
CASE REPORT

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RESPONSE TO PACLITAXEL IN ADENOID CYSTIC CARCINOMA OF THE SALIVARY GLANDS

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Abstract: *Background.* Paclitaxel is not considered to be an active drug in adenoid cystic carcinoma (ACC) of the salivary glands. We report 2 consecutive cases of patients with ACC who responded to paclitaxel.

Methods. The patients were: (1) a 58-year-old man with recurrent ACC who developed pulmonary metastases, had progressive disease after a good response to first-line chemotherapy, and then achieved a partial response to weekly single-agent paclitaxel; and (2) a 46-year-old woman with extensive thoracic ACC metastases who achieved a significant response after 2 cycles of paclitaxel chemotherapy.

Results. The first patient died of progressive disease approximately 4 months after completing paclitaxel therapy, and the second patient had disease control after 6 cycles of paclitaxel.

Conclusions. Systemic weekly paclitaxel produced a significant response in 2 patients with ACC of the head and neck, and its use in this disease merits further study. ©2007 Wiley Periodicals, Inc. *Head Neck* 30: 810–814, 2008

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Adenoid cystic carcinoma (ACC) of the head and neck is a malignant neoplasm arising from the mucus-secreting cells of the major and minor sali-

vary glands. It accounts for 5% to 10% of all neoplasms of the salivary glands, and most commonly (60% of cases) originates in the minor salivary glands, frequently in the oral cavity.¹ The natural history of the disease is often indolent, although in some cases the biology is more aggressive and the clinical course more rapid.

Even in cases of indolent ACC, there is an almost inevitable tendency to recur and progress relentlessly. These tumors are usually treated with aggressive surgical resection and adjuvant radiotherapy. Chemotherapy is typically reserved for metastatic disease and locoregional recurrences not amenable to further surgery or radiotherapy. Because of the relative rarity of this disease, there are limited clinical trial data to define the exact role of chemotherapy. A recent phase II clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG) in which patients with locally recurrent or metastatic salivary gland malignancies were treated with paclitaxel on a 21-day schedule suggested that ACC tumors are unresponsive to paclitaxel.² On the basis of this trial, paclitaxel is considered to be an inactive agent in ACC, although very little other literature exists assessing its efficacy in this disease.

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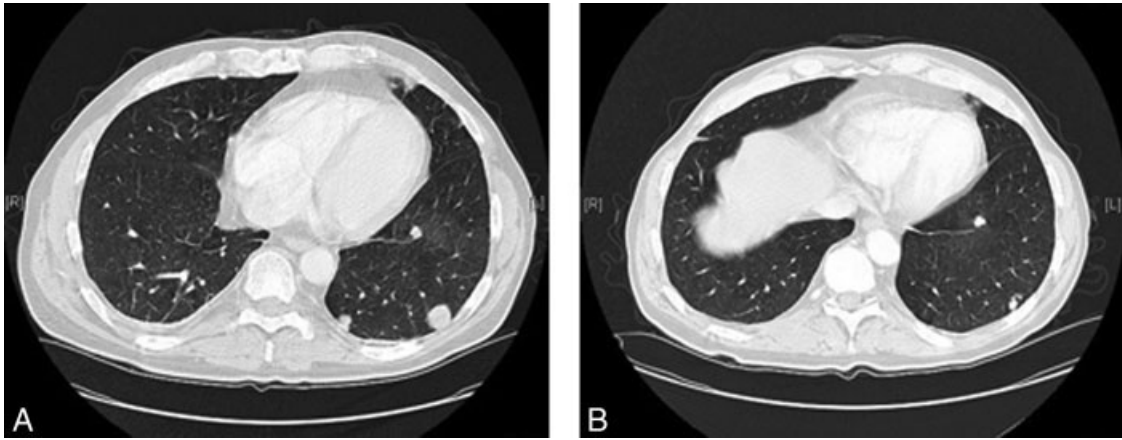


FIGURE 1. Case 1. (A) Pretreatment CT scan, with large pulmonary nodules. (B) CT scan after 2 cycles of paclitaxel therapy.

We present here 2 consecutive cases of advanced ACC that responded to weekly single-agent paclitaxel chemotherapy.

CASE REPORTS

Case 1. A 58-year-old man initially presented in 2002 at age 54 with several months of progressive difficulty chewing solid foods, as well as bleeding of the right hard palate. He was initially felt to have a periodontal abscess, but after a course of antibiotics failed to produce a response, he underwent a biopsy of the right anterior palate, and the pathological examination, performed at the University of Washington, revealed ACC with perineural invasion. A CT scan of the head and neck revealed a destructive mass within the right hard palate, extending into the right maxillary sinus antrum, with extensive destruction of the alveolar portion of the right maxillary bone. There was no crossing over the midline and no extension to the pterygopalatine fossa noted. Additionally, there was no evidence of cervical lymphadenopathy.

He underwent a right hemimaxillectomy, and pathology confirmed ACC, with perineural invasion and tumor present at the surgical margins. He subsequently received adjuvant neutron radiotherapy at a dose of 19.2 neutron Gray. Approximately 1 year later, he developed radiographic evidence of recurrence in the pteryoid plate region. He underwent a right posterior maxillectomy, and tumor was found to be extensively present at the margins. He had another local recurrence 2

months later, in the anterior maxillary region, involving the orbital rim and floor. He underwent further resection with a right maxillectomy, and tumor was again extensively present at the surgical margin. He received postoperative gamma knife radiotherapy at the end of 2003.

He remained free from progression until late 2004, when he was found to have extensive local recurrence in the right maxillary sinus region, as well as distant metastatic disease with multiple pulmonary and pleural nodules. He began palliative chemotherapy with cisplatin 80 mg/m² on day 1 and vinorelbine 25 mg/m² on days 1 and 8 of each 3-week cycle. He received 4 cycles, with a near-complete response in his lungs, as well as good radiological and symptomatic improvement in the maxillary region. In mid-2005, however, he developed aphasia and was found on MRI to have multiple hemorrhagic brain metastases.

He received whole-brain radiotherapy, with resolution of his neurological symptoms, and went on to have further gamma knife radiotherapy to the brain metastases. Restaging images of the chest were performed and revealed new pulmonary nodules. In August 2005 he began second-line palliative chemotherapy with paclitaxel (90 mg/m² on days 1, 8, and 15 of each 28-day cycle). After 2 cycles, he had a 50% reduction in the size of his pulmonary metastases (Figure 1). He received 2 further cycles but had progression of his pulmonary nodules at the end of the 4 cycles. He tolerated the therapy well overall.

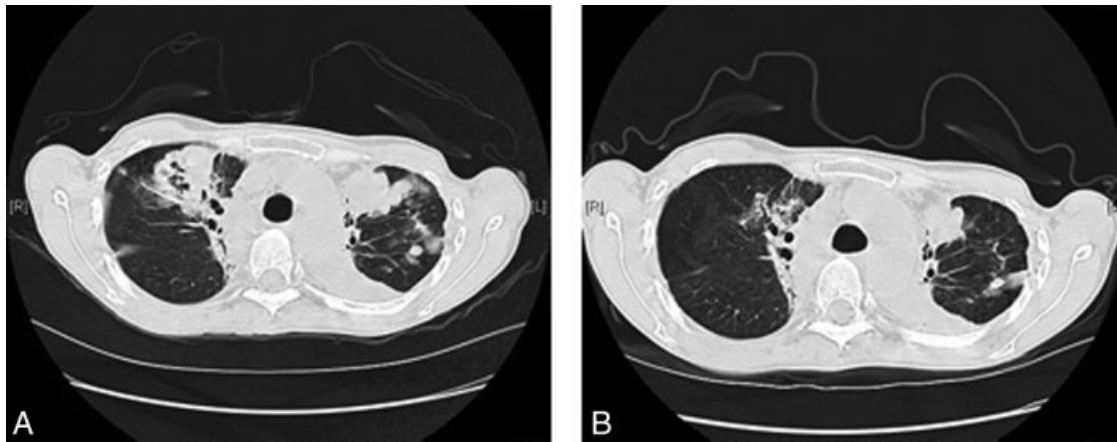


FIGURE 2. Case 2. (A) Pretreatment chest CT scan, with large bilateral lung lesions. (B) CT scan after 2 cycles of weekly paclitaxel therapy.

He did not respond to third and fourth lines of chemotherapy and died approximately 4 months after completion of the paclitaxel.

Case 2. A 46-year-old woman presented in 1989 at age 29 with a submandibular mass, which was biopsied, with the results described by the patient as benign (no report available). The mass grew slowly over several years, and in 1995 it began to enlarge rapidly. After a fine-needle aspiration revealed malignant cells, she underwent a resection of the left submandibular space and selective neck dissection through levels 2, 3, and 4. Pathologic examination at the University of Washington revealed ACC in 3 separate tumor nodules within the submandibular gland measuring 1.5, 1.0, and 1.0 cm respectively, with a predominantly solid growth pattern, a high nuclear grade, high mitotic rate, vascular invasion with tumor thrombosis, and perineural invasion. None of the 5 lymph nodes removed were involved. A CT scan of the head and neck did not show any lymphadenopathy. She received adjuvant neutron beam radiotherapy with a total tumor bed dose of 19.2 neutron Gray delivered by a 3-field submandibular field technique.

She did well until 5 years later, when she was found to have multiple pulmonary nodules on a chest X-ray. She underwent a thoracoscopic biopsy, which showed metastatic ACC. She underwent weekly therapy with single-agent vinorelbine, which initially resulted in a small response, but after 6 months there was evidence of disease progression. The patient elected an approach of expectant observation, and she was followed until late 2003, at which time she was found to have a

large ovoid left chest mass abutting the atrium and pulmonary veins as well as a possible atrial thrombus. She elected a nontraditional treatment based on organic juices, potassium, levothyroxine, liothyronine, niacin, pancreatin, acetyl pepsin, Lugol's solution, castor oil, and coffee enemas. During the first year of this therapy, she had slow progression of her pulmonary and mediastinal metastases with encasement of the left pulmonary veins and left lower lobe collapse. In late 2004, she also developed a pericardial effusion that resulted in tamponade, and she underwent pericardiocentesis and balloon pericardiotomy, which yielded bloody fluid without malignant cells seen on cytologic examination.

She was offered therapy with liposomal doxorubicin, but she declined this. She developed progressive dyspnea and was found to have complete collapse of her left lung. In mid-2005 she was referred for hospice care and underwent palliative neutron radiotherapy to the lungs, mediastinum, and chest wall at a dose of 15 neutron Gray. She had a good response radiologically and symptomatically and disenrolled from hospice care.

In June 2006, however, her dyspnea progressed, and the left lung cavity was found to be almost entirely occupied by tumor, with complete compression of the pulmonary veins. In August 2006, she began second-line palliative therapy with single-agent paclitaxel (90 mg/m² on days 1, 8, and 15 of each 28-day cycle). After 2 cycles, a restaging CT scan was performed, which showed a significant improvement in her bilateral lung lesions (Figure 2). She also had improvement of her shortness of breath and fatigue. She received an additional 4 cycles of paclitaxel and main-

tained disease control. She developed mild peripheral neuropathic pain of the right arm but otherwise tolerated therapy well.

DISCUSSION

The clinical course of ACC of the salivary glands is often indolent but typically progressive, characterized by local or distant recurrences as many as 10 years or more after initial definitive therapy. Although optimal treatment has not been established, the best results to date have involved surgical resection with adjuvant radiotherapy for localized disease. This approach often results in a significant period of disease-free survival,³ but the disease almost inevitably relapses, as illustrated by 5-year survival rates of 64% to 85% but 20-year rates of only 12.5%.^{3,4} Once patients develop unresectable local recurrences or distant metastases, the prognosis is generally very poor, although some patients live for more than 10 years with metastatic disease. Because a survival benefit has not been shown with systemic chemotherapy, it is usually reserved for symptomatic or rapidly progressive disease. Several small trials have demonstrated responses to platinum compounds and anthracyclines, alone or in combination.⁵

In a recent study by Nakashima et al, ACC cells in a xenograft model were found to exhibit upregulation of stathmin, an intracellular protein involved in the regulation of microtubule dynamics.⁶ The activity of this protein is modulated by phosphorylation in response to a number of different signaling pathways, and as such it is thought to play a key role in microtubule-dependent cellular processes. Its overexpression in ACC suggests that microtubule-dependent mechanisms may in part underlie the abnormal biology of the disease, thus providing a possible rationale for therapy with taxanes.

A limited amount of clinical trial data exists evaluating the activity of taxanes in ACC. In the largest study to date, patients with recurrent or metastatic salivary gland carcinomas were treated with paclitaxel at a dose of 200 mg/m² IV every 21 days for a minimum of 4 cycles as part of an ECOG phase II trial. Of the 50 patients treated, 14 had ACC, and none of them achieved an objective response. On the basis of this study, the authors of a review of systemic therapy in salivary gland cancers concluded that paclitaxel appears to be an inactive agent in ACC.⁵

However, another study evaluated the use of paclitaxel, in combination with carboplatin, on a

21-day schedule in 14 patients with recurrent salivary gland malignancies, 10 of whom had ACC, and 2 of these patients achieved partial responses (lasting 5 and 12 months).⁷ Another study, a small case series of patients undergoing definitive chemoradiotherapy for ACC, demonstrated locoregional control in 4 of the 5 patients at 3 years using carboplatin and paclitaxel.⁸ In a case report, a patient with recurrent ACC of the sublingual gland was treated with intraarterial cisplatin and docetaxel and concomitant external beam radiotherapy and achieved a complete response.⁹ Although these studies are small, and taxanes were used in combination with other therapies, it appears that these drugs may have activity in ACC. We present here 2 consecutive cases of patients with ACC who responded to single-agent paclitaxel, lending further support to the possibility that taxanes may have activity in some patients with ACC. These responses are particularly noteworthy in that they occurred in the second-line setting, where patients are less likely to respond than with initial chemotherapy.

It may be that paclitaxel is more effective given as a weekly dose than every 3 weeks, which is a possible explanation for the responses seen in our patients compared with the lack of response in the ECOG trial, although the sample sizes are not large enough to make meaningful comparisons.

CONCLUSION

We report 2 consecutive cases of patients with advanced ACC of the head and neck that achieved a significant clinical and radiologic response to weekly single-agent palliative paclitaxel. On this basis, we believe that weekly paclitaxel is an active agent in some cases of ACC and that its use warrants further study in this disease.

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