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PHASE II STUDIES OF BLEOMYCIN, IFOSFAMIDE AND CIS-PLATINUM IN ADVANCED AND RECURRENT CERVICAL CARCINOMA

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Abstract

We report the results of phase II studies using a combination of ifosfamide, cis-platinum and bleomycin (BIP) in advanced and recurrent cervical cancer. Fifty-one patients have been studied. In 37 patients with disease not amenable to radical local therapy 27 objective responses (73%) were seen with 7 complete responses. Eleven of 14 patients (79%) with primary inoperable disease had at least a 50% reduction in tumour bulk prior to radical local radiotherapy. All patients experienced alopecia, nausea and vomiting. Other toxicity included myelosuppression, infection, reduction in renal function and disturbance of consciousness. There was no evidence that primary chemotherapy enhanced the acute toxic effects of pelvic radiotherapy. These data indicate that BIP is highly active in cervical cancer and can be used for effective palliation and cytoreduction in more than 70% of patients.

Key words: Uterine cervical cancer; advanced or recurrent, bleomycin, ifosfamide, cis-platin.

Cervical carcinoma accounts for around 4% of all malignancies in women in the UK and is the commonest gynaecological malignancy. Stage specific 5-year survival for treated women with this disease has not altered over the last 20 years. Any improvements in overall survival that have occurred reflect a trend towards early diagnosis rather than improvements in treatment. A significant proportion of women will relapse after primary therapy. In this group prognosis is particularly poor with 1-year survival of less than 15% (5). Therefore, we believe that there are 3 potential roles for chemotherapy in this disease: as palliative treatment in symptomatic recurrent disease, as primary therapy in patients presenting with bulky early or advanced stage disease and as adjuvant therapy in patients with early stage disease where adverse prognostic features are identified.

Chemotherapy is often the treatment of choice in women with recurrent disease. Early studies of chemotherapy in this setting demonstrated both complete and partial responses with single agent and combination chemotherapy. However, overall response rates in these studies rarely exceeded 25% for single agents and 50% for combination regimens (3, 4). Furthermore, duration of remission was short with a median in most studies of around 12 weeks. Several recent studies, including one from our own centre, have confirmed the effectiveness of two agents, cis-platinum and ifosfamide, in cervical cancer (1, 2, 9). Both agents show response rates of around 30% with a significant number of complete responses. In the single agent phase II studies reported for these drugs, a number of patients with complete responses have experienced significant long term duration of remission. In addition, palliation of symptoms associated with recurrent disease has been reported (2). The most effective combination regimens have been those that combine cis-platinum and bleomycin with other active chemotherapeutic agents (6, 13). Response rates up to 66% have been demonstrated for such combinations.

Important factors which may account for treatment failures in primary disease are tumour bulk and the presence of extra-pelvic metastases at the time of primary treatment. Strategies to improve radical local therapy have centred on improving local control with radiation sensitizers. None has been shown to convincingly improve survival apart from hydroxyurea which may improve local control and survival in patients shown to be free of para-aortic metastases at the time of primary treatment (11). Para-aortic irradiation with tumoricidal doses has been

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reported to produce unacceptable toxicity (10). Thus there is potential for systemic treatment in this setting. Primary chemotherapy prior to radical local radiotherapy has potential to cytoreduce bulky tumours and sterilize extrapelvic metastatic disease which may improve survival.

In an attempt to improve the treatment of advanced cervical cancer, we combined ifosfamide and cis-platinum, the 2 most active agents in cervical cancer, with bleomycin (BIP). The results of this phase II study are reported. The aims of the study were to assess the response rate, duration of response and toxicity of the combination in recurrent cervical cancer no longer amenable to radical local therapy and to explore the feasibility of giving BIP as primary therapy prior to conventional treatment in patients with bulky early and advanced stage disease.

Material and Methods

Between February 1985 and June 1987, 37 patients with biopsy proven cervical cancer no longer amenable to radical local treatment were entered into this study. The patient characteristics are shown in Table 1. With the exception of one patient with 4B disease all patients had received previous treatment. The sites of recurrent disease are documented in Table 1. Follow-up is complete to 30th June 1987 except for one patient who emigrated after achieving a partial response. She has been censored at her last date of follow-up for all analysis.

Patients received treatment with bleomycin, ifosfamide and cis-platinum (Figure). Mesna 8 g/m^2 was administered concurrently with the ifosfamide infusion and continued for a further 12 h to prevent urothelial toxicity. All patients received 2 courses of treatment unless there was definite evidence of progression with a maximum of 6 courses of treatment being given to responders. Dose modification was carried out in the form of 30% dose reduction if the blood count fell below 2.8×10^9/l and/or creatinine clearance was less than 40 ml/min at day 28, or in the form of delaying treatment.

Fourteen patients with biopsy proven untreated inoperable primary disease were also entered into the study to test the feasibility of giving BIP as primary chemotherapy. The patient characteristics are shown in Table 1. The patients were treated with either 2 or 3 courses of BIP depending on clinical response and then received conventional radical local radiotherapy comprising brachytherapy and whole pelvic teletherapy. Treatment scheduling and dose modifications were as for patients with recurrent disease.

Patients were assessed clinically and whenever possible using radiological methods which included computed axial tomography, conventional radiology and ultrasound. In cases of pelvic disease when there was doubt as to the extent of response examination under anaesthetic was carried out, by at least 2 clinicians, with biopsy of previously involved areas. WHO criteria for toxicity and UICC criteria for response were used.

Data was recorded prospectively on proformas and

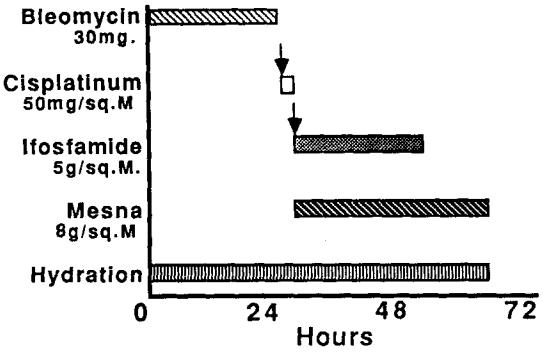

Fig. 1. BIP regimen.

Table 1

Patient characteristics

	Recurrent (n=37)	Primary (n=14)
Mean age (range)	40 (24–74)	46 (30–69)
Mean Karnofsky (range)	86 (70–100)	93 (90–100)
Histology		
Sq. well	4	0
Sq. mod	9	3
Sq. poor	20	8
Adeno.	2	1
Unknown	2	2
Original FIGO stage		
1B	17	0
2A	3	0
2B	6	7
3A	1	1
3B	4	4
4	2	1
Unknown	4	1
Previous treatment		
None	1	14
Surgery	6	0
Surgery/RT	19	0
RT	11	0
Site of disease		
Primary	2	14
Pelvic recurrence	24	0
Regional nodes	8	1
Metastatic nodes	5	1
Lung	6	0
Assessment method		
Clinical	12	9
CXR	6	0
CT scan	23	5
Ultrasound	4	0

Sq = squamous, Adeno = adenocarcinoma, RT = radiotherapy, CXR = chest radiogram, Well = well differentiated, Mod = moderately differentiated, Poor = poorly differentiated, CT = computed axial tomography

Table 2

Toxicity with BIP

Major toxicity		
Hair loss	Complete, reversible	95 % of patients
	Moderate, patchy	5 % of patients
Nausea and vomiting	Transient	92% of courses
	Required IV support	8% of courses
Haematological	Blood transfusion	11% of courses
	WCC nadir 2.1×10^9	15 days
Central nervous system	Confusion diorientation (nomogram not used)	1 patient

	WHO grade			
Other toxicity (% courses affected)	0	1	2	3
Infection	87	6	4	3
Diarrhoea	62	26	12	0
Stomatitis	75	24	1	0
Oesophagitis	92	6	2	0
Fever	81	11	8	0
Haematuria	81	10	9	0

stored on computer in the West Midlands CRC Clinical Trials Unit. Data was analysed using the BMDP statistical package and StatWorks for the Apple Macintosh computer.

Results

Response—recurrent disease. Thirty-five patients were available for response. Two patients who died during the first course of chemotherapy were not available for assessment of response and are considered to be treatment failure.

Twenty-seven of the evaluable patients had responses giving an overall response rate for the 37 patients of 73% (95% CI = 59–87%). There were 7 documented complete responses (CR). Five patients had static disease during treatment with the remaining 5 patients (includes 2 treatment failures) showing evidence of progression during therapy. The median number of courses to response was 2 (range 2–5).

Nineteen patients were evaluable for duration of response. Six of 7 who achieved a CR were evaluable for response duration. Three have progressed at 3, 7 and 10 months from the date that response was documented. The remaining 3 patients are in complete remission at 10, 11 and 13 months' follow-up. All patients who achieved partial responses (PR) have progressed with a median duration of response of 6.1 months (SE 1.1 months). The remaining 8 patients (1 CR and 7 PR) went on to receive radiotherapy in an effort to consolidate the response. Four have progressed, the median duration of response being 9.6 months (SE 0.75 months).

Response—primary disease. Eleven of 14 patients (79% with 95% CI = 58–100%) showed at least 50% reduction in primary tumour bulk following chemotherapy. One patient showed no change in disease bulk after 2 courses of chemotherapy and one patient was treated with radiotherapy after only 1 course due to progression of disease. The remaining patient refused further chemotherapy after bleomycin and cis-platinum during her first course. The median number of courses given was 2 (range 1–4).

Survival. In patients with recurrent disease 28 of 37 have died with a median overall survival, defined as the time from day one treatment until death or date of censor, of 10.13 months (SE 0.49 months). Eighteen of 27 responding patients have died (median survival 11.81 months, SE 0.98 months), whereas all of the non-responders have died (median survival 6.38 months, SE 0.31 months).

Effect of previous irradiation. Response was not related to whether the site of disease had been subject to previous irradiation. Forty-five areas of disease in 35 patients were assessed for response. Twenty of 26 lesions (77%) in previously irradiated sites and 9/15 lesions (60%) in non-irradiated sites showed objective response to treatment.

Toxicity. Thirty-seven patients received a total of 153 courses of treatment. Three patients died after the first course of chemotherapy. One patient with central pelvic recurrence and pulmonary metastases died 5 weeks after the first course with massive vaginal hemorrhage. A second patient died 17 days after the first treatment course of lobar pneumonia. Her white cell count on admission was 10.5×10^9/l. It was felt that myelosuppression secondary to treatment was a contributory factor. The final patient, who had impaired renal function at the start of treatment, developed renal failure secondary to an episode of cis-platinum induced acute tubular necrosis and died 4 weeks after treatment.

Detailed toxicity was recorded in the first 19 patients in 63 treatment courses. Toxicity consisted primarily of nausea and vomiting, alopecia, myelosuppression, reduction in renal function and disturbance of consciousness (Table 2). One patient developed ifosfamide/mesna associated disturbance of consciousness. Retrospective analysis of the case records for this patient confirmed that this event could have been predicted with the encephalopathy nomogram developed in this unit (8). Of the remaining 16 patients no unexpected toxicity was encountered. Two of these patients were inadvertently treated with up to 3 times the usual dose of ifosfamide. Both developed reversible CNS toxicity of WHO grades 2 and 3 and infections of grade 3 severity. One patient was not given further treatment because of grade 2 renal toxicity.

Toxicity in the primary chemotherapy patients was similar to that seen in patients with recurrent disease. Radiotherapy was delayed for one week due to leukopenia in the one patient who received 4 courses of BIP. There were no delays of radiotherapy in patients receiving 2 or 3 courses of BIP and there was no evidence that primary chemotherapy enhanced the acute toxic effects of pelvic radiotherapy.

Discussion

This study has demonstrated that bleomycin, ifosfamide and cis-platinum can be safely and effectively combined to treat cervical cancer. Phase II studies of ifosfamide in recurrent cervical cancer conducted in several centres have demonstrated that the drug is highly active in this disease (2, 9). Furthermore, ifosfamide displays in-vitro synergism with cis-platinum (7). A major gynecologic oncology group study has established that cis-platinum is one of the most active single agents in cervical cancer (1). Data from this group have shown that there is no dose response enhancement with this drug the optimal dose being 50 mg/m^2 given every 21 days. The drug also gives good response in previously irradiated sites of disease. Bleomycin also has single agent activity in recurrent cervical cancer which may be optimized by administration as a 24 h infusion. Regimens including bleomycin and cis-platinum give objective response rates of 40–60% (6, 13). The toxicities of all 3 drugs are predictable, manageable and non-crossreacting. Therefore, it was logical to combine these drugs.

The response rate in this study is higher than has been reported for other cis-platinum containing regimens. The fact that the overall response rate for recurrent cervical cancer in this study was 73% (95% CI = 59–87%) suggests that this regimen may be an advance in identifying more active combinations in this disease. This compares favourable with combinations containing cis-platinum and bleomycin either with vincristine or vinblastine which have shown response rates in the order of 40–60% (6, 13).

Though high rates of response have been demonstrated it is apparent that survival duration is similar to that seen in most other series. However, 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. Though this trial did not set out to assess this aspect of treatment it is noteworthy that many patients reported relief from one of the more troublesome symptoms of recurrent disease, namely severe pelvic pain. Further trials are required in order to optimize symptomatic relief and minimize subjective toxicity from chemotherapy in recurrent disease.

The major toxicities of the regimen were hair loss, nausea and vomiting and myelosuppression. In the majority of cases toxicity was predictable and manageable. However, there were 2 deaths which were at least in part attributable to chemotherapy toxicity. This serves to emphasize the need in future trials for adequate assessment of quality of life in patients treated with palliative chemotherapy. The white cell count nadir was found to occur at around 15 days and to have recovered in the majority of cases between 21 and 28 days following treatment. Therefore, this regimen can safely be administered on a 3 to 4 weekly basis. Other toxicities were relatively uncommon and rarely severe.

A potential role for chemotherapy as primary treatment in bulky early or advanced cervical cancer has been suggested (12). Patients with bulky and advanced disease are at high risk of having extra-pelvic spread, which is not amenable to radical local therapy at the time of diagnosis and of developing central pelvic recurrence after primary treatment. Primary chemotherapy by producing cytoreduction and sterilizing extra-pelvic metastases may improve prognosis in patients who are not curable with radical local therapy. There are several requirements for chemotherapy to be used in this way. The chemotherapy should be highly active, and cause significant, rapid reduction in tumour bulk in the majority of patients. Administering chemotherapy prior to radical local treatment, delays potentially curative treatment. If the chemotherapy is not sufficiently active some patients will progress further during this period. BIP caused response in 73% of patients with recurrent disease, and a further 13.5% were static while on treatment with 13.5% progressing during treatment. In addition, patients who responded invariably had evidence of this within 3 courses. Therefore, if BIP was used as primary therapy, an early change to local treatment could be carried out if response had not been noted. Primary chemotherapy should also be tolerable to the patient. The toxicity of BIP is acceptable. Patients experience temporary hair loss, but otherwise the side effects seen in this study were no greater than those seen with other highly active regimens. At this time there is no evidence to support the view that primary chemotherapy improves survival in patients treated with radical local radiotherapy. This question can only be satisfactorily answered by large prospective randomized trials.

In summary BIP is a highly active combination in recurrent cervical cancer producing objective response in 73% of patients. The toxicity of the regimen is acceptable. The regimen has potential for use as primary chemotherapy in patients with bulky early or advanced disease. This hypothesis is currently being tested in a prospective randomized multi-centre trial initiated by this group.

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REFERENCES

1. Bonomi P., Bruckner H., Cohen C., Marshall R., Blessing J. and Slayton R.: A randomized trial of three cisplatin regimens in squamous cell carcinoma of the cervix. Proc. Am. Soc. Clin. Oncol. 18 (1982), 110.
2. Coleman R. E., Harper P. G., Gallagher C. et al.: A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother. Pharmacol. 18 (1986), 280.
3. De Palo G.: Medical treatment of advanced carcinoma of the cervix. A review. Tumori 63 (1977), 215.
4. De Vita V. T., Wasserman T. H., Young R. C. and Carter S. K.: Perspectives on research in gynaecologic oncology. Cancer 38 (1976), 509.
5. Di Saia P. J., Morrow C. P. and Townsend D. E.: Synopsis of gynecologic oncology, p. 74. John Wiley and Sons, New York 1975.
6. Friedlander M. L., Kaye S. B., Sullivan A. et al.: Cervical carcinoma: A drug-responsive tumour experience with combined cisplatin, vinblastine and bleomycin therapy. Gynecol. Oncol. 16 (1983), 275.
7. Goldin A.: Ifosfamide in experimental tumour systems. Semin. Oncol. 9 (Suppl. 1) (1982), 14.
8. Meanwell C. A., Blake A., Kelly K. et al.: Prediction of ifosfamide/mesna encephalopathy. Eur. J. Cancer Clin. Oncol. 22 (1986), 815.
9. — Mould J. J., Blackledge G. et al.: Phase II study of ifosfamide in cervical cancer. Cancer Treat. Rep. 70 (1986), 727.
10. Piver S. M. and Barlow J. J.: High dose irradiation to biopsy confirmed aortic node metastases from carcinoma of the uterine cervix. Cancer 39 (1977), 1243.
11. — — Vongtama, V. and Blumenson L.: Hydroxyurea: A radiation potentiator in carcinoma of the uterine cervix. Am. J. Obstet. Gynecol. 147 (1983), 803.
12. Tattersall M. H. N.: The integration of surgery, radiotherapy and chemotherapy in the treatment of advanced gynaecological cancer. Aust. NZ. J. Obstet. Gynaec. 24 (1984), 158.
13. Vermorken J. B., Mangioni C., van Oosterom A. T. et al.: Vincristine, bleomycin, mitomycin C and cisplatin (VBMP) in squamous cell carcinoma of the uterine cervix (SCCUC). Proc. 2nd. European Conference on Clinical Oncology Abstract 05-20 (1983), 50.