Chapter 13

Systemic Therapy for Salivary Gland Cancer

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Outline

Introduction

Salivary gland tumors are a group of heterogeneous neoplasms that constitute less than 1% of all cancers diagnosed globally (WHO 2005). The behavior of these tumors varies widely depending on their location, histology, and tumor biology. The tumors can involve both the major salivary glands (parotid, submandibular, and sublingual) and the minor salivary glands. The most common location is the parotid gland, which accounts for approximately 80% of all the salivary gland tumors (Guzzo, et al. 2010). Tumors involving the minor salivary glands are rare but are also more likely to be malignant. Salivary gland tumors include both benign and malignant neoplasms and they are classified according to the World Health Organization (WHO) system (WHO 2005). This chapter will focus on the use of systemic therapy in the treatment of salivary gland cancers.

Epidemiology and Risk Factors

The global annual incidence rates for salivary gland cancers (SGC) vary between 4 and <0.05 per 100,000 (Parkin, et al. 2002). It has been suggested that radiation exposure, viral infections, diet, and genetic predisposition may play a role in the development of these rare cancers. The association between radiation exposure and SGC was first identified in atomic bomb survivors in Hiroshima (Saku, et al. 1997). Subsequently SGC has been reported in patients receiving radiation to the head and neck region for both cancers and benign conditions (Schneider, et al. 1998).

Viral infections have been shown to be associated with the development of SGCs. Lymphoepithelial carcinoma is an SGC that is strongly associated with Epstein–Barr Virus (EBV) infection in areas endemic to the virus (WHO 2005). Epidemiologic studies have shown that patients with the human immunodeficiency virus (HIV) are also more likely to develop SGCs (Serraino, et al. 2000). The human papillomavirus (HPV) has been identified in some mucoepidermoid carcinomas (Brunner, et al. 2012, Isayeva, et al. 2013); however, this has not been a consistent finding (Jour, et al. 2013). Similarly, HPV has been rarely identified in other SGCs (Hafed, et al. 2012). At this time, it is not clear if there is a significant association between HPV and SGCs.

Environmental carcinogens have also been shown to be associated with SGCs. Tobacco smoke exposure has been associated with the

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development of Warthin tumor (Pinkston and Cole 1996, WHO 2005). Exposure to nickel and rubber manufacturing have been reported to be risk factors for SGCs (Horn-Ross, et al. 1997). In addition, professionals such as hair dressers and beauticians are reported to have higher risk of developing SGCs (Swanson and Burns 1997).

Molecular Biology of Salivary Gland Tumors

SGCs consist of variety of different tumors and there is considerable variation in the type of molecular changes identified in these tumors. These molecular changes include fusion genes, oncogenic mutations, and alterations in gene amplification or expression. Some of these molecular alterations are specific to the tumor type and could help establish the diagnosis in the absence of a histologic diagnosis; others have been identified as potential therapeutic targets.

Fusion genes are relatively rare molecular events in malignant epithelial tumors. The *MYB-NFIB* fusion gene has been identified in adenoid cystic carcinoma (ACC) and appears to be specific to this tumor type (Persson, et al. 2009). The *MYB-NFIB* fusion gene activates the transcription of a variety of genes downstream to *MYB*, which includes *BCL2*, *KIT*, *CD34*, *BIRC3*, and *MYC* (Stenman 2013). These genes are important in activation of cell proliferation, differentiation, and apoptosis. The *MYB* gene has been reported to be activated in the vast majority (80%) of all ACCs either by gene fusion or by other mechanisms. Mucoepidermoid carcinoma (MEC) is characterized by the *CRTC-MAML2* fusion gene and both constituent genes have role in cell cycle (Enlund, et al. 2004). The *CRTC1* is a cAMP response element binding protein (CREB) co-activator that regulates genes involved in cell proliferation and differentiation in response to stimulus from growth factors and cytokines (Coxon, et al. 2005). The *MAML2* gene is a co-activator for the *NOTCH* gene which also plays a major role in cell cycle as well as in oncogenesis. The oncoprotein resulting from this gene fusion has transforming activity in both in-vitro and in-vivo experiments. Recently the *ETV6-NTRK3* gene fusion was identified in mammary analogue secretory carcinoma (MASC) and the chimeric tyrosine kinase resulting from this fusion has shown transforming activity as well (Skalova, et al. 2010). Targeting the IGF1R pathway has been shown to effectively inhibit the transforming activity of this fusion kinase (Tognon, et al. 2011).

Over-expression of the epidermal growth factor receptor (*EGFR)* gene is the most common genomic abnormality reported in SGCs, it is identified in approximately 70% of all SGCs (Locati, et al. 2009b). However, activating mutations involving the tyrosine kinase domain of the *EGFR* gene are rare. Other genes that have been reported to be over expressed or amplified in SGC include *HER2*, *VEGF*, and *C-KIT* (Press, et al. 1994, Lim, et al. 2003, Skalova, et al. 2003, Dagrada, et al. 2004, Freier, et al. 2005). VEGF expression is an independent prognostic factor and high expression is associated with inferior outcomes. C-Kit expression is found in the majority of high grade ACCs (90%). Expression of estrogen and progesterone receptors has been reported in some SGCs, though this is a rare finding.

Clinical Presentation

The clinical presentation for SGC depends on the site of origin and involvement of adjacent structures. Approximately half of all major SGCs arise in the parotid gland and they usually present as a painless mass arising in the parotid, submandibular, or sublingual gland. Around 90% of all salivary gland tumors arise in the parotid gland and about 25% of them are malignant (2005). In the case of submandibular salivary gland, the proportion of SGCs is about 45%, 70–90% in sublingual gland tumors and 50–75% in minor salivary gland tumors (Guzzo, et al. 2010). If the mass is associated with facial nerve palsy then it is likely to be a malignant SGC. Similarly presence of associated lymphadenopathy also indicates malignant SGC.

Tumors arising from minor salivary glands are more likely to be malignant than tumors arising in major salivary glands. More than half of all minor salivary gland tumors arise within the oral cavity. Symptoms for minor SGCs vary according to the location. Oral tumors may present as a painless submucosal tumor, minor SGCs in the nasopharynx can cause facial pain, nasal obstruction, and bleeding, and tumors in the hypopharynx can result in hoarseness of voice and dyspnea. Minor SGCs in the nasopharynx are also more likely to present at an advanced stage with invasion of the skull

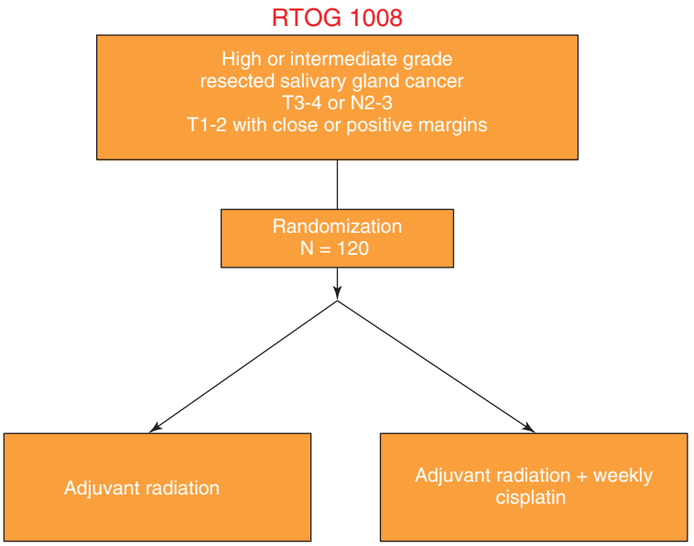

Figure 13.1. The role for concomitant chemotherapy with adjuvant radiation is being evaluated by the RTOG 1008 clinical trial.

base, intracranial and cranial nerve involvement (Schramm and Imola 2001). A thorough initial assessment with history and physical exam could help estimate the extent of the disease and the likelihood of it being a malignant tumor. Tissue diagnosis will have to be established and this can achieved in most cases with fine needle aspiration cytology. Imaging scans such as computerized tomography (CT) and/or magnetic resonance imaging (MRI) may be needed to establish the TNM stage of the disease.

Treatment

Treatment of SGCs depends on the location, tumor histology, and the extent of disease involvement. Whenever possible, a complete surgical resection with clear margins is the preferred treatment approach for SGCs. In patients with SGCs that are unresectable or medically inoperable, definitive radiation remains the treatment of choice. Concurrent chemotherapy with a platinum agent can be considered in patients with good performance status; however, there is insufficient evidence to support this approach over definitive radiation alone.

ADJUVANT TREATMENT

There is no established role for adjuvant chemotherapy alone in patients with resected SGCs, though this approach may be considered with concomitant adjuvant radiation. Adjuvant radiotherapy is indicated in patients with high risk features such as high grade tumors, advanced disease stage, adenoid cystic carcinoma histology, and skin or nerve invasion. In addition, patients with T2 or greater SGCs involving the submandibular, sublingual, and minor salivary glands are potential candidates for adjuvant radiotherapy. The role for concomitant chemotherapy with adjuvant radiation has not been established but is currently being evaluated by the RTOG 1008 clinical trial (Figure 13.1) (Rodriguez, et al. 2008). This randomized phase II trial will compare adjuvant radiotherapy with concurrent cisplatin chemotherapy to adjuvant radiotherapy alone in patients with resected SGCs. Results from this trial are expected to be available soon.

TREATMENT OF METASTATIC DISEASE

Cytotoxic chemotherapy is primarily used in the treatment of advanced stage disease that cannot be treated with definitive surgical resection or radiation. However, the optimal chemotherapy regimen in the treatment of SGCs has not been established. Given the rarity of these tumors there have been no large randomized trials to establish the survival benefit from cytotoxic chemotherapy treatment. The primary role for chemotherapy treatment is to palliate symptoms in patients with metastatic SGC. Small phase II trials and case series have

studied the use of both monotherapy and combination chemotherapy in the treatment of SGCs. In addition tumor histology in SGCs appears to determine sensitivity to chemotherapy treatment. Treatment with single agent paclitaxel appears to be effective in patients with mucoepidermoid carcinomas and adenocarcinoma but it has not shown activity against ACC (Gilbert, et al. 2006, Laurie, et al. 2011). Similarly, treatment with cisplatin was shown to be associated with increased toxicity but no better efficacy than mitoxantrone, epirubicin, or vinorelbine in patients with ACCs (Table 13.1).

Single agent paclitaxel, cisplatin, doxorubicin, mitoxantrone, vinorelbine, and methotrexate have all shown activity in the treatment of SGCs. The response rate is modest and ranges between 10 and 40% (Schramm, et al. 1981, Licitra, et al. 1991, Vermorken, et al. 1993, Verweij, et al. 1996, Airoldi, et al. 2001). The choice of agent will depend on the tumor histology and the patient's ability to tolerate the agent. In general, any one of these agents can be considered for the treatment of SGCs, except in the case of ACCs where paclitaxel is not particularly effective.

Combination chemotherapy is generally associated with better tumor response rate compared to single agent chemotherapy but it is also associated with a higher incidence of adverse effects (Table 13.1). Several different combinations of platinum, anthracycline with or without other agents including cyclophosphamide, and 5-fluorouracil have been evaluated in the treatment of advanced stage SGCs. The most common regimen being

Table 13.1. Chemotherapy in the treatment of metastatic or recurrent salivary gland cancers.

Agent(s)	ACC		MEC		ADC	
	N	No of objective responses	N	No of objective responses	N	No of objective responses
Cisplatin (Schramm et al. 1981, Suen and Johns 1982, Kaplan et al. 1986, Licitra et al. 1991, de Haan et al. 1992, Jones et al. 1993)	66	28	7	2	8	0
Paclitaxel (Gilbert et al. 2006)	14	0	14	3	17	5
Gemcitabine (van Herpen et al. 2008)	21	0	–	–	–	–
Vinorelbine (Airoldi et al. 2001)	13	2	–	–	5	2
Mitoxantrone (Mattox et al. 1990, Verweij et al. 1996)	50	5	–	–	–	–
Epirubicin (Vermorken et al. 1993)	20	2	–	–	–	–
CAP (Alberts et al. 1981, Kaplan et al. 1986, Dreyfuss et al. 1987, Belani et al. 1988, Creagan et al. 1988, Licitra et al. 1996)	36	9	16	8	29	19
CAP + 5FU (Dimery et al. 1990)	7	3	1	1	9	4
Carboplatin/paclitaxel (Ruzich et al. 2002)	10	2	1	0	2	1
Cisplatin/vinorelbine (Airoldi et al. 2001)	9	4	1	0	4	3
Cisplatin/gemcitabine (Laurie et al. 2010)	10	2	4	1	8	3
Cisplatin/5FU (Hill et al. 1997)	11	0	—	–	–	–

ACC = Adenoid cystic carcinoma
MEC = Mucoepidermoid carcinoma
ADC = Adenocarcinoma

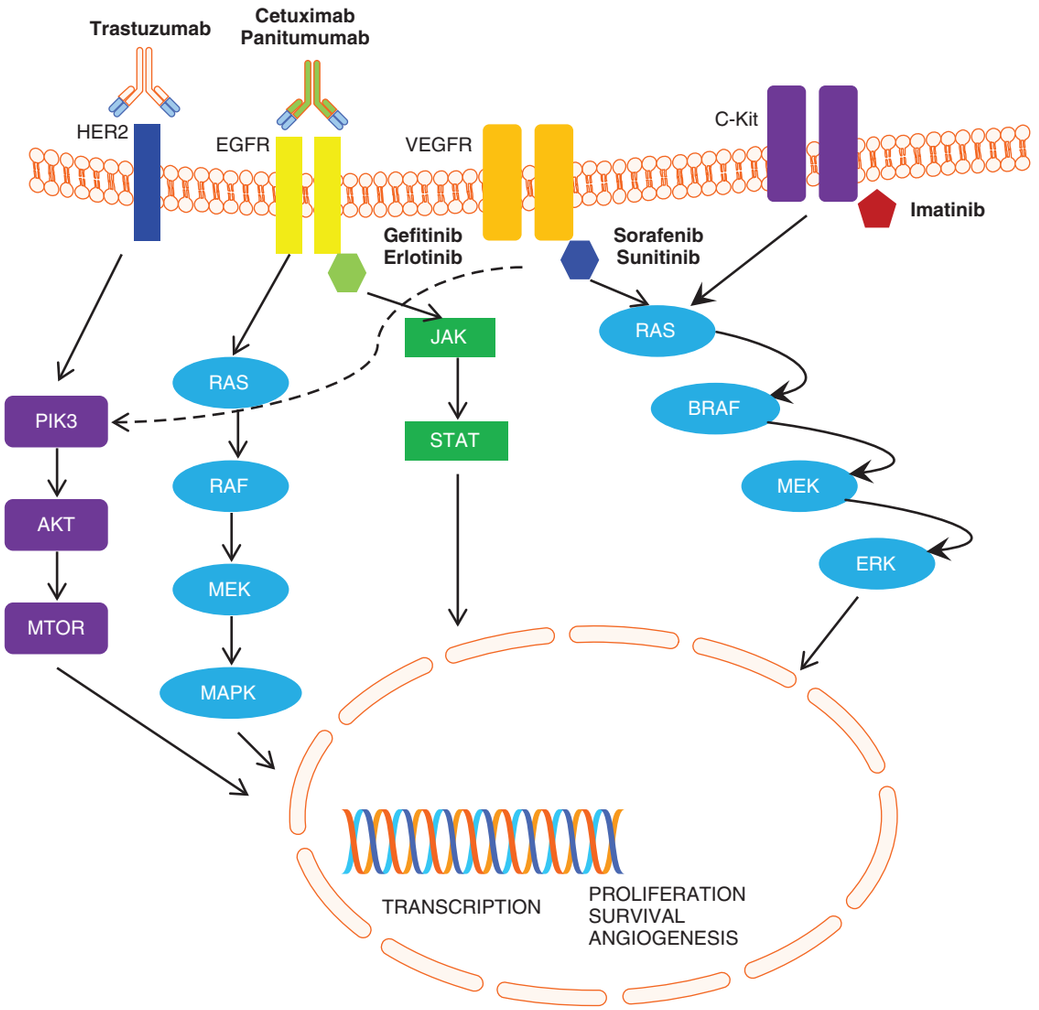

Figure 13.2. Activated signaling pathways and their inhibitory agents in advanced salivary gland cancers.

cyclophosphamide, doxorubicin, and cisplatin (CAP) given on day 1 of a 28-day cycle (Dreyfuss, et al. 1987, Licitra, et al. 1996). The overall response rate ranges between 30 and 40% for all patients with advanced stage SGCs. In addition, the response rates may vary according to the histologic type with some histologic types such as adenocarcinomas showing a better response rate of approximately 60%.

In general, our approach has been to use combination chemotherapy in patients who are symptomatic from the disease and single agent chemotherapy in all other patients. In patients who have an indolent disease that is asymptomatic, close monitoring without any systemic therapy would be appropriate.

TARGETED THERAPY

The field of oncology has been revolutionized by the advent of molecularly targeted therapy (Figure 13.2). Some of these agents have been evaluated in patients with SGC. The majority of these studies involve agents targeting receptor tyrosine kinases in advanced stage salivary gland cancers. So far, molecularly targeted treatment approaches have not shown any significant activity or improvement in survival outcomes (Table 13.2).

Table 13.2. Targeted therapy in the treatment of metastatic or recurrent salivary gland cancers.

Agent	Molecular Target	N	Tumor type	Response rate	Comment
Imatinib (Pfeffer et al. 2007)	CKIT	26	ACC	–	No significant activity
Gefitinib (Jakob et al. 2014)	EGFR	29	SGC	–	No significant activity
Cetuximab (Locati et al. 2009a)	EGFR	30	SGC	–	No significant activity
Trastuzumab (Haddad et al. 2003)	HER2	15	SGC	–	No significant activity
Lapatinib (Agulnik et al. 2007)	HER2	40	SGC	–	No significant activity
Sorafenib (Thomson et al. 2013)	VEGFR	23	ACC	8.3%	Significant toxicity
Sunitinib (Chau et al. 2012)	VEGFR	14	ACC	–	No significant activity
Bortezomib (Argiris et al. 2011)	Proteasome	25	ACC	–	No significant activity

ACC = adenoid cystic carcinoma
MEC = mucoepidermoid carcinoma
ADC = adenocarcinoma
SGC = salivary gland cancer

Targeting *C-KIT*

ACCs have been reported to have C-kit expression and individual case studies have reported response to treatment with imatinib (Mino, et al. 2003). Phase II trials evaluating single agent imatinib for the treatment of ACCs did not report any significant treatment response (Pfeffer, et al. 2007). The combination of imatinib with cisplatin in a phase II trial was reported to have a partial response in 5 out of 28 evaluable patients with ACC and 19 had stable disease (Ghosal, et al. 2011). Overall, prospective studies have not shown any significant treatment benefit with imatinib for patients with ACC.

EGFR Inhibition

Gefitinib is an EGFR tyrosine kinase (TK) inhibitor and has shown activity in patients with lung and pancreatic cancers. EGFR over-expression has been reported in patients with MEC and ACCs. Treatment with gefitinib in a phase II trial did not report any significant objective response in patients with advanced stage SGCs. Stable disease was reported in 10 (34%) patients (Jakob, et al. 2014).

EGFR inhibition can also be achieved by cetuximab which is an anti-EGFR monoclonal antibody. Treatment with cetuximab was not associated with treatment response in a phase II trial with 30 patients with SGCs (Locati, et al. 2009a). Disease stabilization was reported in 24 (80%) patients and 15 (50%) patients had disease stabilization for at least 6 months.

HER2 Inhibition

Her2 expression has been reported in MEC and salivary duct cancers (Glisson, et al. 2004, Jaehne, et al. 2005). A phase II trial was initiated to evaluate trastuzumab, a monoclonal antibody targeting HER2 for patients with HER2 expression positive SGCs (Haddad, et al. 2003). The study closed early due to low rates for HER2 expression positive tumors. In one patient with Her2 positive MEC, partial response was reported, which lasted for over 2 years. In addition, there have been case studies reporting benefit from trastuzumab in combination with chemotherapy for patients with salivary duct carcinomas.

Lapatinib is a small molecule dual kinase inhibitor for *HER2* and *EGFR* that was evaluated in a phase II trial for patients with metastatic SGCs (Agulnik, et al. 2007). Of the 40 patients enrolled in the multicenter phase II trial, none of them had a treatment response, 15 patients with ACC had stable disease, and 8 patients with non ACC had stable disease. The treatment outcomes did not correlated with either EGFR or HER2 expression in this study.

Multi Kinase Inhibition

Sorafenib and sunitinib are multi kinase inhibitors that have been evaluated in patients with advanced stage ACCs. Sorafenib was evaluated in 23 patients with ACC and 2 patients had partial response with a median progression free survival of 13 months (Thomson, et al. 2013). In another study, 14 patients with ACC were treated with sunitinib and

no treatment responses were reported but 5 patients had disease stabilization (Chau, et al. 2012).

Both of these treatments were difficult to tolerate, more than half the patients receiving sorafenib developed grade 3 or higher toxicity. The authors did not recommend further evaluation of sorafenib in this patient population. Similarly sunitinib also had a significant toxicity profile with 3 patients removed from the study due to toxicity and 10 patients required dose reductions.

Proteasome Inhibition

Bortezomib is a 26S proteasome and *NF-κB* inhibitor that had shown pre-clinical activity against ACC tumors in combination with doxorubicin. A phase II trial evaluated treatment with both single agent bortezomib and in combination with doxorubicin in the treatment of patients with incurable ACC (Argiris, et al. 2011). Of the 24 patients treated with single agent bortezomib, none had an objective response and stable disease was reported in 15 patients. One patient out of 10 receiving the combination therapy had a partial response.

Summary

- Systemic therapy in the treatment of SGCs is primarily limited to patients with metastatic or recurrent disease.
- The role for chemotherapy in the adjuvant setting is unclear and could be considered in patients with high risk features after tumor resection. The RTOG 1008 trial may help shed more light on this issue when results from this study become available.
- In patients with metastatic or recurrent SGCs the choice of chemotherapy is dependent on several factors including clinical course and histology. Some patients have an indolent course and can be observed without any systemic therapy. In patients with symptomatic and/or progressive disease both combination and single agent cytotoxic chemotherapy can be considered.
- In patients with ACC both paclitaxel and gemcitabine have not shown activity and should be avoided.
- The CAP regimen has shown activity against ACC, acinic cell carcinoma, adenocarcinomas, and malignant mixed tumors.
- Agents such as cisplatin, 5-FU, and methotrexate seem to provide better response in patients with MEC and undifferentiated tumors.
- Molecularly targeted therapy holds significant promise in the treatment of SGCs but so far, none of the available agents have shown any significant activity.
- A better understanding of the molecular biology of salivary gland cancers could lead to better treatment options in the future. The rarity and heterogeneity of SGCs pose major challenges to achieving this goal but persistent efforts are needed to achieve better outcomes for the patients.

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