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CASE REPORT

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Salivary gland carcinoma treated with concomitant chemoradiation with intraarterial cisplatin and docetaxel

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Abstract Malignant neoplasms of the salivary gland are uncommon entities in which surgical resection of the primary lesion has been accepted as a standard therapeutic option. The efficacy of radiation and systemic chemotherapy has been limited for patients with recurrent, metastatic, or unresectable disease because of unfavorable response rates and the short duration of the response. We treated one patient with recurrent adenoid cystic carcinoma arising from the sublingual gland and one patient with primary adenocarcinoma arising from the parotid gland with transfemoral intraarterial chemotherapy, based on full-dose cisplatin and docetaxel and concurrent external-beam radiotherapy. The doses of cisplatin and docetaxel in the two patients were 80–100 mg/m^2 and 10–15 mg/m^2, respectively. Docetaxel was infused first, followed by cisplatin. Both patients obtained complete responses. Although complications such as mucositis, anorexia, neutropenia, and ischemic colitis were observed, they were well tolerated and manageable. The concomitant chemoradiotherapy of cisplatin and docetaxel seemed to be a practicable option for patients with recurrent and unresectable salivary gland carcinomas.

Key words Salivary gland carcinoma · Intraarterial chemoradiation · Cisplatin · Docetaxel

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Introduction

Primary malignant neoplasms of salivary gland origin are relatively uncommon, accounting for 10% to 15% of all salivary gland tumors.[1] These tumors arise from the parotid, submandibular, and sublingual glands and minor salivary glands, which are distributed throughout the upper aerodigestive tract. The most common histological types include adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma, followed by acinic cell carcinoma, salivary duct carcinoma, and carcinoma expleomorphic adenoma.[1,2] Their biological and clinical behaviors are extremely variable, depending on the histological subtype and grade, and the anatomic site. Locoregional recurrence and distant metastasis are the most common causes of treatment failure for most tumors.[3]

Standard treatment has been complete surgical excision and additional radiation therapy in selected patients with a positive surgical margin, local recurrence, or high-grade malignancy. Systemic chemotherapy, based on cisplatin or cisplatin in combination with other agents including doxorubicin, vinorelbine, and fluorouracil, has benefited certain patients with advanced disease caused by recurrent, metastatic, and unresectable tumors. However, the complete response (CR) rate with conventional systemic chemotherapy remains low, at less than 20%.[4–6] Recent reports have shown that intraarterial full-dose infusion of cisplatin with concurrent radiation therapy dramatically improves locoregional control in advanced head and neck squamous cell carcinomas, demonstrating a CR rate of over 80%.[7,8] However, the efficacy of intraarterial concomitant chemoradiation for salivary gland carcinoma has yet to be established. Here, we report two patients with primary parotid gland adenocarcinoma and recurrent adenoid cystic carcinoma of the sublingual gland who showed a marked response to concomitant chemoradiation, with the intraarterial infusion of cisplatin and docetaxel and sodium thiosulfate neutralization.[7,8]

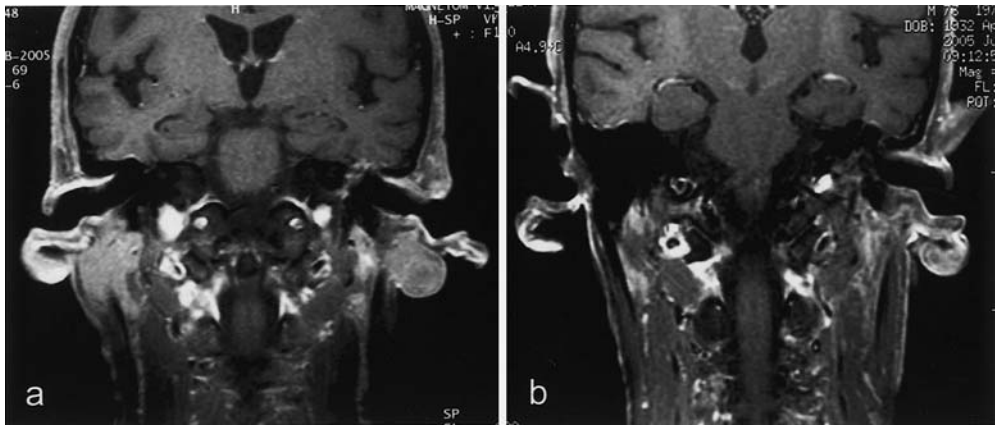

Fig. 1a,b. Magnetic resonance imaging (MRI) **a** before and **b** after treatment in case 1. T1-weighted image after treatment demonstrated a sclerotic change in the left auricle

Case reports

Case 1

A 72-year-old man was referred to our hospital with left parotid swelling of 3 months' duration. There was a hard mass with poor mobility without tenderness, approximately 35 mm in diameter in the left postauricular region. The skin around the mass was markedly congestive. Chronic otitis media with effusion was observed in the left middle ear. There were no mass lesions in the nasopharynx. He had a history of left facial palsy lasting for 4 years before the initial visit to our hospital. There was no remarkable family history and there were no abnormalities in laboratory data. Magnetic resonance imaging (MRI) disclosed an expansive mass with heterogeneous low signal intensity on T1- and T2-weighted images, and mild enhancement with gadolinium on a T1-weighted image (Fig. 1a). Cutting-needle biopsy, using a biopsy gun (Magnum; BARD, Tempe, AZ), was performed, revealing a histological diagnosis of adenocarcinoma (Fig. 2). Because imaging analyses indicated that the parotid lesion involved skin around the auricle with some invasion to the parapharyngeal space, complete resection was determined to be difficult and, consequently, intraarterial chemoradiation was selected for his treatment. Therefore, he was treated with external irradiation by a linear accelerator, using 4-megavolt photon beams with a wedged-pair technique (7.1 to 7.3 cm in width and 7.2 cm in length), and he received 60 Gy in 30 fractions in 7 weeks. Intraarterial infusion of cisplatin and docetaxel by transfemoral catheterization was performed a total of three times, at intervals of 7 to 10 days, during the time he received the external radiotherapy. Each intraarterial infusion was performed by the standard femoral artery approach under local anesthesia. The tip of a 4-Fr diagnostic catheter was positioned in the left external carotid artery, just proximal to the branching of the posterior auricular artery. The doses of cisplatin and docetaxel were 80 mg/m^2 and 10 mg/m^2 , respectively, for the initial two times, and the doses were increased to 100 mg/m^2 and 15 mg/m^2, respectively, for the last infusion, as there was a lack of severe toxic events with the two initial infusions. Cisplatin was infused at 5 mg/min after the infusion of docetaxel at 1.5 mg/min. An intravenous infusion of sodium thiosulfate (20 g) was commenced simultaneously with the cisplatin. On the day following the first infusion, he presented with abdominal pain and bloody diarrhea. Colonoscopy showed erosion and ischemic ulcer in the transverse colon. Biopsy revealed a diagnosis of ischemic colitis. He recovered well with supportive care and treatment with broadspectrum antibiotics by the time of the second intraarterial infusion. Grade III mucositis and anorexia (requiring total parenteral nutrition), and grade III neutropenia (requiring injection of granulocyte-colony-stimulating factor) were also observed during therapy. Magnetic resonance imaging (MRI) after completion of the therapy demonstrated sclerotic changes in the left postauricular subcutaneous tissue (Fig. 1b). Follow-up investigations over 8 months showed no regrowth or distant metastasis.

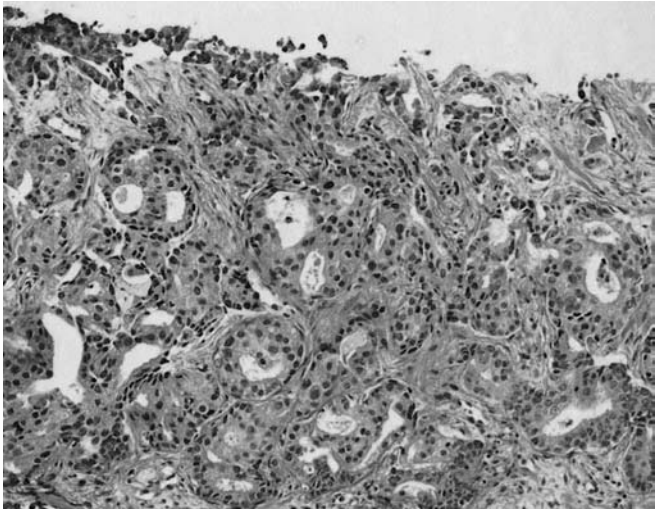

Fig. 2. Biopsy sample from case 1, illustrating tubular and cribriform structures composed of tumor cells with hyperchromatic nuclei and abundant cytoplasm. H&E, × 200

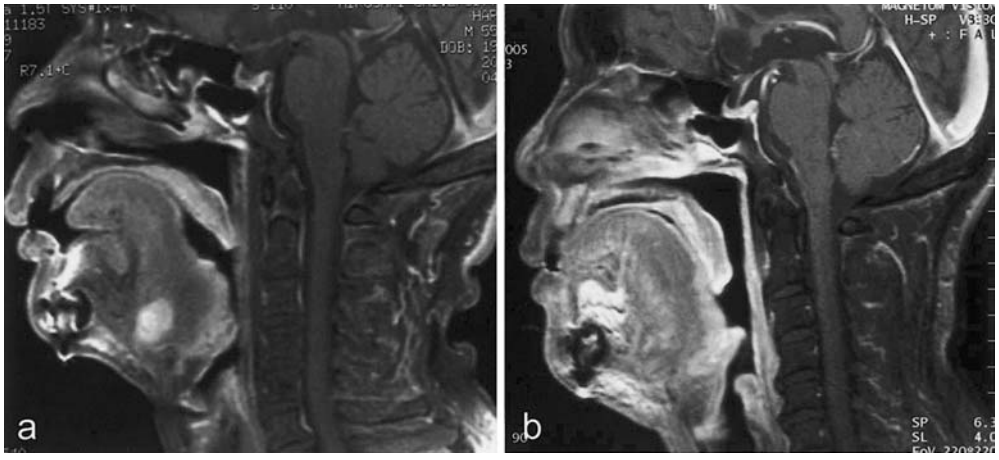

Fig. 3a,b. MRI **a** before and **b** after treatment in case 2. The recurrent tumor located behind the pedicled myocutaneous flap had vanished after external radiation and four courses of intraarterial chemotherapy

Case 2

A 51-year-old man was initially seen with the chief complaint of swelling of the right side of the oral floor, which had been gradually increasing for 6 months. He had no pain, facial nerve impairment, or lymph node enlargement. On palpation, there was a soft mass with good mobility, approximately 30 × 20 mm in size, in the submucosa of the right oral floor. MRI disclosed a relatively demarcated mass with heterogeneous high signal intensity in the right sublingual gland on a T2-weighted image. Cutting-needle biopsy, using a biopsy gun (BARD), revealed a histological diagnosis of adenoid cystic carcinoma. Systemic examination failed to detect any metastatic lesions, and extensive resection with neck dissection was performed. The defect of the oral cavity was reconstructed with a pedicled myocutaneous flap of the right greater pectoral muscle. An appropriate surgical margin was taken and no positive nodes were detected, although extensive perineural invasion was shown histologically. MRI 3 years after this initial treatment disclosed a well-demarcated mass, approximately 15 mm in diameter, with high signal intensity on a T2-weighted image, in the basal tongue (Fig. 3a). Because the lesion was diagnosed as a recurrent tumor and he wished to avoid the possibility of complications caused by total glossectomy, such as swallowing disorder and speech disorder, chemoradiotherapy was selected for the therapy. He was treated with external irradiation by a linear accelerator, using 4-megavolt photon beams with a three-field technique: lateral opposed fields for the primary tumor and upper neck (15 cm in width and 12.5 cm in length) and a matching anterior lower neck field (19 cm in width and 9 cm in length) with conventional fractionation (2 Gy/day, five times/week). After irradiation of 40 Gy, the fields were changed to avoid the spinal cord and he received a further 10 Gy. Finally, the primary site received a boost to 66 Gy with lateral opposed fields (7.1 cm in width and 5 cm in length). Concurrent intraarterial infusion of cisplatin and docetaxel by transfemoral catheterization was carried out a total of four times. Selective intraarterial infusion was performed with a coaxial catheter system. A microcatheter (Prowler Plus; Cordis, Miami Lakes, FL) was cannulated into the right lingual artery through a 4-Fr diagnostic catheter positioned in the right external carotid artery. Cisplatin was commenced at a dose of 80 mg/m^2 for the first infusion and was increased to 100 mg/m^2 from the second infusion. Docetaxel was infused at 15 mg/m^2 each time. Docetaxel was infused first, followed by cisplatin. The infusion velocity was identical to that in case 1. Simultaneously with cisplatin, sodium thiosulfate (20 g) was infused intravenously. His treatment was complicated by grade III anorexia, skin reaction, and mucositis (requiring total parenteral nutrition). The two initial infusions were carried out during the period of external radiation. Because a limited area with gadolinium enhancement was detected on MRI after the second infusion, two additional intraarterial infusions were consequently performed within 1 month after the external radiation treatment. The subsequent clinical course over 7 months has been uneventful without high signal area and gadolinium-enhancement on MRI (Fig. 3b).

Discussion

We have reported two patients with major salivary gland carcinoma treated with intraarterial chemoradiation of cisplatin and docetaxel. They responded very well despite their histological and clinical differences. There have been only a few reports about intraarterial chemotherapy in salivary gland carcinoma, although intraarterial full-dose cisplatin infusion with concurrent radiotherapy has been accepted as a powerful therapeutic option for patients with advanced head and neck squamous cell carcinoma, demonstrating an excellent CR rate.[7,8] It has been reported that the effect of intraarterial cisplatin infusion is limited when it is performed without concurrent radiotherapy in adenoid cystic carcinoma.[9] The present observations suggest that intraarterial concomitant chemoradiation therapy may dramatically improve the locoregional control of advanced salivary gland carcinoma.

Beacuse this treatment modality requires simultaneous intravenous infusion of sodium thiosulfate for systemic

cisplatin neutralization, nephrotoxicity is thought to be mild despite the high dose of cisplatin. Actually, there were no critical complications including renal toxicity in the present patients, although severe skin reaction and mucositis eventually impeded weekly intraarterial infusion in case 2. We also observed bloody diarrhea after the first infusion in our 72-year-old patient. He was diagnosed with ischemic colitis by colonoscopic examination. We could not clarify the apparent association between the drug infusion and the ischemic colitis. It has been reported that colitis was associated with docetaxel-based systemic chemotherapy in patients with metastatic breast cancer and some cases of colitis were critical.[10] In this context, although our patient recovered quickly with conservative treatment, consideration of the risk of ischemic colitis may be required when using docetaxel as an intraarterial agent, especially in aged patients with a higher risk of cardiovascular disorders.

It is well known that the combination of docetaxel with cisplatin will have enhanced clinical activity in various types of tumor, including head and neck squamous cell carcinoma.[11] Although the efficacy of docetaxel as a single or combination agent has not yet been established in salivary gland carcinoma, systemic combination therapy of paclitaxel and carboplatin manifests certain responses in recurrent and metastatic salivary gland carcinomas.[12,13] Our experiences also imply that docetaxel is potentially useful in combination with platinum agents. Previous investigations have indicated that taxoids such as docetaxel and paclitaxel exhibit a radiosensitising effect by stabilizing microtubules and accumulating cells to the radiosensitive phase of the cell cycle (G2/M).[14,15] This radiation susceptibility is, contradictorily, inhibited at low concentrations of docetaxel, implying that intraarterial docetaxel infusion directly inducing a high intratumoral concentration potentially confers augmented antisurvival activity in cancer cells. Biologically, docetaxel treatment followed by cisplatin demonstrates a synergistic effect on cell survival inhibition, with increased intracellular platinum accumulation compared to cisplatin followed by docetaxel, and docetaxel improves the multidrug resistance induced by single treatment with cisplatin.[16] In this context, docetaxel should be infused fisrt, followed by cisplatin. We commenced cisplatin at a lower dose (80 mg/m^2) than the established dose in single intraarterial usage (100–150 mg/m^2),[7,8] because of the possibility that a combination of these agents would amplify toxicity. However, we increased the dose of cisplatin to 100 mg/m^2 in both patients because of the lack of critical complications. Our findings here suggest that the current doses seemed to be associated with acceptable and manageable toxicity. The follow-up period was short in both of our present patients; therefore, further investigations are needed in order to evaluate the impact of the novel therapeutic approach used here on long-term prognosis in patients with salivary gland carcinoma.

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