Anti-Cancer Drugs 2002, **13,** pp. 491–495

Clinical report

Mitoxantrone and cisplatin in recurrent and/or metastatic salivary gland malignancies

Claudia Gedlicka,[1] Birgit Schüll,[2] Michael Formanek,[1] Johannes Kornfehl,[1] Martin Burian,[1] Birgit Knerer,[1] Edgar Selzer,[3] Werner Scheithauer[2] and Gabriela V Kornek[2]
Departments of [1]Otorhinolaryngology, [2]Internal Medicine I/Division Oncology and [3]Radiation Therapy, University of Vienna, 1090 Vienna, Austria.

A phase II study was performed to assess the safety and efficacy of mitoxantrone and cisplatin in locally recurrent and/or metastatic carcinomas of the salivary glands. Between May 1997 and March 2001, a total of 14 patients were entered on this trial. All of them had previously undergone radical resection and 10 were subsequently treated with adjuvant radiation therapy with (n=3) or without (n=7) concomitant chemotherapy. Therapy according to the study protocol consisted of mitoxantrone given as i.v. bolus on day 1 at a dose of 12 mg/m^2 and cisplatin given as 90-min infusion at a dose of 30 mg/m^2 on days 1–3. We observed two partial responses (14.3%) and stabilization of disease in nine patients (64.3%); progression during therapy was noted in only three cases (21.4%). The median time to progression was 15 months (range 2–36) and the median survival time was 27 months (range 4–54). Myelosuppression was commonly observed. Leukocytopenia occurred in all patients, and was grade 3 or 4 in three (21%) and four (29%) patients. WHO grade 3 thrombocytopenia and anemia was seen in three (21%) and four (29%) patients, respectively. Non-hematologic toxicity was in general mild to moderate except for two cases (14%) of grade 3 nausea and vomiting; overall incidence rates were nausea and vomiting (n=14), stomatitis (n=6), diarrhea (n=3), alopecia (n=11), infection (n=7), increase of serum creatinine (n=3), and peripheral neuropathy (n=3). The combination of mitoxantrone and cisplatin seems to be an active and fairly well-tolerated regimen for the treatment of advanced salivary gland cancers. According to the observed high rate of abrogating progressive disease for a long duration, and the resulting promising progression-free and overall survival time, further investigation seems warranted. [© 2002 Lippincott Williams & Wilkins.]

Key words: Cisplatin, mitoxantrone, palliative chemotherapy, salivary gland carcinoma.

Correspondence to GV Kornek, Department of Internal Medicine I, Division of Oncology, University of Vienna, Waehringer Guertel 18–20, 1090 Vienna, Austria.
Tel/Fax: (+43) 40400 5462;
E-mail: Gabriela.Kornek@akh-wien.ac.at

Introduction

Carcinomas of the salivary glands are rather uncommon, representing 5–10% of the head and neck malignancies.[1,2] They are characterized by slow but progressive growth, and are known to show late local recurrences and distant metastases. The standard therapy consists of radical resection followed by adjuvant radiation therapy in selected cases.[3,4] Despite improved results with more aggressive local treatment, the prognosis for patients suffering from advanced carcinomas of the salivary glands remains poor. Given the relative rarity of these tumors, data concerning the activity of single agents in the treatment of these malignancies are limited. Cisplatin, doxorubicin and 5-fluorouracil (5-FU) are the most active single agents used for the treatment of patients with salivary gland malignancies.[1,2,6] Combination chemotherapy regimens frequently used are the PAC regimen (cyclophosphamide, doxorubicin and cisplatin)[7,8] and the CF regimen (cisplatin plus 5-FU).[9,10] Although responses have been reported, the experience with systemic chemotherapy is limited. Therefore, the identification of new active agents and/or drug combinations with a superior therapeutic index remains a principal goal of investigational efforts.

Mitoxantrone is an anthraquinone antineoplastic agent with structural and functional similarities to anthracyclines. Because it is less cardiotoxic than anthracyclines, mitoxantrone has been investigated extensively in various malignancies such as lymphomas, breast cancer and nasopharyngeal carcinomas.[11–14] Analogous to the PAC regimen, we combined mitoxantrone with cisplatin, and evaluated the efficacy and tolerance of this combination in

patients with recurrent and/or metastatic salivary gland carcinomas.

Patients and methods

Patients eligible for this trial had histologically confirmed carcinoma of the salivary glands with inoperable recurrent and/or metastatic disease. All patients were required to be aged $\leqslant 75$ or younger, to have a WHO performance status <3 and to have an expected survival time of >12 weeks. Adequate bone marrow (neutrophils $>2000/\mu$l, thrombocytes $>100\,000/\mu$l), as well as adequate renal and liver function (creatinine <1.5 mg/dl, creatinine clearance 70 ml/h and bilirubin <1.5 mg/dl) were required. Previous surgery and radiation therapy with or without concomitant chemotherapy were allowed if therapy was completed at least 3 months before trial with full resolution of toxicity.

Treatment protocol

The chemotherapy regimen consisted of mitoxantrone 12 mg/m^2 given as rapid i.v. infusion on day 1 and cisplatin 30 mg/m^2 administered as a 90-min infusion on days 1–3. A maximum of 6 courses were given every 4 weeks. Cisplatin was preceded and followed by an infusion of 1000 ml normal saline and electrolyte substitution to prevent kidney tubuli destruction. All patients were supported with 5-HT$_3$ antagonists and dexamethasone.

Toxicity and dosage modifications guidelines

Adverse reactions were evaluated according to WHO standard criteria. If the absolute neutrophil count was $<2000/\mu$l or platelet count was $<100\,000/\mu$l, treatment could be delayed for up to 2 weeks. Drug doses were reduced by 25% in case of febrile neutropenia grade 4 if the lowest platelet count was $<25\,000/\mu$l or any severe (WHO grade >2) non-hematologic toxicity was observed in the previous cycle. The dose of cisplatin was reduced by 25% if the creatinine clearance was $<50\%$.

Pretreatment and follow-up evaluation

Pretreatment evaluation included a complete medical history and physical examination with measurement of all tumor-associated lesions. Laboratory evaluation consisted of a complete blood count with platelet count and leukocyte differential count, and an 18-function biochemical profile. Imaging procedure consisted of computed tomographic (CT) scan or magnetic resonance imaging (MRI) of the head and neck, chest X-ray, sonography of the abdomen, and CT scan of the site of metastases. Complete blood cell counts and differential counts were performed on the day of treatment and 10 days after infusion for nadir control. Biochemical profiles were assessed before each treatment cycle. Tumor size was measured by CT scan or MRI every 3 months.

Assessment of response

The primary efficacy end point was response rate. A complete response (CR) required the complete disappearance of all objective evidence of disease on two separate measurements at least 4 weeks apart. A partial response (PR) was defined as a $>50\%$ reduction in the sum of the product of the perpendicular diameters of measurable lesions without a CR, no progression of any lesion by $>25\%$ or the appearance of any new lesions, confirmed by two separate measurements that were 4 weeks apart. Progressive disease (PD) was defined as the enlargement of any existing measurable lesion by $>25\%$ or the development of new metastatic lesions. Stable disease (SD) was any measurement that did not fulfill the criteria for PR or PD. Secondary efficacy endpoints included the time to progression (calculated from the start of treatment to the time of progression or relapse) and overall survival.

Results

Patients characteristics

Fourteen patients were entered on this trial, all of whom were evaluable for toxicity assessment and response evaluation. The demographic data, sites of metastatic tumor and prior therapies are listed in Table 1. The median age was 62 years (range 33–69) and the median WHO performance status was 1 (range 0–2). The predominant sites of primary tumor were parotid gland ($n=6$), submandibulary gland ($n=5$), upper alveolar comb ($n=2$) and orbita ($n=1$). Nine patients presented with distant metastases (lung, liver, bone and renal) with ($n=4$) or without ($n=5$) local recurrences and five patients had local

Table 1. Patient characteristics

	No. of patients
Entered/evaluable	14/14
Age (years)	
median	62
range	33–69
WHO performance status	
0	5
1	7
2	2
Time to progression (months)	
median	15
range	0–29
Sites of relapse/tumor	
lymph node ± locoregional	5
lung	2
locoregional and lung	4
other sites of metastases	3
Prior treatment	
surgery	4
surgery+radiation	7
surgery+radio/chemotherapy	3

relapse without distant metastases. All patients had previously undergone radical resection, 10 of whom also had adjuvant radiation therapy with (n=3) or without (n=7) concomitant chemotherapy. A total of 52 cycles were administrated to the 14 patients. The median number of treatment cycles was 4 (range 1–6) and the median duration of follow-up at the time of this analysis was 22 months (range 8–54 months).

Response to treatment

The best response to treatment was PR in two patients (response duration 27 and 14 months, respectively) yielding an overall response rate of 14.3%. Disease stabilization for a median duration of 15 months (range 3–27) was seen nine patients (64.3%), whereas disease progressed during chemotherapy in only three patients (21.4%). The median time to progression for all patients was 15 months (range 2–36). See Table 2.

Survival

As of November 2001, with a median follow-up duration of 22 months (range 8–54), six of 14 patients were still alive (43%) and eight patients had died because of PD. In five patients who experienced a relapse after a treatment-free interval period of more than 6 months the same regimen was re-introduced. Patients who showed an early relapse after or a disease progression during treatment received gemcitabine (n=4). The median survival was 27 months (range 4–54).

Table 2. Treatment results

Response	*N* (%)
CR	0 (0)
PR	2 (14.3)
No change	9 (64.3)
PD	3 (21.4)
Median time to progression [months (range)]	15 (2–36)
Median survival [months (range)]	27 (3–52)

Toxicity

All 14 patients, who received a total of 52 cycles, were assessable for toxicity. Adverse events associated with treatment are listed in Table 3.

Myelosuppression was commonly observed. Leukopenia occurred in all patients and was grade 3 in three patients (21%) and grade 4 in four patients (29%). The median nadir WBC count was 2700/μl (range 600–22 300). Neutropenia was seen in 12 patients (85%), and was grade 3 in three patients (21%) and grade 4 in one patient (7%). The median nadir count of neutrophils was 1100/μl (range 100–20 000). Neutropenic fever occurred in seven patients (50%), but none of these patients required i.v. antibiotics. Thrombocytopenia was seen in 12 patients (85%) and was grade 3 in three patients (21%). The median nadir platelet count was 140 000/μl (range 28 000–356 000). Twelve patients (85%) experienced anemia and four patients had a severe anemia requiring packed red blood cell transfusion.

Non-hematologic side effects were in general mild to moderate and in all cases fully reversible. Gastrointestinal symptoms were the most frequently encountered toxicities. Nausea and vomiting were mild or moderate except in two patients (14%) and generally responsive to standard antiemetic medication. Mild or moderate stomatitis was observed in six patients (43%) and mild diarrhea was noted in three patients (21%). Constipation and peripheral neuropathy was seen three patients (21%) each. Eleven patients experienced alopecia, but complete hair loss was seen in only one patient. A transient increase of the serum creatinine level was observed in only three patients (21%).

Treatment was prematurely discontinued in three cases because of early progression and five patients

Table 3. Highest grade of toxicity experienced

	Grade 1 [*n* (%)]	Grade 2 [*n* (%)]	Grade 3 [*n* (%)]	Grade 4 [*n* (%)]
Leukocytopenia	2 (14)	5 (36)	3 (21)	4 (29)
Neutropenia	2 (14)	6 (43)	3 (21)	4 (29)
Thrombocytopenia	3 (21)	6 (43)	3 (21)	–
Anemia	6 (43)	2 (14)	4 (29)	–
Nausea/vomiting	7 (59)	5 (36)	2 (14)	–
Stomatitis	4 (29)	2 (14)	–	–
Diarrhea	3 (21)	–	–	–
Alopecia	6 (43)	4 (29)	1 (7)	–
Infection	4 (29)	3 (21)	–	–
Constipation	2 (14)	1 (7)	–	–
Creatinine increase	3 (21)	–	–	–
Peripheral neuropathy	3 (21)	–	–	–

(36%) had at least one treatment delay of 1 week; the total number of delayed courses was 14 (27%). The reasons for delayed treatment courses were hematologic toxicity in four patients and personal reasons in one patient. The dose of cisplatin was reduced by 25% according to the criteria described above in two patients after the third and fourth course.

Discussion

The standard therapy for malignant salivary gland tumors of the head and neck is focused on locoregional treatment options, including surgery and adjuvant radiation.[1–4] Surgical results for low-grade malignancies are good, but for high-grade tumors postoperative radiotherapy is usually indicated. The local recurrence rate of high-grade salivary gland tumors treated with surgery alone is at least 30% and late distant metastases can occur. Relapses might be reduced by providing the patient with postoperative radiotherapy.[3,4] Chemotherapy is indicated in the case of local recurrence with inoperability of the tumor and/or development of distant metastases.[2–5]

Because of the rarity of these diseases (only 5–10% of all head and neck malignancies), data concerning the effect of chemotherapy are limited, especially with regard to various histologic types. Therefore, performing clinical trials with adequate numbers of patients (the numbers of patients in published trials varies from 4 to 36) is difficult and our series is no exception. The overall response to chemotherapy averages 0–100% in published trials.[6–10,15–18]

Cisplatin, doxorubicin and 5-FU are the agents with the best-documented single activity.[7,8] The most frequently used combination regimens are the PAC and CF regimen.[7–10]

In 1996, Verweij on behalf of the EORTC presented a phase II study with 32 patients receiving mitoxantrone yielding an overall response rate of 12% and stabilization of disease in 69%.[15] Since combination regimens (especially the PAC regimen) resulted in higher response rates than single agents, and due to the structural and functional similarity of mitoxantrone to the anthracyclines, we investigated the combination of cisplatin and mitoxantrone.

Two PRs (14.3%) of long duration (14 and 27 months, respectively) could be achieved. In nine patients (64.3%) SD with a median duration of stabilization of 15 months (range 3–27) was observed. The apparent long-term control of disease and the fact that only three patients (21.4%) progressed under chemotherapy suggests that the combination of cisplatin and mitoxantrone may be active in salivary gland carcinomas. It seems noteworthy that after a median follow-up time of 22 months (range 8–54 months), six of 14 patients (43%) are still alive.

With regard to tolerance of treatment, neutropenia was the most common and dose-limiting toxicity associated with this combination regimen, being grade 3 or 4 in 21 or 29%, respectively. Non-hematologic adverse events were generally mild to moderate, except two patients who experienced grade 3 nausea/vomiting.

In conclusion, the results of this phase II trial indicate that cisplatin and mitoxantrone is an effective and fairly well-tolerated regimen for disseminated or recurrent salivary gland malignancies. In view of the observed high rate of abrogation of PD and the long-term disease control in patients with PR and SD, further investigation of this regimen seems warranted.

References

1. Schantz SO, Harrison LB, Forastiere A. Cancer of the head and neck. In: De Vita VT, Hellmann S, Rosenberg SA, eds. *Cancer: principles & practice of oncology*. Philidelphia, PA: Lippincott 2001: 789–917.
2. Everett E, Vokes EE, Ralp R, *et al*. Head and neck cancer [Review]. *N Engl J Med* 1993; **328**: 184–94.
3. Spiro RH, Huvos AG, Strong EW. Adenoid cystic carcinoma of salivary gland origin: a clinico-pathologic study of 242 cases. *Am J Surg* 1974; **128**: 512–20.
4. Chou C, Zhu G, Luo M, Xue G. Carcinoma of the minor salivary glands: results of surgery and combined therapy. *J Oral Maxillofac Surg* 1996; **54**: 448–53.
5. Posner MR, Ervin TJ, Weichselbaum RR, *et al*. Chemotherapy of advanced salivary gland neoplasms. *Cancer* 1982; **50**: 2261–4.
6. Schramm VL, Strodes C, Myers E. Cisplatinum therapy for adenoid cystic carcinoma. *Arch Otolaryngol* 1981; **107**: 739–741.
7. 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.
8. Licitra L, Cavina R, Grandi C, *et al*. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinomas. *Ann Oncol* 1996; **7**: 640–2.
9. Triozzi PL, Brantley A, Fisher S, Cole B, Crocker I, Huang AT. 5-Floururacil, cyclophosphamide and vincristine for adenoid cystic carcinoma of the head and neck. *Cancer* 1987; **59**: 887–90.
10. Hill ME, Constenla DO, A'Hern RP, *et al*. Cisplatin and 5-floururacil for symptom control in advanced salivary adenoid cystic carcinoma. *Oral Oncol* 1997; **33**: 275–8.
11. McLaughlin P, Hagemeister FB, Ramaguera JE, *et al*. Fludarabine, mitoxantrone and dexamethasone: an effective new regimen for indolent lymphoma. *J Clin Oncol* 1996; **14**: 1262–8.
12. Smith D, Leyland-Jones B, Shak S, *et al*. MMM (mitomycin/mitoxantrone/methotrexate): an effective new regimen in the treatment of metastatic breast cancer. *Oncology* 1993; **50**(suppl 1): 9–15.
13. Yoa-Pu Hu O, Chang SP, Law CK, *et al*. Pharmacokinetic and pharmacodynamic studies with mitoxantrone in the treatment of patients with nasopharyngeal carcinoma. *Cancer* 1992; **69**: 847–53.
14. Dugan M, Choy D, Ngai A, *et al*. Multicenter phase II trial of mitoxantrone in patients with advanced nasopharyngeal carcinoma in Southeast Asia: an Asian-Oceanian Clinical Oncology Association Group Study. *J Clin Oncol* 1993; **11**: 70–6.
15. Verweij J, Mulder PHM, Graeff A, *et al*. Phase II study on mitoxantrone in adenoid cystic carcinomas of the head and neck. *Ann Oncol* 1996; **7**: 867–9.
16. Airoldi M, Pedani F, Succo G, *et al*. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies. *Cancer* 2001; **91**: 5 41–7.
17. Airoldi M, Fornari G, Pedani F, *et al*. Paclitaxel and carboplatin for recurrent salivary gland malignancies. *Anticancer Res* 2000; **20**: 37781–84.
18. De Haan LD, De Mulder PH, 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.

(Received 22 January 2002; accepted 5 March 2002)