The Journal of Laryngology & Otology (2009), ***123***, *250–252*.

doi:10.1017/S0022215108002314

Clinical Record

Biological therapy of salivary duct carcinoma

M Nashed, R J Casasola

Abstract

Background: The incidence of human epidermal growth factor receptor 2 positivity in salivary duct carcinoma ranges from 25 to 100 per cent and is associated with a poor outcome. Salivary duct carcinoma has significant pathological similarities to ductal carcinoma of the breast.

Methods and results: A 49-year-old man developed lung and liver metastasis a few months after surgery and adjuvant radiotherapy for salivary duct carcinoma of the parotid gland. There was no response to palliative chemotherapy with doxorubicin. We followed the biological model of breast cancer, whereby two-thirds of human epidermal growth factor receptor 2 positive patients respond to a combination of docetaxel and human epidermal growth factor receptor 2 blocker (trastuzumab). A durable, complete response was achieved with this combination. A rationalised treatment approach targeting the biological characteristics of salivary duct carcinoma had proven successful.

Key words: Salivary Duct; Carcinoma; Trastuzumab; Docetaxel; Her-2

Introduction

Salivary duct carcinoma is a rare tumour of the salivary glands and represents 1–3 per cent of all malignant salivary tumours.[1] Salivary duct carcinoma has significant pathological similarities to ductal carcinoma of the breast. Two-thirds of patients present with advanced disease, and there is a high risk of both local (48 per cent) and distant (48 per cent) recurrence. The five-year overall survival of stage I, II, III and IV disease is 42, 40, 30 and 23 per cent, respectively.[1] In view of the poor overall survival figures for this disease, a structured therapeutic approach should be developed to improve the outcome of this disease.

The human epidermal growth factor receptor (HER-2/neu) gene is involved in the control of cell growth and development.[2] Amplification of this gene leads to over-expression of the membrane protein, which can be detected using immunocytochemistry (ICC). Over-expressed human epidermal growth factor receptor 2 can be targeted by using a monoclonal antibody, trastuzumab.[3]

In salivary duct carcinoma, the incidence of human epidermal growth factor receptor 2 over-expression ranges from 25 to 100 per cent (Table I), and is associated with early development of distant metastasis and reduction of the five-year survival rate.[1–4] The wide range of human epidermal growth factor receptor 2 positivity in salivary duct carcinoma may be explained by the use of different staining techniques and antibodies. The discordance between levels of human epidermal growth factor receptor 2 positivity detected by and by fluorescent in situ hybridization (FISH) could in some cases be related to either of two factors. Firstly, an increased sensitivity of the antigen retrieval methods could be interpreted as a false positive ICC. Secondly, a false negative FISH might be encountered as an over-expression of a protein, and could be induced by either an increased transcription of its gene or through an inhibition of protein degradation.[4] Therefore, a negative human epidermal growth factor receptor 2 status by FISH analysis does not invalidate a strongly positive ICC.

Case report

A 49-year-old man presented with a three-month history of a swelling in the right parotid gland, which measured 10×15 cm. There was no cervical lymphadenopathy. The rest of the clinical examination was unremarkable.

The full blood count, electrolytes, and kidney and liver functions were all within normal ranges. Fine needle aspiration cytology confirmed the lesion's malignant nature. There was no evidence of metastatic disease on computed tomography scanning.

Therefore, the patient underwent total parotidectomy and a modified neck dissection.

Histopathological examination showed a 40 mm, poorly differentiated salivary duct carcinoma ex-pleomorphic adenoma. Extramural vascular invasion and involvement of the deep resection margin were detected. Fourteen out of 75 nodes were affected at levels two, three and five, with extra-capsular invasion demonstrated in 10 nodes. The cancer was strongly positive for human epidermal growth factor receptor 2 and negative for ICC by estrogen receptor (ER).

In view of the positive deep surgical margin and extra-capsular nodal spread, the patient received a course of post-operative adjuvant radiotherapy, with 50 Grays in 20 fractions to the right parotid and neck over 28 days.

Five months later, the patient developed neck recurrence and lung metastasis (Figure 1a). Therefore, he was treated with five cycles of palliative chemotherapy, with doxorubicin 75 mg/m^2 on a three-weekly basis. His disease progressed while receiving this chemotherapy, with development of

From the Oncology Department, Ninewells Hospital & Medical School, Dundee, Scotland, UK.
Accepted for publication: 8 February 2008. First published online 11 April 2008.

TABLE I

HER-2 STATUS (BY ICC AND FISH) IN SALIVARY DUCT CARCINOMA: PUBLISHED CASE SERIES

Study	Pts (*n*)	ICC (*n* (%))		FISH +ve (*n* (%))
		−ve	+ve	
Skalova *et al.*[4]	11	0 (0)	11 (100)	4 (36)
Dagrada *et al.*[5]	18	7 (39)	11 (61)	8 (73)
Jaehne *et al.*[1]	34	18 (53)	16 (47)	
Hellquist *et al.*[6]	9	0 (0)	9 (100)	
Etges *et al.*[7]	5	1 (20)	4 (80)	
Skalova *et al.*[8]	15	1 (7)	14 (93)	
Barnes *et al.*[9]	12	9 (75)	3 (25)	
Felix *et al.*[10]	30	11 (37)	19 (63)	
Total	134	47 (35)	87 (65)	

HER-2 = human epidermal growth factor receptor 2; ICC = immunocytochemistry; FISH = fluorescent in situ hybridization

liver metastasis (Figure 1c). In view of his tumour's human epidermal growth factor receptor 2 positivity, he was then treated with weekly trastuzumab 2 mg/kg, with an initial stabilisation of his disease. Unfortunately, after five months, the disease progressed in his neck, liver and lungs. Thereafter, he was treated with a combination of docetaxel (100 mg/m^2) and trastuzumab (6 mg/kg) on a three-weekly basis. After six cycles, complete resolution of the lung and liver metastases was achieved (Figure 1b and d), with minimal residual disease in the neck. There was no significant toxicity and the patient's performance status was maintained throughout the treatment period.

At the time of writing, the patient was still alive, 20 months after diagnosis of metastatic disease, and was receiving three-weekly trastuzumab.

Discussion

Docetaxel plus trastuzumab is an established combination for the treatment of advanced breast cancer.[11] This is based on a synergistic interaction between trastuzumab and taxanes.[12] Two-thirds of patients positive for human epidermal growth factor receptor 2 respond to a combination of docetaxel and human epidermal growth factor receptor 2 blocker.[13] Due to the pathological similarities between ductal carcinoma of the breast and salivary duct carcinoma,[1] the present case was treated with the same combination, achieving complete resolution of the metastatic disease.

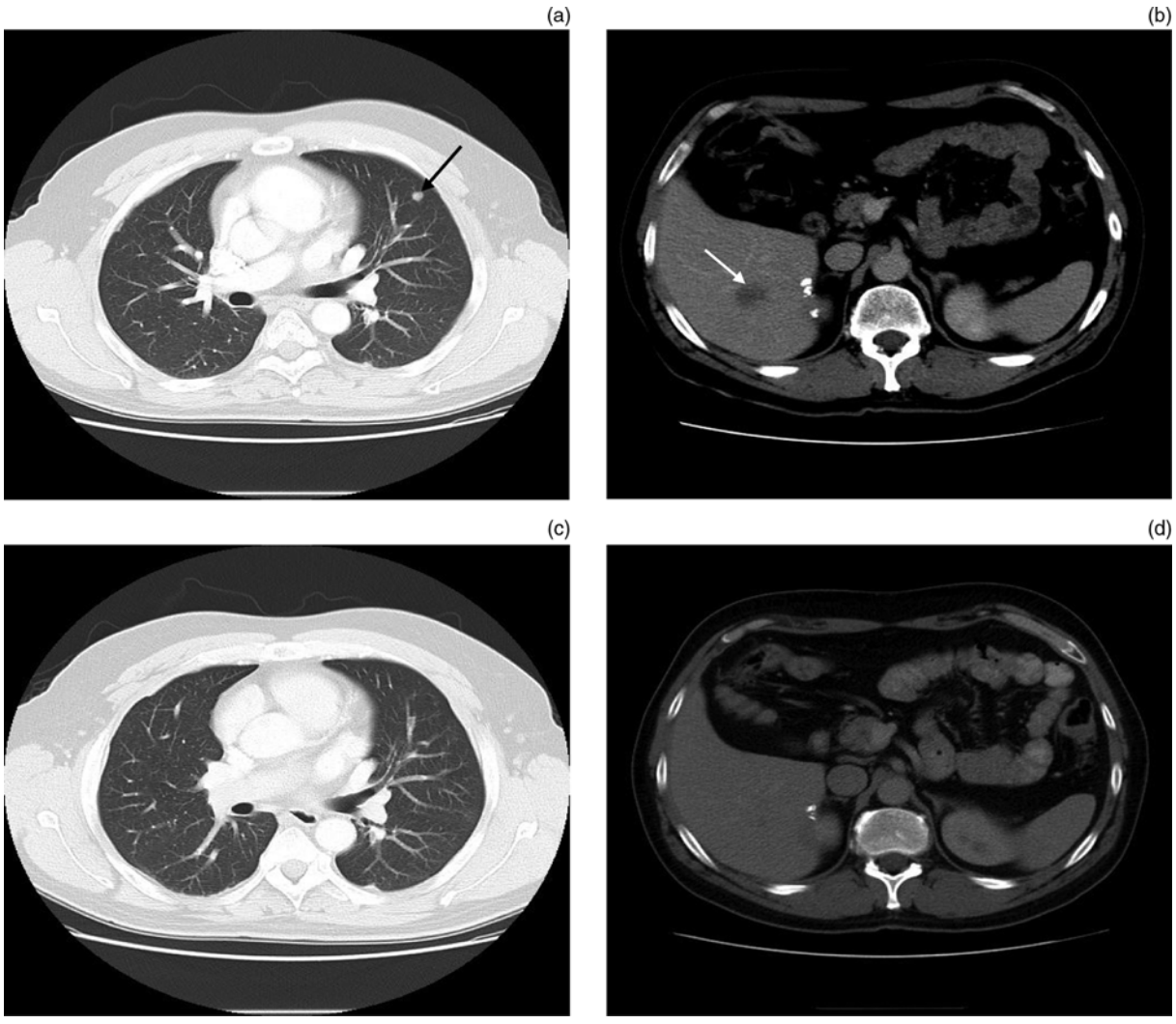

FIG. 1

Pre-treatment (a) and (b) and post-treatment (c) and (d) axial computed tomography scans. Arrows point to lung (a) and liver (b) metastases.

https://doi.org/10.1017/S0022215108002314 Published online by Cambridge University Press

- **The incidence of human epidermal growth factor receptor 2 positivity in salivary duct carcinoma is 25–100 per cent and is associated with a poor outcome**
- **Salivary duct carcinoma has significant pathological similarities to ductal carcinoma of the breast**
- **A 49-year-old man developed lung and liver metastasis a few months after surgery and adjuvant radiotherapy for salivary duct carcinoma of the parotid gland**
- **A durable, complete response was achieved with a combination of docetaxel and human epidermal growth factor receptor 2 blocker (trastuzumab)**
- **A rationalised treatment approach targeting the biological characteristics of salivary duct carcinoma proved successful**

Alternative and more effective therapeutic modalities should be explored for the treatment of salivary duct carcinoma, through targeting the biological characteristics of this aggressive type of cancer. To our knowledge, this is the first report of the use of human epidermal growth factor receptor 2 blocker in combination with docetaxel for the treatment of salivary duct carcinoma of the parotid gland. Based on the good outcome of the reported case, oncologists should be encouraged to explore such treatment for the management of this aggressive cancer.

References

1 Jaehne M, Roeser K, Jaekel T, Schepers JD, Albert N, Loning T. Clinical and immunohistologic typing of salivary duct carcinoma: a report of 50 cases. *Cancer* 2005;**103**: 2526–33
2 De Potter CR. The neu-oncogene: more than a prognostic indicator? *Hum Pathol* 1994;**25**:1264–8
3 Pegram MD, Lipton A, Hayes DF, Weber BL, Baselga JM, Tripathy D *et al*. Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. *J Clin Oncol* 1998;**16**:2659–71
4 Skalova A, Starek I, Vanecek T, Kucerova V, Plank L, Szepe P *et al*. Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry. *Histopathology* 2003;**42**:348–56
5 Dagrada GP, Negri T, Tamborini E, Pierotti MA, Pilotti S. Expression of HER-2/neu gene and protein in salivary duct carcinomas of parotid gland as revealed by fluorescence in-situ hybridization and immunohistochemistry. *Histopathology* 2004;**44**:301–2
6 Hellquist HB, Karlsson MG, Nilsson C. Salivary duct carcinoma – a highly aggressive salivary gland tumour with overexpression of c-erbB-2. *J Pathol* 1994;**172**:35–44
7 Etges A, Pinto DS Jr, Kowalski LP, Soares FA, Araujo VC. Salivary duct carcinoma: immunohistochemical profile of an aggressive salivary gland tumour. *J Clin Pathol* 2003; **56**:914–18
8 Skalova A, Starek I, Kucerova V, Szepe P, Plank L. Salivary duct carcinoma – a highly aggressive salivary gland tumor with HER-2/neu oncoprotein overexpression. *Pathol Res Pract* 2001;**197**:621–6
9 Barnes L, Rao U, Contis L, Krause J, Schwartz A, Scalamogna P. Salivary duct carcinoma. Part II. Immunohistochemical evaluation of 13 cases for estrogen and progesterone receptors, cathepsin D, and c-erbB-2 protein. *Oral Surg Oral Med Oral Pathol* 1994;**78**:74–80
10 Felix A, El-Naggar AK, Press MF, Ordonez NG, Fonseca I, Tucker SL *et al*. Prognostic significance of biomarkers (c-erbB-2, p53, proliferating cell nuclear antigen, and DNA content) in salivary duct carcinoma. *Hum Pathol* 1996;**27**:561–6
11 Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M *et al*. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005;**23**: 4265–74
12 Pegram MD, Konecny GE, O'Callaghan C, Beryt M, Pietras R, Slamon DJ. Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. *J Natl Cancer Inst* 2004;**96**:739–49
13 Sato N, Sano M, Tabei T, Asaga T, Ando J, Fujii H *et al*. Combination docetaxel and trastuzumab treatment for patients with HER-2-overexpressing metastatic breast cancer: a multicenter, phase-II study. *Breast Cancer* 2006; **13**:166–71

Address for correspondence:
Dr M Nashed,
Oncology Department,
Ninewells Hospital & Medical School,
Dundee DD1 9SY, Scotland, UK.

E-mail: m.nashed@nhs.net

Dr M Nashed takes responsibility for the integrity of the content of the paper.
Competing interests: None declared