ROLE OF CHEMOTHERAPY IN ADVANCED CERVICAL MALIGNANCY

By

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SUMMARY

A prospective study was conducted at the Eden Hospital to assess the role of chemotherapy followed by radical surgery (when possible) in advanced carcinoma of the cervix. A combination chemotherapy of Methotrexate and Mitomycin C was tried on 104 patients with stages IIb, IIIa & IIIb cervical carcinoma. The overall clinical response (complete and partial) was evident in 56 (53.8%) cases. Subsequent radical surgery was possible in these cases. In other words, radiotherapy could be avoided in about a half of these 104 cases. A follow-up of between 3 months and 5 years is being presented. An overall 5-year survival was 43.5%; and the respective figures for stages IIb, IIIa, & IIIb were 50.0%, 42.9%, and 33.3% respectively. The authors suggest the use of combination chemotherapy to 'down-stage' advanced cervical malignancy to make them amenable to radical surgery. This would improve the quality of life in long term survivors in comparison to those who are treated with radiotherapy alone.

Introduction

Carcinoma of the cervix happens to be the commonest gynaecological malignancy in Indian women. Most of the cases present themselves at the advanced stage of the disease. Although the prognosis of early carcinoma of the cervix has been reported to be fairly good, over 65% of patients with FIGO stage III or IV will die from their disease within 5 years (Kottmeier, 1985).

Radiotherapy is the treatment of choice for advanced cervical carcinoma. But recent advances in radiotherapeutic facilities are not available in most of the institutions in India. Even when the facility is there, there are some specific contraindications to radiotherapy. These had led the authors to investigate the role of chemotherapy in advanced cervical malignancy.

A number of cytotoxic agents have been tried, either singly or in combinations. Response rates of between 15 and 40 per cent have been reported with several single agents including cisplatin, methotrexate, vincristine, mitomycin C and bleomycin. With the combination

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Accepted for publication on 2-6-89.

regimens of these agents there is further improvement in the tumour regression rate. But an ideal combination is yet to be found (Thigpen *et al*, 1987).

The present study assessed the effectiveness of the combination regimen of methotrexate and mitomycin C in advanced cancer of the cervix. The choice of these two cytotoxic agents was based on the fact that they act at two different phases of the cell cycle. Methotrexate, an antimetabolite, acts in the S-phase of the cell cycle; whereas Mitomycin C, an antibiotic, is a non phase-specific agent acting mainly in the G_2-phase. They also differ in their biochemical sites of action in the cell. Using this combination, this study also assessed the subsequent operability rate, the quality of life and survival during 1 to 6 years of follow-up.

Patients and Methods

One hundred and four patients with histologically confirmed carcinoma of the cervix, initially unsuitable for radical surgery, were studied during the years 1982 to 1988. The staging was carried out according to FIGO recommendations and all the patients belonged between stages IIb and IIIb. 99 patients had squamous cell carcinoma and the rest 5 had adenocarcinoma.

The median age of the 104 patients was 45 (range 24-64) years. 84 patients were para 3 or above, 20 were para 1 & 2, and 4 women were nulliparous. Most of the patients belonged to the low socioeconomic class and with less than average nutritional status.

All the patients were admitted to hospital for treatment. None of the patients had received chemotherapy or radiotherapy previously. The routine pretreatment investigations included a complete blood count, blood glucose, blood urea, serum creatinine, liver function tests, chest roentgenogram, intravenous urography, examination under anaesthesia (EUA) and cystoscopy. The blood counts and the serum biochemical screen for renal and liver functions were repeated every week during the chemotherapy. Abdomino-pelvic ultrasound was carried out where appropriate. Patients with impaired renal function or deranged liver function tests were not included in the series.

The performance status was ascribed as per the recommendations by the International Union Against Cancer (1977).

Grade 0: normal activity, no analgesia.

Grade 1: slight activity restriction, able to carry out light work.

Grade 2: activity restricted but less than 50% time in bed, unable to work.

Grade 3: severely restricted activity, more than 50% time in bed.

Grade 4: completely disabled.

The chemotherapy regimen is detailed in Table I. During the course of treatment, fresh whole blood was transfused from time to time as required. Intravenous infusions of aminoacids solution (Hermin) and sometimes, serum albumin were also prescribed as required.

TABLE I
Chemotherapy Regimen

Day	Drug
1, 3, 5, 9, 13, 17.	Inj. Methotrexate 50 mg intramuscularly.
7, 11, 15, 19.	Inj. Mitomycin C 10 mg dissolved in 540 ml of 5% dextrose solution—infused intravenously over a period of 6 hours.

In assessing the tumour response to chemotherapy, the following criteria was used:

Complete response (CR)

Complete resolution of all known tumour deposits and malignant effusions.

Partial response (PR)

Fifty per cent or more reduction in tumour size, measured as the product of the two maximal perpendicular diameters of the cervical growth; no new deposits.

No change (NC)

Less than 50% or no change in the size of the major indicator lesion.

Progression (PD)

Enlargement of lesions and/or appearance of a new ones.

After the completion of each course of chemotherapy, the performance status and the tumour response were assessed. An abdominal radical hysterectomy and pelvic lymphadenectomy (where possible) were performed after assessing the feasibility of the operation by EUA after chemotherapy. The patients with histologically positive (metastasis) lymph node/s were further sent for palliative radiation. Those who showed no response or progressive disease during chemotherapy were sent for radiotherapy.

The patients were followed-up regularly. The survival was calculated from the date of completion of chemotherapy to the time of analysis for each patient. Five (5) cases were lost to follow-up. Thus, the follow-up of between 3 months and 5 years of 99 patients have been presented.

Results

Response to chemotherapy

Table II details the clinical stage of the 104 patients and the response to chemotherapy. Out of 51 patients with stage IIb disease 36 (70.6%) responded (complete and partial response) to chemotherapy and 7 (13.7%) had no change, while 8 (15.7%) patients had progressive disease. 1 patient died of progressive disease during chemotherapy. Clinical response to chemotherapy was evident in 13 (40.6%) patients with stage IIIa and in 6 (28.6%) patients with stage IIIb cervical carcinoma. 1 patient with stage IIIa died during chemotherapy. Thus, the overall response rate was 53.8%.

The majority of tumour responses were clearly evident on clinical examination. Factors possibly predicting response to chemotherapy were disease stage and histological features of the

TABLE II
Clinical Stage and Tumour Response

Stage	No.	Tumour Response CR	PR	NC	PD
IIb	51	6	30	7	8
IIIa	32	0	13	8	11
IIIb	21	1	6	7	7
	104	7 (6.7%)	49 (47.1%)	22 (21.1%)	26 (25.0%)

CR: Complete response
PR: Partial response
NC: No change
PD: Progressive disease

primary tumour, i.e., nuclear grade, number of mitoses, degree of lymphocytic infiltration, fibroblastic response and histologic type. Histology was reported by a senior pathologist. Fibroblastic response and lymphocytic infiltration were found to be significantly related to the response to chemotherapy. There were only five patients with adenocarcinoma, and it is not possible to say whether the response of these cell types was similar to that of squamous tumours.

Subsequent treatment

Table III documents the subsequent treatment following completion of chemotherapy. Radical hysterectomy and pelvic lymphadenectomy was performed in 56 (53.8%) patients, comprising 7 complete responders and 49 partial responders. 9 patients had lymph node metastases on histopathological examination of the removed specimen—they received adjuvant pelvic radiotherapy post-operatively. 46 (44.2%) patients who did not respond to chemotherapy were treated by radiotherapy.

Survival

Survival by disease stage has been shown in Table IV. At the time of analysis, follow-up results of between 3

TABLE III
Response to Chemotherapy and Subsequent Treatment

Response to chemotherapy	Subsequent Treatment				
	Total	RHPL	RHPL + ADJ. R/T	R/T	Death during chemotherapy
Complete	7	7	—	—	—
Partial	49	40	9	—	—
No change	22	—	—	22	—
Progressive disease	26	—	—	24	2
	104	47 (45.2%)	9 (8.6%)	46 (44.2%)	

RHPL: Radical hysterectomy and pelvic lymphadenectomy.
RHPL + ADJ. R/T: RHPL plus adjuvant radiotherapy.
R/T: Radiotherapy.

TABLE IV
Survival of 99 Patients

Time	STAGE IIb (n = 49)		STAGE IIIa (n = 30)		STAGE IIIb (n = 20)	
	No.	%	No.	%	No.	%
3 months	48/49	98.0	29/30	96.7	19/20	95.0
6 months	31/35	88.0	21/25	84.0	14/16	87.5
1 year	24/33	72.7	16/24	66.7	9/15	60.0
2 years	18/23	64.3	13/22	59.1	8/14	57.1
3 years	13/23	56.5	8/17	47.1	6/13	46.1
4 years	11/21	52.4	7/15	46.7	4/11	36.4
5 years	5/10	50.0	3/7	42.9	2/6	33.3

months to 5 year were available. 5 patients were lost to follow-up. Out of 23 patients, who had been followed-up for more than 5 years, 10 were surviving. Thus, the overall 5-year survival was 43.5%. The corresponding individual figures for stages IIb, IIIa & IIIb were 50.0%, 42.9% & 33.3% respectively. All of these 10 five-year survivors had responded to chemotherapy and were treated by radical surgery. None of them had lymph node involvement at the time of surgery.

Discussion

The role of chemotherapy in the treatment of cancer of the cervix is not clear (Barker, 1983). This study demonstrated a 53.8% overall response rate to Methotrexate-Mitomycin C chemotherapy in 104 patients with advanced carcinoma of the cervix. Although a higher response rate has been reported with cis-platin based regimens, Rustin *et al* (1987) admitted that this was at the expense of considerable toxicity to the aggressive chemotherapy. In the present study, the regimen was simpler to administer than the 3 or 4 drug combinations, and significant toxicity was limited to a very few patients.

The interesting finding in the present study was that the regression of growth by chemotherapy in an advanced stage of the disease could lead them to being operable in 53.8% of cases. It can be concluded that at least half of the patients with advanced carcinoma of the cervix can have the benefit of radical surgery with a prior course of chemotherapy with the combination regimen of Methotrexate and Mitomycin C. The hazards of surgery is more easily remediable than radiotherapy. The quality of life (as assessed by the performance status) has been found to be much better with chemotherapy plus surgery than with radiotherapy. In the present study, radiotherapy could be avoided in about a half of the patients with advanced cervical malignancy by 'down-staging' the disease with the use of a combination chemotherapy which made radical surgery possible. Unfortunately, there is no way at present of predicting which patients would benefit from chemotherapy.

Although the survival figures found in this study are slightly on the lower side than those reported by Kottmeier (1985), the results are difficult to compare. However, the survival of stage IIb disease is significantly lower than those of Kottmeier's (1985) collection from different centres. Since many of the stage IIb patients are still alive and are being followed-up, it would be premature at present to conclude that this group is better treated with radiotherapy.

Some patients with advanced cervical carcinoma are becoming long-term survivors. Due consideration has to be paid as regards the quality of life during this period. Radiotherapy is the treatment of choice in advanced inoperable cervical malignancies. The hazards of radiotherapy (both short-term and long-term) are well-known. The present study highlights the use of a combination chemotherapy to 'down-stage' the disease to make the operable in at least a half of the cases.

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