Review Article

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Dentistry Section

Human Epidermal Growth Factor Receptor 2 (*HER2/neu*) in Salivary Gland Carcinomas: A Review of Literature

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ABSTRACT

The aim of our study is to assess the relation of human epidermal growth factor receptor 2 or *HER2/neu* with the development of salivary gland carcinomas and use of Herceptin in the treatment of these cancers. A literature search was conducted using MEDLINE accessed via the National Library of Medicine PubMed interface searching for articles from 1994 up to 2014 relating to the existence of *HER-2* protein and gene in salivary gland carcinomas and *HER2/neu* targeted therapy, written in English language. Almost all the studies in literature reported a frequent over expression and amplification of *HER2*/nue in salivary duct carcinomas (SDC) compared to other salivary gland cancers. Herceptin given as a monotherapy was not effective. The data on Herceptin combined chemotherapy are potentially promising but inadequate to evaluate drug activity, as patients also received a variety of cytotoxic agents. Therefore, Herceptin contribution to tumour response outcomes could not be precisely determined and the total number of cases is not sufficient. It is recommended that further work involves a large series of *HER2/neu* positive salivary gland cancers (randomized control trial) treated with chemotherapy with and without Herceptin. This might need multi-institutional cooperation.

Keywords: ErbB-2, Herceptin, Salivary gland neoplasm, Salivary duct carcinoma

INTRODUCTION

The majority of salivary gland tumours are benign in nature. While malignant salivary gland tumours account for up to 11% of all head and neck cancers, reporting for nearly 10,000 cases per year in United States [1]. Salivary gland carcinomas metastasize to distant organs in 20% of salivary gland malignancies [2]. These tumours recur despite combined medical therapy [3]. The recurrences can rarely be avoided even with a successful use of chemotherapy treatment [4-5]. Therefore, other effective treatment options are needed to prevent the recurrence of such cancers. Salivary gland cancers are histologically similar to certain types of breast cancers [6]. The use of anti-*HER2* therapy is currently approved in over expressing breast cancers [7]. The *HER2* proto-oncogene present on chromosome 17q, this gene encodes a membrane receptor protein, which is a member of the epidermal growth factor receptor family, and it is over expressed in variety of epithelial malignancies [8]. *HER2* has no ligand but is capable of heterodimerization with any of the other three HER proteins and can thus participate in effecting a signal transduction cascade with diverse the effect that potentiate the malignant phenotype [9]. For the last two decades, *HER-2/neu* in salivary gland neoplasms was poorly investigated. The aim of our study is to assess the relation of *HER2/neu* with the development of salivary gland carcinomas and applicability of Herceptin in the treatment of these cancers.

MATERIALS AND METHODS

A literature search conducted using MEDLINE accessed via the National Library of Medicine PubMed interface (http://www.ncbi.nlm.nih.gov/pubmed), searching for articles relating to the existence of *HER-2* protein and gene in salivary gland carcinomas and *HER2/neu* targeted therapy, written in English. We used the following search string (*HER2/neu* in salivary gland cancers) and we took all the articles using these keywords in their title. We also used the "Related Articles" feature of PubMed to identify further references of interest within the primary search (125 related articles). These references were obtained and from their bibliographies pertinent secondary results were also included. The process was repeated until no further new articles could be identified.

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No statistical analysis is presented as the collected data is different and the results cannot be compared. Further, no randomized controlled trials to assess the possibility of using the anti-*HER2/neu* therapy in the treatment of salivary gland cancers were found in the literature. Our search has identified only 39 studies available in written literature dating from 1994-2014.

Press et al., [10] reported that archival tissues resected from 58 patients with mucoepidermoid carcinoma of salivary glands were evaluated for *HER-2/neu* gene amplification by fluorescence in situ hybridization (FISH) and for gene expression by immunohistochemistry (IHC) in a blinded fashion. They followed-up and compared the information with the results of these analyses to determine whether there were significant associations. Over expression, identified as membrane immunostaining by IHC was observed in 22 of 58 (38%). MEC gene amplification was observed in 12 (21%) cases. Eleven of the 12 cases with gene amplification were also immunostained for *HER-2/neu*. Both gene amplification ($p = 0.0001$, $p < 0.0001$) and immunostaining ($p < 0.0001$, $p < 0.0001$) were correlated with shorter disease-free interval and poorer overall patient survival, respectively. Multivariate analysis showed that *HER-2/neu* immunostaining and amplification were markers of poor prognosis independent of histopathological grade, tumour size, and involvement of regional lymph nodes.

Giannoni et al., [11] have followed 71 patients with minor salivary gland tumours of the palate. A significant difference between *her2/nue* over expression in benign and malignant tumours was observed ($p=0.01$). Over expression of c-erbB-2/neu oncogene was noted in 38% (16 of 42) of malignant tumours and was significantly associated with aggressive tumour behaviour ($p < 0.001$). Only 1 out 18 is over expressed in benign tumours. Multivariate analysis of significant factors revealed that gender, tumour stage and c-erbB-2/neu oncogene over expression were jointly predictive of survival.

They investigated other markers and showed that only *HER-2/neu* over expression was significantly associated with their biologic aggression.

Shintani et al., [12] studied 16 cases of adenoid cystic carcinomas (ACC) using IHC and found that *HER2/neu* is over expressed in all cases. They mentioned that tubular and cribriform patterns over expressed a large amount of *HER-2/neu* protein and strong staining mainly observed in tumours cells of invasive area.

Skálová et al., [13] have evaluated 15 cases of SDC for *HER2/neu* over expression using IHC with Hercep-test. Over expression was observed in all cases but one case of salivary duct carcinoma (SDC) in most neoplastic cells. Suggesting that anti-*HER2/neu* therapy with Herceptin is beneficial for patients with aggressive SDC.

Jaehne et al., [14] reported a pilot-study consisting of four patients with different clinical courses. Patients were examined in regard to their histopathological features and *HER2* gene amplification. Three out of four patients died due to tumour at 2.4, 5.5, 8.2 y after initial diagnosis. The remaining patient died tumour-free six years after diagnosis. Two patients with an early recurrent and distant metastasis showed a high *HER2* expression compared with the rest. They concluded that a distinct correlation between *HER2* gene-amplification and clinical course could be observed and recommended further analysis.

Dori et al., [15] presented 32 samples of ACC. Only five (16%) cases were noticed with *HER-2/neu* over expression. Four cases scored 1+ and one case scored 2+.

Haddad et al., [16] have preformed a phase II study with Herceptin (Trastuzumab). Fourteen patients were enrolled having advanced, incurable salivary gland tumours with 2+ or 3+ *HER2/neu* expressions in their tumours. The study closed early when they realized that the majority of cases did not over express *HER2*-neu but they documented one partial response in a patient with metastatic MEC, concluding that single agent was not enough.

Nguyen et al., [17] reported 42 patients with mucoepidermoid carcinoma of major and minor salivary glands, they stated that positive *HER-2/neu* occurred in patients with high-grade MEC, whereas low-grade carcinomas was correlated with negative or weak staining. Concluding that over expression of *HER2/neu* may serve as prognostic marker in salivary gland MEC.

Etges et al., [18] reported five SDCs all showed *HER2/neu* over expression except for the one with a long term survival (10 years), therefore they concluded that *HER2/neu* overexpression was associated with poor prognosis. Aggressive behaviour, recurrence, metastatic potential seem to be associated with *HER-2* oncoprotein.

Glisson et al., [19] have screened 137 tumours with different histological subtypes for *HER2/neu* expression; the overall *HER2/neu* over expression was 17% (23 of 137), whereas it was only 8% in the three most common histological subtypes. It was distinctly rare in the most common subtypes ACC 4% (3 of 70) and it was very common in SDC 83% (10 of 12). This observation was consistent with the typical high-grade histological features and aggressive behaviour of this subtype. Further it was stated that tumours originating from excretory duct had a higher frequency of *HER2/neu* over expression (55%) than tumours from intercalated duct (7%) suggesting that trastuzumab will not have a major role in salivary gland cancers of intercalated duct origin.

Jaehne et al., [20] reported 50 cases of SDCs. 20.6% of the probes with positive *HER-2/neu* expression were (+++) positive and statistically linked (p=0.05) with early local disease recurrence, distant metastasis and survival rates.

Cornolti et al., [21] have studied 13 cases of SDCs all arising from the parotid gland. With IHC, 10 cases showed over expression (grade 3+) of *HER2/neu*protein, whereas 3 were negative for this protein (grade 0/1+). Using FISH amplification of *HER/2 neu* gene was found in 8 of the 10 grade 3+ cases, whereas none of the cases negative for the protein according to IHC had amplification of the gene. Demonstrating that *HER2/neu* protein is frequently over expressed in SDC and associated in most cases with *HER2/neu* gene amplification.

Johnson et al., [22] reported 12 previously diagnosed SDCs were evaluated by IHC and chromogenic in situ hybridization (CISH) to detect whether the protein expression is related to gene amplification. A total four cases were positive by IHC and CISH. The remaining eight cases were negative by IHC and no gene amplification with CISH. Suggesting that a role for Herceptin based therapy may exist in some SDC patient.

Vidal et al., [23] have analysed archival tumour specimens of 20 patients with ACC and 17 patients with (non-ACC), all treated with lapatinib. For ACC, no *HER2* amplification was detected while in non-ACC patients only 3 (18%) were *HER2* amplified and all had stained 3+ for *HER2* by IHC.

Locati et al., [24] have investigated 139 patients with primary, recurrent and/or metastatic salivary gland carcinomas by IHC of *HER2* protein. In 26 cases IHC was complemented by FISH. *HER2* expression, mostly sustained by gene amplification, correlated with SDC in 44% of cases and adenocarcinoma NOS in 21%.

Clauditz et al., [25] have constructed a tissue microarray from 994 carcinomas and 205 adenomas of salivary glands. Using FDA approved reagents for IHC and FISH to detect over expression and gene amplification. *HER2* was over expressed in 39 of 915 (4.26%) and amplified in 9 of 915 interpretable salivary gland carcinoma (0.98%). *HER2* over expression caused by gene amplification was observed in about 20% of patients with SDC while all other entities were mainly rare.

Kim et al., [26] have reported a case of carcinoma arising from warthin tumour in 79-year-old man. A left superficial parotidectomy showed a solid mass as infiltrative ducts with few foci of malignant transformation and *HER2* FISH showed a focal amplification. This was suggested as the first case of SDC arising from warthin tumour.

Ettl T et al., [27] regarding activity of the tumour-suppressor gene PTEN they have investigated 287 carcinomas of the major and minor salivary glands for deletion and loss of PTEN expression using FISH, IHC and the results were correlated to EGFR and *HER2*. Genomic deletion of PTEN, in particular Homogenous deletion ($p<0.001$) predominantly occurred in tumours with increased gene copy number of EGFR (60.0%) and / or amplification of *HER2* (63.0%). Loss of PTEN expression was frequently found in tumours over expressing EGFR (28.6%) and /or *HER2* (52.6%). Concluding that reduced PTEN function in different type of salivary gland carcinoma indicates unfavourable prognosis and it might affect targeted therapy.

Hashimoto et al., [28] have examined *HER2* over expression and *HER2* amplification by IHC and CISH in 31-carcinoma ex-pleomorphic adenoma (CXPA) with ductal differentiation. *HER2* amplification was more prevalent in extracapsular CXPA (9/18 cases; 50%) than intracapsular CXPA (1/5 cases; 20%), intraductal CXPA (2/8 cases; 25%) or atypical Pas (0/7 cases; 0%). Suggesting that *HER2* may play a critical role in the progression of CXPA, and *HER2* amplification may be an additional prognostic indicator of CXPA.

Ettl et al., [29] have evaluated protein gene status of *HER2* and other biomarkers by IHC and dual colour FISH in tissue microarrays of 286 carcinoma of the salivary glands. Amplification of *HER2* was found 35.5% of SDC. Overall, over expression and increased gene copy of *HER2* characterize high-grade malignancy and unfavourable prognosis.

Agulnik et al., [30] have screened 60 patients. They found 29 of 33 (88%) ACC and 28 of 29 (97%) nonACC patients expressed

EGFR and/or erbB2. Forty patients with progressive disease were enrolled onto the study. Among 19 assessable ACC patients, there were no objective responses, 15 patients (79%) had stable disease (SD), nine patients (47%) had SD > or = 6 months, and four patients (21%) had progressive disease (PD). For 17 assessable nonACC patients, there were no objective responses, eight patients (47%) had SD, four patients (24%) had SD > or = 6 months, and nine patients (53%) had PD. They suggest that efforts should be made to gain better understanding into the biology of this heterogeneous group of malignancies.

Prat et al., [31] reported a case of SDC with extensive cervical lymph node involvement. Patient underwent resection and radiotherapy. Multiple pulmonary metastatic lesions were detected after 6 months. A (CR) was reached with trastuzumab based combination therapy and no evidence of disease progression was observed after 14 months. They concluded that trastuzumab based combination therapies should be considered for advanced SDC.

Nashed et al., [32] reported a 49-year-old man with SDC that developed lung and liver metastasis a few months after surgery and adjuvant radiotherapy. There was no response to palliative chemotherapy with doxorubicin. They followed the biological model of breast cancer, were they used a combination of docetaxel and trastuzumab. A durable, complete response was achieved with this combination. Targeting the biological characteristics of salivary duct carcinoma had proven successful.

Sharon et al., [33] presented a patient with T1N2bM0 carcinoma ex pleomorphic adenoma underwent surgery and adjuvant radiation therapy. Multiple metastases to bone were documented later. IHC-test proved tumour was strongly *HER2/neu* positive, so the patient was treated with trastuzumab, capecitabine, and zoledronic acid. Total resolutions of symptoms were achieved and repeat FDG-PET scan interval disease resolution. This case demonstrates the successful long-term treatment of carcinoma ex pleomorphic adenoma (CXPA) with targeted therapy with trastuzumab in combination with chemotherapy.

Firewane et al., [34] reported a 61-year-old male with a history of salivary gland tumour who presented after 20 y of complete surgical resection with kidney mass. He was treated with primary surgical excision including nephrectomy and adjuvant clinical trial with placebo. CT-guided biopsy showed adenocarcinoma with *HER2/neu*, 3+ by IHC. The patient was treated successfully with trastuzumab with near-complete response.

Suzuki et al., [35] have evaluated (EGFR), phosphorylated EGFR (p-EGFR), *HER2*, and phosphorylated forms of Akt (p-Akt) and mammalian target of rapamycin (p-mTOR) in 47 salivary gland tumours using IHC. EGFR over expression was found in 51% of the tumours (24/47); in particular, EGFR (HER1) over expression occurred in mucoepidermoid (7 out of 7) and salivary duct carcinomas (9/12). Although EGFR amplification was not detected by FISH analysis, increased copy number due to polysomy of chromosome 7, which houses EGFR, was observed in 4 of the 24 tumours with EGFR over expression; this polysomy occurred most frequently in salivary duct carcinomas (3 out of 9). *HER2* over expression was observed in 21 % (10/47) of all tumours; in these 10 tumours, *HER2* gene amplification was found in seven cases. P-Akt was found in 51 % (24/47) of all tumours, most frequently in mucoepidermoid carcinomas (six out of seven). P-mTOR was found in 57 % of the latter (four out of seven). Finally, it concludes that phosphoprotein mapping of components in the EGFR/*HER2*–Akt–mTOR pathways may be a useful guide to select appropriate targeting regimens.

Limaye et al., [36] have reported 13 patients with SDC and *HER2/neu* expression by IHC of 1–3+ were treated with trastuzumab in adjuvant (n = 8) or palliative (n = 5) setting. All of cases underwent FISH testing for *HER2/neu* gene amplification. They propose that *HER2/neu* status be examined routinely in all patients with SDCs and the treatment be directed accordingly.

Kadowaki et al., [37] reported a metastatic CXPA with SDC component. Multiple pulmonary metastatic lesions were detected after surgery trastuzumab-based chemotherapy was initiated because it showed strong positivity for *HER2* protein and *HER2* gene amplification. Finally it has had a durable (CR). This report suggests a potential utility of trastuzumab-based chemotherapy for *HER2*-positive CXPA.

Perissinatti et al., [38] have recorded 13 patients with SDC over expressing *HER2* treated with trastuzumab as a single agent (n=3) with no objective responses and in combination with chemotherapy (n=10) three patients had partial responses with the duration of 3 to 6 months. Ten of these had 3+ IHC or *HER2* gene amplification by FISH. They found that radiographic review couldn't asses the efficiency of the treatment. Stating that trastuzumab should undergo prospective therapeutic clinical trials in SDC.

Golusinski et al., [39] reported Study group consisted of 51 patients with the salivary glands cancer. *HER2* expression was found in 10% of tumours. They conclude that *HER2* expression in malignant tumours of the salivary glands, especially in SDC may be of use in future implementation of new-targeted therapies based on monoclonal antibodies.

Otsuka et al., [40] performed statistical analysis and IHC examination of 16 patients with SDC. The three year disease-free survival (DFS) and cause –specific survival (CSS) rates were 29.2% and 72.7% respectively. They concluded that receptors could be suitable molecular targets of systemic therapy for patients with frequent expressions of *HER-2* SDC.

Agulnik and Siu et al., [41] made an update on systemic therapy regarding salivary gland carcinomas. They mentioned an association with *HER2* oncoprotein with biological aggressiveness and poor prognosis in most series.

Laurie SA and Licitra et al., [42] reviewed the literature in 2006 and reported that responsiveness to systemic therapy may vary among different subtypes. They found a paucity of high-quality data regarding the role of systemic therapies in palliative management of salivary gland carcinomas, and a need for high quality clinical trials in salivary gland carcinomas, responsiveness to systemic therapy may vary among different subtypes.

Lee et al., [43] tested two patients with salivary gland carcinomas, one had *HER2/neu* overexpression the other one was negative. The patient with *HER2/neu* overexpression had a worse prognosis. Trastuzumab was given in adjuvant sitting and proved to be an effective treatment. Concluding *Her2* overexpression is associated with a poor prognosis. And targeted therapy should be considered in adjuvant sittings.

Ettl et al., [44] studied 316 salivary gland carcinomas for predictors of cervical lymph nodes metastasis and correlated *her2* number of gene gain with metastasis to the cervical lymph nodes. Concluding that histological subtypes is crucial for decisions regarding neck dissection and new molecular may indicate elective therapy of the neck.

Falchook et al., [45] reported a resolution in a patient with SDC receiving a combination of trastuzumab, lapatinib and bevacizumab. The treatment was well tolerated except for grade 2 diarrhea and mucositis, which required lapatinib dose reduction. The response was achieved in spite of extensive previous therapy, which included trastuzumab and/or chemotherapy. Warranting further investigations of non-cytotoxic alternative treatment of *HER-2* SDC, particularly those not responsive to trastuzumab monotherapy.

Krishnamurthy J et al., [46] reported a 72-year-old male diagnosed with SDC after receiving Herceptin based chemotherapy the patient had a partial response and no signs of progression nine months

after therapy. This response was achieved in spite of prior extensive therapy; suggesting Herceptin based chemotherapy is a potential therapeutic option for treating SDC.

Nakano, et al., [47] evaluated MAML2 fusion status in 31 cases using reverse transcriptase-polymerase chain reaction, and *HER2* and EGFR status using IHC and CISH. Irrespective of MAML2 fusion status, all seven high-grade MEC had an increased gene copy number of either *HER2* or EGFR. They conclude that *HER2* or EGFR gene abnormality may play an important role in the development of high-grade MEC.

Cros J et al., [48] identified high level of *HER2* protein expression in salivary duct carcinoma. Recurrent mutation of oncogenes was found less than 1% of samples had *HER2* mutations.

DISCUSSION

Salivary gland carcinomas recur despite combined medical therapy [3]. Therefore, other effective treatment options are needed to prevent the recurrence of such cancers. Salivary gland cancers are histologically similar to certain types of breast cancers [6]. The use of anti-*HER2* therapy is currently approved in over expressing breast cancers [7]. This has caused an interest in studying anti-*her/2* in the treatment of salivary gland carcinomas. Our review has identified twelve studies that correlated the existence of *HER2/neu* and the clinical outcome of salivary gland carcinomas, 11 out 12 studies reported it association with poor prognosis and aggressive behaviour. Almost all the studies in literature reported a frequent over expression and amplification of *HER2*/nue in SDC compared to other salivary gland cancers. *HER2/neu* is mainly uncommon in other histological subtypes despite the wide range of reports, which could be explained by the differences in IHC methodology and scoring criteria; and issues with antigen retrieval, sample size, intrinsic biologic variability and type of antibody used. Regarding the clinical application of Herceptin in *HER2/neu* positive salivary gland carcinoma our search has identified 11 studies in literature; all of these studies were case reports and case series. 2 out of 11 studies used Herceptin as a monotherapy, Haddad et al., [16] used the Herceptin alone in phase II trials suggesting that Herceptin given as a single agent was not enough in treating salivary gland tumours overexpressing *HER2/neu*, Perissinotti et al., [38] also used Herceptin as a single agent and as combined chemotherapy in a series of cases (n=13) and reported no objective response in patients treated with Herceptin alone (n=3). This might be due to the multidisciplinary nature of cancer management. Falchook GS et al., [45] reported a patient responding to a unique non-cytotoxic combination of Herceptin, lapatinib and bevacizumab, Suggesting that it could be helpful particularly in those not responsive to Herceptin monotherapy. Nevertheless, this type of combination still needs further investigations. 9 out of 11 studies used Herceptin as combined chemotherapy; almost all of these studies reported a complete response to the combination. The data presented are potentially promising but inadequate to evaluate drug activity, as patients also received a variety of cytotoxic agents. Therefore, Herceptin contribution to tumour response outcomes could not be precisely determined and the total number of cases is not sufficient. The lack of strong evidence for the use of Herceptin as routine practice in the treatment of salivary gland carcinomas is due to limited clinical evidence available to date in the literature; This may be due to the rarity of such tumours. It is recommended that further work involves a large series of *HER2/neu* positive salivary gland cancers (randomized control trial) treated with chemotherapy with and without Herceptin. It might need a multi-institutional cooperation in order to do so.

CONCLUSION

HER2/neu over-expression is frequent in SDC and it is usually associated with poor prognosis and aggressive behaviour. Herceptin-based combined chemotherapy showed promising results in the literature but the role of Herceptin in the combination could not be quantified, as the patients in almost all trials received other cytotoxic agents. It is recommended that further work involves a large series of *HER2/neu* positive salivary gland cancers (randomized control trial) treated with chemotherapy with and without Herceptin.

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