B-ENT, 2011, **7**, 1-6

Cyclophosphamide, doxorubicin, and cisplatin in advanced salivary gland cancer

D. Debaere[1], *V. Vander Poorten*[2], *S. Nuyts*[3], *E. Hauben*[4], *J. Schoenaers*[5], *P. Schöffski*[1] *and P. M. J. Clement*[1]

[1]Department of General Medical Oncology, [2]Department of Otorhinolaryngology-Head and Neck Surgery, [3]Department of Radiation Oncology, [4]Department of Pathology, Leuven Cancer Institute, [5]Department of Maxillofacial Surgery, University Hospitals Leuven, Catholic University Leuven, Belgium

Key-words. Salivary glands; carcinoma; neoplasm metastasis; drug therapy; cisplatin

Abstract. *Cyclophosphamide, doxorubicin, and cisplatin in advanced salivary gland cancer. Objectives*: Advanced salivary gland cancer is a rare disease that comprises different histopathological tumour types; correspondingly, data on palliative systemic treatment are scarce. Combination chemotherapy with cyclophosphamide, doxorubicin, and cisplatin (CAP) has been reported to induce a reasonable response rate, although fewer than 100 cases have been described. We conducted a retrospective review of advanced salivary gland cancer patients treated with CAP.
Methodology: Fifteen consecutive patients with recurrent, locally advanced, or metastatic progressive salivary gland cancer treated with CAP were identified over a five-year period. The mean age at start of treatment was 53.5 years, and the male/female ratio was 11/4. The most common histological subtypes were adenoid cystic carcinoma and adenocarcinoma not otherwise specified (NOS), with the parotid gland as the most frequently affected anatomical site.
Results: A response rate of 60% was achieved, with one complete and eight partial responses and six stable diseases according to RECIST criteria. No patient progressed under treatment. An average of 5.4 treatment cycles were administered; median time to progression after ending CAP was 6.6 months, and median overall survival was 15.1 months. Patients with adenocarcinoma NOS appeared to benefit more than patients with adenoid cystic carcinoma, but had a shorter time to progression. Except for neutropenia with neutropenic fever and alopecia, no NCI-CTC grade III or IV toxicity was observed.
Conclusion: This retrospective study confirms the clinically meaningful efficacy of CAP in advanced adenocarcinomas NOS of the salivary gland in routine practice, with acceptable safety levels.

Introduction

Malignant tumours of the salivary glands are rare, but still comprise 3-6% of all head and neck cancers in adults, an incidence that has remained stable over recent decades. The disease affects 1.0 males and 0.7 females per 100 000 patients per year.[1] Malignant tumours can arise from the major salivary glands (parotid, submandibular, and sublingual glands) or the minor salivary glands located in the submucosa of the upper aerodigestive tract. Tumour histology is classified according to the World Health Organization's Histological Classification of Salivary Gland Tumours, which was established in 1972 and revised in 2005. Among 24 different histological subtypes, adenocarcinoma not otherwise specified (NOS), adenoid cystic carcinoma, and mucoepidermoid carcinoma occur most frequently.[2]

Primary therapy consists of surgery with or without radiotherapy.[3,4] Metastasis occurs most frequently in the lung, but also in the liver, bone, and brain, and once metastasis occurs, the prognosis is usually poor. Since salivary malignancies are rare, no standard chemotherapeutic regimen for metastatic disease has been validated in phase III clinical trials. Treatment options are based on retrospective studies or infrequent phase II trials.[5] Single-agent therapies with cisplatin, mitoxantrone, epirubicine, vinorelbine, cyclophosphamide, or paclitaxel have all demonstrated antitumour activities.[6-11] Adenoid cystic carcinoma appears to be more chemoresistant than other histological subtypes; two phase II studies with paclitaxel and gemcitabine failed to demonstrate antitumour activity in adenoid cystic carcinomas,[11,12] in spite of case reports describing response following paclitaxel treatment.[13]

Response rates with CAP (cyclophosphamide, doxorubicin, cisplatin) combination chemotherapy are listed in Table 1. However, only one phase II trial has been published examining CAP in 22 patients with predominantly adenoid cystic carcinomas of the salivary gland. Partial responses were observed in 27%

Table 1

Results of CAP (+/- 5fluoro-uracil) in salivary gland cancer according to histology

Article	# Patients	OR	Adca	MEC	ACC	Other
Licitra[14]	22, CAP	6/22	2/2 SD	1/1 PR	3/12 PR, 5/12 SD, 4/12 PD	2/7 PR, 3/7 SD, 2/7 PD
Alberts[15]	5, CAP	5/5	1/3 CR, 2/3 PR	/	/	1/2 CR, 1/2 PR
Dreyfuss[16]	13, CAP	6/13	3/4 response	/	3/9 response	/
Belani[17]	8, CAP	5/8	1/1 CR	2/3 CR, 1/3 PR	1/4 PR, 3/4 PD	/
Tsukuda[18]	14, CAP	5/14	?	/	?	/
Kaplan[19]	4, CAP	3/4	1/1 PR	1/2 PR, 1/2 SD	/	1/1 PR
Creagan[20]	34, Cisplatin based	13/34	2/7 CR, 4/7 PR, 1/7 regression	1/2 PR, 1/2 regression	/	2/4 PR, 2/4 regression

CAP: cyclophosphamide-adriamycin-cisplatin; OR: overall response; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; Adca: adenocarcinoma; MEC: muco-epidermoid carcinoma; ACC: adenoid cystic carcinoma.

of patients, with a median response duration of 7 months and a median survival of 21 months.[14] Other studies were retrospective and discovered response rates ranging from 27% to 63%, including some complete responses, with response duration from 5 to 16 months and overall survival varying from 6 to 21 months.[15-20] Addition of 5-fluoro-uracil (5FU) to CAP did not appear to induce higher response rates; rather, it resulted in more toxicity, including two toxic deaths.[21] To date, no randomised trials comparing CAP with single-agent therapy or other combinations have been conducted.

Given the paucity of data described above, we wished to investigate the efficacy of therapeutic strategies. We retrospectively reviewed patients with advanced salivary gland cancer treated with CAP and analyzed responses in various histological subtypes.

Materials and methods

We reviewed retrospectively all files of patients with recurrent, locally advanced, or metastatic salivary gland cancer treated with the CAP regimen between January 2005 and October 2009 at the University Hospitals of Leuven, Belgium.

Chemotherapy consisted of cyclophosphamide (600 mg/m^2), doxorubicin (50 mg/m^2), and cisplatin (50 mg/m^2), repeated every three weeks. Chemotherapy was continued for a total of six or eight cycles, or until disease progression or development of unacceptable toxicity.

All patients had regular follow-ups by three-month physical exams and CT scans, except for one patient, who was followed with chest X-rays. Response was determined according to the Response Evaluation Criteria In Solid Tumours (RECIST) criteria.[22] Time to progression was determined as the time from the start of the first CAP cycle until disease progression, or censored at the date of last follow-up if the patient was not progressive at the time of evaluation. Overall survival time was determined as the time from the start of the first CAP cycle until death, or censored at the date of last follow-up if the patient was still alive.

Toxicity is routinely recorded in patient files in our institution and is scored by the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 3.0).

Results

Seventeen patients received systemic therapy for recurrent, locally advanced, or metastatic salivary gland cancer between 2005 and 2009. Among these, fifteen received CAP, two for locally recurrent disease, and thirteen for progressive metastatic disease. Two patients were rechallenged with CAP treatment later. Patient characteristics and outcomes are listed in Table 2 and Table 3.

Mean age at the time of treatment initiation was 53.5 years (range 22-77 years). Most affected patients were male, with a male/female ratio of 11/4. The most common histological subtypes were adenoid cystic carcinoma (n = 6, 40%) and adenocarcinoma NOS (n = 6,

Table 2

Patient characteristics: age, gender, histology, and primary tumour site

Patient	Age (yr)/ gender	Histology	Primary tumour site
1	39/M	Adenocarcinoma NOS	Parotid
2	64/M	Salivary duct carcinoma	Parotid
3	61/F	Adenocarcinoma NOS	Parotid
4	62/M	Adenocarcinoma NOS	Parotid
5	22/F	Adenocarcinoma NOS	Parotid
6	52/M	Adenoid cystic carcinoma	Parotid
7	57/M	Adenoid cystic carcinoma	Parotid
8	64/M	Adenocarcinoma NOS	Submandibular
9	40/M	Adenoid cystic carcinoma	Sinus maxillaris/orbita
10	44/M	Adenoid cystic carcinoma	Nasopharynx
11	47/F	Polymorphic low grade adenocarcinoma	Parotid
12	77/M	Adenoid cystic carcinoma	Submandibular
13	55/F	Adenoid cystic carcinoma	Parotid
14	59/M	Adenocarcinoma NOS	Parotid
15	59/M	Acinic cell carcinoma	Parotid

40%), with the parotid gland (n = 11, 73.3%) being the most frequent primary tumour site.

Treatment was started upon metastatic disease or local recurrence observation, except for five patients (4/6 of the adenoid cystic carcinoma and 1/6 of the adenocarcinoma NOS) with lung metastases as the single metastatic site, in whom a "watch and wait" policy was first adopted. In these patients, CAP was initiated after a median of 9.6 months after detection of the metastases. In two patients with adenoid cystic carcinoma, chemotherapy was withheld for a period of 31.8 months and 53 months given the slow evolution of disease.

Except for two patients who were metastasized at the time of

Table 3

Best response, time to progression, localisation of progression, and overall survival

Patient	**Number of CAP cycles**	**Best response**	**TTP (days)**	**Localisation of PD after CAP**	**OS (days)**
1	8x CAP	PR	260	Brain	492
2	6x CAP	PR	192	Lung, bone	394
3	1x CAP/2x CAP (80%~NF) + Pegfilgrastim/3x AP(80%~NF)	PR	197	Lung	453
4	6x CAP	CR	352	Local, lung	508*
	+5x CAP Doxo - >Caelyx, cum dose Doxo)	PR	156	Lung	"
5	6x CAP	PR	170	Brain metastasis	235*
6	6x CAP	PR	260	Liver, lung, bone, spleen	596
	+ 4x CAP (cum dose Doxo)	PR	151	Omentum, peritoneum, mesenterium	"
7	6x CAP	SD	479	Bone	532*
8	6x CAP	PR	224	Lung, lymph nodes (stable bone)	276
9	6x CAP	SD	700	01/2007: local	1658*
10	3x CAP	SD	277	Local, intracerebral extension	290
11	6x CAP	SD	193	Local disease progression	247
12	3x CAP (80%~moderate general condition at start)	SD	67	Stop therapy (general deterioration)	67
13	3x CAP - 3x CAP (80%~NF)	PR	139*	No progression	139*
14	2x CAP	SD	140	Lung, brain	540
15	1x CAP - 4x CAP (75%~NF) - 1x CAP (65%~NF)	PR	383	Local nasopharyngeal	580*

LN: lymph node; PR: partial response; CR: complete response; SD: stable disease; TTP: time to progression; OS: overall survival; CAP: cyclophosphamide, doxorubicin, cisplatin; AP: doxorubicin, cisplatin; NF: neutropenic fever.
* Censored data.

diagnosis, initial treatment consisted of chemoradiotherapy based on cisplatin in one patient and of local surgery and/or local radiotherapy in all other patients. One patient was pretreated with gemcitabine, one with cisplatin/5-FU, and two patients had palliative radiotherapy for bone metastases prior to CAP treatment.

After failure of CAP, five patients received second line chemotherapy, two patients underwent surgery, two had radiotherapy for bone metastases, and four patients received whole-brain radiotherapy.

An average of 5.4 CAP cycles was administered, ranging from two to eight courses, resulting in a total response rate of 60% (9/15). We observed one complete response (1/15, 6.7%) and eight partial responses (8/15, 53.3%). The remaining patients (6/15, 40%) had stable disease as the best response. No patient progressed during active treatment with CAP. Median time to progression was 6.6 months (range 1.4-23.3 months), and median overall survival time was 15.1 months (range 2.2-55.3 months).

Two patients with relapse after initial response to CAP were rechallenged with the same regimen. One patient with an adenoid cystic carcinoma, who initially had a partial response, received only four additional CAP cycles because the maximum cumulative dose of doxorubicin was reached. For the second patient with an adenocarcinoma NOS, who initially displayed a complete response, doxorubicin was replaced by the less-cardiotoxic liposomal doxorubicin. Both patients exhibited a partial response after rechallenge. The best response was taken into consideration for each patient. Histological responses were observed in 5/6 adenocarcinoma NOS, 2/6 adenoid cystic carcinoma, 1/1 salivary duct carcinoma, and 1/1 acinic cell carcinoma.

Nearly all patients with an adenocarcinoma NOS benefited from the therapy; 1/6 patients had a complete response and a partial response at rechallenge, while 4/6 patients exhibited a partial response. In one patient, CAP was discontinued after two cycles due to a suspicion of progressive disease in the lungs. Retrospectively, however, the disease was stable according to RECIST criteria, and remained stable until 20 weeks after discontinuation of CAP; at that point brain metastasis was observed, along with disease progression in the lungs. Median time to progression was 6.6 months in this subgroup, and median overall survival was 15.8 months.

Patients with adenoid cystic carcinoma showed a lower response rate: 2/6 achieved a partial response, whereas 4/6 cases remained stable. One patient with partial response was rechallenged at progression, resulting in a second partial response. Median time to progression was 8.7 months in this subgroup, with a median overall survival of 13.7 months. One patient with adenoid cystic carcinoma had a poor survival of only 2.2 months (67 days) after initiation of CAP. In this patient, treatment was started 31.8 months after the occurrence of lung metastases ("watch and wait" policy), but was stopped at the patient's request.

After discontinuation of chemotherapy, most patients showed progression of known local or metastatic lesions. In total, three patients with adenocarcinoma NOS developed brain metastases, and whole-brain radiotherapy was administered. The CAP regimen was discontinued due to infectious complications in one patient with tumour necrosis. This patient developed local progression with involvement of the brain, and was also treated with radiotherapy. At the time of evaluation, six patients were still alive, one of which was still free of progression.

Adverse events included gastrointestinal intolerance, haematological events, and fatigue. No grade three or four gastrointestinal toxicity was observed. Five patients developed grade four neutropenia, associated with neutropenic fever grade three, which was well managed with intravenous antibiotics. Haematological toxicity resulted in a dose reduction to 80% in three patients. No grade three or four anaemia or thrombocytopenia was observed. However, one patient developed a myocardial infarction without ST segment elevation on ECG, partly due to underlying aortic stenosis associated with treatment-induced anaemia and severe physical exercise. Fatigue grade three occurred in one patient.

Discussion

Metastatic salivary gland disease is a rare condition, and thus data on the effectiveness of chemotherapy are limited and most studies are retrospective. Molecular signalling pathways are under investigation, and the results of these studies are still too preliminary to draw conclusions for clinical practice.[23] There are no rigorous comparative studies

between molecular therapy and chemotherapy. Combination chemotherapy appears to induce higher response rates, but generally leads to higher toxicity rates than single agents.[5-21]

Although CAP is the most frequently studied regimen, fewer than 100 cases have been published (Table 1). In the current study we describe data from an additional 15 patients treated with this regimen. Comparison is difficult with previous studies of CAP in locally advanced or metastatic disease due to the small sample sizes of all available series. Any difference in response rate could therefore be explained by chance, and the investigations are purely explorative. The doses and treatment intervals in most previously published series differed slightly in comparison to the CAP regimen that was used in the present study. However, the difference in histological subtypes is likely the most important factor to take into account when assessing the probability of a response to treatment with this regimen.

In our series, adenoid cystic carcinoma (6/15) and adenocarcinoma NOS (6/15) were the most common histological subtypes, with the parotid gland (11/15) as the most frequent primary tumour location. Nearly all patients with adenocarcinomas NOS obtained a partial or complete response. Upon retrospective analysis, the one patient who was considered progressive was discovered to have stable disease after two cycles. Only 2/6 patients with adenoid cystic carcinoma obtained a partial response, which is much lower than the frequency obtained in patients with adenocarcinoma. Although response according to histology is not always recorded and data on this subject are scarce, it is evident from all available data (Table 1), including the present series, that a very large proportion of adenocarcinoma cases respond very well to CAP, while the response rate is generally lower in adenoid cystic carcinoma. Therefore, patients with adenocarcinoma may derive more benefit from chemotherapy.

In our opinion, the decision to start palliative chemotherapy in locally advanced or metastatic disease should take into account the histology and its expected natural evolution. Patients with adenoid cystic carcinoma in our series had less-favourable response rates, but exhibited a longer time to progression. This result could reflect less-efficient tumour shrinkage in tumours with a large proportion of resting cells, such as adenoid cystic carcinoma, compared to more efficient tumour shrinkage in rapidly growing tumours, such as adenocarcinomas. A "watch and wait" policy was invoked in five patients in our series with metastatic disease limited to the lungs, with a median interval of 9.6 months. One "watch and wait" patient had an adenocarcinoma NOS and experienced a shorter interval of 3.2 months. The other patients had adenoid cystic carcinoma; in two of them chemotherapy was withheld for much longer periods of 31.8 months and 53 months. This result, again, is consistent with the indolent spontaneous course of some adenoid cystic carcinoma, especially if only the lungs are affected.[24]

Our recommendation is that a "watch and wait" policy may be an appropriate strategy for selected asymptomatic patients with adenoid cystic carcinoma, whereas in other histological subtypes (especially adenocarcinoma NOS), or when rapid disease progression is observed, palliative chemotherapy should not be postponed.

Conclusion

In conclusion, our retrospective study confirms a clinically meaningful effect of CAP chemotherapy in patients with advanced adenocarcinomas NOS of the salivary gland, accompanied by a favourable toxicity profile. Our data support the use of the CAP regimen as the standard of care in the palliative treatment of these patients in routine practice, and as a reference arm in future randomised clinical trials. A "watch and wait" policy should be considered in asymptomatic patients with adenoid cystic carcinoma, since the response rate to CAP chemotherapy is much lower in these patients.

Acknowledgements

We acknowledge Dr N. Claes, General Hospital St Jan, Bruges for kindly providing the data of the patient treated at her department.

References

1. Cooper JS, Porter K, Mallin K, Hoffman HT, Weber RS, Ang KK, Gay EG, Langer CJ. National Cancer Database report on cancer of the head and neck: 10-year update. *Head Neck.* 2009;31(6):748-758.
2. Barnes L, Everson JW, Reichard P, Sidransky D, Eds. *World Health Organization Classification of Tumours. Pathology and genetics. Head and neck tumours*. IARC Press, Lyon, France: 2005.
3. Delbouck C, Roper N, Aubert C, Souchay C, Choufani G, Hassid S. Unusual presentation of adenoid

cystic carcinoma of the maxillary antrum. *B-ENT.* 2009;5(4):265-268.
4. Dequanter D, Andry G, Lothaire P, Larsimont D, Deraemaecker R. Wide localized excision and reconstruction for minor salivary gland tumours. *B-ENT.* 2005;1(4):187-190.
5. Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. *J Clin Oncol.* 2006;24(17):2673-2678.
6. Licitra L, Marchini S, Spinazzè S, Rossi A, Rocca A, Grandi C, Molinari R. Cisplatin in advanced salivary gland carcinoma. A phase II study of 25 patients. *Cancer.* 1991;68(9):1874-1877.
7. Verweij J, de Mulder PH, de Graeff A, Vermorken JB, Wildiers J, Kerger J, Schornagel J, Cognetti F, Kirkpatrick A, Sahmoud T, Lefebvre JL. Phase II study on mitoxantrone in adenoid cystic carcinomas of the head and neck. EORTC Head and Neck Cancer Cooperative Group. *Ann Oncol.* 1996;7(8):867-869.
8. Vermorken JB, Verweij J, de Mulder PH, Cognetti F, Clavel M, Rodenhuis S, Kirkpatrick A, Snow GB. 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(9):785-788.
9. Airoldi M, Pedani F, Succo G, Gabriele AM, Ragona R, Marchionatti S, Bumma C. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. *Cancer.* 2001;91(3):541-547.
10. Spiers AS, Esseltine DL, Ruckdeschel JC, Davies JN, Horton J. Metastatic adenoid cystic carcinoma of salivary glands: case reports and review of the literature. *Cancer control.* 1996;3(4):336-342.
11. Gilbert J, Li Y, Pinto HA, Jennings T, Kies MS, Silverman P, Forastiere AA. Phase II trial of taxol in salivary gland malignancies (E1394): a trial of the Eastern Cooperative Oncology Group. *Head Neck.* 2006;28(3):197-204.
12. van Herpen CM, Locati LD, Buter J, Thomas J, Bogaerts J, Lacombe D, de Mulder P, Awada A, Licitra L, Bernier J, Vermorken JB. Phase II study on gemcitabine in recurrent and/or metastatic adenoid cystic carcinoma of the head and neck (EORTC 24982). *Eur J Cancer.* 2008; 44(17):2542-2545.
13. Till BG, Martins RG. Response to paclitaxel in adenoid cystic carcinoma of the salivary glands. *Head Neck.* 2008;30(6):810-814.
14. Licitra L, Cavina R, Grandi C, Palma SD, Guzzo M, Demicheli R, Molinari R. Cisplatin, doxorbicin and cyclophosphamide in advanced salivary gland carcinoma: A phase II trial of 22 patients. *Ann Oncol.* 1996; 7(6):640-642.
15. Alberts DS, Manning MR, Coulthard SW, Koopmann CF, Herman TS. Adriamycin/cis-platinum/cyclophosphamide combination chemotherapy for advanced carcinoma of the parotid gland. *Cancer.* 1981; 47(4):645-648.
16. 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(12): 2869-2872.
17. Belani CP, Eisenberger MA, Gray WC. Preliminary experience with chemotherapy in advanced salivary gland neoplasms. *Med Pediatr Oncol.* 1988;16(3):197-202.
18. Tsukuda M, Kokatsu T, Ito K, Mochimatsu I, Kubota A, Sawaki S. Chemotherapy for recurrent adeno- and adenoidcystic carcinomas in the head and neck. *J Cancer Res Clin Oncol.* 1993;119(12):756-758.
19. Kaplan MJ, Johns ME, Cantrell RW. Chemotherapy for salivary gland cancer. *Otolaryngol Head Neck Surg.* 1986;95(2):165-170.
20. Creagan ET, Woods JE, Rubin J, Schaid DJ. Cisplatin-based chemotherapy for neoplasms arising from salivary glands and contiguous structures in the head and neck. *Cancer.* 1988;62(11):2313-2319.
21. Dimery IW, Legha SS, Shirinian M, Hong WK. Fluorouracil, doxorubicin, cyclophosphamide, and cisplatin combination chemotherapy in advanced or recurrent salivary gland carcinoma. *J Clin Oncol.* 1990;8(6): 1056-1062.
22. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumours. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000;92(3):205-216.
23. Prenen H, Kimpe M, Nuyts S. Salivary gland carcinomas: molecular abnormalities as potential therapeutic targets. *Curr Opin Oncol.* 2008;20(3): 270-274.
24. van der Wal JE, Becking AG, Snow GB, van der Waal I. Distant metastases of adenoid cystic carcinoma of the salivary glands and the value of diagnostic examinations during follow-up. *Head Neck.* 2002; 24(8):779-783.

Paul Clement, M.D., Ph.D.
General Medical Oncology
University Hospitals Leuven
Herestraat 49
3000 Leuven, Belgium
Tel.: + 32 16 34 69 03
Fax: +32 16 34 69 01
E-mail: paul.clement@uzleuven.be