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Case report

COMBINED SYSTEMIC TREATMENTS IN TWO PATIENTS WITH DUCTAL SALIVARY CARCINOMA

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Abstract

Ductal carcinomas, a variant of salivary gland cancer, are characterized by concurrent androgen receptor (AR) positivity and overexpression of HER2, making them potential targets for tailored therapies extensively explored in literature. We present two consecutive cases of patients diagnosed with inoperable metastatic ductal carcinoma, both displaying HER2 overexpression and AR positivity, who underwent combination therapy involving chemotherapy and dual targeted agents.

Both patients diagnosed with centralized inoperable ductal carcinoma were retrospectively analyzed and received trastuzumab, docetaxel, leuprolide and bicalutamida as first-line therapy until progression, defined by RECIST criteria. The first patient exhibited a partial response, with a 34% reduction in nodal metastases, remaining progression-free for 20 months. Despite rapid progression on initial treatment lines, the second patient achieved a partial response with a 35% reduction in metastases upon receiving third-line therapy, sustaining a progression-free interval. Importantly, both patients tolerated the treatment regimen well without severe acute toxicities. Although they responded favorably to the combined therapy, the addition of antiandrogen, anti-HER2, and chemotherapy did not appear to enhance efficacy. The use of combined target therapy seems to be effective in selected patients, but this indication requires further investigation through prospective studies.

Key words: salivary duct carcinoma, HER2, androgen receptor, targeted therapy, treatment sequencing

Resumen

Tratamientos sistémicos combinados en dos pacientes con carcinoma salivar ductal

Los carcinomas ductales son una variante histológica de cáncer de glándula salival que frecuentemente expresan el receptor androgénico a nivel nuclear y sobre expresan HER2 en inmunohistoquímica, mostrando sensibilidad a terapias dirigidas a estos blancos en múltiples series de casos. En este trabajo, se presentan 2 casos consecutivos de pacientes con estos marcadores, tratados con terapia combinada de quimioterapia y doble terapia dirigida.

Ambos pacientes con carcinoma ductal metastásico no operable, con sobreexpresión de HER2 y receptor androgénico positivo por inmunohistoquímica, recibieron como primera línea trastuzumab, docetaxel, leuprolide y bicalutamida hasta la progresión, los criterios progresión y respuesta fueron adecuados a RECIST 1.1. El primer paciente mostró una respuesta parcial, con una

reducción del 34% de las metástasis ganglionares, permaneciendo libre de progresión durante 20 meses. A pesar de la rápida progresión en las líneas de tratamiento iniciales, el segundo paciente logró una respuesta parcial con una reducción del 35% de las metástasis al recibir la terapia de tercera línea, manteniendo un intervalo libre de progresión. Es importante destacar que ambos toleraron bien el régimen de tratamiento sin toxicidades agudas graves.

A pesar de la respuesta observada en ambos pacientes, la combinación de dos o más agentes no aumentaría la efectividad del tratamiento dirigido solo monoterapia. La terapia con múltiples drogas dirigidas puede ser efectiva en pacientes muy seleccionados, pero se requiere mayor investigación para respaldar su indicación.

Palabras clave: carcinoma ductal salival, HER2, receptor de andrógenos, terapia dirigida, secuenciación del tratamiento

Salivary gland carcinomas represent a subset of head and neck malignancies, accounting for 5% of cases[1]. Their prognosis is multifactorial, influenced by histology, grade, and resection quality[2]. With over 20 histological subtypes characterized by distinct biological behaviors, understanding the features of each subtype is critical for effective management[3].

Salivary duct carcinoma (SDC) is a frequent variant of adenocarcinoma, characterized by its aggressive nature, shares morphological and molecular similarities with breast carcinomas[4]. Patients often present with advanced disease and exhibit overexpression of HER2 and AR nuclear expression, being AR the predominant biomarker in 85-95% of cases[5]. Expression of both HER2 and AR (HER^+/AR^+) is reported in a significant proportion of SDC cases, yet the precise biological implications remain elusive[6]. Treatment options for SDC include androgen deprivation therapy for AR expression and HER2-targeted therapy for HER2 overexpression, mirroring approaches used in breast cancer management[7].

The optimal treatment sequencing for dual HER2 and AR expression in SDC remains uncertain. While initial HER2 inhibition followed by androgen deprivation therapy shows promise, comprehensive utilization strategies are lacking in current literature. However, the use of trimodal therapy has not yet been described in the available literature.

In this study, we present two HER^+/AR^+ cases between the years 2012 and 2022 treated with combined target therapy. Our objective is to demonstrate the potential efficacy of dual-targeted therapy in improving treatment response rates and to provide insights into personalized treatment approaches for this challenging malignancy.

Biomarker determination followed the reporting templates outlined by the American College of Pathologists guidelines[8]. HER2 positivity was defined either by positive immunohistochemical interpretation or an immunohistochemistry score of 3+. Androgen receptor positivity was confirmed by positive immunohistochemistry, demonstrated through nuclear expression.

Patients received first-line treatment comprising a combination therapy regimen consisting of trastuzumab at a dose of 6 mg/kg, paclitaxel 175 mg/m^2, bicalutamide 50 mg/day, and leuprolide 7.5 mg administered every 28 days. At disease progression, patients continue under double blockade with abiraterone 1000 mg/day, leuprolide 7.5 mg, and trastuzumab 6 mg/kg in the second-line setting. Patient one continues the third line with TDM-1 3.6 mg/kg, abiraterone 1000 mg/day and leuprolide 7.5 mg. Additionally, all therapies were concomitantly administered with zoledronic acid 4 mg every 28 days.

TC scans were performed with Aquilion 64 Multislice Helical Tomograph (Toshiba, Otawara, Japan) at baseline and every 3-4 month. Non-ionic intravenous (ev) contrast medium was administered in the selected studies. RadiAnt DICOM Viewer software (64-bit) was used for image analysis and processing. Disease assessment evaluation will be determined locally according to RECIST v1.1 (Response Evaluation Criteria in solid Tumors) criteria defining progression free survival as the time from beginning of treatment to progression.

Clinical case 1

A 57-year-old male presented with a left latero-cervical tumor. Biopsy confirmed a diagnosis of poorly differentiated carcinoma. Imaging studies revealed cervical adenopathy, left supraclavicular cavity involvement, pulmonary metastases, and osteoblastic changes in first cervical vertebra. PET-CT findings indicated extensive meta-

static disease involving cervical and mediastinal lymph nodes, as well as pulmonary metastases.

Staging classified the disease as stage IV salivary gland cancer with metastases to the lungs. High-grade ductal carcinoma with positive nuclear expression of androgen receptor, GATA3, and HER2 overexpression was confirmed (Fig. 1). Initial treatment with paclitaxel, trastuzumab, bicalutamide, and leuprolide resulted in left cervical nodal and pulmonary disease progression after four cycles (Fig. 2A). Second-line therapy comprising abiraterone, leuprolide, and prednisone in combination with continued trastuzumab achieved pulmonary disease progression with worsening symptomatology after four cycles. Further treatment with TDM-1, abiraterone, and leuprolide achieved left cervical nodal partial response with symptomatic improvement after 4 cycles. Maintained stable disease with mild symptoms during the last follow-up, following completion of nine cycles of third-line therapy.

The patient's informed consent was obtained and has the approval from the ethics committee for its publication.

Clinical case 2

A 53-year-old male presented in December 2022 with a right cervical mass. PET-CT imaging revealed multiple bilateral latero-cervical lymphadenopathies. Directed laryngoscopy and subsequent biopsy confirmed salivary ductal carcinoma with positive expression of androgen receptor and HER2 (Fig. 1).

Staging identified metastatic involvement in the bones and lungs, categorizing the disease as stage IV. First-line treatment with paclitaxel, trastuzumab, bicalutamide, leuprolide. After six cycles the patient presented partial response in the left cervical and right axillary nodal metastasis (Fig. 2B). Subsequently, the patient underwent maintenance therapy with trastuzumab, leuprolide, and bicalutamide, completing a total of six cycles before experiencing progression of lymph node lesions after twenty months. Second-line treatment with TDM-1, abiraterone, and leuprolide resulted in stable disease after two cycles, with no significant acute toxicities observed.

The patient's informed consent was obtained and has the approval from the ethics committee for its publication.

Discussion

In this article we presented two patients with initial metastatic salivary gland ductal carcinoma HER2^{+}/AR^{+} selected for trimodal systemic treatment, which included anti-HER2 therapy, androgen deprivation therapy, and taxane-based chemotherapy. They demonstrated sensitivity to combined treatment at first line or advanced without major toxicity, suggesting that this approach could be considered for metastatic or relapsed cases.

While evidence specifically for trimodal treatment is lacking, existing data indicate favorable response rates with anti-HER2 therapy combined with chemotherapy compared to androgen deprivation therapy alone[9]. Studies have shown that the combination of anti-HER2 therapy with docetaxel yields higher response rates (71%)[10], compared to androgen deprivation therapy (13%)[11, 12]. Notably, continuing HER2

Figura 1 | Hematoxylin and eosin 40X microphotography showing the duct formation in salivary gland cancer, followed by positive immunohistochemistry staining for HER2 and AR receptors. For HER, the microphotograph was digitally magnified in order to clearly show the membrane staining of HER2 and the line in this case is 60 um

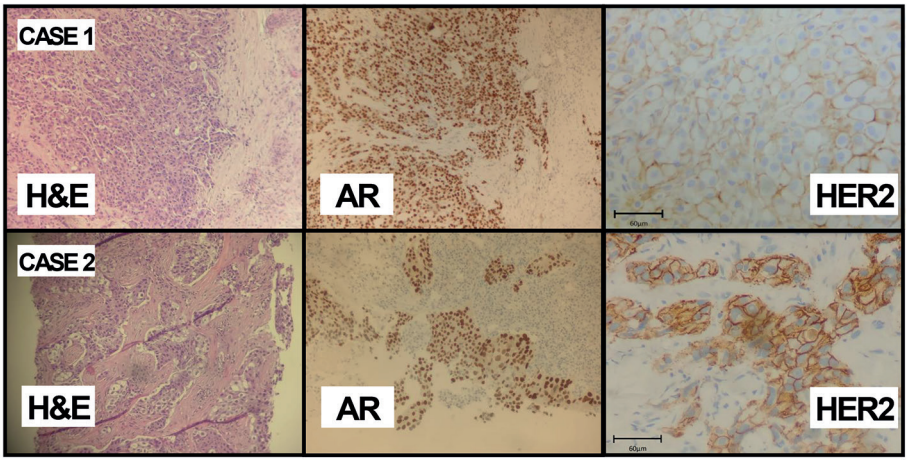
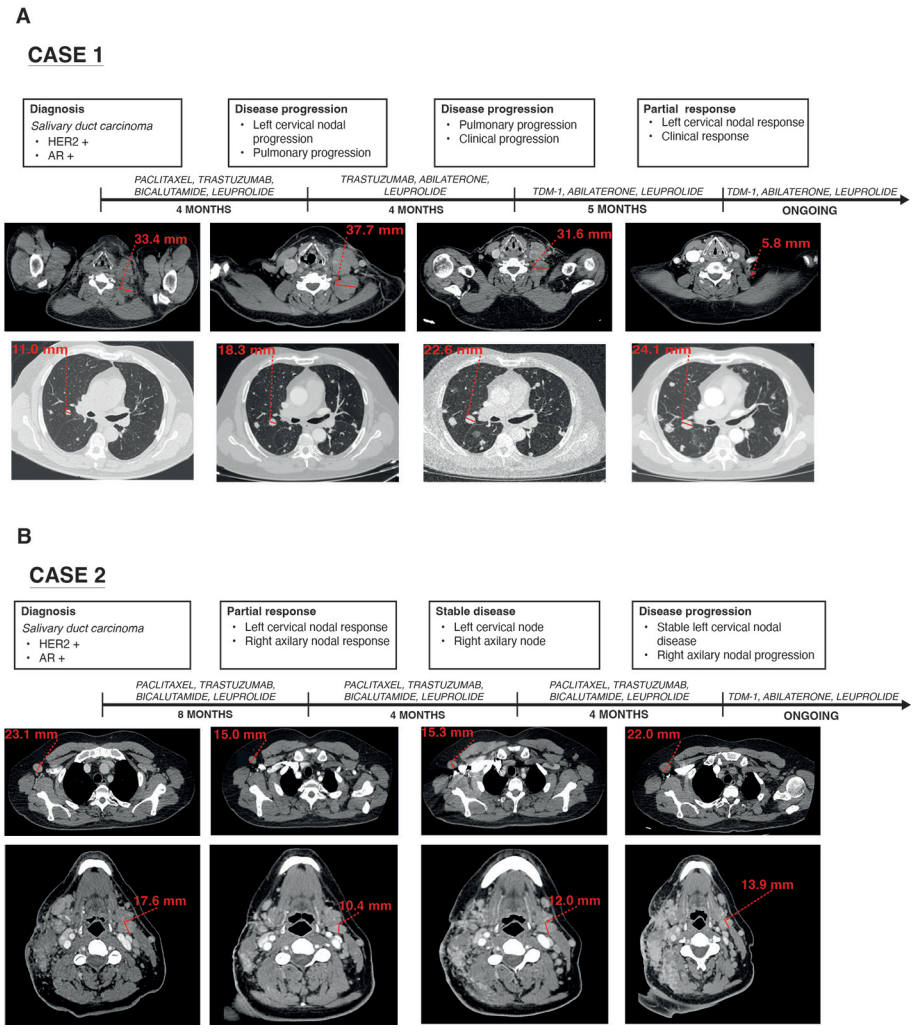


Figure 2 | A-B: Timeline for both cases illustrating responses to treatment in lung and nodal lesions



blockade in subsequent lines of therapy has demonstrated clinical benefit, with objective response rates and median PFS indicating its efficacy[13].

For patients exhibiting HER2⁺/AR⁺ profile, selecting the appropriate treatment modality presents a challenge for physicians, as both modalities have shown responses in ductal and adenocarcinomas NOS, albeit with no direct comparisons published to date. A recent large retrospective cohort study involving patients with both markers revealed a higher proportion of responses with anti-HER2 therapy as first-line treatment compared to androgen deprivation therapy[14]. Additionally, a previous study investigating trastuzumab-emtansine demonstrated activity in ductal patients previously treated with trastuzumab[13].

Although this study is limited by its design and small sample size, it is essential to acknowledge that the absence of a control group restricts definitive conclusions. The observed responses in the two patients cannot be attributed only to a synergistic effect between treatments; rather, they may be explained by the sensitivity to one of the drugs. Nonetheless, the results obtained with trimodal therapy underscore the importance of precise patient selection for this combination, emphasizing its potential benefits with tolerable side effects.

In patients with metastatic ductal carcinoma of the salivary gland, trimodal treatment represents a viable strategy, yielding responses in

the majority of patients with acceptable toxicity profiles. Further research is warranted to elucidate optimal treatment sequencing and refine therapeutic strategies for improved outcomes in this patient population.

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Conflict of interest: None to declare

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