SUCCESSFUL TREATMENT OF PULMONARY METASTATIC SALIVARY DUCTAL CARCINOMA WITH TRASTUZUMAB-BASED THERAPY

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Abstract: Background. Salivary ductal carcinoma (SDC) is an uncommon malignant tumor of the salivary glands. Although there is no known standard of care for the treatment of advanced disease, the vast majority of patients with SDC may be offered palliative systemic therapy. We report a case of epidermal growth factor receptor 2 (HER2)-positive metastatic submandibular SDC with a complete and durable clinical response to treatment with trastuzumab in combination with chemotherapy.

Methods and Results. A 62-year-old man was diagnosed with SDC of the left submandibular gland with extensive cervical lymph node involvement. The lesion was completely resected, and the patient underwent postoperative radiotherapy. After 6 months, multiple pulmonary metastatic lesions were detected. A complete response was reached with trastuzumab-based combination therapy, and no evidence of disease progression has been observed after 14 months of initiation of systemic therapy.

Conclusion. Trastuzumab-based combination therapies should be considered for advanced SDC.

Keywords: trastuzumab; salivary ductal carcinoma; HER2; chemotherapy

Malignant salivary gland tumors are relatively rare, accounting for less than 5% of the tumors arising in the head and neck area.1 Approximately one fourth of parotid tumors and one half of submandibular tumors are malignant. In general, malignant salivary gland tumors are histologically diverse tumors that can be divided into those that might originate from the intercalated ducts (which include adenoid cystic carcinoma and adenocarcinoma) and those of secretory duct origin (mucopidermoid carcinoma, squamous cell carcinoma, and SDC).2 The treatment of salivary gland malignancies remains primarily surgical. Postoperative radiotherapy improves locoregional control for patients with advanced-stage tumor, inadequate margins, or poor prognostic features such as perineural invasion. Because of their rarity, there are limited data to define a role of
systemic therapy in the palliative management of malignant salivary gland tumors.

**CASE REPORT**

A 62-year-old white man was initially seen for evaluation of a left submandibular mass, which had been present for 6 months and had shown a gradual painless increase in size over the previous 2 months. A cervical and thoracic CT scan showed a 2.0-×-2.0-cm left submandibular mass with multiple enlarged ipsilateral cervical nodes. No pulmonary lesions were observed. A complete resection of the left submandibular gland with an ipsilateral-modified radical neck dissection was performed. The specimen showed cribriform arrangement of pleomorphic epithelioid tumor cells with prominent nucleoli and coarse chromatin (Figure 1A). Metastases with extracapsular extension were confirmed in 7 of 10 cervical lymph nodes by histological examination. Immunohistochemistry (IHC) analyses showed that the tumor was HER2+ (Herceptest) (Figure 1B), and estrogen receptor negative and progesterone receptor negative. The average percentage of cells that stained positively for Ki-67 was 75%. In addition, amplification of the HER2 gene was detected by fluorescence in situ hybridization test (PathVysion; Vysis, Downers Grove, IL). On the basis of these findings, a final diagnosis of salivary ductal carcinoma (SDC) of the left submandibular gland with extensive cervical lymph node involvement was established.

The patient was referred for conventional adjuvant radiotherapy. The primary site received a dose of 66.6 Gy, and all draining lymph nodes at risk received a dose of 54 Gy. The patient was followed-up for 6 months without evidence of recurrence until he was seen with an acute upper respiratory infection in the emergency department. A thoracic X-ray revealed multiple bilateral pulmonary metastatic lesions, confirmed by thoracic CT scan (Figure 2A). The workup was completed with a cervical CT scan and a bone scan, both of which were negative. Systemic treatment with paclitaxel (80 mg/m²/weekly; days 1, 8, 15), carboplatin (area under the curve [AUC] 2, weekly; days 1, 8, 15), and trastuzumab (4 mg/kg dose-loading and 2 mg/kg/weekly; days 1, 8, 15 and 22) was initiated. A posttreatment CT scan obtained 3 months later revealed a complete response of all pulmonary metastatic lesions (Figure 2B). The patient completed a total of 6 cycles and continued main-

**DISCUSSION**

SDC is an uncommon malignant tumor of the salivary glands located predominantly in the parotid gland and occasionally in the submandibular gland. SDC is characterized by distinctive pathologic and clinical features. The most important histologic attribute of this neoplasm is its striking resemblance to breast carcinoma of the ductal type.

Clinically, SDC exhibits a male predominance and occurs at a mean age of 60 years. SDC is an
aggressive disease associated with cervical lymph node involvement at presentation, and a high rate of local and distant recurrence.

Although there is no known standard of care for the treatment of advanced disease, the vast majority of patients with SDC may be offered palliative systemic therapy. Most studies show response rates to standard cytotoxic agents (cisplatin, carboplatin, paclitaxel, doxorubicin) in the range of 15% to 30%, and these responses are usually short lived.\(^7\)

HER2 is a member of the epidermal growth factor (EGF) family of receptor tyrosine kinases, which also includes EGF receptor (EGFR; HER1 and erbB1), HER3 (erbB3), and HER4 (erbB4). Nearly 25% of invasive ductal carcinomas of the breast exhibit HER2 gene amplification. This molecular feature has been associated with a more aggressive clinical outcome.\(^8,9\) Trastuzumab, a humanized monoclonal antibody, binds with high affinity to the extracellular domain of HER2, inhibiting the proliferation of human tumor cells that overexpress HER2. Treatment with trastuzumab improves survival when combined with taxanes in advanced disease or in combination and/or sequentially after chemotherapy in the adjuvant setting in HER2\(^{+}\) breast cancer.

SDC commonly overexpresses HER2 by IHC, and this molecular feature has been correlated with an aggressive behavior.\(^10\) Indeed, immunohistochemical analysis of 137 cases of malignant salivary gland tumors show that, in contrast to the 3 most common subtypes (adenoid cystic, adenocarcinoma, and mucoepidermoid), SDC appears to strongly overexpress HER2 in more than 80% of tissue samples (10/12).\(^11\) The predictive value of these findings has been suggested in a phase II study of trastuzumab monotherapy in advanced HER2\(^{+}\) malignant salivary gland tumors, in which 2 patients with progressive SDC had stabilization of disease for 6.1 and 9.3 months, respectively.\(^1,12\)

We report a case of HER2\(^{+}\) metastatic submandibular SDC with a complete and durable clinical response to initial treatment with trastuzumab in combination with paclitaxel and carboplatin, followed by maintenance therapy with trastuzumab. Because of the low feasibility of conducting a prospective clinical trial in this particular histologic subtype, trastuzumab-based combination therapies should be considered for this rare tumor of the head and neck region.

REFERENCES


FIGURE 2. (A) Detection of pulmonary metastases and response to systemic treatment. A thoracic CT scan reveals multiple bilateral pulmonary metastatic lesions. (B) After treatment with trastuzumab-based combination therapy, a complete radiological response of all pulmonary lesions is observed.