REVIEW

Recent advances in the treatment of salivary gland cancers: Emphasis on molecular targeted therapy

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Summary Salivary gland cancers include tumors of different histologic characteristics and biological behavior. Radical surgery, followed or not by radiation therapy, represents the main treatment approach for this disease. The role of systemic chemotherapy is less clearly defined since trials of single-agent chemotherapy have consistently shown low response rates. Polychemotherapy is likely to induce a higher response rate, but does not improve survival. The determination of the molecular abnormalities underlying the different subtypes of salivary gland cancers might lead to more active targeted therapies. C-kit is overexpressed in a wide percentage of salivary gland carcinomas, but clinical trials with single-agent imatinib have been negative. ErbB1 and ErbB2 are also frequently overexpressed in salivary gland cancers and this has provided the rationale for clinical trials with trastuzumab, cetuximab, gefitinib, lapatinib. Finally, new pathways, such as vascular endothelial growth factor, might be worth targeting and clinical trials with anti-angiogenic agents are ongoing.

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Introduction

Malignant salivary gland neoplasms account for <0.5% of all malignancies and approximately 3–5% of all head and neck cancers. Tumors of the salivary glands may arise either from the major (parotid, submandibular, and sublingual) or from the minor glands (oral mucosa, palate, uvula, floor of mouth, posterior tongue, retromolar area, peritonsillar area, pharynx, larynx, and paranasal sinuses).1,2 Salivary gland carcinomas (SGCs) represent the most heterogeneous group of tumors of any tissue in the body,3 and the WHO classification has been recently updated, listing 24 different histologic subtypes, some of which are very rare.4 The main four histopathologic types are: (1) mucoepidermoid carcinoma (MEC) that represents 29–34% of malignant tumors; (2) adenoid cystic carcinoma (ACC) which accounts for approximately 20%; (3) adenocarcinoma which includes a few variants, namely: acinic cell carcinoma,
polymorphous low-grade adenocarcinoma, adenocarcinoma not otherwise specified (NOS), rare adenocarcinomas; (4) salivary duct carcinoma. In general, cancers of intercalated duct origin (ACC, adenocarcinoma) are low grade and biologically indolent compared with those derived from secretory duct (salivary duct cancer, MEC). Tumor grading of salivary carcinomas is correlated with myoepithelial elements, whose presence indicates low grade. A higher tumor grade appears to be correlated with a more aggressive behavior only in some histotypes, such as MEC and adenocarcinoma. Overall, clinical stage, particularly tumor size, may be the main prognostic parameter for salivary gland cancers and may be more important than histologic grade. However, the prognosis also depends on other factors. In fact, a number of studies have emphasized the importance of oncogenes in the initiation and/or progression of the development of salivary gland tumors. The mutation of oncogenes, and the overexpression of growth factors or growth factor-binding receptors, such as epidermal growth factor receptor (EGFR or ErbB1), ErbB2, vascular endothelial growth factor (VEGF), c-Kit have been identified as important factors in the genesis of salivary gland tumors. Kasamatsu et al. investigated candidate genes associated with salivary adenoid cystic carcinomas using combined comparative genomic hybridization and oligonucleotide microarray analyses. This study suggests that the combination of copy number and gene expression profiling provides an improved strategy for gene identification in salivary gland ACC. The determination of these markers should help in guiding new therapeutic strategies in patients with salivary gland tumors. Among histologic subtypes, ACC qualifies as an often indolent tumor, that invades diffusely and often metastasizes to the lung, although the growth rate is very slow. Spontaneous regression of histologically confirmed lung metastases from adenoid cystic carcinoma has been anecdotally reported. Moreover, a retrospective analysis of 94 cases of ACC evaluated the correlation between the site of distant metastasis and its impact on outcomes. Median survival times among patients with isolated lung metastases and patients with bone metastases with or without lung involvement were 54 and 21 months, respectively (p = .04). This observation suggests that patients with bone involvement with or without lung metastases may have worse outcomes than patients with lung metastases alone. A possible explanation of these results could lie in the modulation of the expression of genes critical to the metastatic process in different anatomic sites.

Salivary gland carcinomas are managed primarily with surgical resection and, if indicated by pathological findings, adjuvant radiation. Systemic therapy is generally reserved for locoregional recurrence and/or metastatic disease. Both single agent and combination chemotherapy have been used, with response rate of 15–50%. Given the rarity of these tumors and the variability in natural history of metastatic disease, it has been difficult to define the survival benefits of cytotoxic agents. Therefore, there is a need to better understand the biology of these cancers and to develop therapeutic approaches based on relevant targets. With the emergence of molecular targeted therapy, these tumors have become excellent candidates for trials of investigational drugs.

In this paper we want to discuss the main concepts about all the aspects of the management of salivary gland cancers, with particular emphasis on recent advances in the medical approach.

Surgery

Surgery represents the mainstay of the treatment of salivary gland malignancies. The aim of surgical procedures should be the complete excision of tumor with an adequate margin, (i.e.: 0.5–1 cm according to histology and site). Such parameters can be easily achieved in case of minor, or submandibular, or sublingual salivary glands, even though in many cases flaps are required to repair the defect. In case of involvement of the parotid gland there are some controversies due to the management of the facial nerve which should be preserved unless in case of preoperative facial palsy, and/or either skin infiltration or intraoperative evidence of nerve involvement.

The management of the neck plays an important role in the surgical treatment of salivary gland neoplasms. A neck dissection should be always planned in case of preoperative evidence of lymph node involvement; in patients without nodal involvement, a prophylactic neck dissection can be set up in case of >4 cm tumors, high-grade malignancies, preoperative facial palsy and skin infiltration.

Radiotherapy

Post-operative radiation therapy may improve local control and increase survival rates for patients with high-grade tumors, positive surgical margins, or perineural invasion. Fast neutron-beam radiation or accelerated hyperfractionated photon beam schedules have been reported to be more effective than conventional X-ray therapy in the treatment of unresectable, or recurrent malignant salivary gland tumors. The Dutch Head and Neck Oncology Cooperative Group has evaluated the role of post-operative radiation therapy in patients surgically treated for salivary gland cancer. In this study, post-operative radiotherapy significantly improved 10-year local control compared with surgery alone in T3-4 tumors (84% vs. 18%), in patients with close (95% vs. 55%) and incomplete resection (82% vs. 44%), in patients with bone invasion (86% vs. 54%), and perineural invasion (88% vs. 60%). Local control was not correlated with the interval between surgery and radiotherapy. No dose-response relationship was shown. Post-operative radiotherapy significantly improved regional control in patients with pathologic neck nodal involvement (pN+) (86% vs. 62% for surgery alone). These findings show that post-operative radiotherapy with a dose of at least 60 Gy is indicated in patients with invasion, and lymph nodes involvement.

Chemotherapy

The role of chemotherapy in the management of salivary gland cancers remains uncertain. Chemotherapeutic agents, such as doxorubicin, paclitaxel, 5-fluorouracil clearly have some degree of activity in this disease, but responses are generally in the range of 15–50%, and of short duration. The activity profile of most of the drugs does not change...
across histologic subtypes. One exception is possibly represented by pacitaxel, which is believed to be more active in MEC than in other histologies.\textsuperscript{22} While anthracyclines are often recommended as active agents in ACC, little data exist for these drugs.\textsuperscript{23} Cisplatin shows a moderate activity with 20\% response rate in the locoregional treatment of SGCs, compared to a 7\% response rate in metastatic disease. Moderate activity was seen with single agent mitoxantrone and vinorelbine with responses ranging between 10\% and 15\%. The combination of cisplatin, doxorubicin, and cyclophosphamide has provided an overall response rate of 27\%. In a small randomized phase II trial comparing cisplatin-vinorelbine with vinorelbine alone, more responses were reported with the combination, but the difference was not significant. These data seem to support the idea that combination therapy may lead to higher response rates, but is not clearly superior to single-agent therapy with regards to survival. More recently, docetaxel has been evaluated in vitro in salivary cancer cell lines\textsuperscript{24} and a pro-apoptotic effect, partly mediated by the Fas-pathway, has been demonstrated. These results have paved the way to clinical trials with docetaxel in patients with salivary cancers. Two complete responses and two partial responses, with duration ranging between 18 and 27 months, were reported in a series of four chemo-naïve patients with locally recurrent high-grade salivary gland cancers treated with docetaxel alone.\textsuperscript{25} Estrogen-receptor positivity is not frequent at all in salivary gland tumors. However, a response to tamoxifen has been reported. Expression of androgen receptors has been described and responses to anti-androgen therapy by androgen-receptor positive adenocarcinoma of the salivary gland and salivary duct carcinoma have been reported.\textsuperscript{26} There are some ongoing phase II clinical trials, that are evaluating new combinations of agents, such as capecitabine plus oxaliplatin, and cisplatin or carboplatin in combination with gemcitabine, in patients with locally advanced, recurrent, or metastatic malignant salivary gland cancers; the results of these studies are awaited.

**Biologic drugs interference with Kit, ErbB2, EGFR, VEGF- pathways**

**Kit-pathway**

C-kit expression appears as a common feature in salivary gland cancers as it is expressed in approximately 80\% of adenoid cystic carcinoma.\textsuperscript{27} Kit overexpression is likely to be implicated in the pathogenesis of these carcinomas, although genetic mutation which is seen in gastrointestinal stromal tumors (GIST) is not the mechanism of kit activation. Jeng et al. identified kit expression in ACC (20 cases of 25) and myoepithelial tumors (2 cases of 2).\textsuperscript{27} Similarly, in another series of 30 ACC patients, kit expression was demonstrated in 90\% of the archival tumor specimens but, again, no mutations were identified.\textsuperscript{28} The tyrosine kinase inhibitor imatinib, which selectively suppress the activity of Abelson (ABL), platelet-derived growth factor receptor (PDGFR) and KIT\textsuperscript{29,30} has been clinically evaluated also in salivary gland cancers. In a phase II clinical trial, 16 patients with unresectable or metastatic ACC were treated with imatinib 400 mg orally bid.\textsuperscript{31} Half of the patients had mild to moderate toxicities, such as nausea, fatigue, edema, diarrhea, headache, dyspnea. No objective responses were observed in 15 evaluable patients; stable disease was observed in 9 patients, whereas 6 patients had progressive disease after two cycles. Despite the high prevalence of kit expression in ACC, the study was clearly negative, probably due to the lack of kit genetic alteration. In fact, patients with GIST responded to imatinib when the tumors had specific activating mutations of kit.\textsuperscript{32} Conversely, a multicenter phase II trial in patients with recurrent or metastatic adenoid cystic carcinomas strongly overexpressing Kit is ongoing. Among six assessable patients, who were treated with imatinib 400 mg bid, three patients had stable disease after 3 months of treatment; one patient, who was resistant to cisplatin–5-fluorouracil combination, had a 42\% tumor reduction.\textsuperscript{33} However, response to imatinib in GIST patients is known to sometimes occur only after several months of treatment and prolonged tumor stabilization can be looked at as a satisfactory outcome.

In vivo studies also evaluated the synergistic effect of imatinib in combination with chemotherapeutic drugs, such as cisplatin. Head and neck cancer cell lines were demonstrated to have a response ranging from additive to synergistic when imatinib and cisplatin were combined.\textsuperscript{34} On the basis of these preclinical data, a phase II clinical trial combining the two drugs has been conducted. Eighteen patients with advanced ACC received imatinib alone at an initial dose of 800 mg daily for 2 months and then cisplatin at the dose of 80 mg/m² every month. Of 17 evaluable patients, two developed progressive disease on imatinib alone and were taken off study. Three patients showed a partial response with imatinib plus cisplatin, and one of these remained on imatinib for 27 months. Twelve patients had stable disease.\textsuperscript{35}

**EGFR/ ErbB2 pathway**

The ErbB family of transmembrane tyrosine kinase receptors consists of four members: ErbB1, ErbB2, ErbB3, and ErbB4.\textsuperscript{36,37} Expression of ErbB1 and/or overexpression of ErbB2 occur to varying degrees in epithelial malignancies, where they promote tumor cell growth/survival, and in certain tumors predict for a poor clinical outcome.\textsuperscript{38,39} Upon ligand binding, ErbB receptors form hetero- or homodimers resulting in the autophosphorylation of specific tyrosine residues within the conserved catalytic kinase domains of ErbB receptors. ErbB2, the only member of the ErbB family without an exogenous ligand, is the preferred heterodimer partner for other ErbB receptors where it amplifies the biologic signal. Since ErbB2-containing heterodimers exert potent growth and survival effects, simultaneous inhibition of ErbB2 and ErbB1 is an appealing therapeutic strategy.\textsuperscript{40}

**Trastuzumab**

ErbB2 expression in salivary gland tumors seems to be of varying importance.\textsuperscript{6,41,42} Kamio et al. reported ErbB2 overexpression together with an elevated proliferation rate to be associated with unfavourable clinical course in salivary gland tumors.\textsuperscript{43} This was observed also in nine tumor specimens examined in another study.\textsuperscript{44} In other reports, fre-
quency of ErbB2 expression in salivary gland tumors, which was detected by either immunostaining or fluorescence in situ hybridization, has been variable. Rates of 7–56% in adenoid cystic, 30–38% in mucoepidermoid, and 23% in terminal ductal adenocarcinoma subtypes have been documented. In two reports, overexpression and/or amplification of ErbB2 was an independent marker of poor prognosis in mucoepidermoid and adenoid cystic carcinomas. A retrospective analysis of 50 cases demonstrated that the intensity of ErbB2 expression correlated significantly with the clinical course of patients. Finally, a large analysis of 137 salivary tumors demonstrated that the overall frequency of overexpression for ErbB2 was 17% (23 of 137), whereas it was only 8% in the three most common histological subtypes. In particular, the overexpression was distinctly rare in adenoid cystic carcinoma (4%). Instead, 10 of 12 salivary duct cancers (83%) were positive for ErbB2. This observation is consistent with the typical high-grade histological features and aggressive behavior of this subtype as well as with histogenic similarity to breast cancer.

Taken together these data provided the rationale for the use of trastuzumab, a recombinant monoclonal antibody directed against ErbB2 that enhanced the response rate to cytotoxic agents in ErbB2–positive breast cancer, in patients with incurable salivary gland cancer. In a phase II clinical trial, 14 patients with salivary gland cancers that overexpressed ErbB2 received weekly trastuzumab therapy. One of three patients with mucoepidermoid cancer had a partial response that is ongoing after 45 months, whereas two additional patients with salivary duct cancer had stable disease lasting 24 and 40 weeks, respectively.

**Gefitinib**

A majority of ACC have a high expression level of ErbB1 and ErbB1-targeted therapy may hold promise in the treatment of this disease. Twenty-nine patients (19 of whom with ACC) with incurable salivary gland cancer were accrued in a phase II trial of gefitinib, an orally active ErbB1-inhibitor given at the dose of 250 mg daily. Toxicity was mild to moderate. In particular, grade 1–2 rash was observed in 76% of patients and grade one diarrhea in 79%. Among 24 evaluable patients, 13 had stable disease and 11 progressed after 2 months of treatment. Gefitinib was associated with a 53% stable disease rate (10/19) in ACC, which was maintained for ≥16 weeks in 26% (5/19) of the patients in this cohort.

**Cetuximab**

Cetuximab (Erbitux, C225), a human-murine chimeric monoclonal antibody to ErbB1, has been tested in a phase II study in 30 patients with recurrent and/or metastatic salivary gland tumors (23 ACC, 2 mucoepidermoid, 3 myoepithelial, 1 cystoadenocarcinoma and 1 acinic cell carcinoma). Among 22 patients evaluable for response after at least 3 months of treatment, 11 patients had stable disease, nine had progressive disease, while two patients refused to continue after 1 month.

**Lapatinib**

Lapatinib (GW572016) is an orally active small molecule that reversibly inhibits ErbB1 and ErbB2 tyrosine kinases. Recently, a phase II study was conducted in 34 patients with progressive, recurrent or metastatic adenoid cystic cancer expressing ErbB1 and/or ErbB2, who were treated with lapatinib 1500 mg daily. The most frequent adverse events were diarrhea (54%), pain (52%), fatigue (52%), lymphopenia (39%), anemia (34%), hyperglycemia (38%) and dyspnea (34%). Among 14 ACC patients evaluable for response, nine had stable disease, three had progressive disease and two died prior to cycle 2. These data show that lapatinib is well tolerated, with tumor stabilization achieved by 64% of patients.

**VEGF-pathway**

VEGF, which is a key regulator of tumor-induced endothelial cell proliferation and vascular permeability, is frequently upregulated in human cancers. Lim et al. evaluated the prognostic value of VEGF in a series of 45 patients with salivary gland carcinoma. Univariate analysis showed that age, lymph node metastasis, vascular invasion, p53, Ki-67 and VEGF expression correlated with prognosis. Multivariate analysis demonstrated that VEGF was an independent prognostic factor for patients with salivary gland carcinomas and this points to the need of clinical studies with antiangiogenic agents in the treatment of advanced salivary gland carcinomas.

**Targeting the proteasome-bortezomib**

Bortezomib (PS-341, Velcade) is a selective inhibitor of the 26S proteasome which is involved in the ubiquitin-proteasome degradation pathway. Bortezomib-induced inhibition of NF-κB activity may be important for inhibition of the growth of ACC. In a recent clinical study, 25 patients with incurable ACC were enrolled and treated with bortezomib at the dose of 1.3 mg/m² on days 1, 4, 8 and 11, every 21 days, until progression. Doxorubicin at the dose of 20 mg/m² on days 1 and 8 was added at the time of progression. After treatment with bortezomib alone, 16 patients (64%) had stable disease, seven progressed and two were not evaluable. The median progression-free survival was 8.5 months. In four evaluable patients who received bortezomib plus doxorubicin, one partial response and two stable diseases were observed, while one patient died 7 months after starting treatment without documented disease progression. Bortezomib was well tolerated and resulted in disease stabilization in a high percentage of patients when given alone, although no objective responses were recorded.

**Conclusion**

Salivary gland cancers represent a fairly heterogeneous group of tumors with frequently different biologic behaviors. However, most of the more frequently observed subtypes are generally indolent and oligosymptomatic also after recurrence and in presence of metastases, thus justifying a "watch and wait policy" to be carried out until clear evidence of disease progression. Given the lack of large studies and of strict clinical evidences, the participation of patients with advanced disease to multicenter cooperative studies should be largely encouraged. For the time being, neither conventional chemotherapy, nor newer...
costly targeted drugs are to be considered satisfactory approaches. A major breakthrough in the treatment of these tumors can only be achieved by the determination of the molecular abnormalities underlying the different subtypes of salivary gland cancers, which might lead to more active and specific targeted therapies.

References


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