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A phase II study of ifosfamide, 5-fluorouracil and leucovorin in patients with recurrent nasopharyngeal carcinoma previously treated with platinum chemotherapy

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Abstract

The aim of this study was to evaluate the efficacy and toxicity of ifosfamide, 5-fluorouracil (5-FU) and leucovorin (IFL) as a second-line chemotherapy regimen in patients with recurrent undifferentiated nasopharyngeal carcinoma (NPC) previously treated with platinum/5-FU. Between June 1997 and February 1999, 18 patients were entered into the study. 3 patients had loco-regional recurrence, 12 had distant metastases and 3 had both loco-regional recurrence and distant metastases. All patients had previously received platinum/5-FU as adjuvant or palliative treatments. The IFL regimen consisting of ifosfamide 1.2 g/m^2 (with mesna), 5-FU 375 mg/m^2 and leucovorin 20 mg/m^2 for 5 days and was repeated every 21 days. The dose of ifosfamide was escalated to 1.4 and 1.6 g/m^2 in subsequent cycles according to the bone marrow toxicity, and the dose of 5-FU to 450 and 525 mg/m^2 according to the severity of mucositis. Patients received a median of 3 cycles of IFL (range: 2–6), with a median total ifosfamide dose of 21 g/m^2 (range: 13–46) and a median total 5-FU dose of 6.75 g/m^2 (range: 4.1–14.7). The median follow-up was 10 months (range: 4–25). 9 patients (50%) achieved a partial response and 1 patient (6%) achieved a complete response, with an overall response rate of 56% (95% confidence interval (CI): 32–80%). For those patients who responded to IFL, 8 had subsequent disease progression on follow-up, with a median response duration of 7.1 months (95% CI: 5.3–8.9). The median time to progression for all patients was 6.5 months (95% CI: 4.2–8.7). 12 patients are still alive with an estimated 1-year survival probability rate of 51%. Treatments were well tolerated, only 1 patient had grade 3 emesis. None of the patients had grade 3/4 anaemia, leucopenia or thrombocytopenia, although IFL was discontinued in 1 patient because of persisting thrombocytopenia. IFL is an effective second-line regimen in patients with recurrent NPC and is well tolerated with mild toxicity. Combining platinum and IFL in chemonaïve patients may further improve the overall response rate and duration and is worth investigating in future trials.

Keywords: Nasopharyngeal carcinoma; Recurrence; Palliative chemotherapy; Ifosfamide; 5-Fluorouracil; Leucovorin

1. Introduction

Nasopharyngeal carcinoma (NPC) of an undifferentiated type is responsive to a wide range of chemotherapeutic agents, with response rates ranging from 38 to 91% using combination chemotherapy in the setting of loco-regional recurrence and/or distant metastases [1–9]. A higher response rate is commonly observed with the use of platinum-based regimens than with non-platinum-based regimens. Although platinum-based regimens, especially the combination of platinum and 5-fluorouracil (5-FU), have been widely adopted as the first-line chemotherapy regimen in the treatment of recurrent NPC, the choice of a second-line regimen in patients with an unsatisfactory response to platinum or in those previously treated in an adjuvant setting by platinum-based chemotherapy remains unclear. Despite a large number of publications addressing the efficacy of different chemotherapy regimens in NPC, very few reports had specifically studied the efficacy of second-line chemotherapy in patients previously treated with platinum-based regimens.

Ifosfamide is an analogue of cyclophosphamide that possesses a spectrum of toxicities and clinical activity different from that of its parent compound. Significant haemorrhagic cystitis was the dose-limiting factor in

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phase I trials until the introduction of the uroprotective agent mesna. Activity has been demonstrated for ifosfamide in a variety of tumours, including testicular cancer, sarcoma, lymphoma, lung cancer, paediatric tumours, and gynaecological malignancies. Recent studies also demonstrated an activity of ifosfamide in head and neck cancers [10–13]. However, studies of ifosfamide-based chemotherapy in NPC, have been sparse. 5-FU is also active against a wide range of tumours, and in combination with cisplatin, has a high activity in head and neck cancers including NPC. The cytotoxic effect of 5-FU can be enhanced further by modulation using low-dose leucovorin. In this study, we chose to investigate the combination of ifosfamide, 5-FU and leucovorin as a second-line chemotherapy regimen in patients with advanced recurrent NPC pretreated with platinum/5-FU chemotherapy.

2. Patients and methods

2.1. Patient characteristics

Between June 1997 and February 1999, 18 patients with advanced recurrent NPC (loco-regional disease and/or distant metastases) were treated with the study regimen ifosfamide, 5-FU and leucovorin (IFL). The inclusion criteria were: histologically proven NPC (undifferentiated or poorly differentiated carcinoma), completed radical treatment, disease recurrence or progression after previous platinum-based chemotherapy given as part of the primary treatment and/or treatment for recurrence, recurrent disease not amenable to other salvage treatments such as surgery or re-irradiation, measurable disease on clinical or radiological grounds, age 18 years or above, Karnofsky performance score of 60 or above, adequate haematological reserve (white cell count $\geqslant 3\times10^9$/l and platelet count $\geqslant 100\times10^9$/l), and completion of other forms of therapy including chemotherapy at least 4 weeks before entering study. The study protocol was approved by the institution ethics committee and all patients gave informed consent prior to entry into the study. The baseline patient characteristics are summarised in Table 1.

2.2. Treatment

IFL was given as a 5-day in-patient treatment with a 21-day cycle. The starting IFL dose was ifosfamide 1.2 g/m^2 infused over 4 h, leucovorin 20 mg/m^2 as an intravenous bolus, 5-FU 375 mg/m^2 infused over 20 h, all were given daily for 5 days. Mesna was given intravenously at a dose of 300 mg/m^2 before commencing ifosfamide infusion and thereafter at a 4-h interval for a total of four doses. 5-HT_3 antagonist was given 15 min before ifosfamide as prophylaxis against emesis. A white cell count $\geqslant 3\times10^9$/l and a platelet count $\geqslant 100\times10^9$/l were required before each cycle, and if the cell counts fell below these levels then treatment was delayed for 1 week or longer until recovery.

The dose of ifosfamide was escalated to 1.4 g/m^2 and then to 1.6 g/m^2 in the subsequent cycle if the white cell count was $\geqslant 3\times10^9$/l and the platelet count $\geqslant 100\times10^9$/l at the end of cycle and if there was no delay of the cycle secondary to slow bone marrow recovery and/or neutropenic fever. The dose of 5-FU was escalated to 450 mg/m^2 and then to 525 mg/m^2 in the absence of severe

Table 1
Patient characteristics

	n (%)
Gender (*n*)	
Male	16 (89)
Female	2 (11)
Age (years)	
Median (range)	46 (34–64)
Performance score (KPS)	
Median (range)	75 (60–100)
No. of relapse (*n*)	
First relapse	11 (61)
Second relapse	7 (39)
Disease sites (*n*)	
Loco-regional	3 (17)
Distant metastases	12 (67)
Loco-regional and distant metastases	3 (17)
No. of disease sites (*n*)	
One	9 (50)
Two	8 (44)
Three	1 (6)
Previous radiation therapy (*n*)	
Radical radiotherapy to nasopharynx/neck	18 (100)
Re-irradiation to nasopharynx	2 (11)
Re-irradiation to neck	2 (11)
Palliative radiotherapy to bone	2 (11)
Previous platinum chemotherapy (*n*)	
Neoadjuvant/adjuvant Rx	3 (17)
Adjuvant after salvage Rx	2 (11)
Neoadjuvant/adjuvant Rx + Rx for relapse	2 (11)
Rx for relapse	11 (61)
Platinum-based regimen (*n*)	
Cisplatin/5-FU	13 (72)
Carboplatin/5-FU	2 (11)
Cisplatin or carboplatin/5-FU	3 (17)
Total no. of platinum cycles received (*n*)	
Three	6 (33)
Four	3 (17)
Five	4 (22)
Six	3 (17)
> Six	2 (11)
Follow-up time (months)	
Median (range)	10 (4–25)

Rx, chemotherapy.

mucositis (grade 2 or above) in the preceding cycle. The dose of leucovorin was not escalated.

Response assessment was performed after three and six cycles according to WHO criteria. Patients with at least a partial response after three cycles would receive three more cycles of chemotherapy. Treatment was stopped if progression was documented at any time or after a maximum of six cycles.

2.3. Evaluation of response/toxicity and follow-up

Blood tests including complete blood picture, renal and liver function tests were performed between each cycle, as well as at the end of the cycles. Toxicity of treatment was graded after each cycle according to WHO grading. Urinalysis was performed prior to chemotherapy and monitored throughout the administration of chemotherapy to document the presence and extent of haematuria. For microscopic haematuria with urine red blood cell (RBC) $\leqslant 25/\mu l$, an additional dose of mesna at 300 mg/m^2 was administered q4 h until haematuria was resolved. Chemotherapy was discontinued if there was persistent haematuria that did not respond to an additional dose of mesna or if urine RBC exceeded 25/μl. In patients with documented microscopic haematuria that resolved after an additional dose of mesna, further chemotherapy was continued with a higher dose of mesna (400 mg/m^2 every 4 h$\times$5).

Response assessment was performed as described above. For patients with multiple disease sites, the worst response site was taken as the overall response. Patients were followed-up monthly in the first year after completion of treatment and thereafter every 2 months. Clinical examination was carried out during each visit, whilst relevant blood tests and imaging were carried out every 2–3 months.

The following endpoints were used in the evaluation of efficacy: response rate, response duration, time to progression and survival. The probability of survival or time to progression was calculated by the Kaplan–Meier method. Response duration refers to patients with a documented response to IFL and was calculated from the day chemotherapy was started until the date of progression or last follow-up in those without disease progression. Time to progression refers to all patients and was similarly calculated. Likewise, survival time was calculated from the first day of chemotherapy until the date of death or last follow-up.

3. Results

18 patients were recruited into the trial from June 1997 to February 1999 and all were evaluable for toxicity and response. All patients had received previous platinum-based chemotherapy; 3 for neoadjuvant and/or adjuvant treatment, 2 for adjuvant treatment after salvage of earlier recurrences (neck dissection for recurrent neck node in one, and resection of lung metastasis in the other), 2 for both neoadjuvant/adjuvant treatment and recurrence and 11 for recurrence. 13 patients had previously received cisplatin at a dose of 100 mg/m^2 on day 1 and 5-FU at a dose of 1 g/m^2 on days 1–3, 2 patients had carboplatin at a dose of 300 mg/m^2 on day 1 and 5-FU at a dose of 1 g/m^2 on days 1–3 and 3 patients had cisplatin/5-FU initially but switched to carboplatin/5-FU later because of nephrotoxicity. The number of courses of platinum/5-FU received ranged from 3 to 10, with a median of 4.5. The response rate to platinum chemotherapy in those with assessable disease was 31% (4/13).

A total of 65 cycles of IFL was administered to 18 patients with a median of three treatment cycles per patient (range: 2–6). 13/18 (72%) of patients received at least three cycles, whilst 4/18 (22%) received the maximum six cycles. The median total ifosfamide dose received by patients was 21 g/m^2 (range: 13–46) and the median total 5-FU dose was 6.75 g/m^2 (range: 4.1–14.7). The median follow-up duration was 10 months (range: 4–25).

The overall response rate to IFL was 56% (10/18, 95% CI: 32–80%). One patient (6%) with liver metastases had a complete response to IFL, whereas 9 patients (50%) had a partial response. One patient with axilla lymphadenopathy achieved a good partial response after six cycles of IFL and went on to receive additional radiotherapy to the axilla, and remains disease free at 25.3 months. 7 patients (39%) had static disease whereas 1 patient had disease progression during chemotherapy. For those who responded to IFL, 8 had subsequent disease progression on follow-up; the median response duration was 7.1 months (95% CI: 5.3–8.9), with a range of 3.9–25.3 months. The median time to progression for the whole group was 6.5 months (95% CI: 4.2–8.7), with a range of 3–25.3 months. At the time of analysis, 12 patients (67%) are still alive and the median survival has not yet been reached. The estimated 1-year survival probability rate was 51%.

The time interval between the completion of previous platinum-based chemotherapy and the initiation of IFL ranged from 6 weeks to 25 months with a median of 10 months. No correlation was found between this time interval and the response rate to IFL, with a 55% (6/11) response rate observed for a time interval of $\leqslant 12$ months compared with a 57% (4/7) rate for a time interval of >12 months. There was also no correlation between the response to IFL and the previous response to the platinum regimens: the response rate to IFL was 50% (2/4) in those who previously responded compared with 44% (4/9) in those who did not respond ($P=0.69$, McNemar test).

Table 2
Response to IFL according to specific disease sites[a]

Disease site	*n* of patients (%)	CR	PR	SD	PD	CR + PR (%)	Patients not assessed
Nasopharynx	3 (17)	0	0	2	1	0	0
Neck nodes	6 (33)	0	2	3	1	2 (33)	0
Axilla nodes	1 (6)	0	1	0	0	1 (100)	0
Lung	11 (61)	0	6	5	0	6 (55)	0
Liver	4 (22)	1	3	0	0	4 (100)	0
Bone	3 (17)	0	0	1	0	0	2

[a] CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The time interval between the completion of the primary radiotherapy and disease recurrence ranged from 4 to 128 months with a median of 27 months. A higher response rate to IFL was observed in patients with a longer time from completion of primary radiotherapy to recurrence. The response rate to IFL was 70% (7/10) in those with time interval >24 months compared with 38% (3/8) in those $\leqslant 24$ months, but the difference was not statistically significant ($P=0.34$, Fisher's Exact test).

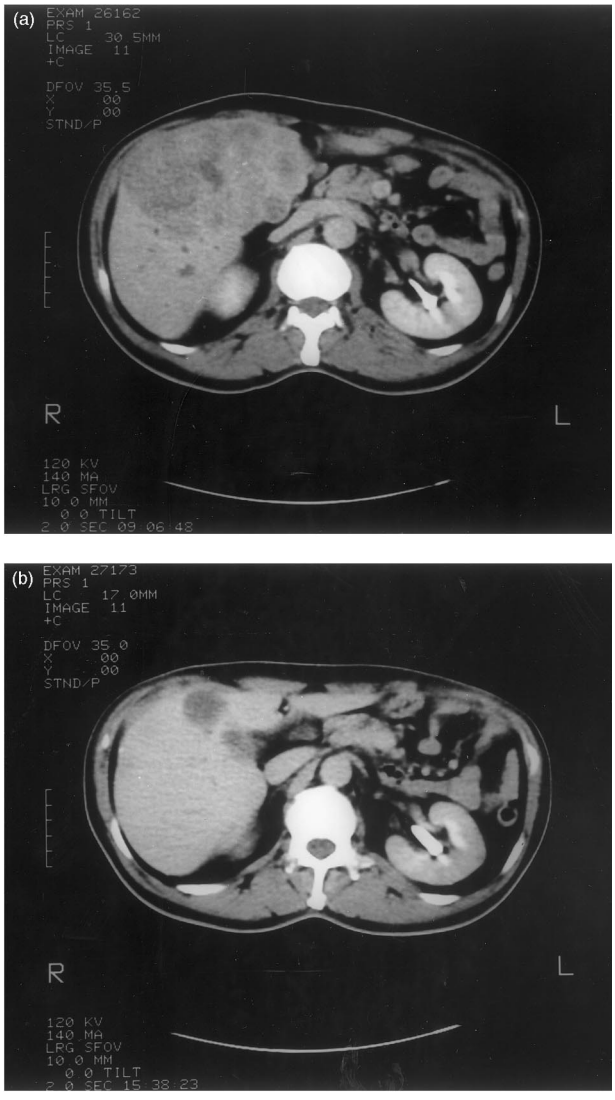

Fig. 1. Response to ifosfamide, 5-fluorouracil and leucovorin (IFL) in a patient with liver metastases: (a) before IFL treatment; (b) after three cycles of IFL.

9 patients had significant symptoms due to disease prior to IFL treatment, including 4 with liver metastases, 4 with loco-regional disease and 1 with bone metastases. After chemotherapy, 5 patients (56%), including the 4 patients with liver metastases and 1 patient with loco-regional disease, had good symptomatic relief with an improvement in performance status.

Table 2 shows the response rate to IFL according to specific disease sites. There are altogether 26 assessable sites in 18 patients, including 9 loco-regional disease sites and 17 distant metastatic sites (axilla, liver, lung and bone). A higher response rate to IFL was observed in patients with distant metastases 11/17 (65%) compared with those with loco-regional disease 2/9 (22%). Patients with liver metastases appear to be more responsive, with all 4 patients responding to IFL, including one complete response. The responses observed in patients with liver metastases were also more dramatic with significant reduction in size of tumour and hepatomegaly, accompanied by normalisation of liver enzymes and symptomatic relief. Fig. 1 shows pre- and postchemotherapy computed tomography (CT) scans of a patient with a partial response to the study regimen.

Treatments were generally well tolerated by patients. There were no WHO grade 3 or 4 anaemia, leucopenia and thrombocytopenia. One patient (6%) had a persistent low platelet count (between 70 and 80×10^9/l) after three cycles of IFL and further chemotherapy was discontinued. No patient had neutropenic fever as a result of chemotherapy and there were no treatment-related deaths. Severe emesis (grade 3) was observed in only 1 patient (6%). All patients developed alopecia and total alopecia (grade III) was observed in 12 patients (67%). 4 patients (22%) had transient microscopic haematuria during chemotherapy that resolved after increasing the dose of mesna.

4. Discussion

There have been few reports on the use of ifosfamide-based chemotherapy in NPC compared with other head and neck cancers. Liu and colleagues reported using single-agent ifosfamide at a dose of 2 g/m^2 for 4 days in 33 patients with recurrent NPC, including 18 chemonaïve patients [14]. 31 patients were evaluable and the overall response rate was 45%, with a complete response rate of 6% and a partial response rate of 39%. Stein and associates combined cisplatin at a dose of 50 mg/m^2 with ifosfamide at a dose of 3 g/m^2 both given for 2 days, in 18 young African blacks with advanced NPC. This group of patients are younger (median age 20 years) and have predominantly bone metastases (83%) [15]. After treatment with cisplatin–ifosfamide, a 15% complete response rate was achieved and good remission was observed in another 44% of patients. The median response duration was 29 weeks and median survival was 59 weeks.

The current study is the first report on the efficacy of ifosfamide in a homogeneous group of patients previously treated by platinum for NPC. The response rate observed with IFL in this study compares favourably with the reported response rates to platinum-based chemotherapy in NPC [2–9]. It also compares favourably with the observed response rates to newer agents such as paclitaxel, for which a response rate of 22% was reported when used as a single agent [16], and a response rate of 59% when combined with carboplatin [17]. However, strict comparison with other chemotherapy regimens is of limited value because of different selection criteria and the relative small sample sizes in these studies.

The two main indications for chemotherapy in patients with disseminated disease are effective prolongation of survival and good palliation of symptoms, thereby improving the quality of life. Although a high response rate has been commonly observed with the occasional observation of long-term responders after the use of platinum-based chemotherapy in NPC, there has been no randomised study documenting a survival benefit with the routine use of chemotherapy in recurrent NPC. In addition, the effectiveness of chemotherapy in symptom palliation and the resulting quality of life are seldom reported in phase II studies.

Our findings, along with other reports, suggest ifosfamide to be an effective agent in NPC, although the response duration in recurrent disease still tends to be brief with a limited effect on survival. Nevertheless, use of IFL in the palliative setting would still be beneficial if toxicities are mild and effective palliation of symptoms can be achieved. In this study, the use of IFL was restricted to second-line regimens in patients previously treated by platinum/5-FU. Although quality of life was not assessed in this study, IFL was found to be beneficial in some patients with symptomatic disease, especially in those with extensive liver metastases causing jaundice and abdominal distention. The good remission observed in patients with liver metastases is of particular importance as liver metastases has been reported to be a predictor of short survival in metastatic NPC [18].

In summary, the study regimen IFL appears to be an effective second-line treatment in patients with recurrent NPC previously treated by platinum-based regimens, and is worth considering in patients with significant symptoms not controlled by other means. The benefit of IFL in patients with asymptomatic recurrent disease is unclear and needs to be studied further. A prospective study comparing IFL and platinum/5-FU as first-line chemotherapy in patients with recurrent NPC is worthwhile. Combining IFL and cisplatin as first-line chemotherapy may lead to higher response rates in recurrent NPC, as well as achieving a more durable response and is also worth investigating in future trials.

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