Update and perspectives on non-surgical treatment of salivary gland malignancies

Attualità e prospettive nel trattamento non chirurgico dei carcinomi delle ghiandole salivari

M. AIROLDI, G. CORTESINA[1], C. GIORDANO[1], F. PEDANI[1], A. CAVALOT[1], P. MARCATO[1], F. BEATRICE[2], C. BUMMA
Department of Medical Oncology, S. Giovanni Antica Sede Hospital, Turin
[2] ENT Clinic, University of Turin
[3] ENT Department, Giovanni Bosco Hospital, Turin, Italy

Key words

Salivary gland carcinoma • Radiotherapy • Chemotherapy • Biological therapy

Parole chiave

Tumori ghiandole salivari • Radioterapia • Chemioterapia • Terapia biologica

Summary

Surgery is the treatment of choice for major and minor salivary gland malignancies. Herein, the role of radiation and medical treatment in the multidisciplinary management of salivary gland tumours is discussed. Neutron irradiation and hyperfractionated external beam mega voltage irradiation improve local control. Combination of three dimensional conformal radiotherapy and intensive-modulated radiation therapy provide better local tumour delineation, better field design to encompass the tumour allowing dose escalation to target while sparing the surrounding normal tissue. Cisplatin-based chemotherapy provides a response rate ≥ 45%, in a palliative setting. Concomitant chemo-radiotherapy could improve local control. Recent studies evaluated the expression of molecular targets in salivary gland carcinomas (c-kit = 53-90%, EGFR = 25-85%, c-erb-B2 = 11-57%, p53 = 11-67%, H ras = 18%); these targets are very important since new targeted drugs are now available. Anti-androgen therapy might have a role in the management of patients with ductal carcinoma. These new targeted drugs could be integrated with chemotherapy and radiotherapy in the treatment of locally advanced/metastatic salivary gland malignancies.

Riassunto

Nei carcinomi delle ghiandole salivari la chirurgia rimane l'opzione principale. In questo lavoro si analizzano le potenzialità e le prospettive delle terapie radianti e mediche nonché le loro possibili integrazioni. La radioterapia con neutroni e quella iperfrazionata sono in grado di migliorare il controllo locale. Le nuove tecniche di radioterapia (3D-CRT e IMRT) permettono di erogare alte dosi con risparmio di tossicità per i tessuti sani. La chemioterapia palliativa con combinazioni comprendenti cisplatino determina risposte oggettive nel 35-45% dei casi. Un uso concomitante alla radioterapia potrebbe aumentare il controllo locale. In questi carcinomi sono diffusamente presenti alcuni *targets* (c-kit = 53-90%, EGFR = 25-85%, c-erb-B2 = 11-57%, p53 = 11-67%, H ras = 18%) verso i quali disponiamo di nuovi farmaci. Nel carcinoma duttale si può ipotizzare l'utilizzo di una terapia anti-androgenica. Infine si prospettano le possibili integrazioni di questa terapia biologica con chemioterapia e radioterapia.

Introduction

Surgery is the treatment of choice for major and minor salivary gland malignancies[1]; the ability of the well-trained head and neck surgeon to excise salivary gland malignancies, in any site, has probably not changed significantly over the last 20 years, although the availability of cutaneous, subcutaneous, osteocutaneous, and innervated muscle flaps has made reconstruction much easier, in those patients requiring very radical operations. Radiation therapy is indicated post-operatively for patients with high-grade neoplasms, involving surgical margins, local soft tissue, osseous, perineural, or lymphatic metastases. In unresectable cases, radiation therapy is the treatment of choice. Chemotherapy has a palliative role. The overall incidence of distant metastases is about 25%. The lungs are favoured sites for metastases, although bone, liver, central nervous system (CNS) and other organs may become involved. Loco-regional recurrences, in selected cases, may be managed with further surgery or radiotherapy but long-term remissions are rare (<10%). However, most patients with recurrent or metastatic salivary gland cancer can be treated with chemotherapy with a palliative endpoint. Herein, the role of radiation and medical treatment is

discussed in the multidisciplinary management of salivary gland tumours. This integration is very important since, despite advances in loco-regional treatment, the 5-year survival of patients with high-grade histological pattern (adenoid cystic carcinoma, malignant mixed tumour, high grade adenocarcinoma, undifferentiated carcinoma, high grade mucoepidermoid carcinoma) or locally advanced disease is approximately 50%.

Radiotherapy

Photon or electron beam post-operative radiation therapy can lead to 34-74% improvement in local control [2].

A review of the literature on inoperable tumours showed loco-regional control rates of 4-54% with low-LET (Linear Energy Transfer) (photons, electrons) [3 4]. The most effective non-surgical treatment for inoperable salivary gland neoplasms, especially adenoid cystic carcinoma, is neutron beam [5 6]. A prospective clinical trial showed that neutron irradiation is superior to high-energy X-rays in the treatment of macroscopic salivary gland lesions (local control 64% vs 31%; 2-year overall survival 68% vs 25%) [5]. However, it is well known that such treatment is available at only a few centres. Bulky salivary tumours can also be successfully palliated by the combined use of localized hyperthermia and external beam radiotherapy or brachytherapy [7 8]. The permanent implantation of iodine-125 sources or the use of after-loading low- or high-dose rate removable iridium-192 implants may produce effective palliation [9].

The use of hyperfractionated external beam mega voltage irradiation consisting of multiple daily 160 cGy fractions for a total tumour dose of 65 to 70 Gy in 5-6 weeks has also recently been proposed, with excellent local control rates [10].

Three-dimensional (3D) conformal radiation therapy allows radiation therapy fields to conform to the shape of the target area; it achieves isodose distributions that maximally cover the target while minimally irradiating normal tissue, and uses beams-eye treatment planning to avoid underdosage of any area of the target volume. Therefore, we have a combination of better local tumour delineation, better field design to encompass the tumour, and a technique that allows dose escalation to target while sparing the surrounding normal tissue.

Palliative chemotherapy

In combined chemotherapy for head and neck cancer, salivary carcinoma shows a poor clinical outcome, and it has been suggested that the sensitivity and/or mechanism of resistance to anti-cancer drugs are different between these two conditions. P-glycoprotein expression is associated with multidrug resistance and in salivary gland malignancies is an inherent phenotype caused both by high levels of P-glycoprotein induction and activated production during treatment, while that in squamous cell carcinoma is an acquired phenotype chiefly caused by induction of P-glycoprotein [11].

With regard to advanced loco-regional or metastatic salivary gland carcinomas, only small series of patients, treated uniformly with single agent chemotherapy, have been reported. Cisplatin is considered the most active drug and is the "backbone" of polychemotherapeutic regimens; in 1981-1982 cisplatin has been reported to provide a response rate up to 70% in case series with fewer than 15 cases each [12 13].

In 1991, Licitra et al. showed that cisplatin provided an overall response rate of 16% in 25 consecutive patients; in 19 patients, not previously treated with chemotherapy, the response rate was 21%. Response duration was between 5 and 9 months and median overall survival time was 14 months [14].

As single agents, epirubicin and mitoxantrone are reported to provide a 10% response rate (Table I) [15-17].

Tannock and Sutherland reported objective responses in 4 out of 12 patients following fluorouracil administration but the estimates of tumour response are not clearly described [18].

Cyclophosphamide + vincristine + 5-fluorouracil combination has not been proven more effective than single agent chemotherapy [19]; the addition of cyclophosphamide appears to enhance the efficacy of adriamycin alone [20] (Table I).

We have recently shown a moderate activity of vinorelbine [21 22]. A series of 20 patients (13 male, 7 female, median age 61 years, range 27-64) with recurrent adenocarcinoma-like tumours of major (10 patients) and minor (10 patients) salivary gland origin (13 adenoid cystic carcinoma, 5 adenocarcinoma, 1 malignant mixed tumour, 1 undifferentiated carcinoma) were treated with vinorelbine at the dose of 30 mg/m^2 iv weekly. Of these patients, 16 had previously been treated with surgery plus radiation, 3 with surgery plus radiotherapy plus novantrone and 1 with radiotherapy alone. Nine patients had local recurrence, 2 local relapse plus metastases and 9 metastases alone. The site of metastases were: lung (7 cases), bone (1 case), lung+bone (2 cases) and lung+bone+lymph node+skin (1 case). Overall, 174 courses were given (median 9, range 6-19). Responses were: partial response (PR) in 4 patients (20%) with a median duration of 6 months (3-9), 9 no change (NC) (45%) with a median duration of 3.5 months and 7 progressive disease (PD) (35%). The median survival duration was 10 months for PR/NC

Table I. Results of chemotherapy in salivary gland tumours.

Drug(s)	Complete + Partial remissions	References
Cisplatin	16%	14
Epirubicin	10%	15
Mitoxantrone	5-12%	16,17
Vinorelbine	20%	22
Paclitaxel	18%	33
CYC+5-FU+VCR	25%	19
Adriamycin+CYC	38%	20
Cisplatin+5-FU	0%	32
Cisplatin+Adriamycin+CYC	27-46-50%	24-26
Cisplatin+Adriamycin+5-FU	37%	27
Cisplatin+Epirubicin+5-FU	44%	28
Cisplatin+Adriamycin+CYC+5-FU	50%	31
Cisplatin+Adriamycin+Bleomycin	33%	30
Cisplatin+Vinorelbine	44%	23
Cisplatin+VP-16+Bleomycin	45%	29
Carboplatin+Paclitaxel	14%*	33

* >50% Cisplatin pre-treated; CYC: cyclophosphamide; VCR: vincristine

patients, 4 months for non-responders. Median overall survival was 7 months. The treatment was well tolerated and toxicity was manageable.

Cisplatin and vinorelbine have been shown to have a synergistic activity both in vitro and in vivo.

Between April 1993 and April 1997, 36 patients in a phase II randomized trial received either cisplatin 80 mg/m^2, on day 1, plus vinorelbine 25 mg/m^2, on days 1 and 8 (every 3 weeks) for a minimum of 3 cycles (16 patients; arm A), or vinorelbine, 30 mg/m^2/week, for a minimum of 9 weeks (20 patients; arm B). This study population comprised 23 males and 13 females, median age 59 years (range 20-74) and a median Eastern Cooperative Oncology Group (ECOG) performance status of 1 (range 0-2). Of these patients, 4 had been previously treated with surgery or radiotherapy, 27 had been treated with surgery plus radiotherapy, and 5 had been treated with surgery plus radiotherapy plus mitoxantrone. As far as concerns tumour type, 18 patients had major salivary gland tumours, and 18 had a minor salivary gland tumour; 9 patients had adenocarcinoma, 22 had adenoid cystic carcinoma, 1 had a malignant mixed carcinoma, 3 had undifferentiated carcinoma and 1 had a mucoepidermoid carcinoma. The site of recurrence was local (16 patients), local plus metastases in 5 patients and metastases only in 15 patients. These characteristics were well balanced between the two arms [23]. In arms A and B, a complete response (CR) was observed in 3 patients (19%) and no patient, respectively; a PR was observed in 4 (25%) and 4 patients (20%), respectively; no change was observed in 6 (37.5%) and 9 patients (45%), respectively; and progressive disease was observed in 3 (19%) and 7 patients (35%), respectively. The median duration of the CR was 15+ months (range 6-27+) and for PR the median duration was 7.5 months (range, 3-11+) and 6 months (range 3-9) in arms A and B, respectively. The median overall survival durations for arms A and B were 11 months (range 3-29+) and 8.5 months (range 2.5-16), respectively; a significant difference in >12 months survival was noted in arm A ($p<0.05$). At 2 years, 19% of patients treated with the combination were alive whereas in the vinorelbine alone arm, no patient was still alive at 2 years. The survival curve analysis showed a trend ($p=0.058$) toward better survival in the cisplatin plus vinorelbine arm. The median survival for patients achieving CR was 19+ months; the median survival of patients achieving a PR was 12.5 months for arm A and 9 months for arm B. Patients with an ECOG performance status of 0-1 had a median survival of 10.5 months, which was statistically better ($p<0.05$) than patients with an ECOG performance status of 2 (median survival time, 4.5 months).

Grade 2-3 nausea and emesis was statistically higher ($p<0.001$) in arm A; there was no significant difference with regard to other side-effects between the two treatment arms.

Chemotherapy regimens including cisplatin, adriamycin, and cyclophosphamide have shown significant efficacy with overall response rates of 27-50% [24-26]. Chemotherapy regimens combining cisplatin, adriamycin or epirubicin+ 5-fluorouracil achieved over-

all response rates between 37 and 47% [27 28]; comparable results were obtained with the combinations of cisplatin, bleomycin and adriamycin or VP-16 (Overall Response Rate – ORR = 33-45%) [29 30]. The 16 evaluable patients with recurrent or non-resectable salivary gland malignancies were treated with a combination of fluorouracil, adriamycin, cyclophosphamide, and cisplatin. A total of 111 courses of chemotherapy were given, yielding one complete (6%) and seven partial responses (44%) [31]. The median duration of the objective response was 32 weeks and the median overall survival was 72 weeks. Haematologic toxicity was significant and 7 patients (44%) developed neutropenic fever; 3 patients (18%) developed an increase in serum creatinine >1.5 mg/dl during the course of treatment. Response duration, or overall patient survival, of this intensive regimen was comparable to that in other published therapeutic trials concerning this disease.

The combination of cisplatin and fluorouracil, the most commonly used regimen in squamous cell head and neck cancer, yielded disappointing results in terms of objective response rates [32].

Taxol is an efficacious drug, in salivary gland carcinomas, especially in mucoepidermoid carcinoma and adenocarcinoma [33]; given the promising response rates obtained in other diseases, paclitaxel and carboplatin seem to be a logical combination to be used in advanced salivary gland tumours. A total of 14 patients (10 male, 4 female; median age 55 years, range 20-70) with recurrent carcinomas of major (9 patients) and minor (5 patients) salivary gland origin (histology: 1 adenocarcinoma, 10 adenoid cystic carcinoma, 2 undifferentiated carcinoma, 1 mucoepidermoid carcinoma) were treated by us with carboplatin area under curve (AUC) 5.5 and paclitaxel 175 mg/m^2 (3-hour infusion) on day 1 (interval=3 weeks) [34]. All patients had previously been submitted to surgery and radiotherapy and 8 treated with a cisplatinum combination. One had a local lesion, 7 loco-regional recurrence and metastases and 6 had only metastases. Overall, 65 courses were given (median 5; range 2-6). The responses were: PR in 2 patients (14%) lasting 5 and 12 months, 7 NC (50%) with a median duration of 8.5 months (range 5-12), and 5 PD (36%). The median survival time was 13.5 months for PR/NC patients, 6 months for non responders; median overall survival was 12.5 months (3-17+). The treatment was well tolerated and toxicity was manageable. Our study suggests that this combination has a moderate efficacy; the poor results were probably due to the high percentage of adenoid cystic carcinoma with distant metastases and to the large number of patients previously treated with chemotherapy for recurrence. Second-line chemotherapy was ineffective.

In murine salivary gland carcinoma, docetaxel has proven to be effective; no data have been reported in humans [35].

In metastatic/recurrent disease, the following conclusions can be drawn [36]:

- cisplatin, anthracyclines, paclitaxel and vinorelbine are the most effective agents;
- chemotherapy regimens combining cisplatin, anthracycline or vinorelbine are well tolerated with objective responses that appear to be superior to those observed after mono-chemotherapy; our randomized trial has confirmed this hypothesis. Triple therapy is probably not more effective than double combined therapy. Combination regimens are more toxic than single-agent chemotherapy;
- responses are more frequent in chemotherapy-naive patients and in cases with loco-regional disease; adenoid cystic carcinoma seems less chemosensitive than adenocarcinoma; mucoepidermoid carcinoma responds to the drugs effective in squamous cell head and neck carcinoma even if the response rate is lower;
- median CR duration is 7-18 months;
- patients achieving stable disease can achieve a transient subjective improvement;
- despite the absence of an apparent survival benefit, palliation of pain and local disease is frequently pronounced;
- the optimal drug combination remains to be defined;
- patients with bulky disease, impaired performance status, or marginal nutritional status might be best treated by supportive care.

Neo-adjuvant chemotherapy

Response to neo-adjuvant chemotherapy in squamous cell carcinoma of the head and neck predicts a better prognosis and permits a conservative treatment, but it has been shown to have no impact on survival [37].

Nine patients were treated with cisplatin, doxorubicin, and 5-fluorouracil combination chemotherapy; one complete remission (11%) and 2 partial remissions (22%) were observed [27]. In recurrent/metastatic disease, this regimen led to the same response rate.

There may also be a role for neo-adjuvant chemotherapy in selected patients who have inoperable primary tumours, although more effective chemotherapy regimens must be used. The responsiveness to a neo-adjuvant scheme could be important to plan the subsequent chemotherapy concomitant with radiotherapy or in an adjuvant setting.

Adjuvant chemotherapy

Triozzi et al. [19] evaluated the efficacy of combination chemotherapy consisting of intravenous boluses of cyclophosphamide and vincristine and continuous i.v. infusion of 5-fluorouracil as adjuvant therapy after radiation therapy in 13 patients who had incomplete resection of either primary or recurrent adenoid cystic carcinoma.
No distant metastases developed in the patients treated with adjuvant chemo-therapy whereas distant metastases had developed in historical controls with comparable periods of follow-up. The response rate of this regimen in recurrent disease (25%) seems to be too low to obtain a favourable outcome in an adjuvant setting. In squamous cell head and neck carcinoma, adjuvant chemotherapy remains experimental and overall survival has not improved despite the possibility that the distant metastases rate may decrease [38].
We have recently reported the feasibility of adjuvant cisplatin+ VP-16 after chemo-radiation of undifferentiated carcinoma of the parotid gland [39].

Concomitant chemo-radiation therapy

In locally advanced head and neck cancer, a recent meta-analysis has shown a significant benefit of chemotherapy concomitant with conventional radiotherapy versus radiotherapy alone [37].
Two recent and well-conducted randomised trials [40 41] have investigated concurrent cisplatin and conventional radiotherapy, in an adjuvant setting, versus conventional post-operative radiotherapy in patients with high risk of recurrence. Clinical outcomes were better in the combination arm.
We have recently reported personal data following concomitant radio-chemotherapy in locally advanced undifferentiated carcinomas of the parotid gland [39]. Undifferentiated carcinoma is a poor-prognosis lesion. In patients treated with radical surgery and adjuvant post-operative radiotherapy, the 5-year survival is 33%. Results in inoperable T_3-T_4N_{0-1} lesions, treated with radiotherapy alone are very disappointing.
Six patients with T_{3-4} N_{0-1} inoperable lesions were treated with conventional radiotherapy (64-70 Gy, 2 Gy per fraction 5 times a week) and concomitant cisplatin (100 mg/m^2, days 1, 22 and 43). Four weeks after radiotherapy, adjuvant chemotherapy (cisplatin 80 mg/m^2, day 1 + VP-16 100 mg/m^2, days 1, 3, 5 at 3-week intervals, for 3 cycles) was given. A median dose of 66 Gy was delivered, and all patients received 3 courses of cisplatin during radiotherapy. Five out of 6 patients received all three chemotherapeutic adjuvant courses. Two months after the end of treatment, 3 CR (50%), 2 PR (33%) and 1 NC (16%) were observed. Median CR and PR duration was 26 and 10 months, respectively. Median overall survival was 18 months. No severe acute or late toxicity was observed. We had only one refusal before the third adjuvant planned course, probably due to the low mucosal toxicity of cisplatin and VP-16 at the adopted dose level. The impact of the whole treatment on survival is difficult to define. Due to the histologic type and the bulky lesions, we could expect a very poor prognosis. It was encouraging to have observed three long-term complete responses, without severe late side-effects.
These results indicate that chemotherapy may be another effective way to enhance radiotherapy.

New targets

Recent studies have evaluated the expression of molecular targets in salivary gland carcinomas; these targets are very important since new targeted drugs are now available.
In squamous cell head and neck cancer, these drugs have obtained a response rate between 6% and 20% and a disease stabilization of 25% to 40% (Table II). Proteins encoded by tyrosine-kinase receptors, such as c-kit, are widely expressed in salivary gland malignancies (Table III). The c-kit protein, a receptor type tyrosine kinase that plays an important role in the development of haematopoietic cells, melanocytes and germ cells, is expressed in mastocytosis, gastrointestinal stromal cell tumours, and several other tumours. Gain-of-function mutations in exon 11 and exon 17 have been shown as a mechanism of c-kit activation in some tumours. Although varying in intensity of staining, c-kit expression was identified very often in adenoid cystic carcinoma, lymphoepithelioma-like carcinomas and myoepithelial carcinomas [42-44]. By DNA sequencing, genetic alterations of the c-kit juxtamembrane domain (exon 11) and the tyrosine kinase domain (exon 17) were not found in all three types of salivary carcinoma that had c-kit expression. c-kit expression was noted in 90% of adenoid cystic carcinomas; an association between the presence of at least 50% c-Kit positive neoplastic cells and grade 3 or a solid growth pattern was observed; c-kit immunostaining may be a valuable adjunctive tool for differentiating salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma which does not express c-kit [45]. Imatinib mesylate (Glivec™ is the commercial name) was identified as a potent protein kinase inhibitor of c-kit, the platelet-derived growth factor, and v-Abl; phase I and II trials in chronic myeloid leukemia proved the validity of this concept. In gastrointestinal stromal tumours, which have a high c-kit expression, this drug has proven highly effective. The role of this drug in ade-

Table II. Results of new targeted drugs in squamous cell head and neck cancer.

Target	Drug	Objective responses	No change
EGFR			
	Cetuximab	14%	40%
	Iressa	20%	35%
	OSI 774	13%	29%
p53			
	Onyx-015	14%	40%
	Ad-p53	12%	35%
Ras			
	SCH 66366	17%	
VEGFR			
	SU 5416	6%	25%

Table III. Molecular Target expressions in salivary gland malignancies.

c-kit	= 53-75-90%* (27% with +++)
EGFR	= 25-60-85%
c-erb-B2	= 11-20-57%
p53	= 11-31-67%
H ras	= 18%**

Salivary Duct Carcinoma: EGFR = 92%; TGF-α = 67%; AR = 92%
* Adenoid cystic carcinoma – especially G3; ** Mucoepidermoid carcinoma.

noid cystic carcinoma has not been investigated but it is extremely important to explore the activity especially in the more aggressive types.

The Epidermal Growth Factor (EGF) is an important mediator of cell growth, differentiation, and survival. Among the peptide growth factors, EGF and tumour growth factor-alpha (TGF-α) are believed to be the main endogenous ligands that result in EGFR receptor EGFR-mediated stimulation for tumour growth and progression, angiogenesis, cell survival, and metastasis. The frequency of positive EGFR staining in salivary gland tumours is different (Table III), probably due to the different methods of evaluation; as far as concerns salivary carcinomas, EGFR was reported in 85% of adenoid cystic carcinomas even if a positivity of 20-30% was more frequently described [46-48]. A variety of agents have been developed over the last few years that inhibit the EGFR signal, such as monoclonal antibody (Cetuximab) directed against its external ligand-binding domains and synthetic tyrosine-kinase inhibitors that act directly on the cytoplasmatic domain of EGFR (Iressa, OSI 774). These agents, in vitro and in vivo, are able to reduce tumour cell growth by inducing apoptosis and to modulate inhibition of production of angiogenetic factors. Anti-EGFR agents are currently under investigation in phase II/III trials combined with standard chemotherapy and radiotherapy, as radiosensitizers, in patients with head and neck (Table II), lung, renal, gastric and prostate cancer.

These agents can improve the efficacy of platinoids, taxanes and anthracyclines cytotoxic; these groups of cytostatics are the most effective in salivary gland malignancy [49 50]. Cetuximab (IMC-225), a chimeric monoclonal antibody that specifically binds to the EGFR with high affinity, overcomes resistance to cisplatin in cisplatin-refractory advanced head and neck squamous cell carcinoma [51].

Protein kinase A inhibitors and VEGFR inhibitors have a synergistic effect in combination with EGFR inhibitors [52 53]; multitarget therapy seems very interesting.

COX-2 inhibitors enhance antitumoural activity of EGFR and HER-2/neu inhibitors [54 55]. COX-2 inhibitors, show promise in combination with radiation therapy and inhibit angiogenesis [56 57].

The HER2 oncogene is differently expressed in salivary gland malignancies [58-60] (Table III); its overexpression correlates with poor prognosis. We have monoclonal antibodies and tyrosine kinase inhibitors for the erbB-2 receptor which could be used alone or in combination for salivary gland malignancies.

The p53 tumour suppressor gene may be involved in salivary gland carcinogenesis, and its oncoprotein expression is an independent indicator of clinical aggressiveness in patients with carcinoma of the parotid gland. The p53 expression is associated with certain histological types (adenocarcinoma, pleomorphic adenoma, salivary duct carcinoma), advanced tumour stage and high-cell proliferative activity [59 61]. p53 gene replacement therapy (adenovirus-p53) and strategies aimed specifically at enhancing viral replication in cells with defective p53 protein (ONIX-015) have been explored in clinical trials.

H-ras mutations, predominantly at codon 12, were detected in 18% of mucoepidermoid carcinomas; mutations were observed more often in high grade lesions [62]. Ras overexpression correlates with radio-resistance; farnesyl transferase inhibitors, are able to enhance tumour radiosensitivity [63]. These drugs can also revert acquired resistance to either paclitaxel and epothilones [64].

Vascular Endothelial Growth Factor inhibitors (mono-clonal antibodies and tyrosine kinase inhibitors) combined with radiation show a very favourable interaction in the tumour model system [65].

Salivary duct carcinoma is a high grade aggressive malignancy of the major salivary glands. The microscopic features are remarkably similar to those of mammary ductal carcinoma, suggesting that these tumours may share antigenic or hormonal features [66]. This tumour frequently expresses androgen receptor (90%), EGFR (90%) and TGF-α (67%) [67, 68] suggesting the presence of an androgen receptor-mediated TGF-α/EGFR autocrine pathway in these neoplasms. The same tumour expresses Prostatic Acid Phosphatase (PAP)(58%) and Prostatic-Specific Antigen (PSA) (18%), indicative of a close immunophenotypic homology between this cancer and prostatic carcinoma [69]. These observations raise the possibility that anti-androgen therapy, possibly with anti-EGFR therapy, might have a role in the management of patients with disseminated disease.

Perspectives of combined treatments

Cisplatin-based chemotherapy can enhance radiation therapy, and some new target therapies can obtain the same result. In inoperable lesions, we could integrate radiation therapy with medical treatments; a comparable strategy could be evaluated in the post-operative adjuvant setting.

New target drugs, if proven effective in salivary gland malignancies, could be used in the adjuvant setting of high risk patients.

Neo-adjuvant medical regimens could be used in locally advanced lesions to obtain a down-staging.

Palliative treatments could integrate new target drugs.

Phase I and II studies, with these new agents, will be very important.

References

1 Spiro RH, Dubner S. *Salivary gland tumors*. Curr Opin Oncol 1990;2:589-95.

2 Guillamondegui OM, Byers RM, Luna MA, Chiminazzo M Jr, Jesse RH, Fletcher GH. *Aggressive surgery in treatment for parotid cancer: the role of adjuvant postoperative radiotherapy*. Am J Roentgenol Radium Ther Nucl Med 1975;123:49-54.

3 Rossman KJ. *The role of radiation therapy in treatment of parotid carcinomas*. Am J Roentgenol Radium Ther Nucl Med 1975;123:492-9.

4 Shidnia H, Hornback NB, Hamaker R, Lingerman R. *Carcinoma of the major salivary gland*. Cancer 1980;45:693-7.

5 Laramore GE, Krall JM, Griffin TW, Duncan W, Richter MP, Saroja KR, et al. *Neutron versus photon irradiation for unresectable salivary gland tumor: report of an RTOG-MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council*. Int J Radiat Oncol Biol Phys 1993;27:235-40.

6 Koh W-J, Laramore G, Griffin T. *Fast neutron radiation for inoperable and recurrent salivary gland cancers*. Am J Clin Oncol 1989;12:316-9.

7 Gabriele P, Amichetti M, Orecchia R, Valdagni R. *Hyperthermia and radiation therapy for inoperable or recurrent parotid carcinoma. A phase I-II study*. Cancer 1995;75:908-13.

8 Armstrong JG, Harrison LB, Spiro RH, Fass DE, Strong EW, Nori D. *Brachytherapy for malignant tumors of salivary gland origin*. Endocurie Hypertherm Oncol 1990;6:19-23.

9 Goffinet DR. *Salivary gland neoplasms. Radiation therapy*. Proc 4th Conference Head Neck, Toronto, July 28-August 1, 1996:726-32.

10 Wang CC, Goodman M. *Photon irradiation of unresectable carcinomas of salivary glands*. Int J Radiat Oncol Biol Phys 1991;21:569-76.

11 Uematsu T, Hasegawa T, Hiraoka Y, Komatsu F, Matsuura T, Yamada A-S, et al. *Multidrug resistance gene 1 expressions in salivary gland adenocarcinomas and oral squamous-cell carcinomas*. Int J Cancer 2001;92:187-94.

12 Suen JY, Johns ME. *Chemotherapy for salivary gland cancer*. Laryngoscope 1982;92:235-9.

13 Schramm VL, Srodes C, Myers EN. *Cisplatin therapy for adenoid cystic carcinoma*. Arch Otolaryngol 1981;107:739-41.

14 Licitra L, Marchini S, Spinazzè S, Rossi A, Rocca A, Grandi C, et al. *Cisplatin in advanced salivary gland carcinoma*. Cancer 1991;68:1874-7.

[15] Vermorken JB, Verweij J, de Mulder PHM, Clavel M, Cognetti F, Schornagel J. *Epirubicin in patients with advanced or recurrent adenoid cystic carcinoma of the head and neck: a phase II study of the EORTC Head and Neck Cancer Cooperative Group*. Ann Oncol 1993;4:785-8.

[16] Verweij J, Vermorken J, de Mulder P, Schornagel J, Clavel M, Cognetti F, et al. *Phase II studies of epidoxorubicin and mitoxantrone in locally advanced or metastatic adenoid cystic carcinoma of the head and neck*. Ann Oncol 1996;7:876-8.

[17] Mattox DE, Von Hoff DD, Balcerzak SP. *Southwest Oncology Group of mitoxantrone for treatment of patients with advanced adenoid cystic carcinoma of the head and neck*. Invest New Drugs 1990;8:105-7.

[18] Tannock IF, Sutherland DJ. *Chemotherapy for adenoid cystic carcinoma*. Cancer 1980;46:452-4.

[19] Triozzi PL, Brantley A, Fisher S, Cole B, Crocker I, Huang AT. *5-fluorouracil, cyclophosphamide, and vincristine for adenoid cystic carcinoma of the head and neck*. Cancer 1987;59:887-90.

[20] Posner MR, Ervin TJ, Weichselbaum RR, Fabian RL, Miller D. *Chemotherapy of advanced salivary gland neoplasms*. Cancer 1982;50:2261-4.

[21] Airoldi M, Bumma C, Bertetto O, Riella AM, Gabriele P, Succo G, et al. *Vinorelbine for recurrent adenocarcinoma-like salivary gland malignancies*. Oral Oncol Eur J Cancer 1996;32B:213-4.

[22] Airoldi M, Bumma C, Bertetto O, Gabriele P, Succo G, Pedani F. *Vinorelbine treatment of recurrent salivary gland carcinomas*. Bull Cancer 1998;85:892-4.

[23] Airoldi M, Pedani F, Succo G, Gabriele AM, Ragona R, Marchionatti S, et al. *Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies*. Cancer 2001;91:541-7.

[24] Licitra L, Bonfante V, Spinazzè S, Bidoli P, Grandi C, Molinari R, et al. *Cyclophosphamide, doxorubicin, and cisplatin for advanced salivary gland carcinomas*. Proc Am Soc Clin Oncol 1991;10:204.

[25] Dreyfuss AI, Clark JR, Fallon BG, Posner MR, Norris CM, Miller D. *Cyclophosphamide, doxorubicin, and cisplatin combination chemotherapy for advanced carcinomas of salivary gland origin*. Cancer 1987;60:2869-72.

[26] Creagan ET, Woods JE, Schutt AJ, O'Fallon JR. *Cyclophosphamide, adriamycin, and cis-diamminedichloroplatinum (II) in the treatment of advanced nonsquamous cell head and neck cancer*. Cancer 1983;52:2007-210.

[27] Veenok AP, Tseng A, Meyers FJ, Silverberg I, Boles R, Fu KK, et al. *Cisplatin, doxorubicin, and 5-fluorouracil chemotherapy for salivary gland malignancies: a pilot study of the Northern California Oncology Group*. J Clin Oncol 1987;5:951-5.

[28] Airoldi M, Pedani F, Brando V, Gabriele P, Giordano C. *Cisplatin, epirubicin and 5-fluorouracil combination chemotherapy for recurrent carcinoma of the salivary gland*. Tumori 1989;75:252-6.

[29] Creagan ET, Schutt AJ, Richardson RL, Schaid DJ. *Phase II trial of VP-16, bleomycin, and cisplatin in patients with advanced nonsquamous cell head and neck neoplasms*. Am J Clin Oncol 1993;16:291-4.

[30] de Haan LD, de Mulder PHM, Vermorken JB, Schornagel JH, Vermey A, Verweij J. *Cisplatin-based chemotherapy in advanced adenoid cystic carcinoma of the head and neck*. Head Neck 1992;14:273-7.

[31] Dimery IW, Legha SS, Shirinian M, Hong WK. *Fluorouracil, doxorubicon, cyclophosphamide, and cisplatin combination chemotherapy in advanced or recurrent salivary gland carcinoma*. J Clin Oncol 1990;8:1056-62.

[32] Hill ME, Constenla DO, A'Hern RP, Henk JM, Rhys-Evans P, Breach N, et al. *Cisplatin and 5-fluorouracil for symptom control in advanced salivary adenoid cystic carcinoma*. Oral Oncol 1997;33:275-8.

[33] Jennings T, Li Y, Pinto H, Kies M, Mansour E, Forastiere A. *Phase II trial of paclitaxel in advanced or metastatic salivary gland malignancies: an Eastern Cooperative Oncology Group study*. Proc Am Soc Clin Oncol 2001;20:236.

[34] Airoldi M, Fornari G, Pedani F, Marchionatti S, Gabriele P, Succo G, et al. *Paclitaxel and carboplatin for recurrent salivary gland malignancies*. Anticancer Res 2000;20:3781-4.

[35] Piechocki MP, Lonardo F, Ensley JF, Nguyen T, Kim H, Yoo GH. *Anticancer activity of docetaxel in murine salivary gland carcinoma*. Clin Cancer Res 2002;8:870-7.

[36] Airoldi M, Brando V, Giordano C, Gabriele P, Bussi M, Cortesina G. *Chemotherapy for recurrent salivary gland malignancies: experience of the ENT Department of Turin University*. ORL 1994;56:105-11.

[37] Pignon JP, Bourhis J, Domenge C, Designe L. *Chemotherapy added to locoregional treatment for head and neck squamous cell carcinoma. Three meta-analyses of updated individual data*. Lancet 2000;355:949-55.

[38] Agarwala SS. *Adjuvant chemotherapy in head and neck cancer*. Hematol Oncol Clin North Am 1999;13:743-52.

[39] Airoldi M, Gabriele AM, Gabriele P, Pedani F, Marchionatti S, Succo G, et al. *Concomitant chemoradiotherapy followed by adjuvant chemotherapy in parotid gland undifferentiated carcinoma*. Tumori 2001;87:14-7.

[40] Bernier J, van Glabbeke M, Domenge C, Wibault P, Ozsahin M, Matuszewska K, et al. *Results of EORTC phase III trial 22931 comparing, postoperatively, radiotherapy to concurrent chemo-radiotherapy with high dose cisplatin in locally advanced head and neck carcinomas*. Eur J Cancer 2001;37(Suppl.6):S267.

[41] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, Kish JA, et al. *Postoperative concurrent radiochemotherapy in high-risk SCCA of the head and neck: initial report of RTOG 9501/intergroup phase III trial*. Proc Am Soc Clin Oncol 2002;21:226.

[42] Jeng Y-M, Lin C-Y, Hsu H-C. *Expression of the c-kit protein is associated with certain subtypes of salivary gland carcinoma*. Cancer Letters 2000;154:7-11.

[43] Holst VA, Marshall CE, Moskaluk CA, Frierson HF. *Kit protein expression and analysis of c-kit gene mutation in adenoid cystic carcinoma*. Mod Pathol 1999;12:956-60.

[44] Locati LD, Licitra L, Tamborini E, Quattrone P, Tovaglieri A, Bossi P, et al. *Tyrosine kinase and hormonal receptors as therapeutic molecular targets in salivary gland carcinomas*. Ann Oncol 2002;13(Suppl.3):33.

[45] Penner CR, Folpe AL, Budnick SD. *C-kit expression distinguishes salivary gland adenoid cystic carcinoma from polymorphous low-grade adenocarcinoma*. Mod Pathol 2002;15:687-91.

[46] Vered M, Braunstein E, Buchner A. *Immunohistochemical study of epidermal growth factor receptor in adenoid cystic carcinoma of salivary gland origin*. Head & Neck 2002;24:632-6.

[47] Mori M, Naito R, Tsukitani K, Okada Y, Hayashi T, Kato K. *Immunohistochemical distribution of human epidermal growth factor in salivary gland tumours*. Virchows Arch A 1987;411:499-507.

[48] Yamada K, Iwai K, Okada Y, Mori M. *Immunohistochemical expression of epidermal growth factor receptor in salivary gland tumours*. Virchows Arch A 1989;415:523-31.

[49] Baselga J, Norton L, Masui H, Pandiella A, Coplan K, Miller WH, et al. *Antitumor effects of doxorubicin in combination with anti-epidermal growth factor receptor monoclonal antibodies*. J Natl Cancer Inst 1993;85:1327-33.

[50] Fan Z, Baselga J, Masui H, Mendelsohn J. *Antitumor effect of anti-epidermal growth factor receptor monoclonal antibodies plus cis-diamminedichloro-platinum on well established A431 cell xenografts*. Cancer Res 1993;53:4637-42.

[51] Mendelsohn J, Shin DM, Donato N, Khuri F, Radinsky R, Glisson BS, et al. *A phase I study of chimerized antiepidermal growth factor receptor monoclonal antibody C225 in combination with cisplatin in patients with recurrent head and neck squamous cell carcinoma*. Proc Am Soc Clin Oncol 1999;18:389A.

[52] Bianco C, Bianco R, Tortora G, Damiano V, Guerrieri P, Montemaggi P, et al. *Antitumor activity of combined treatment of human cancer cells with ionizing radiation and anti-epidermal growth factor receptor monoclonal antibody C225 plus type I protein kinase A antisense oligonucleotide*. Clin Cancer Res 2000;6:4343-50.

[53] Ciardiello F, Bianco R, Damiano V, Fontanini G, Caputo R, Pomatico G, et al. *Antiangiogenic and antitumor activity of anti-epidermal growth factor receptor C225 monoclonal antibody in combination with vascular endothelial growth factor antisense oligonucleotide in human GEO colon cancer cells*. Clin Cancer Res 2000;6:3739-47.

[54] Mestre JR, Subbaramaiah K, Sacks PG, Schantz SP, Tanabe T, Inoue H, et al. *Retinoids suppress epidermal growth factor-induced transcription of cyclooxygenase-2 in human oral squamous carcinoma cells*. Cancer Res 1997;57:2890-5.

[55] Vadlamudi R, Mandal M, Adam L, Steinbach G, Mendelsohn J, Kumar R. *Regulation of cyclooxygenase-2 pathway by HER2 receptor*. Oncogene 1999;18:305-14.

[56] Milas L, Kishi K Hunter N, Mason K, Masferrer L, Tofilon PJ. *Enhancement of tumor response to gamma-radiation by an inhibitor of cyclooxygenase-2 inhibitor*. J Natl Cancer Inst 1999;91:1326-31.

[57] Masferrer JL, Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, et al. *Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors*. Cancer Res 2000;60:1306-11.

[58] Karja V, Syrjanen S, Kataja V, Syrjanen K. *C-erbB-2 overexpression in salivary gland tumours*. ORL 1994;56:206-12.

[59] Kamio N. *Coexpression of p53 and c-erbB-2 proteins is associated with histological type, tumour stage, and cell proliferation in malignant salivary gland tumours*. Virchows Arch 1996;428:75-83.

[60] Press MF, Pike MC, Hung G, Zhou JY, Ma Y, George J, et al. *Amplification and overexpression of HER-2/neu in carcinomas of the salivary gland: correlation with poor prognosis*. Cancer Res 1994;54:5675-82.

[61] Gallo O, Franchi A, Bianchi S, Boddi V, Giannelli E, Alajmo E. *p53 oncoprotein expression in parotid gland carcinoma is associated with clinical outcome*. Cancer 1995;75:2037-44.

[62] Yoo J, Robinson RA. *H-ras gene mutations in salivary gland mucoepidermoid carcinomas*. Cancer 2000;88:518-23.

[63] Cohen-Jonathan E, Muschel RJ, McKenna W, Evans SM, Cerniglia G, Miok R, et al. *Farnesyltransferase inhibitors potentiate the antitumor effect of radiation on a human tumor xenograft expressing activated HRAS*. Radiat Res 2000;154:125-32.

[64] Moasser MM, Sepp-Lorenzino L, Kohl NE, Oliff A, Balog A, Su DS, et al. *Farnesyl transferase inhibitors cause enhanced mitotic sensitivity to taxol and epothilones*. Proc Natl Acad Sci USA 1998;95:1369-74.

[65] Gorski DH, Beckett MA, Jaskowiak NT, Calvin DP, Mauceri HJ, Salloum RM, et al. *Blockade of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation*. Cancer Res 1999;59:3374-8.

[66] Lewis JE, McKinney BC, Weiland LH, Ferreiro JA, Olsen KD. *Salivary duct carcinoma. Clinicopathologic and immunohistochemical review of 26 cases*. Cancer 1996;77:223-30.

[67] Kapadia SB, Barnes L. *Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma*. Mod Pathol 1998;11:1033-8.

[68] Fan C-Y, Melhem MF, Hosal S, Grandis R, Barnes L. *Expressions of androgen receptor, epidermal growth factor receptor, and transforming growth factor alpha in salivary duct carcinoma*. Arch Otolaryngol Head Neck Surg 2001;127:1075-9.

[69] Fan C-Y, Wang J, Barnes L. *Expression of androgen receptor and prostatic specific markers in salivary duct carcinoma. An immunohistochemical analysis of 13 cases and review of the literature*. Am J Surg Pathol 2000;24:579-86.

■ Received: 13 January 2003
Accepted: 13 February 2003

■ Address for correspondence: Dr. M. Airoldi, Divisione di Oncologia Medica, Ospedale San Giovanni Antica Sede, Via Cavour 31, 10123 Torino, Italy. Fax: +39 011 6333591. E-mail: mario.airoldi@jumpy.it