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Phase II studies of ifosfamide alone and in combination in cancer of the cervix*

G. Blackledge, E. J. Buxton, J. J. Mould, J. Monaghan, M. Paterson, J. Tobias, C. Alcock, D. Spooner, and C. A. Meanwell

West Midlands Cancer Research Campaign Clinical Trials Unit, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Edgbaston, Birmingham, United Kingdom

Summary. A series of phase II studies using ifosfamide (IFX) as a single agent and in combination with cisplatin and bleomycin (BIP) in advanced and recurrent cervical cancer have been coordinated at the West Midlands CRC Clinical Trials Unit (Birmingham, UK). The aims of these studies were to identify single agents and combination regimens that may be of value for palliation and have potential for use as neoadjuvant and adjuvant therapy at the time of primary treatment. A total of 79 patients with disease non-amenable to radical local therapy were treated with single-agent IFX or the BIP combination. In 30 patients treated with single-agent IFX, 10 objective responses (30%) were seen, with 1 complete response. In 49 patients treated with BIP, 34 objective responses (69%) were seen, with 10 complete responses (20%). Toxicity included alopecia, nausea and vomiting, myelosuppression, infection, reduction in renal function and disturbance of consciousness. These data indicate that IFX is highly active in cervix cancer and, in combination with bleomycin and cisplatin, can be used for effective palliation and cytoreduction in >70% of patients. IFX-containing regimens have potential for use as neoadjuvant and adjuvant therapy in patients at high risk of recurrence with conventional treatment. These hypotheses are currently being tested in prospective randomised trials.

Introduction

The annual registration rate of cases of invasive cervical cancer in the United Kingdom and Wales has remained consistent over the past 25 years, with around 4,000 cases being registered annually [15]. Stage-specific 5-year survival of women treated for this disease has not altered over the last 20 years. In our region, overall 5-year survival has risen from 40% to 52% in the period 1957–1981 [13], probably reflecting a trend towards early diagnosis (stage 1B and 2A registrations rose from 50% to 63%) rather than more effective treatment. The prognosis in women with recurrent disease is particularly poor, with a 1-year survival of <15% [5]. These data suggest that surgery and radiotherapy alone, the traditional cornerstones of management, do not constitute the optimal therapeutic approach to this disease.

Systemic chemotherapy has traditionally been reserved for palliative treatment in women with recurrent or advanced-stage disease that is not amenable to local radical therapy. Early studies of chemotherapy in this setting demonstrated both complete (CR) and partial (PR) responses to single-agent and combination chemotherapy, but overall response rates rarely exceeded 25% for single agents and 50% for combination regimens [3, 4]; furthermore, durations of remission were short. In an effort to improve the results of treatment, we coordinated a series of collaborative studies whose broad aims were to identify single agents and combinations of high activity that might be of value in the palliation of tumours no longer amenable to radical local therapy. This report describes a coordinated series of studies investigating the activity of ifosfamide (IFX) alone and in combination with cisplatin and bleomycin (BIP) in recurrent cervical cancer.

Rationale

Single-agent IFX: activity and toxicity in cervical cancer

IFX is a highly active oxazaphosphorine derivative and structural analogue of cyclophosphamide that has demonstrated activity in a variety of malignancies [10]. It produces less myelosuppression than cyclophosphamide, and the dose-limiting toxicity of haemorrhagic cystitis can be virtually eliminated by concurrent administration of

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Offprint requests to: G. Blackledge. West Midlands Cancer Research Campaign Clinical Trials Unit, Queen Elizabeth Hospital, Queen Elizabeth Medical Centre, Edgbaston, Birmingham, United Kingdom

Table 1. Single-agent IFX study: patient characteristics

Number of patients	30
Mean age (range)	49 (25–71) years
Median Karnofsky status (range)	80% (60%–100%)
Histology:	
Sq, Well	3
Sq, Mod	14
Sq, Poor	13
Previous treatment:	
None	2
Surgery + DXT	7
DXT	27
Chemotherapy (CDDP + etoposide)	1
Previous chemotherapy for recurrence (bleomycin, doxorubicin mitomycin C)	2

Sq, squamous; Well, well differentiated; Mod, moderately differentiated; Poor, poorly differentiated; DXT, radiotherapy; CDDP, cisplatin

Table 2. BIP study: patient characteristics

Number of patients	49
Median age (range)	41 (24–74) years
Karnofsky status:	
100%	13
90%	19
80%	10
70%	7
Histology:	
Sq, Well	4
Sq, Mod	11
Sq, Poor	25
Adeno	4
Unknown	5
Original FIGO stage:	
I B	23
2	14
3	5
4	2
Unknown	5
Previous treatment:	
None	1
Surgery	6
Surgery/DXT	19
DXT	22
DXT/Chemotherapy	1

Sq, squamous; Well, well differentiated; Mod, moderately differentiated; Poor, poorly differentiated; Adeno, adenocarcinoma; DXT, radiotherapy

Table 3. BIP regimen

Fluid	Volume	Additions	Infusion time (h)
D saline	3 l	30 mg bleomycin	24
0.9% Saline	0.1 l	50 mg/m^2 CDDP	0.5
0.9% Saline	1 l	0.01 l 10% magnesium sulphate	4
Mannitol 20%	0.2 l		2
D saline	3 l	5 g/m^2 IFX	
		3 g/m^2 mesna	24
D saline	1 l	3 g/m^2 mesna	12

D saline, 4% dextrose with 30 mmol sodium chloride; CDDP, cisplatin

mesna [9]. Since cyclophosphamide has demonstrated activity in cancer of the cervix [4], IFX was selected as an agent to be tested in this disease.

Phase II study of BIP in cervical cancer

In an attempt to improve the treatment of advanced and recurrent cancer of the cervix, we combined IFO and cisplatin, the two most active agents in this disease, with bleomycin. Several studies, including that from our own centre, have confirmed the activity of IFX in cervical cancer [2, 12]. Response rates of around 30% were demonstrated, with a significant number of complete responses. A major Gynecologic Oncology Group study established cisplatin as one of the most active single agents in this disease [1]. Data from this group have demonstrated that the optimal dose is 50 mg/m^2 given every 21 days. The drug is also active in previously irradiated sites of disease. In the single-agent phase II studies reported for these drugs, a number of patients with complete responses experienced significant long-term remission. In addition, palliation of symptoms associated with recurrent disease has been reported [2]. Bleomycin also has single-agent activity in recurrent cervical cancer [17]. The most effective combination regimens have been those that combine cisplatin and bleomycin with other active chemotherapeutic agents [7, 16]; response rates of up to 66% have been demonstrated for such combinations. Furthermore, IFX displays in vitro synergism with cisplatin [8]. The toxicities of all three drugs are predictable and non-cross-reactive; therefore, it was logical to combine them. The aims of the study were to assess the response rate, duration of response and toxicity of the BIP combination in the treatment of women with cervical cancer no longer amenable to radical local treatment.

Patients and methods

Single-agent IFX. A total of 30 patients with symptomatic, progressive squamous-cell carcinoma of the cervix no longer amenable to surgery or radiotherapy were entered into this phase II study [12]. Patient characteristics are shown in Table 1. In all patients, renal function was normal (serum creatinine values of <120 mmol/l, serum urea levels of <8.0 mmol/l and creatinine clearance of $\geq$ 50 ml/min) and bone marrow reserves were adequate (WBC, >3.5 × 10^9/l; platelet count, >100 × 10^9/l; haemoglobin concentration, >11.0 g/l). None of the patients had been treated with chemotherapy or radiotherapy for at least 8 weeks prior to study entry. Before treatment, bidimensionally measurable disease was identified and documented using plain radiography, abdominal ultrasonography, rectosonography and computed tomography. Corroborative clinical measurements were made by the investigators.

After prehydration with 1 l dextrose saline over 2 h, patients were treated with IFX (5 g/m^2) given as an infusion in 3 l dextrose saline over 24 h. Treatment was repeated every 21 days. Mesna (5 g/m^2) was added to the IFX infusion solution, followed by a further 3.2 g/m^2 in 1 l dextrose saline that was infused over 12 h to prevent serious and delayed urothelial toxicity. No dose reductions were carried out. Treatment was delayed for 1 week if there were signs of bone marrow suppression or renal impairment (parameters lower than the pre-treatment values listed above). Patients were given a minimum of two cycles of treatment before evaluation of response; if no evidence of disease progression was seen, a maximum of six treatment cycles were given. Response, duration of

Table 4. Response to single-agent IFX in 30 patients

Response	Irradiated site	Non-irradiated site	Overall
Complete	0	1	1
Partial	4	6	9
Stable disease	9	9	10
Disease progression	9	4	9
Inevaluable (early death)	0	2	1

Table 5. Single-agent IFX toxicity expressed as the percentage of courses affected

	WHO grade:				
	0	1	2	3	4
Haemoglobin	75	13	7	5	0
WBC	65	14	11	8	2
Platelets	96	4	0	0	0
Central nervous system	57	32	8	2	1
Nausea and vomiting	5	18	63	14	0
Infection	95	4	0	0	1
Haematuria	72	23	3	2	0
Diarrhoea	85	9	5	0	0
Alopecia	4	8	20	68	0

WBC nadir at 10–14 days was $<3.0 \times 10^9$ in 15 patients assessed; during this period, treatment of three patients was delayed by 1 week due to leukopoenia

Table 6. BIP toxicity expressed as the percentage of courses affected

	WHO grade:				
	0	1	2	3	4
Haemoglobin	37	35	20	7	1
WBC	63	20	12	2	3
Platelets	94	2	1	1	2
Renal	94	2	3	1	0
Central nervous system	32	37	24	6	1
Nausea and vomiting	0	6	87	7	0
Infection	82	8	5	4	1
Haematuria	70	24	5	1	0
Diarrhoea	71	22	7	0	0
Stomatitis	85	12	2	1	0
Oesophagitis	92	6	2	0	0
Fever	81	11	8	0	0
Skin	83	16	1	0	0

Toxicity was assessed in 186 (88%) treatment courses. All patients experienced grade 3 or 4 alopecia, blood transfusions were given in 23% of treatment courses and a WBC nadir of 2.1×10^9 was determined at 15 days (31 courses assessed)

response, survival and toxicity were defined according to UICC and WHO criteria [14].

BIP study. A total of 50 patients with recurrent or advanced carcinoma of the uterine cervix were entered into this study. One patient was later found to be ineligible on the grounds that radiotherapy had been delivered to the measurable lesion 2 weeks prior to initiation of chemotherapy. With the exception of one case of stage IV b disease, all patients had received previous treatment. One patient had previously been treated with six courses of IFX (5 g/m^2) and had achieved a complete response lasting 32 months. Follow-up was complete to January 1, 1988, except for one patient who emigrated after achieving a partial response; she was censored at her last date of follow-up for all analysis. In all, 14 patients with biopsy-proven, untreated, inoperable primary disease were also entered into the study to test the feasibility of giving BIP as neoadjuvant chemotherapy. All patient characteristics are shown in Table 2.

Patients were treated with bleomycin (30 mg), IFX (5 g/m^2) and cisplatin (50 mg/m^2) (Table 3). To prevent serious and delayed urothelial toxicity, 8 g/m^2 mesna (reduced to 6 g/m^2 after December 1986) was given concurrently with the IFX infusion and continued for a further 12 h. If the WBC count was $<2.8 \times 10^9$/l or the platelet count was $<150 \times 10^9$/l and/or the creatinine clearance was <40 ml/min at day 28, a 30% dose reduction was carried out or treatment was delayed. Three patients with recurrent disease (six treatment cycles) received IFX in fractionated doses over 5 days because of impaired renal function. Patients received a standard anti-emetic regimen of intravenous high-dose metoclopramide (7 mg/kg per 24 h), dexamethasone (8 mg at the start of treatment, then 4 mg q 8 h for 24 h) and lorazepam (2 mg at the start of treatment, repeated as required). Further oral anti-emetics were provided as required after discharge from hospital. All patients received two courses of treatment unless there was definite evidence of progression, for a maximum of six cycles in responding patients.

Patients were assessed clinically and using imaging methods that included computed tomography, chest X-ray and ultrasound. In cases of pelvic disease in which there was doubt as to the extent of response, examination with the patient under anaesthesia was carried out, with biopsy of previously involved areas. Response, duration of response and survival were defined according to UICC and WHO criteria. Apart from central nervous system toxicity, which was graded according to the criteria of Meanwell et al. [11], toxicity was assessed using WHO criteria. Informed consent was obtained from all patients. Data were recorded prospectively on proformas and stored on computer in the West Midlands CRC Clinical Trials Unit. All analyses were carried out using the BMDP statistical package [6].

Results

Single-agent IFX

One CR (duration, 32 months) and nine PRs were observed, with an overall median response duration of 6.5 months. All patients showing objective evidence of response and four patients with static disease reported subjective improvement of disease-related symptoms. The median survival of responding patients was 11 months. Detailed response data are shown in Table 4. Objective response rates for lesions arising in previously non-irradiated sites (15 of 28) were significantly higher than those for lesions arising in previously irradiated sites (4 of 22) ($P = 0.018$; Fisher's exact test, two-tailed).

In all patients, haemorrhagic cystitis and haematological and gastrointestinal toxic effects were manageable (Table 5). Treatment was delayed for 1 week due to treatment-related toxicity on 7 occasions out of 101 cycles. Four treatment delays occurred due to mild, reversible impairment of renal function and three were due to leukopenia. Complete but reversible alopecia was experienced by 22 of the 30 patients. There were two treatment-related deaths: one due to infection during the period of myelosuppression in a patient with peritonitis and severe central nervous system (CNS) toxicity, and one due to CNS toxicity without complicating factors. An additional patient developed severe CNS toxicity that resolved spontaneously. The clinical and EEG features of IFX/mesna-associated CNS toxicity have been described in detail by Meanwell et al. [11].

BIP study

Of the 50 patients, 49 were evaluable for response. The ineligible patient had received recent radiotherapy to the index lesion. Of the 49 evaluable patients, 34 showed an objective response to treatment, giving an overall response rate in 49 patients of 69% (95% confidence interval, 56%–82%). There were ten CRs. Six patients showed disease stabilisation during treatment, seven showed progressive disease and two showed rapidly progressive disease with early death. The median number of courses to first evidence of response was 2 (range, 1–5). Of 34 patients who responded (9 with a CR and 15 with a PR), 24 were evaluable for response duration. The median duration of response from the date on which treatment started was 8.4 months (SE, 1.84 months; range, 1.2–23.2+ months). The remaining ten patients (one with a CR and nine with a PR) went on to receive radiotherapy in an effort to consolidate or improve response and were therefore ineligible for assessment of response duration. Of 49 patients, 33 died, with a median overall survival, defined as the time from day 1 of treatment until death or date of censoring, of 10.2 months (SE, 0.78 months; range, 0.7–31.2+ months). Response was not related to previous irradiation of the site of disease. A total of 57 areas of disease were assessed for response; 25 of 36 lesions (69%) in previously irradiated sites and 13 of 21 lesions (62%) in non-irradiated sites showed objective response to treatment.

In all, 49 patients received a total of 211 cycles of treatment. Detailed toxicity data were available for 186 treatment cycles (Table 6). Toxicity consisted primarily of nausea and vomiting, myelosuppression, reduction in renal function, alopecia and disturbance of consciousness. Blood transfusion was required in 23% of courses and the WBC nadir (assessed in 31 treatment courses) was found to be 2.1×10^9/l and occurred around day 15 following treatment, with recovery by days 21–28. Six patients developed grade 3 and one patient, grade 4 IFX/mesna-associated encephalopathy. In all cases complete, spontaneous recovery occurred. Grade 1/2 CNS toxicity was observed in the majority of patients; this adverse effect may have been caused by the anti-emetic regimen. All patients experienced grade 3 or 4 alopecia. Two patients died of infection associated with myelosuppression: one, after the first treatment course, and the other, during the third treatment cycle. Two other patients died after the first course of chemotherapy: one succumbed to massive vaginal haemorrhage and the other, who had impaired renal function at the start of treatment, developed renal failure secondary to an episode of cisplatin-induced, acute tubular necrosis. Two further patients were inadvertently treated with up to three times the usual dose of IFX and experienced CNS toxicity of grades 2 and 3 and infections of grade 3 severity; one of these patients was not given further treatment because of grade 2 renal toxicity.

Discussion

These studies demonstrated that IFX can be safely and effectively used as a single agent and in combination to treat cervical cancer. The initial study identified IFX as one of the most active single agents in the treatment of this disease, with an overall objective response rate of 33% (95% confidence interval, 16%–50%). The median duration of response (6.5 months) and median survival for responding patients compare favourably with values for single-agent cisplatin in this setting. Response rates for disease in previously irradiated sites were significantly lower than those for disease arising in non-irradiated sites (54%; 95% confidence interval, 35%–73%); this suggested that IFX might be of value as part of a neoadjuvant regimen given before radical, local treatment with radiotherapy.

After the activity of IFX had been established, the feasibility of combining it with other active drugs was explored. Bleomycin and cisplatin were chosen based on the results of phase II studies from other centres and in vitro data suggesting synergism between IFX and cisplatin. The overall response rate with BIP was 69% (95% confidence interval, 56%–82%), a value that is higher than that previously reported for other cisplatin-containing regimens and compares favourably with that obtained using combinations containing cisplatin and bleomycin plus either vincristine or vinblastine, which have shown response rates on the order of 40%–66% [7, 16]. Furthermore, ten patients (20%) achieved a complete remission. This suggests that BIP may represent an advance in the identification of more active combinations for treating cancer of the cervix.

The main toxicities of IFX comprised myelosuppression, alopecia, nausea and vomiting and haematuria, but these were manageable in the majority of patients. Mild, reversible CNS toxicity was seen in the majority of patients, but severe and potentially life-threatening CNS toxicity was observed in three patients. Further studies of IFX/mesna CNS toxicity conducted at this centre have established that severe toxicity can be reliably predicted on the basis of pre-treatment serum albumin and creatinine levels [11]. The major toxicities of treatment with BIP were similar to those of single-agent IFX. However, in the majority of cases toxicity was tolerable. The WBC nadir was found to occur at around 15 days and to have recovered in all cases between 21 and 28 days following treatment. Therefore, this regimen could safely be given every 3–4 weeks for up to six cycles. Other toxicities were relatively uncommon and rarely severe. However, there were two deaths that were at least in part attributable to chemotherapeutic toxicity; this serves to emphasize the need in future trials for adequate assessment of quality of life in patients treated with palliative chemotherapy.

Although high rates of response were demonstrated, it is apparent that survival duration was similar to that seen in most other series. In assessing the benefits of chemotherapy in recurrent cervical cancer, it is necessary to quantify the substantial benefit that may be derived from the relief of disease-related symptoms. Although these trials did not set out to assess this aspect of treatment, it is noteworthy that in the single-agent IFX study, palliation of disease-related symptoms was achieved in half of the patients treated, and many patients treated with BIP reported relief from one of the more troublesome symptoms of recurrent

disease, namely, severe pelvic pain. Further trials are required for the optimisation of symptomatic relief and minimisation of subjective toxicity due to chemotherapy in patients with recurrent disease.

In summary, IFX is a highly active single agent in cervical cancer and, in combination with other active agents, produces response rates of around 70%. Highly active chemotherapy such as BIP may potentially be useful in primary disease. In advanced and bulky early-stage disease, neoadjuvant chemotherapy may improve survival by cytoreducing the central tumour and eradicating extrapelvic metastases. In patients with early-stage disease who are at high risk of recurrence due to lymphatic spread, survival may be improved by adjuvant chemotherapy. We are currently testing these hypotheses in prospective, randomised, multi-centre trials using this regimen.

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