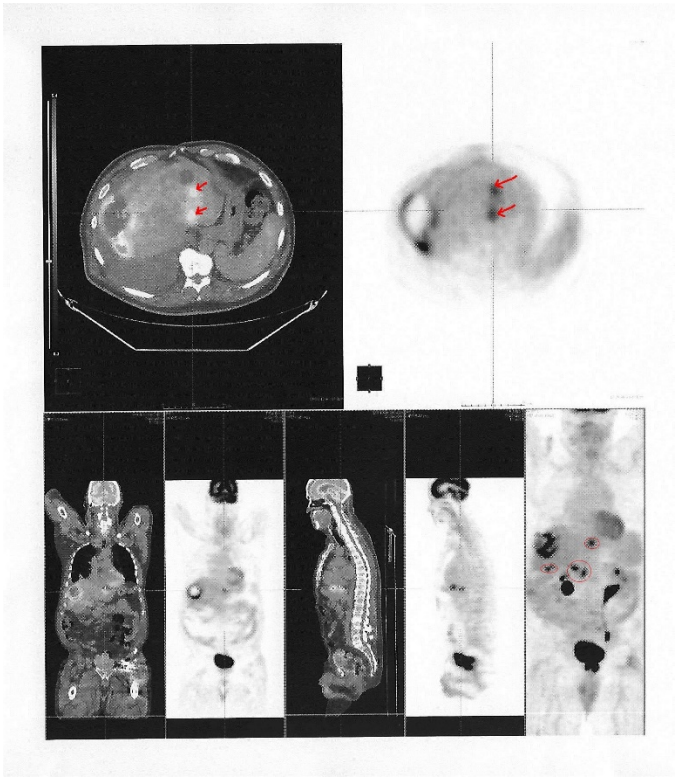
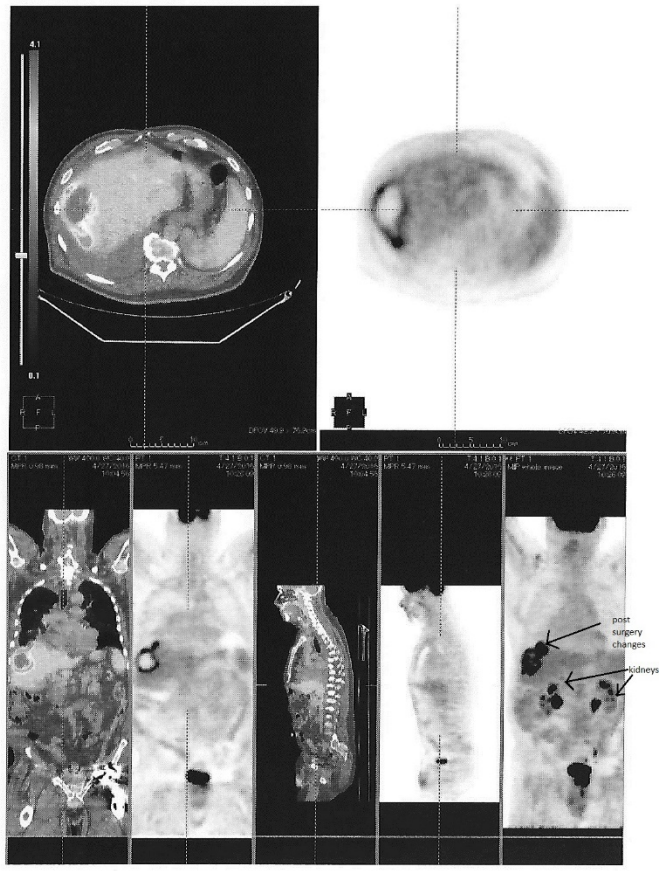


Figure 2.



Conclusion

Malignant salivary gland tumors are rare but highly aggressive cancers that tend to metastasize frequently. Standard treatment for these cancers consists of surgical resection with or without adjuvant radiation. The results of such treatment are disappointing with more than 2/3rds of patients dying with recurrent disease within 3 years. T-DM1 is associated with efficacy and improved safety compared with traditional chemotherapy in the second line setting of metastatic HER2 positive metastatic breast cancer.[17-19] Our case demonstrates the use of T-DM1 in HER2 overexpressing salivary gland cancer is both well tolerated and effective.

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