Oral Oncology 60 (2016) 142–145

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Editorial

Unmet needs for patients with salivary gland cancer

The rarity and heterogeneity of salivary gland cancers creates a difficult challenge for informing management guidelines and advancing drug and other therapy development for this entity of malignancies. These factors figure prominently as to why we have unmet needs for patients with salivary gland cancer. Salivary gland cancers comprise less than 5% of head and neck cancers and approximately 0.5% of all malignancies [1,2]. They can arise in the major salivary glands, which consists of the parotid, submandibular, or sublingual glands, or in one of the minor salivary glands present throughout the aerodigestive tract. This group of tumors can vary in histology, molecular drivers, behavior, and response to therapy. Many historical studies "lumped" patients with a spectrum of salivary gland cancers for sample size purposes, failing to fully appreciate the impact of this heterogeneity on the reported results and compromising what could have been learned.

The World Health Organization (WHO) classifies salivary gland cancers into 24 distinct histologic subtypes [3]. Mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), and adenocarcinomas account for greater than 75% of salivary gland malignancies. Salivary gland cancers either arise from the secretory ducts/acinar and ductal cells (MEC) or the intercalated ductal tissue/myoepithelial and basal cells (ACC and adenocarcinoma). Tumors predominantly of myoepithelial composition are considered to be biologically low-grade, while tumors with minimal myoepithelial components are considered to be biologically high-grade [4].

Molecular features

In addition to being a histologically and prognostically diverse group of tumors, salivary gland cancers have diverse molecular features. A common genetic alteration in MEC is the translocation of t(11;19)(q21;p13), which creates a fusion between the *CRTC1* gene and the *MAML2* gene resulting in the formation of the MECT1-MAML2 fusion protein [5,6]. The MECT1-MAML2 fusion protein activates the transcription factor CREB, which leads to upregulation of AREG, which then activates oncogenic EGFR signaling [7]. The presence of this translocation in MEC is associated with a better prognosis. In ACC, the t(6;9)(q22-23;p23-24) translocation in often present [8]. This cytogenetic alteration creates a gene fusion of the MYB and NFIB transcription factors. The translocation leads to upregulated levels of *MYB* expression at both the mRNA transcript and protein level [8,9]. Additionally, over one-third of t(6;9)-negative or MYB-negative ACCs harbor an alteration in another MYB family gene, *MYBL1*, producing a gene expression signature similar to what has been observed in *MYB*- fusion tumors [10,11].

Biologic markers are also differentially expressed. The majority of ACCs possess high c-kit expression [12,13], although inhibitors of *c-kit* have not been promising. High androgen receptor (AR) expression is common in salivary duct carcinomas (SDCs), and although less common, overexpression of the AR is seen in adenocarcinomas [14], allowing for treatment with androgen deprivation therapy. HER2 overexpression is frequently seen in SDCs and a smaller proportion of MECs and adenocarcinomas [15]. EGFR overexpression is present in non-ACC salivary gland cancers [16].

Treatment of locoregional disease

Initial treatment of localized or locally-advanced disease consists of surgery and/or radiation therapy. The role of chemotherapy to improve locoregional control in patients with poorer risk disease is being evaluated in an ongoing randomized phase II/III trial comparing adjuvant radiation to chemoradiation in patients with completely resected salivary gland cancers [NCT01220583].

In patients with unresectable disease or for whom the morbidity of resection would be unacceptable, radiation with photons, photon/electrons, or high conformal techniques is recommended per the National Comprehensive Cancer Network (NCCN) Guidelines on Head and Neck Cancer [17]. Neutron therapy has been studied in the management of advanced salivary gland cancers and had been listed as an option in these guidelines [18]. The randomized trial performed by the Radiation Therapy Oncology Group (RTOG) in the United States and the Medical Research Council (MRC) in Britain suggested that neutrons may be more efficacious than photons in patients with advanced salivary gland cancers. The study randomized 25 patients to fast neutron versus photon therapy and found locoregional control at 10 years to be superior in the group that received neutron radiation, albeit with no difference in overall survival and more toxicity [19]. This study highlights the methodologic limitations of historic trials for these rare tumors. These include a small sample size, a spectrum of histological subtypes allowed, and unbalanced distribution of subtypes between arms despite randomization (for example, acinic cell carcinomas represented over a fifth of the neutron arm and none of the photon arm). Other relevant prognostic factors, such as resectability, tumor size, and primary versus recurrent disease also varied between arms. These methodologic issues prompted questions regarding the robustness of the reported local control advantage, which was particularly relevant given the lack of a survival benefit and increased long-term toxicity with neutrons. There has been a loss of traction with this radiation strategy, such that there is only one neutron facility in the United States at present. More recently, proton and carbon ion therapy are being evaluated as radiotherapy options for locally advanced salivary gland cancers [18]. It will be critical in planning these assessments to avoid methodological limitations like those described above.

http://dx.doi.org/10.1016/j.oraloncology.2016.06.003
1368-8375/

Systemic therapy for recurrent/metastatic disease

Due to the rarity of salivary gland cancers, there is a scarcity of clinical trials to guide systemic therapy [1,2,20] for palliative treatment of locoregional recurrence and/or distant metastatic disease. The available trials are composed of a small number of patients with heterogenous tumor histologies and differing numbers of prior systemic therapies. Many of the studies evaluating treatment in salivary gland cancers were case series or retrospective reviews, rather than true prospective studies. Additionally, studies commonly did not require progression of disease prior to enrollment, making it difficult to appreciate whether disease control was due to treatment versus the natural behavior of indolent tumors.

It is increasingly appreciated that the approach to systemic therapy, including both chemotherapy and targeted therapy, will likely need to vary by the particular subtype of salivary gland cancer based on consideration of the natural behavior, molecular alterations, and availability of clinical data.

Adenoid cystic carcinoma

The natural history of ACC follows a wide spectrum of behavior. Case series estimate a median survival of 3 years when metastatic disease is present [21,22] yet approximately 10% of these patients will survive more than 10 years [23,24]. Patients with indolent disease, minimal symptoms, and particularly pulmonary only metastases are potentially good candidates for management with initial observation and limited application of surgery and radiation, to spare these patients the side effects of palliative systemic therapy that is unlikely to provide significant benefit. Systemic therapy in ACC particularly outside of a clinical trial is typically reserved for patients with progressive disease and/or symptoms that are not amenable to local therapies.

Laurie and colleagues in 2011 published a systematic review of systemic therapy in ACC and highlighted the methodologic limitations and variability of the included studies [20]. The major response rate with both single-agent and combination-agent cytotoxic chemotherapy is low. Objective responses and disease stabilization have been reported with mitoxantrone [11,12], vinorelbine [25], and epirubicin [26] monotherapy. Neither gemcitabine nor paclitaxel when studied have demonstrated a clear therapeutic signal and no major responses were observed [27,28]. Cisplatin has shown objective responses, although its use as a single agent is not favored initially as other agents have comparable activity and are less toxic [20]. Combination regimens containing cisplatin, often in combination with an anthracycline or vinorelbine, have led to major responses in a minority of patients [25,29]. Cisplatin combined with doxorubicin has been evaluated in ACC, and is often administered in combination with cyclophosphamide (CAP) [30,31]. There remain insufficient data to conclude that platinum-based combination regimens lead to improved response rates and clinical benefit compared to single agents in ACC [20].

Targeted therapy has been evaluated in ACC. Although the majority of ACCs exhibit high expression of c-kit, imatinib has shown disappointing efficacy [32–37]. Other targeted agents have not shown efficacy in the treatment of ACC. Phase II studies of the EGFR inhibitors gefitinib [38] and cetuximab [39], as well as the pan-ErbB family inhibitor, lapatinib [40], did not produce major responses. Additionally, bortezomib, a proteasome inhibitor, did not result in any objective responses [41]. While disease stabilization was observed on all of these agents, not all studies required patients to have progressive disease at the time of study entry. Phase II trials evaluating multi-targeted tyrosine kinase inhibitors, including sunitinib [42], sorafenib [43], dovitinib [44], and axitinib [45], have been performed demonstrating both low rates of major response and disease stabilization.

Mucoepidermoid carcinoma

Although low-grade MEC rarely metastasizes, high-grade MEC commonly recurs locally and metastasizes, warranting systemic treatment [46]. However, there are no disease-specific studies evaluating systemic therapy for MEC. In the ECOG phase II trial evaluating single-agent paclitaxel, 25% of patients with MEC had an objective response, compared to no responses among patients with ACC [28]. Cisplatin-based combination regimens have also shown activity. Specifically, responses have been observed with CAP [47], CAP-5-Fluorouracil (FU) [48], cisplatin/doxorubicin/FU [49], and cisplatin/methotrexate/bleomycin [50,51].

Limited targeted therapy has been explored in MEC. One of three patients with a HER2 overexpressing MEC had an objective response to trastuzumab lasting over two years on a phase II trial, while the other two patients exhibited disease progression [52]. The phase II trial of lapatinib included two patients with MEC that expressed EGFR and/or HER2 and neither had a response [40]. Neither of the two patients with MEC who received treatment with cetuximab [39] responded, nor did another two patients who received treatment with gefitinib [53].

Adenocarcinoma

Although the specific histologic subtypes of salivary gland adenocarcinomas were not specified in clinical trials, patients with salivary gland adenocarcinomas who enrolled on trials were presumed to have had high-grade subtypes. Activity has been shown in patients treated with paclitaxel [28], vinorelbine [25], and CAP [29,30,47,54]. No responses to trastuzumab [52], lapatinib [40], cetuximab [39], and gefitinib [53] have been reported. Additionally, there have been case reports of AR-positive adenocarcinoma that have shown response to antiandrogen therapy [55,56]. Abiraterone as second line androgen-deprivation therapy was active in two patients with adenocarcinomas [57]. However, the anti-androgen approach applies more broadly to patients with SDCs that commonly overexpress AR per below.

Salivary duct carcinomas

SDC is an aggressive, high-grade malignancy that commonly presents with lymph node metastases, as well as distant metastases [2]. AR expression is frequently present in SDC. Although there has not been a disease specific clinical trial assessing androgen-deprivation therapy in this histologic subtype, case reports have related objective responses to anti-androgen therapy in patients with SDC [58–60]. There is currently an ongoing phase II clinical trial evaluating androgen-deprivation therapy, specifically bicalutamide and triptorelin, versus chemotherapy in patients with AR-expressing salivary gland cancers in Europe. In the United States, a single arm phase II trial assessing enzalutamide in patients with AR-positive salivary cancers is scheduled to open. Additionally, as HER-2 overexpression and/or amplification have been seen in a significant proportion of SDCs, chemotherapy that incorporated trastuzumab has been observed to lead to objective disease responses in patients with HER-2 expressing SDC [61]. However, as there is no data on the single-agent activity of trastuzumab or randomized data comparing chemotherapy +/− trastuzumab in SDCs, the contribution of trastuzumab in these observed responses is unclear.

Moving forward

In conclusion, there is clearly an unmet need for prospective clinical trials that evaluate systemic therapeutic agents and other