Oral Oncology 66 (2017) 58–63

Contents lists available at ScienceDirect

Oral Oncology

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

Review

Systemic therapy in metastatic salivary gland carcinomas: A pathology-driven paradigm?

Salvatore Alfieri, Roberta Granata, Cristiana Bergamini, Carlo Resteghini, Paolo Bossi, Lisa F. Licitra, Laura D. Locati *

Medical Oncology Unit 3, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
University of Milan, Italy

ARTICLE INFO

Article history:
Received 5 August 2016
Received in revised form 10 December 2016
Accepted 17 December 2016
Available online 19 January 2017

Keywords:
Salivary gland carcinoma
ACC
Metastatic
Systemic
Chemotherapy
Targeted therapy
Androgen deprivation therapy

ABSTRACT

Salivary gland carcinomas (SGCs) represent one of the most complex tumors from a pathological point of view. According to the World Health Organization (WHO) classification (2005), twenty-four malignant histotypes are recognized, almost all characterized by specific morphological and genetic features as well as by particular clinical behavior. Loco-regional relapse and distant metastases are quite common. Distant metastases are diagnosed in 25–55% of the patients and only 20% of them are alive after 5 years. Adenoid cystic carcinoma (ACC) is the most common (60%) malignant histotype observed in patients with metastatic disease, whilst the other histotypes such as mucoepidermoid carcinoma, salivary duct carcinoma, adenocarcinoma, not otherwise specified (NOS), and myoepithelial carcinoma are rarer. The most common therapeutic approach in cases of metastatic disease is systemic chemotherapy, although the results with this type of approach are poor both in terms of response rate and overall outcome. No consensus has yet been reached on what the standard regimen of chemotherapy should be in this setting. New therapies are under investigation e.g. antiangiogenic agents, histone deacetylase inhibitors, and hormonal deprivation treatment. We have focused our review on systemic treatments in ACC and in non-ACC tumors, including in this latter group all SGC histotypes other than ACC.

Introduction

Salivary gland carcinomas (SGCs) are rare. Worldwide annual incidence ranges between <0.05 and 4 per 100,000 people, with an incidence of 1.2 per 100,000 in European countries. From a pathological point of view, SGCs are epithelial tumors. They represent one of the most complex tumors due to the heterogeneity of their origin cells. The luminal part of the glandular acinus is composed of acinar and ductal cells whilst myoepithelial and basal cells wrap the external layer of the acinus. The latest WHO classification comprises 24 malignant histotypes [1], almost all characterized by specific morphological, immunohistochemical and genetic features as well as by particular clinical behavior. This WHO classification is currently under revision, and new histotypes as well as a deeper insight into tumor-specific genetic abnormalities will be included in the new classification. It is commonly thought that sensitivity to chemotherapy may be histotype specific. For example, paclitaxel and gemcitabine are active in mucoepidermoid carcinoma (MEC) and adenocarcinoma, NOS but not in adenoid cystic carcinoma (ACC) [2,3]. Similarly, the expression of molecular targets is histotype-related [e.g. c-kit for ACC, Human Epidermal Growth Factor receptor 2 (HER2) and androgen receptor (AR) for salivary duct carcinoma (SDC), Epidermal Growth Factor Receptor (EGFR) for MEC].

Moreover, the frequency of each histotype among metastatic patients is quite different, with ACC being the most common (60%). Data on systemic treatments (i.e. chemotherapy or targeted therapy) are abundant for ACC whilst they are scarce for the other histotypes, sometimes even non-existent or anecdotal for rarer tumors, such as myoepithelial carcinoma, acinic cell carcinoma or other histotypes of the non-ACC group.

For the purpose of this review and considering just how different the characteristics of ACC are in comparison to the other histotypes, here defined as non-ACC, we have decided to discuss the systemic treatments for these two groups separately.

* Corresponding author at: Medical Oncology Unit 3, Fondazione IRCCS Istituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy.
E-mail address: laura.locati@istitutotumori.mi.it (L.D. Locati).

http://dx.doi.org/10.1016/j.oraloncology.2016.12.016
1368-8375/

ACC

To treat or not to treat a metastatic patient: is this the question?

At present there is little consensus on the best management of metastatic ACC patients. The main concern regards whether to start promptly with treatment or not [4]. This is due to the indolent evolution of this kind of cancer, which is seen in the majority of cases. To date, we have scarce data to classify patients at diagnosis of relapsed and/or metastatic disease for differential prognosis. The site of the disease seems to have a prognostic significance. Better survival outcomes have been reported [5,6] in patients with only lung metastases compared to those with more widespread disease (e.g. liver and bone), regardless of performed treatments, bringing into question whether in this subset of patients a prompt initiation of treatment would be advisable, taking into account the toxicity profile of available systemic treatment options. Recently, Ferrarotto et al. [7] identified a subgroup of ACC patients harboring some specific NOTCH pathway activating mutations with a more aggressive disease phenotype: higher tumor stage at diagnosis, higher risk of relapse and shorter survival with tumors spreading mainly into the bone and the liver. In general, the most common approach in cases of metastatic ACC is a watchful waiting, providing active treatment only to patients with symptomatic and/or rapidly progressing tumors. Systemic chemotherapy is the most popular treatment at this stage; a few experiences of loco-regional therapies, such as lung metastasectomy [8,9] or embolization/radiofrequency ablation of liver lesions [10] have also been reported, although data on the outcome are still scarce. At present, results from clinical trials using targeted agents are still disappointing [Table 1].

Chemotherapy: single or multiple-agent based regimens?

Randomized trials have never been carried out in this setting. Phase II studies have been conducted using a single drug regimen. Cisplatin 100 mg/sm q21 days [11], mitoxantrone 14 mg/sm q21 days [12,13], epirubicin 30 mg/sm weekly [14], and gemcitabine 1250 mg/sm (in a day 1 and 8 schedule) q21 days [2] have been investigated. Among these agents, gemcitabine was not active whilst cisplatin and epirubicin showed quite significant activity even if the response rate (RR) of 70% for cisplatin [11] has been better evaluated by Licitra et al. [15], who reported an overall RR of 15.4% (including 2 complete responses in 13 ACC patients out of 25 enrolled), similar to the activity described for other single chemo-agents in ACC. The range of these results reflects the heterogeneity of patient selection as well as the limited number of enrolled subjects. Other drugs such as paclitaxel 200 mg/sm q21 days [3] and vinorelbine 30 mg/sm intravenously weekly [16] were tested: only the second one showed some activity with a RR of 15.4% (2 partial responders out of 13 ACC patients) whilst no response was found with paclitaxel, indicating against using it in ACC subjects in clinical practice.

Data extrapolated from 4 trials with polychemotherapy [17–20] treating only ACC patients (36 in total) have highlighted cisplatin, anthracyclines, 5-fluorouracil, cyclophosphamide, vincristine, and bleomycin as active and safe agents, in this cancer population. In 13 other studies testing this combination in unselected SGC histotypes (107 ACC patients), these agents were confirmed as being those which work better in ACCs [4]. A combination of cisplatin and anthracycline is the most used in clinical practice. Cisplatin in combination with doxorubicin (or another drug) in a doublet or with another drug in a triplet chemo-regimen exerts a limited activity (RR about 25%) [4]. The most used triple agent-based regimen was CAP (cyclophosfamide 500 mg/sm, doxorubicin 50 mg/sm, cisplatin 50 mg/sm) in 4 studies [21–24]. Only one study with 4 drugs (cyclophosfamide, doxorubicin, cisplatin, 5fluorouracil) has been reported, resulting in a slightly better RR of 42.8%, but without any improvement in survival and with a greater toxicity [25]. Cisplatin should be preferred to carboplatin considering that all studies with carboplatin have showed a lower response rate [26,27].

The results obtained with chemotherapy in ACC patients are overall still unsatisfactory. The activity of combined regimens seems to be superior to monotherapy although toxicities are consistently higher, thus supporting the employment of doublet chemotherapy regimens only in selected patients with good clinical conditions (Performance Status of 0–1) and no major comorbidities. Symptomatic relief is sometimes obtained but no advantage in quality of life has yet been demonstrated. No responses were seen among pre-treated ACC patients questioning the role of a second line chemotherapy.

Table 1
New drugs studied in advanced ACC.

Drug	Target	Number of clinical trials [Ref.][a]	ACC[b] (No.)	RR[c] (%)
Imatinib	KIT	7 [39–44][d]	63	6.3
Lapatinib	EGFR/HER2	1 [35]	19	0
Gefitinib	EGFR	1 [36]	18	0
Cetuximab	EGFR	1 [37]	20	0
Trastuzumab	HER2[e]	1 [38]	2	0
Bortezomib	NF-kB	1 [57]	25	0
Sunitinib	VEGFR/PDGFR	1 [50]	13	0
Sorafenib	BRAF/VEGFR/PDGFR	2 [51,52]	38	11
Axitinib	VEGFR1-3	1 [53]	33	9
Dovitinib	FGFR3	2 [46,47]	67	4.5
Everolimus	mTOR	1 [58]	34	0
Nelfinavir	AKT	1 [59]	15	0
MK-2206	AKT	1 [60]	16	0
Dasatinib	KIT	1 [45]	40	2.5
Vorinostat	HDAC	1 [61]	30	7
Pazopanib	VEGFR1-3/PDGFR/KIT	1 [56]	49	2
Nintedanib	VEGFR/PDGFR/FGFR	1 [54]	13	0
Regorafenib	VEGFR2-3/RET/PDGFR	1 [55]	38	0

[a] All clinical trials mentioned are phase II studies.
[b] ACC: Adenoid cystic carcinoma.
[c] RR,: Response Rate.
[d] Also including case series.
[e] HER2 was evaluated by IHC [38].