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Neoadjuvant bleomycin, ifosfamide and cisplatin in cervical cancer*

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Summary. Patients with advanced and bulky early-stage cancer of the cervix have an unfavourable prognosis, which may be improved by initial neoadjuvant, cytoreductive chemotherapy. In a phase II study, coordinated at the West Midlands CRC Clinical Trials Unit, Birmingham, using ifosfamide (IFX) in combination with cisplatin and bleomycin (BIP) in advanced and recurrent cervical cancer, we demonstrated a response rate of 69%. This regimen produces rapid responses with acceptable toxicity and has potential for use as neoadjuvant therapy prior to radical radiotherapy in patients presenting with advanced and bulky early-stage disease. In an initial pilot study of this approach, 13 of 19 patients (68%) with primary inoperable disease showed significant tumour regression prior to radical local radiotherapy. Interim analysis of the first 66 patients entered into a randomized study evaluating the value of this approach has shown complete clinical tumour resolution after radical radiotherapy in 24/32 patients (75%) treated with up to three cycles of BIP prior to radiotherapy vs 19/34 patients (56%) treated with radiotherapy alone. There was no evidence that neoadjuvant chemotherapy enhances the acute toxic effects of pelvic radiotherapy. This approach has the potential for improving the outlook in patients with poor-prognosis primary disease.

Introduction

In the United Kingdom and Wales, stage-specific 5-year survival for treated women with cervical cancer has not altered over the last 20 years. The outlook is particularly poor in patients who present with advanced and bulky early-stage disease. Failure to cure inoperable cervical cancer may result from suboptimal treatment of the pelvic disease or the existence of metastatic disease outside the treatment fields at the time of diagnosis. In treatment planning, the volume of pelvic disease is one of the most important factors, larger lesions requiring higher doses of radiation to achieve rates of central control similar to those achieved with lower doses in small-volume disease. This principle applies to both central and metastatic disease and is supported by clinical data [14]. Indeed, spread beyond the treatment field at presentation may preclude a cure with pelvic irradiation alone. The incidence of extra-pelvic metastatic spread correlates with both the size and the stage of the primary tumour [10]. Irradiation of para-aortic lymph nodes with effective doses of radiation is associated with unacceptable treatment-related morbidity and mortality, and multiple metastatic sites are not amenable to radiotherapy [11]. Tumours may also be radio-resistant; radiobiological differences between tumours are unpredictable. The limitations of conventional treatments suggest potential roles for systemic, cytoreductive neoadjuvant therapy in patients presenting with bulky early- or advanced-stage disease.

To be useful in this setting, chemotherapy must be highly active since potentially curative conventional therapy is delayed. It must produce a response rapidly to avoid excessive toxicity that, combined with radiotherapy toxicity, might limit the delivery of a radical dose of radiation. It should not enhance the acute or long-term toxicity of radiation but should, at the very least, improve rates of central disease control and, preferably, also confer a survival advantage.

We coordinated a series of collaborative studies using a novel regimen to test the feasibility of this approach and to determine its value in terms of local disease control and survival. This report describes the early results of these studies in primary cervical cancer. The entry criteria for the two studies were identical: all patients had biopsy-proven, inoperable, previously untreated cervical cancer; they were medically fit to receive both treatment modalities, and informed patient consent was obtained before study entry.

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Table 1. Patient characteristics, phase II study (n=20)

Median age (range)		45 (30–68) years
Median ECOG performance status (range)		1 (0–2)
Histology/differentiation	Squamous/good	1
	Squamous/moderate	7
	Squamous/poor	11
	Adenocarcinoma	1
FIGO stage	IIa	4
	IIb	5
	III	7
	IV	4

Table 2. BIP regimen

Fluid	Volume (l)	Additions	Infusion time (h)
D saline	3	Bleomycin 30 mg	24
0.9% Saline	0.1	Cisplatin 50 mg/m^2	0.5
0.9% Saline	1	10% Magnesium sulphate 0.01 l	4
Mannitol 20%	0.2		2
D saline	3	Ifosfamide 5 g/m^2	
		Mesna 3 g/m^2	24
D saline	1	Mesna 3 g/m^2	12

D saline, 4% dextrose with 30 mmol NaCl

Table 3. Patient characteristics, neoadjuvant trial (n=66)

Median age (range)		49 (24–71) years
Median ECOG performance status (range)		1 (0–3)
Histology/differentiation	Squamous/good	3
	Squamous/moderate	12
	Squamous/poor	26
	Squamous/unknown	22
	Adenocarcinoma	3
FIGO stage	IIa	5
	IIb	18
	III	40
	IV	3

Rationale

Phase II study of neoadjuvant BIP

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. In a recent study conducted at this centre, the combination of bleomycin, ifosfamide and cisplatin (BIP) has demonstrated a response rate of 69% in such patients [2]. The regimen produced rapid responses with acceptable toxicity in this setting and clearly had potential for use as neoadjuvant therapy in primary disease. An initial pilot study of this approach was conducted in patients presenting with advanced-stage, previously untreated disease. The aims of the study were to assess the response rate to BIP in previously untreated disease and to test the feasibility of giving the combination as neoadjuvant therapy prior to radical pelvic radiotherapy in women with advanced and bulky early-stage cervical cancer.

Randomized trial of neoadjuvant BIP

The initial pilot study confirmed that neoadjuvant chemotherapy is a feasible approach in the treatment of advanced-stage disease. Acute radiation toxicity did not appear to be enhanced by giving chemotherapy prior to radical radiotherapy, and the activity and toxicity of the regimen were similar to those seen in the phase II study in recurrent disease carried out in our centre. The major unanswered questions about this approach involve whether it improves local disease control and survival. These questions can only be answered by a randomized study. We commenced such a study in 1987, with the aims of assessing the value of neoadjuvant BIP in terms of objective and subjective response, toxicity and survival.

Patients and methods

Phase II study. In all, 20 patients with advanced-stage carcinoma of the uterine cervix were entered in this study. The patient characteristics are shown in Table 1. Follow-up is complete to January 1, 1989. Patients were treated with bleomycin (30 mg), IFX (5 g/m^2) and cisplatin (50 mg/m^2) (Table 2); 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 to prevent serious and delayed urothelial toxicity. 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. Metoclopramide, dexamethasone and lorazepam were given i.v. for antiemesis. All patients received two courses of treatment unless there was definite evidence of progression, with a maximum of three cycles in responding patients. Following chemotherapy, patients received conventional radical, local radiotherapy comprising brachytherapy and whole-pelvic teletherapy.

Patients were assessed clinically and using imaging methods that included computerized tomography, chest X-ray and ultrasound. Response to chemotherapy was assessed clinically immediately prior to commencing radical pelvic radiotherapy. Significant tumour regression was recorded if there had been a reduction in tumour size of >50%. Toxicity was assessed using WHO criteria [9], apart from central nervous system toxicity, which was graded according to the criteria of Meanwell et al. [8]. Informed consent was obtained from all patients. Data were recorded prospectively on pro forma sheets and stored on a computer in the West Midlands CRC Clinical Trials Unit. All analyses were carried out using the BMDP statistical package [5].

Randomized trial. A total of 90 patients with advanced-stage primary carcinoma of the cervix have been entered in this study to date. Data on the first 66 patients entered are presented in this analysis. The patient characteristics are shown in Table 3. Follow-up is complete to January 1, 1989. Patients randomized to receive chemotherapy prior to radiotherapy received up to three cycles of BIP prior to radical pelvic radiotherapy, as in the initial pilot study. All patients received two courses of treatment unless there was definite evidence of progression, with a maximum of three cycles in responding patients. Following chemotherapy, patients received conventional radical, local radiotherapy comprising brachytherapy and whole-pelvic teletherapy. Those randomized to receive radical radiotherapy alone were treated according to the same radiotherapy protocol used for the neoadjuvant therapy group.

Patients were assessed clinically and using imaging methods that included computerized tomography, chest X-ray and ultrasound. Re-

Table 4. Neoadjuvant trial: response

		Post-chemotherapy	Post-radiotherapy
Chemotherapy + radiotherapy group:			
Response	Complete	2	24
	Regression	20	5
	Static	8	1
	Progression	2	2
	Total	32	32
Response rate		69%	91%
95% confidence interval		53%–85%	81%–100%
Radiotherapy group:			
Response	Complete		19
	Regression		14
	Static		0
	Progression		1
	Total		34
Response rate			97%
95% confidence interval			91%–100%

Table 5. Neoadjuvant trial: toxicity (percentage of cycles affected[a])

	WHO grade:				
Toxicity	0	1	2	3	4
Alopecia	3	4	34	50	9
Nausea and vomiting	2	12	73	13	0
CNS	72	5	22	1	0
Infection	84	10	6	0	0
Haematuria	89	9	2	0	0
Renal	97	1	1	0	1
Diarrhoea	93	4	3	0	0
Anemia	70	22	5	3	0
WBC count	82	8	8	1	1
Platelets	99	0	0	0	1

[a] Except alopecia, which was graded according to the worst toxicity grade recorded

sponse was defined according to the same criteria used in the initial pilot study. Toxicity was assessed using WHO criteria, apart from central nervous system toxicity, which was graded according to the criteria of Meanwell et al. [8]. Informed consent was obtained from all patients. Data were recorded prospectively on pro forma sheets and stored on a computer in the West Midlands CRC Clinical Trials Unit. All analyses were carried out using the BMDP statistical package [5].

Results

Phase II study

In all, 13 of 19 patients (68%; 95% confidence interval, 58%–100%) showed at least 50% reduction in primary tumour bulk following chemotherapy. Five patients showed no change in disease bulk after chemotherapy, and one patient was treated with radiotherapy after only one course due to progression of disease. One patient refused further chemotherapy after bleomycin and cisplatin during her first course. An additional patient received a fourth courses after achieving a partial response. The median number of courses given was 2 (range, 1–4).

Toxicity in the neoadjuvant chemotherapy patients was similar to that seen in patients with recurrent disease [2]. Radiotherapy was delayed for 1 week due to leucopaenia in the one patient who received four courses of BIP. There were no delays of radiotherapy in patients receiving two or three courses of BIP, and there was no evidence that neoadjuvant chemotherapy enhanced the acute toxic effects of pelvic radiotherapy.

Randomized trial

In all, 22 of 32 patients (69%; 95% confidence interval, 53%–85%) showed significant clinical regression of the primary tumour following chemotherapy (Table 4). Eight patients showed no change in disease bulk after chemotherapy, and two patients displayed evidence of tumour progression; both of the latter patients progressed through subsequent radical radiotherapy. Subjective response, defined as relief of disease-related symptoms, was seen in 14 of 19 patients (74%) with pelvic pain, in 14 of 26 patients (54%) with discharge and in 18 of 27 patients (67%) with vaginal bleeding at the time of study entry. The median number of courses given was 2 (range, 1–3).

A total of 24/32 patients (75%; 95% confidence interval, 60%–90%) treated with BIP prior to radiotherapy achieved complete clinical resolution of disease following completion of radical radiotherapy (Table 4). In contrast, only 19 of 34 patients (56%; 95% confidence interval, 39%–73%) in the group treated with radiotherapy alone achieved complete clinical resolution of disease following the completion of treatment (Table 4).

Toxicity in the neoadjuvant chemotherapy patients was similar to that seen in patients in the pilot study (Table 5). Radiotherapy was delayed due to leucopaenia in one patient who received neoadjuvant BIP and in one patient randomized to receive radical radiotherapy alone. There was no evidence that neoadjuvant chemotherapy enhanced the acute and late toxic effects of pelvic radiotherapy, with severe toxic events such as treatment-related mortality, bowel toxicity and fistulae being equally distributed between the two treatment arms.

Discussion

Failure to cure inoperable cervical cancer may result from suboptimal treatment of pelvic disease or the existence of metastatic disease outside the treatment fields at the time of diagnosis. Tumour volume is one of the most important factors in determining prognosis in patients with this disease. Not only is the likelihood of achieving local disease control with a given radiation dose related to tumour volume [14], but also the incidence of spread beyond the treatment field at presentation, precluding a cure with pelvic irradiation alone, correlates with both the size and the

stage of the primary tumour [10]. The radiation tolerance of normal tissues adjacent to the tumour limits the delivery of a radical dose to advanced and bulky disease and extrapelvic metastases, if unacceptable treatment-related morbidity and mortality are to be avoided [11]. Tumours may also be radio-resistant; radiobiological differences between tumours are unpredictable. Thus, a potential role for systemic therapy in this setting is apparent.

To be useful, neoadjuvant chemotherapy must be highly active and must produce a response rapidly, with acceptable toxicity, since potentially curative conventional therapy is delayed. Furthermore, it should not enhance the acute or long-term toxicity of radiation but should, at the very least, improve rates of central disease control and, preferably, also confer a survival advantage. Regimens with suitable activity and toxicity for this application are now available [3, 6, 15]. Initial pilot studies from several centres, including our own, with these regimens have confirmed that neoadjuvant chemotherapy is a feasible approach in the treatment of advanced-stage disease [1, 3, 7, 13]. Acute radiation toxicity does not appear to be enhanced by giving chemotherapy prior to radiotherapy, and the activity of most regimens is similar to that seen in phase II studies in recurrent disease.

The major unanswered questions about this approach involve whether it improves local disease control and survival; these can only be answered by randomized studies. In our randomized trial, we showed that the number of patients achieving complete clinical remission of their disease after completion of radical radiotherapy was higher in the group that received neoadjuvant BIP, but it remains to be seen whether this improvement confers a survival advantage. A number of preliminary reports of randomized studies testing the value of neoadjuvant chemotherapy have been presented [4, 12]. On the basis of these limited reports, survival does not appear to be improved. Unfortunately the regimens used in these studies are not the most active that have been reported, and the numbers of patients included were inadequate to ascertain that significant differences in outcome were not missed. Until trials using the most active regimens are completed, the value of this approach will remain unproven.

In summary, we coordinated a series of collaborative studies using a new and novel regimen to test the feasibility of neoadjuvant therapy and to determine its value in terms of local disease control and survival. The activity of the BIP regimen in previously untreated disease was shown to be similar to that seen in patients with recurrent disease, and acute and late radiotherapeutic morbidity and mortality did not appear to be enhanced by this approach. Although resolution of pelvic disease appears to be improved by neoadjuvant BIP, it remains to be demonstrated that neoadjuvant chemotherapy produces a survival advantage. Our randomized study continues to accrue further patients.

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