Systemic therapy for metastatic salivary gland tumors—challenges and novel concepts

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Summary Salivary gland cancers (SGC) are a rare and heterogeneous group of malignancies. Most frequently tumors arise in the parotid gland. The most common histologic subtypes are adenoid cystic carcinoma (ACC) and mucoepidermoid carcinoma (MEC). Rare subtypes include salivary ductal carcinoma (SDC), mammary analogue secretory carcinoma (MASC) and adenocarcinoma not otherwise specified (AC NOS). For locally advanced or metastatic disease, chemotherapy has been the mainstay of therapy. The course of disease differs markedly between the subtypes, especially ACC usually presents as slowly progressing disease. Due to the rarity of these tumors only small phase I/II studies exist, which report efficacy of cytotoxic regimens in advanced SGC. However, due to advances in the understanding of tumor biology and molecular testing, drugable genetic changes like androgen receptor (AR) status, HER2/neu overexpression and neurotrophic tyrosine receptor kinase (NTRK) gene fusion have evolved as potential therapy targets in subsets of SGC. Consequently therapy with androgen receptor blockade (ARB) can be offered to patients with AR expressing tumors. Anti-HER2 therapy with trastuzumab is an option for the treatment of tumors with overexpression of HER2/neu and finally NTRAK inhibitors can be used for tumors harboring a NTRK gene fusion. Taken together, due to the small number of patients, data from large phase III studies for the treatment of SGC are missing. However, promising targeted therapy approaches have been recently undertaken.

Keywords Adenocarcinoma · Treatment · Targeted therapy · Adenoidcystic carcinoma · Mucoepidermoid carcinoma

Epidemiology

SGC represent approximately 6–8% of all head and neck tumors [1]. The incidence in Europe is around 4 per 100,000 people [2]. The majority of tumors arises in the parotid gland (approximately 80%). However, only one quarter of these tumors are malignant. The rate of neoplasms is substantially higher in tumors of the submandibular, sublingual and minor salivary glands [3].

Benign and malignant salivary gland tumors are classified according to the 2017 WHO system. Mucoepidermoid carcinoma (MEC) and adenoid cystic carcinoma (ACC) represent the most frequent salivary gland carcinoma (SGC). SGC are classified according to their clinical behavior into low, intermediate and high grade, with the latter displaying a more aggressive phenotype [1].

The aim of this review is to recapitulate treatment options for ACC and non-ACC, especially focusing on targeted therapies which are already available for subsets of SGCs.

ACC

In the majority of cases, ACC is characterized by its slowly progressing nature. Patients with lung metastases only seem to have better outcomes than patients with more widespread disease [4, 5]. The median overall survival (mOS) of patients with metastatic ACC is reported to be approximately 3 years [5–9].

Especially patients presenting with oligometastatic disease can obtain great benefit from definitive locoregional therapies. In a series of 83 oligometastatic

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head and neck cancer patients, 16 patients with metastatic ACC were included. The 5-year OS after definitive locoregional therapy was 84% in the ACC subset [8].

In patients with slowly progressing disease or without symptom burden due to their malignant disease, it may be feasible to delay treatment due to the indolent course of disease.

Active agents that were tested mainly in phase II studies include cisplatin [10, 11], mitoxantron [12, 13], epirubicin [14] and vinorelbine [15]. However, it has to be kept in mind that disease stabilization was far more common in all these studies than an objective response, which might be due to the slowly progressing nature of this disease [9].

Combination therapy with cisplatin, doxorubicin and cyclophosphamide (CAP) provided overall response rates (ORR) between 18–33% in a total of 4 studies [16–19]. It has to be kept in mind that the triplet therapy is toxic. Replacing cyclophosphamide with 5-fluorouracil (PAF) led to ORR of 33% in ACC [20]. Combining 4 cytotoxic drugs (cisplatin, doxorubicin, 5-fluorouracil and cyclophosphamide; CAPF) led to an increased ORR (43%, 3 out of 7 patients) at the cost of severe toxicity. As a consequence this regimen should not be recommended [21]. A doublet therapy consisting of cisplatin and an anthracycline leads to ORR of roughly 25% [9]. A substitution of cisplatin with the less oto- and nephrotoxic carboplatin may be even less effective, as it was reported in two studies that all ACC patients that received carboplatin instead of cisplatin had no objective response to therapy [22, 23]. Further agents that have only limited activity include gemcitabine and paclitaxel [9, 24]. Taken together, results of chemotherapy in ACC are disappointing with only low response rates and no advantage in quality of life. Furthermore, no responses have yet been reported in previously treated ACC patients [2].

Targeted therapy in ACC

Given the fact that chemotherapy has only limited efficacy in ACC, approaches targeting molecular targets were investigated. Between 60–90% of ACC overexpress c-kit [25, 26]. However, all studies targeting c-kit with either imatinib or dasatinib showed disappointing results with ORR below 5% [27–30]. In addition, neither therapies targeting the epidermal growth factor receptor (EGFR) with gefitinib [31], cetuximab [32] or lapatinib [33], nor the vascular endothelial growth factor (VEGF) 1&2 with sunitinib [34] showed meaningful response rates in previously treated patients. However, response rates of at least 9–11% were reported for sorafenib and axitinib in small phase II studies [31, 35]. Nevertheless, progression after first-line therapy was not required as an inclusion criterion.

Recently, lenvatinib showed modest activity in a phase II trial of 33 previously treated patients with

ACC. The partial response rate was 16%, and in 75% of patients stable disease was achieved. Consequently, lenvatinib represents a possible option for second-line therapy after chemotherapy in ACC.

A more aggressive subset of ACC is defined by NOTCH homologue 1 (NOTCH1) mutation, which occurs in 26% of metastatic ACC [36]. A phase II study investigating the efficacy of ALI01, a NOTCH inhibitor, is still ongoing (NCT03691207).

MEC, salivary duct carcinoma (SDC) and adenocarcinoma not otherwise specified (AC NOS)

In the absence of driver mutations, chemotherapy can be offered to these patients. Again, the available data only derive from small phase II studies including various histological subtypes. Single agents that showed efficacy are cisplatin, paclitaxel [37] and vinorelbine [15]. Presumably more active are combination therapies. These include CAP [16–18, 38, 39] PAF [20, 40], cisplatin/gemcitabine [22] and carboplatin/paclitaxel [41].

Beside the limited data on chemotherapy in this subset of SGC, targeted therapies are under investigation. Overexpression or amplification of human epidermal growth factor receptor 2 (HER2) is reported in up to 30% of MEC, in 40% of SDC and in 20% of AC NOS [42–45]. Overexpression is defined as IHC 3+, or IHC 2+ plus FISH HER2/chromosome 17 ratio >2. Trastuzumab as monotherapy has only limited efficacy with ORR of around 10% [46–48]. A very recent phase II study included 57 SDC patients with HER2 overexpression. The combination treatment of trastuzumab and docetaxel showed promising results with an ORR of 70.2% and mOS 39.7 months. The most common toxicities were hematological adverse events with anemia and neutropenia. In addition treatment with ado-trastuzumab-emtansine (TDM-1) might pose a subsequent option after trastuzumab therapy. A phase II study showed some activity in SDC without previous anti-HER2 therapy [49]. Furthermore, preliminary data of a phase II basket trial presented at ASCO 2019 reported ORR upon TDM-1 of up to 90% in SDC previously treated with trastuzumab (NCT02675829).

AR expression is a frequent event in SDC and AC NOS, with rates of up to 90% [50–52]. Androgen deprivation therapy (ADT) is an option for those patients with AR expression SGC. A small phase II study enrolled 36 patients for combined therapy with bicalutamide and leuprorelin: 94% of patients had SDC and 6% AC NOS. The ORR was 41.7% and the mOS 30.5 months. Toxicities were limited and well manageable [51]. In addition a randomized phase II study comparing chemotherapy (cisplatin/doxorubicin or carboplatin/paclitaxel) vs. ADT (bicalutamide/leuprorelin) in patients with SDC or AC NOS in the first-line setting is ongoing (NCT01969578).

MASC

Mammary analogue secretory carcinoma (MASC) represents a rare subset of SGC and shows similarities to secretory carcinomas of the breast, especially regarding activating gene fusions of NTRK3 gene, with the ETV6-NTRK3 being the most common occurring in up to 99% of all MASCs [53, 54]. According to the preliminary results of phase I/II studies, both the FDA and EMEA approved larotrectinib for solid malignancies with NTRK fusion.

In a study with 55 patients an NTRK gene fusion positive solid cancers 12 patients with MASC were included. ORR was 83% ($n=10$) and 25% ($n=2$) experienced a complete remission [55]. In addition, entrectinib, another NTRK inhibitor proved its efficacy in a pooled analysis of three single arm trials including 54 patients. Seven MASC patients were included, and the ORR in this subset was 86% [56].

Both compounds are well tolerated and no discontinuation due to adverse events occurred [55, 56]. Due to the clinical efficacy and its good safety profile, entrectinib received accelerated approval by the FDA.

Checkpoint inhibitor therapy

The only available data come from a small phase Ib study (KEYNOTE 028) which included 26 programmed death ligand-1 (PD-L1) positive SGC patients. The overall response rate (ORR) was modest with 12%. In total, 3 patients achieved a partial response, and no complete responses were reported. The median PFS was 4 months and the mOS 13 months [57]. In addition, 3 small studies were presented at the ASCO 2019 utilizing CIT in SGCs. However, the results were disappointing. A combination of nivolumab and ipilimumab in recurrent or metastatic ACC showed an ORR of 6% [58]. Another study in ACC patients compared pembrolizumab with or without hypofractionated radiotherapy. Of the 20 included patients, none reached an objective tumor response. However, 65% of patients reached a stable disease (SD) [58]. Another multicentered phase II study included 46 ACC and 52 SGC patients for nivolumab therapy. The reported mPFS was 4.8 months for ACC patients and 1.8 months for SGC patients [58]. Further studies including SGC patients for checkpoint inhibitor therapy (CIT) have completed recruitment, but results are still lacking (KEYNOTE 158 NCT02628067) and NISCAHN (NCT03132038).

Conclusion

SGC are a heterogeneous and rare group of malignancies. Chemotherapy showed minor efficacy and the evaluation of therapy success is limited by the small number of patients. Targeted therapies are on the rise and potential molecular targets such as HER2, NTRK and AR do exist. However, SGC patients should be in-

cluded into clinical trials to further explore potential therapeutic options.

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