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Targeting HER2/neu Oncogene Overexpression With Ado-Trastuzumab Emtansine in the Treatment of Metastatic Salivary Gland Neoplasms: A Single-Institution Experience

Brandon L. Swed, MD¹, Roger B. Cohen, MD¹, and Charu Aggarwal, MD, MPH¹

¹University of Pennsylvania, Philadelphia, PA

INTRODUCTION

Salivary gland neoplasms (SGNs) represent a rare and heterogeneous group of tumors. Approximately 20% to 25% metastasize to distant sites and are generally associated with poor response to treatment.¹ Outcomes with systemic chemotherapy have historically been poor.² With improved understanding of the molecular biology of these tumors, we are beginning to identify promising potential therapeutic targets.

In particular, the human epidermal growth factor receptor 2/neu (HER2/neu) oncogene, one of the tyrosine kinase receptors, is overexpressed in salivary duct carcinomas (44%), salivary gland adenocarcinomas (21%), and adenoid cystic carcinomas (2%), among other subtypes.³ Trastuzumab, a monoclonal antibody that binds to the extracellular domain of HER2/neu, inhibits the proliferation of tumor cells that overexpress HER2/neu.⁴ Patients with HER2/

CORRESPONDING AUTHOR Charu Aggarwal, MD, MPH, Department of Medicine, Division of Hematology-Oncology, University of Pennsylvania, 10-137 Perelman Center for Advanced Medicine, 3400 Civic Center Blvd, Philadelphia, PA 19104; Twitter: @CharuAggarwalMD and @PennCancer_Tweet, charu.aggarwal@uphs.upenn.edu.

AUTHOR CONTRIBUTIONS

Conception and design: Brandon L. Swed, Charu Aggarwal

Provision of study materials or patients: Roger B. Cohen

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Roger B. Cohen

Honoraria: Bristol-Myers Squibb

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Charu Aggarwal

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neu-overexpressing SGNs are often treated with trastuzumab-containing regimens with encouraging results, but disease progression is inevitable, even with a favorable initial response. The antibody-drug conjugate ado-trastuzumab emtansine (T-DM1) is currently approved for treating HER2-positive metastatic breast cancer that has progressed on therapy with trastuzumab. This antibody-drug conjugate selectively directs the cytotoxic drug emtansine to tumor cells with HER2/neu expression, thereby minimizing systemic toxicities.⁵

Given the favorable results seen with ado-trastuzumab emtansine in patients with breast cancer, it is logical to consider administering it to patients with SGNs that overexpress HER2/neu after they have progressed on trastuzumab with or without chemotherapy. Sequential HER2/neu-directed therapy has been successfully used with sustained clinical benefit, albeit in a single patient.⁶ Here we report on the clinical outcomes of seven patients with metastatic SGNs who were treated at our institution with ado-trastuzumab emtansine (Table 1), and we summarize the clinical course and response to therapy of one patient.

CASE REPORT

A 45-year-old man presented with a painless right neck mass in late 2013. Computed tomography (CT) scan of the neck demonstrated a 3.2-cm mass in the right parapharyngeal space arising from the deep lobe of the right parotid gland. Fine-needle aspiration revealed a high-grade carcinoma and positron emission tomography/CT (PET/CT) showed multiple fluorodeoxyglucose (FDG)-avid lymph nodes in the right cervical region. He underwent definitive surgical resection of the parotid tumor and a modified radical neck dissection. Surgical pathology revealed a 3.9-cm high-grade salivary duct carcinoma that was positive for androgen receptor (AR) and HER2/neu (3+) by immunohistochemistry (IHC) staining. Because of the high-risk features of extracapsular nodal extension and close margins, he received adjuvant chemotherapy with cisplatin and radiation therapy once per week in October 2014. Five months later, he developed a solitary biopsy-proven recurrence in the liver for which he underwent left hepatic lobectomy in April 2015. He then went on to develop further disease progression with new retroperitoneal lymphadenopathy and was started on androgen deprivation therapy with bicalutamide and leuprolide. Nodal disease continued to progress over the next 4 months. In July 2015, hormonal therapy was discontinued, and systemic chemotherapy was initiated with carboplatin, paclitaxel, trastuzumab, and pertuzumab. This led to radiographic evidence of a complete response. He continued on maintenance trastuzumab and pertuzumab therapy for 7 months until April 2016 when a restaging PET/CT revealed multiple retroperitoneal lymph nodes indicating tumor progression. He then began therapy with ado-trastuzumab emtansine dosed every 3 weeks and had a complete metabolic response that was first evident at 3 months (Fig 1), with progression-free survival of 29 months that is ongoing. His overall clinical course is depicted in Figure 2.

DISCUSSION

Because of the rarity of metastatic SGNs and the absence of data from prospective clinical trials, there is currently a void in the therapeutic guidelines for managing this disease.

Standard treatment of SGNs involves surgical resection with or without adjuvant radiation therapy. Locoregional recurrence and metastases are common, at which time palliative chemotherapy is considered, but response rates are generally poor, and the duration of response is brief without a clear favorable impact on survival. Given the aggressive nature of these tumors and the limited treatment options upon relapse and metastasis, there has been an increased interest in developing targeted therapies.

Two such targets, the AR and HER2/neu receptor tyrosine kinase, are currently used in clinical practice with variable results.⁷ A relatively large retrospective case series has reported favorable outcomes using androgen deprivation therapy in AR-positive SGNs with good tolerability and an overall survival benefit.⁸ The success of HER2/neu-directed therapy in breast cancer has resulted in multiple case reports that show benefit from using trastuzumab-based regimens in treating SGNs.^{4,9} Despite initial success with targeted therapy, however, progression is inevitable.

Mechanisms of resistance have not been extensively explored. Therefore, it seems reasonable to consider the use of ado-trastuzumab emtansine upon progression on trastuzumab, drawing on its demonstrated activity and clinical benefit in the analogous clinical scenario in patients with advanced HER2/neu-positive breast cancer.¹⁰

By contrast to the previous reports, we describe one of the largest single-institution experiences with HER2/neu-targeted therapy in patients with metastatic SGNs. We describe seven patients with metastatic SGNs, all of whom received and responded objectively to ado-trastuzumab emtansine. Most of our patients (n = 6 of 7) experienced progression after trastuzumab, which highlights the role of sequential HER2/neu therapy described by Almquist et al.⁶ All of our patients' tumors demonstrated HER2/neu overexpression, and most had a high degree of HER2/neu receptor positivity.

In our retrospective case series, there was variability in the methods for HER2/neu testing that reflect the natural evolution of institutional testing practices. Nevertheless, clinical benefit was seen regardless of the method of testing (IHC, fluorescence in situ hybridization, or next-generation sequencing), confirming the role of a HER2/neu-targeted approach. For example, the patient discussed here initially experienced a complete metabolic and radiographic response and derived a sustained clinical benefit with a progression-free survival of 29 months that is ongoing. Progression-free survival in all of our patients ranged from 6 to 29 months, and overall survival ranged from 9 to 33 months. All of the patients experienced varying degrees of neuropathy, which proved to be dose-limiting in patient 2. Thrombocytopenia was another adverse effect of therapy, which led to interruption of therapy in one patient. In summary, our case series suggests that testing for HER2/neu by IHC, fluorescent in situ hybridization, or next-generation sequencing should be performed routinely for metastatic SGNs based on the significant clinical benefit seen in patients with HER2/neu-positive disease, including patients who have progressed on trastuzumab.

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FIG 1.

(A) Initial positron emission tomography/computed tomography (PET/CT) staging in July 2014 without evidence of intra-abdominal metastatic disease. (B) PET/CT in April 2016 revealed multiple retroperitoneal lymph nodes indicating tumor progression. (C) Restaging scan in June 2018 after ado-trastuzumab emtansine shows a complete metabolic response of previously noted metastatic lymphadenopathy.

FIG 2.
Schematic timeline depicting the clinical and therapeutic course in patient 1. RT, radiation therapy.

TABLE 1.

Summary of Patients With SGNs Treated With Ado-Trastuzumab Emiansine at Our Institution

Patient	Demographic Characteristic	Date of Initial Diagnosis	Stage at Diagnosis	Therapy Before T-DM1	Date of Metastatic Diagnosis	Sites of Metastatic Disease	Relevant Molecular Markers	Date of Initial T-DM1 Therapy	Setting of T-DM1 Therapy	Duration of T-DM1 Therapy	Best Response to Therapy	Patient Status
1	45-year-old man; never smoker	Jul 8, 2014	T2N2bM0	Surgical resection with modified radical neck dissection → cisplatin + radiation therapy → left hepatic lobectomy → ADT → carboplatin + paclitaxel + trastuzumab + pertuzumab maintenance	Mar 2, 2015	Liver and lymph nodes	HER2/neu [*] (3+) and positive	Apr 16, 2016	3L	29 months and ongoing	CR	Alive
2	62-year-old man; current smoker, 24 pack-years	Jul 3, 2014	T2N3bM1	Palliative radiotherapy → carboplatin + paclitaxel + trastuzumab maintenance → whole brain radiation therapy	Jul 11, 2014	Bone and brain	HER2/neu fourfold positive [‡] ; (three-to negative amplification) ; AR negative	Dec 15, 2015	3L	25 months	CR	Dead
3	58-year-old man; never smoker	Aug 23, 2012	TxNxM1	Palliative radiotherapy → ADT → carboplatin + paclitaxel + trastuzumab maintenance	Aug 23, 2012	Bone and lymph nodes	HER2/neu [‡] and AR positive	Nov 2, 2015	3L	19 months	PR	Dead
4	59-year-old man; never smoker	Apr 4, 2017	T1N2cM0	Carboplatin + paclitaxel + trastuzumab maintenance	Apr 18, 2017	Bone and lymph nodes	HER2/neu positive [*] (3+)	Oct 19, 2017	2L	10 months and ongoing	PR	Alive
5	50-year-old woman; never smoker	Aug 2, 2013	T2N2bM0	Fluorouracil + cisplatin → stereotactic body radiation to lung metastasis → carboplatin + paclitaxel + trastuzumab maintenance → right occipital lobe resection	Mar18, 2014	Bone, brain, lung, liver, kidney, adrenal gland, and lymph nodes	HER2/neu [‡] (25-fold amplification) and AR positive	Jun 1, 2015	3L	4 months	CR	Dead
6	53-year-old man; never smoker	Apr 11, 2016	T2N2bM0	ADT → carboplatin + paclitaxel + trastuzumab maintenance	May 17, 2016	Bone, lung, liver, and lymph nodes	HER2/neu [§] and AR positive	Jan 5, 2017	3L	3 months	Mixed	Dead
7	67-year-old man; former smoker, 37 pack-years	Dec 7, 2017	T4aN3bM1	Palliative radiotherapy → ADT	Dec 18, 2017	Bone and lymph nodes	HER2/neu [*] (1+) and positive	May 17, 2018	2L	5 months and ongoing	PR	Alive

Abbreviations: 2L, second-line therapy; 3L, third-line therapy; ADT, androgen deprivation therapy; AR, androgen receptor; CR, complete response; SGN, salivary gland neoplasm; T-DM1, ado-trastuzumab emiansine.

^{*}Detected by immunohistochemistry.

[‡]Detected by next-generation sequencing.

[‡]Method of detection unknown.

[§]Detected by fluorescence in situ hybridization.