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## Clinical report

# Ifosfamide and mitoxantrone in the treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck

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**A phase II study was performed to assess the safety and efficacy of ifosfamide and mitoxantrone in recurrent and/or metastatic squamous cell carcinomas of the head and neck. Treatment consisted of ifosfamide 1500 mg/m$^2$ in 1000 ml saline, infused over 60 min and mesna 20% of the total dose of ifosfamide in three doses for 3 days combined with mitoxantrone 12 mg/m$^2$ given as a short infusion on day 1. Treatment courses were repeated every 4 weeks until a total of six cycles. Twenty-two patients entered this trial, 13 of whom had received chemo- and radiation therapy, and nine patients who underwent radiation therapy with or without prior surgery. We observed no objective response, with the exception of two patients who experienced minor response (reduction of tumor size of 25%). The dose-limiting toxicity was myelosuppression with grade 3/4 leukocytopenia in seven patients (32%) and grade 3/4 neutropenia in 15 (68%). Severe organ toxicity except alopecia (91%) was not observed. Ifosfamide combined with mitoxantrone does not improve the therapeutic armentarium in recurrent squamous cell carcinoma of the head and neck. [© 2001 Lippincott Williams & Wilkins.]**

*Key words*: Head and neck cancer, ifosfamide, mitoxantrone, palliative chemotherapy.

## Introduction

There are over 500 000 new cases of head and neck cancer each year worldwide.[1] Two-thirds of patients will present with local or regional advanced disease at the time of diagnosis. Even after aggressive treatment, including surgery, radiotherapy or both, more than 60% of these patients develop either locoregional recurrence or distant metastasis. Once tumor relapse occurs the survival rate of patients with head and neck cancer remains poor.[2] In the case of locoregional recurrence or distant metastasis and after failure of initial therapy, chemotherapy plays a major role.[3,4] More effective systemic treatments could lead to enhanced local control and provide better palliation for patients.

Several antineoplastic drugs and combinations, including bleomycin, cisplatin, carboplatin, methotrexate and others, have shown their capacity to induce antitumoral responses in this disease, but the duration of tumor regression is brief and significant improvements in survival directly attributed to chemotherapy have been difficult to achieve.[5,6] Therefore, the identification or development of new active agents or drug combinations with a superior therapeutic index remains a principal goal of investigational efforts.

Ifosfamide resembles a structural isomer of cyclophosphamide with a broader range of antitumor activity, including testicular cancer and sarcomas of the soft tissue and bone. The improved therapeutic index is largely due to the lower myelosuppressive potential of ifosfamide over its parent compound. In contrast to single-agent settings with much less impressive responses, a recent study combining ifosfamide, cisplatin and paclitaxel achieved an overall response rate of 57%, suggesting an additive antitumor activity of ifosfamide to the paclitaxel/cisplatin combination.[7] Since all chemotherapy-pretreated patients had received a combination regimen consisting of docetaxel and cisplatin we decided to combine ifosfamide with the topoisomerase II inhibitor mitoxantrone, which was found to be an active and tolerable drug in the treatment of patients with advanced

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nasopharyngeal carcinoma, producing an overall response rate comparable to that of other single-agent regimen used in the treatment of advanced head and neck cancer.[8]

## Patients and methods

### Patient selection

Patients with histologically confirmed head and neck squamous cell cancer (HNSCC) were eligible when definitive local treatment, including surgery, radiotherapy, chemotherapy or all, failed or when distant metastasis were present regardless of previous therapy. The patients had to have at least one measurable lesion. All patients were required to be aged $\leqslant 75$ years, to have a WHO performance status of $\leqslant 2$, an expected survival of $>12$ weeks, and to have adequate bone marrow (leukocyte count $\geqslant 4000/\mu$l, absolute granulocyte count $\geqslant 2000\ \mu$l and platelet count $\geqslant 100\ 000/\mu$l, renal (serum creatinin level of less than 1.5 mg/dl) and liver function (total bilirubin level of $<1.5$ mg/dl, transaminase levels of $<2\times$ the upper limits of normal). Informed consent was obtained from the patient according to the institutional regulation.

### Pretreatment and follow-up evaluation

Pretreatment evaluation included a complete medical and physical examination with measurement of all tumor-associated lesions. Laboratory evaluation consisted of a complete blood count with platelet count and a leukocyte differential count, an 18-function biochemical profile, prothrombin and partial thromboplastin time, fibrinogen, and assays of the tumor markers carcinogenic antigen (CEA) and SCC. Imaging procedures included chest X-ray, bone scan and computed tomography plus ultrasound of the abdomen. Complete blood counts and differential counts were performed every 2 weeks; biochemical profiles and tumor markers were assessed before each treatment cycle. Patients were evaluated clinically after each cycle. Radiographs or scans of areas of disease were evaluated after every treatment courses.

### Treatment protocol

Therapy consisted of ifosfamide given as a 60-min infusion at a dose of 1500 mg/m$^2$ on days 1–3 and mitoxantrone as short infusion at a dose of 12 mg/m$^2$ on day 1. Prior to and after ifosfamide administration, patients were hydrated with 1000 ml of normal saline solution. Patients also received mesna 20% of the total ifosfamide dose in three doses for 3 days (prior to, and 4 and 8 h after ifosfamide infusions). Antiemetic therapy was administered routinely on days 1–3, and consisted of serotoninantagonists and steroids. Courses were repeated every 4 weeks until a total of six cycles or progression of disease.

### Toxicity and dosage modifications guidelines

Adverse reactions were evaluated according to WHO criteria. Drug doses were reduced by 25% in subsequent cycles if the lowest WBC (absolute granulocyte) count was $<1000/\mu$l, the lowest platelet count was $<50\,000/\mu$l or if any severe (WHO grade $\geqslant 3$) non-hematologic toxicity was observed during the previous cycle. Treatment could be delayed for up to 2 weeks if the WBC count was $<3000/\mu$l or the platelet count was $<90\,000/\mu$l. Any patient who required more than 2 weeks for hematological recovery was taken off study.

### Assessment of response

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.

## Results

### Patient characteristics

From October 1998 to August 1999, a total of 22 patients entered this trial. All patients were considered evaluable for toxicity assessment and 17 for response assessment. The patient demographic details are shown in Table 1. The median age was 58 years (range 36–72 years), the median WHO performance status was 1 (range 0–2). Site of disease at diagnosis and status of disease recurrence are also shown in Table 1: 11 patients had locoregional recurrences, seven patients had lymph node metastasis and four patients showed distant metastasis. All patients had recurrent disease after locoregional treatment: six patients had surgery followed by radiation, five patients had radiochemotherapy, eight patients had surgery plus radiation therapy and three patients had radiation therapy only.

**Table 1**. Patients characteristics

| | *N* |
|---|---|
| No. of patients entered/evaluable | 22/17 |
| Sex | |
| female | 18 |
| male | 4 |
| Age (years) | |
| median (range) | 58 (36–72) |
| WHO performance status | |
| 0 | 6 |
| 1 | 10 |
| 2 | 6 |
| Site of primary tumor | |
| larynx | 3 |
| pharynx | 5 |
| oral cavity | 14 |
| Site of relapse/tumor | |
| locoregional | 11 |
| lymph node | 7 |
| locoregional + lung | 4 |
| Prior treatment | |
| radiation therapy | 3 |
| surgery + radiation therapy | 6 |
| chemo/radiotherapy | 5 |
| all | 8 |

**Table 2**. Objective response related to prior therapy

| | *N* |
|---|---|
| Response | 22 |
| CR | 0 |
| PR | 0 |
| Minor response (25% reduction of tumor size) | 2 (9%) |
| No change | 8 (36%) |
| Progression | 7 (32%) |
| Median time to progression [median (range), months)] | 6 (2–9) |
| Median survival [median (range), months] | 6 (1.5–12) |

**Table 3**. Hematologic toxicity ($n = 22$)

| Toxicity | WHO grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Leukopenia | 5 (23%) | 6 (27%) | 3 (14%) | 4 (18%) |
| Neutropenia | 3 (14%) | 4 (18%) | 7 (32%) | 8 (36%) |
| Thrombocytopenia | 3 (14%) | 3 (14%) | – | – |
| Anemia | 5 (23%) | 4 (18%) | 8 (36%) | – |

### Response to therapy

Responses to therapy are shown in Table 2: three of the 22 patients stopped treatment and were lost for follow-up after two treatment courses and two patients died after the first or second cycle (before response evaluation was performed) probably due to rapid tumor progression. No patient achieved a response to ifosfamide and mitoxantrone, with the exception of two patients who experienced minor responses by reduction of tumorsize of approximately 25%. Eight patients had stable disease for a median time of 6 months (range 3–9 months). For all patients, the median time to progression was 6 months (range 2–9 months) and median survival was 6 months (range 1.5–12 months).

### Toxicity

All patients who had received a total of 71 courses were assessable for toxicity. Hematologic side effects associated with treatment are listed in Table 3. The dose-limiting toxicity was myelosuppression. Leukopenia occurred in 18 patients (82%) and was grade 3 or 4 in seven patients (32%). Neutropenia occurred in 22 patients (100%) and was grade 3 or 4 in 15 patients (68%). Thrombocytopenia grade 1 or 2 was seen in six patients (27%) and anemia grade 3 in eight patients (36%), requiring packed red blood cell transfusion. Six patients (27%) developed infection, all of which recovered after i.v. antibiotic therapy.

Non-hematologic toxic effects (Table 4) included mild to moderate degrees of nausea plus vomiting and stomatits, and rare incidence of diarrhea. A mild degree of peripheral neuropathy occurred in one patient (5%). Grade 3 alopecia developed in 20 patients (91%).

## Discussion

Ifosamide, an analog of cyclophosphamide, has shown antitumor activity in previous trials carried out in chemotherapy-naive patients with head and neck cancer,[9,10] whereas a previous phase II study found mitoxantrone to be an active and tolerable drug in the treatment of patients with advanced nasopharyngeal carcinoma, producing an overall response rate comparable to that of other single-agent regimen used in the treatment of advanced head and neck cancer.[8] Zamboglou *et al*. found that combining intratumoral instillation of mitoxantrone with concurrent radiotherapy could also show a palliative effect in locoregional recurrence of head and neck cancer.[11]

Based on the above-mentioned findings, we initiated a phase II trial to assess the tolerance and activity of a new antineoplastic drug combination of ifosfamide and mitoxantrone. This study failed to demonstrate

**Table 4**. Non-hematologic toxicity ($n=22$)

| Toxicity | WHO grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Nausea | 8 (36%) | 3 (14%) | 2 (9%) | – |
| Vomiting | 5 (23) | 3 (14%) | – | – |
| Diarrhea | – | 2 (9%) | – | – |
| Stomatitis | 4 (18%) | 2 (9%) | – | – |
| Alopecia | – | – | 20 (91%) | – |
| CNS | – | 1 (5%) | – | – |
| Infection | – | 3 (14%) | – | 3 (14%) |

significant activity in patients with advanced recurrent or metastatic HNSCC, albeit in a population which was in most cases heavily pretreated with surgery, radiotherapy, chemotherapy or the combination. No patient achieved a CR or PR (with the exception of minor responses in 9% of the patients who were evaluable for response), although eight patients experienced stable disease for a median of 6 months (range 3–9 months).

The lack of response is disappointing given that other antineoplastic drugs in combination with ifosfamide have demonstrated activity in patients with advanced HNSCC. For example, ifosfamide in combination with cisplatin showed a response rate of approximately 66% in a phase II study.[12] In another phase I/II study the combination of paclitaxel, ifosfamide and cisplatin achieved an overall response rate of 57%.[2,7]

One possible explanation for the observed lack of efficacy could be the fact that all patients had been pretreated, including 13 patients (59%) who had received prior chemotherapy, as compared to other studies where patients had undergone surgery or radiation therapy only. Another possible reason for the poor study outcome might be the coincidence of other poor prognostic features in our patients, because the response rates to chemotherapy in head and neck cancer may vary significantly depending on the patient population.

## Conclusion

The results of this phase II study do not warrant further development of ifosfamide and mitoxantrone for this disease.

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