Dear Group,

Hopefully this works. Below is the full-text June 2006 article that was mentioned earlier. Unfortunately, the links to the tables will probably not work.

Susan

REVIEW ARTICLE

Systemic Therapy in the Palliative Management of Advanced Salivary Gland Cancers

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ABSTRACT

Cancers of the salivary glands are unusual lesions that vary widely in their histologic appearance and molecular characteristics. Likewise, there is a wide spectrum of biologic behavior, ranging from low-grade, minimally invasive tumors, to highly lethal malignancies. There are few data on the role of systemic therapies in the management of these cancers, and chemotherapy is generally reserved for the palliative management of advanced disease that is not amenable to local therapies such as surgery and/or radiation. The majority of patients for whom systemic therapy is considered will have either adenoid cystic carcinoma, mucoepidermoid carcinoma, or high-grade adenocarcinoma. This article will review the available literature regarding the use of palliative chemotherapy
for patients with advanced salivary gland cancer of these histologies, with an emphasis on the potential role of targeted agents. There is a need for a determined, coordinated effort to conduct high-quality clinical trials in patients with these rare cancers.

## INTRODUCTION

Salivary gland cancers (SGCs) are rare neoplasms, accounting for less than 5% of all cancers of the head and neck. They encompass a wide spectrum of histologies with varied biologic behavior and variable responsiveness to systemic therapies. Initial therapy of localized disease consists of surgery and/or radiation therapy, whereas chemotherapy is generally reserved for the palliative treatment of metastatic disease or locoregional recurrence for which further surgery or radiation is not possible.

Because of their rarity, there are limited clinical trial data to help define the role of systemic therapy in the palliative management of SGCs. Trials tend to have enrolled small numbers of patients who are heterogeneous with respect to histology, number of prior systemic therapies, and the proportion with distant metastatic disease versus only locoregional recurrence, all of which hinder the ability to interpret the activity of a therapy. Only one trial exists for most agents or regimens, or if more than one has been reported, they differ in the dose and/or schedule used. Additionally, the histologic classification of SGC was expanded in the early 1990s, leading to difficulties in determining which tumor type is being described in earlier publications; this is of particular relevance for adenocarcinoma and its subtypes. The greatest amount of data exists for adenoid cystic carcinoma (ACC), for which there are phase II trials of agents and regimens specifically tested in this histology, in addition to trials for SGC, on which patients with ACC were an enrolled subgroup. However, in publications spanning 20 years, fewer than 300 patients were identified in a systematic review of all reports of trials performed in patients with ACC; a significant number of these reports are not prospective clinical trials, but rather case series or retrospective reports of institutional experiences. Further, the methodologic quality of most reported clinical trials is variable and often suboptimal. Prospective clinical trial data for the role of systemic therapy in other histologies is scarce, consisting of a few patients in clinical trials that enrolled all histologies of SGCs. Available case series/single-patient case reports should be interpreted cautiously because they may overestimate the true activity due to publication bias in favor of positive results. These limitations need to be considered when interpreting the evidence in support of the use of any systemic therapy in advanced SGC.

This article will review the current role of systemic therapies in the palliative management of three most common histologic subtypes, ACC, mucoepidermoid carcinoma (MEC), and adenocarcinoma, as well as salivary duct carcinoma (SDC), with an emphasis on emerging potential molecular targets. Other histologies will not be discussed, because of a lack of sufficient data from which to draw meaningful conclusions.

## HISTOLOGIC AND MOLECULAR FEATURES OF SALIVARY CANCERS

The WHO classification of malignant epithelial salivary tumors has been updated recently, listing 24 different histologic subtypes. In practice, however, the vast majority of patients are accounted for by only a few histologies. SGCs can be divided into those believed to originate from the intercalated ducts (which include ACC and adenocarcinoma) and those of secretory duct origin (MEC and SDC). Salivary carcinomas with myoepithelial elements are biologically considered low grade, whereas those devoid of myoepithelium are
The frequency of the different histologies varies depending on whether the cancer arises in the major (parotid, submandibular) or minor (mucosal) glands, but overall, MEC, ACC, and adenocarcinoma together represent the majority of all SGC (Table 1). The parotid is the site of origin of most SGCs, although most parotid tumors are benign. A higher tumor grade appears to correlate with a more aggressive clinical course in MEC and adenocarcinoma, but there are conflicting data on the importance of grading according to histologic pattern in ACC.

### Table 1. Relative Frequency (%) of Different Histologic Subtypes of Salivary Gland Cancer According to Site of Origin

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Relative Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEC</td>
<td>50.0</td>
</tr>
<tr>
<td>ACC</td>
<td>20.0</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>10.0</td>
</tr>
<tr>
<td>Salivary Duct Carcinoma</td>
<td>10.0</td>
</tr>
<tr>
<td>Papillary Adenocarcinoma</td>
<td>5.0</td>
</tr>
</tbody>
</table>

There is increasing interest in determining the molecular abnormalities underlying the different subtypes of SGC, in the hopes that this will lead to the discovery of more effective, targeted therapies. For example, the presence of estrogen receptors in normal salivary tissue and in some salivary carcinomas has led to the investigation of the expression of hormonal receptors. Other potential therapeutic targets examined have included the epidermal growth factor receptor (EGFR), her-2 and c-kit. These studies have shown differential expression of such targets in different histologic subtypes (Table 2). Possible explanations for the wide range of reported expression of these targets among studies of the same histology include differences in immunohistochemistry (IHC) methodology and scoring, use of archival samples leading to problems with antigen retrieval, small numbers, and intrinsic biologic variability.

### Table 2. Frequency of Expression of Molecular Targets in Salivary Gland Carcinomas

<table>
<thead>
<tr>
<th>Target</th>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen Receptors</td>
<td>Present</td>
</tr>
<tr>
<td>HER2</td>
<td>Variable</td>
</tr>
<tr>
<td>c-kit</td>
<td>Negative</td>
</tr>
</tbody>
</table>

### ADENOID CYSTIC CARCINOMA

The natural history of ACC of salivary origin may be quite protracted, and is characterized by the possibility of late recurrence, even more than 10 years after initial "curative" therapy. Historically, local recurrence has been reported to occur most commonly, either alone or in combination with distant failure, whereas isolated distant metastases have been less commonly observed; this pattern of relapse may be changing with the increased use of adjuvant radiation. Median survival following the development of metastases is approximately 3 years, but there is a wide spectrum of biologic behavior and resultant clinical course. Although some patients will survive for more than 10 years with metastases, others suffer rapid progression, and up to one third of patients will die within 2 years. Patients with solely pulmonary metastases have a better prognosis compared to those with metastases to bone or other viscera. For those patients with no or few symptoms and indolent disease, and particularly those with only pulmonary metastases, watchful waiting is often the most appropriate recommendation. Single sites of symptomatic metastases may be more appropriately treated with surgery or radiation. Systemic therapy should be reserved for those with symptoms and/or rapidly progressive...
A systematic overview of all reported trials of systemic therapy in ACC has been performed. In prospectively performed clinical trials, objective responses to any cytotoxic agent or regimen are infrequent, whereas stabilization of disease was observed more commonly (Table 3). Rates of disease stabilization need to be interpreted with caution in an indolent cancer; however, this may be only a marker of antitumor activity, depending on the intrinsic growth rate of the cancer without therapy and on the durability of the reported clinical stability. Documenting evidence of progression and its rate before the commencement of therapy will facilitate this assessment.

Mitoxantrone, vinorelbine, and epirubicin appear to have single-agent activity, as manifested by objective responses, stabilization of progressive disease and/or palliation of disease-related symptoms. Paclitaxel appears inactive in ACC. Cisplatin-anthracycline-based combination regimens also have activity in ACC. For example, in five studies of the regimen cisplatin-doxorubicin-cyclophosphamide (CAP) with or without fluorouracil, objective responses were observed in 12 of 43 patients (28%; 95% CI, 17% to 43%). In a small, randomized phase II trial comparing vinorelbine with cisplatin-vinorelbine more responses were reported with the combination, but response rates have wide, overlapping CIs. Overall, the data are insufficient to conclude that combination therapy is superior to single-agent therapy, and the likelihood of additional toxicity of a combination regimen needs to be considered.

Table 3. Treatments for Which Antitumor Activity Has Been Reported in Salivary Gland Carcinoma

As c-kit is expressed in a high proportion (approximately 80%) of ACC, imatinib, an inhibitor of the tyrosine kinase of this target, is of potential interest. However in two phase II studies in which imatinib was administered as a single-agent at 800 mg/d to patients with evidence of c-kit expression by IHC, no objective responses were observed in 27 patients. Disease stabilization in several patients was reported, but it is not clear that evidence of disease progression was required for study entry. There have, however, been case reports of objective responses to this agent. Possible explanations for these disparate findings include varying levels of c-kit expression, the absence of c-kit mutations (at least in exons 11 and 17), the presence of an autocrine activating loop by its ligand stem-cell factor, and the proliferative activity of the patients’ ACC. Further study of this agent appears to be warranted, particularly in patients with clearly progressive disease and high levels of c-kit expression.

Reported levels of EGFR overexpression in ACC has varied from none to 85%. A phase II study of gefitinib in advanced, progressive salivary malignancies has been reported in abstract form. Of the 29 patients enrolled, 19 had ACC. No major objective responses were observed; 10 (53%) of 19 had disease stabilization, which has been maintained for at least 16 weeks in five patients. Correlation between EGFR expression and outcome is pending.

Hormone receptor positivity is virtually absent in ACC. Although a response to tamoxifen has been reported, there are insufficient data to support the routine use of hormonal agents in the treatment of ACC. Finally, overexpression of her-2 was 3% in 130 cases in a pooling of the two largest series of patients with ACC studied, suggesting that it is unlikely that trastuzumab would be a useful therapy in this histology.

MUCOEPIDERMOID CARCINOMA

High-grade MEC is an aggressive malignancy that both metastasizes and recurs locally. Lesions classified as low grade histologically may still rarely metastasize. Tumors arising in the submandibular gland, even if low grade, appear more likely to
metastasize than those from the parotid. Although MEC is one of the most common subtypes of SGC, there are no studies of systemic therapy specific to this histology. This likely reflects the fact that reported incidence rates include low-grade lesions, which are more common, have a lower metastatic potential, and are therefore less likely to require palliative chemotherapy. There is some suggestion, however, that there is a differential responsiveness of this histology when compared with ACC or adenocarcinoma; an example of this is the activity seen with paclitaxel in MEC but not ACC. This highlights the importance of separating SGC histologies in reports of clinical trials. Of agents or regimens studied, single-agent paclitaxel may have activity, as may cisplatin-based combination regimens. Her-2 has been shown to be overexpressed by IHC in up to one third of patients with MEC and gene amplification has been detected by fluorescence in situ hybridization (FISH). Both overexpression by IHC and amplification by FISH may be associated with a worse clinical outcome. One of three patients with MEC that overexpressed her-2 enrolled to a phase II trial of trastuzumab had a confirmed objective partial response lasting for more than 2 years, whereas the others had progression of disease. EGFR also appears to be commonly overexpressed. Of two patients treated with gefitinib, both progressed during therapy. Further studies of agents targeting these receptors are warranted in patients with MEC.

## Adenocarcinoma

The commonly used classifications of salivary tumors list a number of subtypes and variants of adenocarcinoma. These range from indolent, low-grade lesions with little tendency to recur or metastasize, such as acinic cell carcinoma and polymorphous low-grade adenocarcinoma, to aggressive histologies, such as high-grade adenocarcinoma not otherwise specified. In most reports of systemic therapy, it is not stated which subtypes of adenocarcinoma were present in the enrolled patients, and so the differential effect of treatment on these subtypes is unknown. It is likely, however, that most such patients had high-grade adenocarcinoma. Of agents studied in a reasonable number of patients, paclitaxel, vinorelbine, and CAP have demonstrated antitumor activity. These tumors may overexpress EGFR and, to a lesser extent, her-2. However, seven patients treated with trastuzumab progressed during therapy, whereas two patients treated with gefitinib had stabilization of disease. Expression of androgen receptors and of prostate-specific antigen by IHC has been described, and there have been reports of androgen receptor-positive adenocarcinoma of the salivary gland responding to antiandrogen therapy.

## Salivary Duct Carcinoma

SDC is an aggressive malignancy that usually arises in the parotid, has a high tendency to nodal involvement, and usually affects males in their sixth decade. The development of distant metastases is common, and the median survival from diagnosis is approximately 3 years, with most patients dying as a result of the malignancy. Thus although SDC is rare, most patient with this histology may be considered for palliative systemic therapy. Older reports of chemotherapy for salivary cancers did not separate...
SDC from other adenocarcinomas, and so there are few data on the responsiveness of this specific histology to standard cytotoxic agents. In suitable patients, it is reasonable to use the same agents or regimens as listed above for adenocarcinoma.

Androgen-receptor positivity is not uncommon in SDC, whereas estrogen and progesterone receptors are usually not detectable by IHC. SDC commonly overexpresses either EGFR or her-2 by IHC and there is a suggestion that overexpression of her-2 may be associated with a more aggressive phenotype.

In a phase II trial of gefitinib, three patients with SDC were enrolled, and all patients had progressed at the time of first assessment. In a phase II study of trastuzumab in salivary gland cancers overexpressing her-2, two patients with progressive SDC had stabilization of disease for 26 and 40 weeks, respectively. Antiandrogen therapy has been reported to lead to objective responses in SDC.

**ONGOING CLINICAL TRIALS**

Currently, as listed in the database of the National Cancer Institute (http://cancer.gov/clinicaltrials=finding), the following agents were under study in SGC: gemcitabine, either alone or in combination with cisplatin; the combination of capecitabine and oxaliplatin; bortezomib; trastuzumab; and lapatinib, a dual inhibitor of EGFR and her-2.

**CONCLUSIONS AND FUTURE DIRECTIONS**

There is a paucity of high-quality data regarding the role of systemic therapies in the palliative management of SGC. Because there is no clear evidence that such treatment improves survival, the main goals of therapy are the relief and prevention of disease-related symptoms. Thus, particularly in patients with indolent disease and few symptoms, when compromise of a vital structure is not imminent, watchful waiting may be the most appropriate course. Treatment should be reserved for those patients with symptoms and/or rapid disease progression, and due consideration should be given to local therapies such as radiation. If treating outside of a clinical trial, there is some evidence to guide the choice of standard cytotoxic agents. Although the CAP regimen has the greatest amount of data, there is no clear evidence that this offers a therapeutic advantage over single-agent therapy, and the choice should be made bearing in mind the likelihood of additional toxicities. There is little evidence at this time to support the empiric use of costly, targeted agents because they have been insufficiently studied.

There is a need to conduct quality clinical trials in SGC, and every patient should be considered for participation in...
such studies. Priority should be given to studies with a translational component to advance the molecular understanding of these cancers.

Homogenous patient populations, and reporting of each histologic subgroup separately, will aid interpretation of results. For histologies whose clinical behavior may be indolent (such as ACC), documentation of disease progression and its rate should be required before study entry to facilitate assessment of activity. Sufficient numbers of patients with the most infrequent histologies need to be enrolled because there is evidence that different subtypes of SGC may vary in their responsiveness to therapy and their molecular profiles. This will require a concerted, multi-institutional effort, but recent studies in ACC have shown that this can be accomplished.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Collection and assembly of data: Scott A. Laurie, Lisa Licitra
Manuscript writing: Scott A. Laurie, Lisa Licitra
Final approval of manuscript: Scott A. Laurie, Lisa Licitra
Other: Scott A. Laurie, Lisa Licitra

NOTES

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

REFERENCES
INTRODUCTION
HISTOLOGIC AND MOLECULAR CONTENT
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MUCOEPIDERMOID CARCINOMA
ADENOCARCINOMA
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