THE ROLE OF CHEMOTHERAPY IN CERVICAL CANCER — A REVIEW

V Sivanesaratnam

SYNOPSIS

Developments in systemic chemotherapy for cervical cancer have been rather slow. Recurrences occur not only in the pelvis but may become disseminated. As radiotherapy alone cannot be expected to cure these cases, systemic chemotherapy appears to have a logical role in these cases. Various single agents have been used and these have resulted in response rates from 6 to 25%, whilst combination drugs have shown response rates of 55 to 65% in some instances. Results, however, show no long-term benefits. The reasons for the poor response to chemotherapy seen in recurrent cervical cancer are discussed. Neoadjuvant chemotherapy with hydroxyurea as a radiation potentiating agent suggests the possibility of increased cure with combined therapy. Chemotherapy may also play an important adjuvant role in radical surgery for cervical cancer. Preliminary studies using cisplatinum combination drugs as adjuvant therapy in 'high risk' patients appear encouraging and need further evaluation.

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INTRODUCTION

Chemotherapy has a definite place in the therapy of ovarian cancer, but its role in the management of cervical cancer has been somewhat neglected. Radical surgery and radical radiotherapy have made a majority of patients with cervical cancer, especially those with early disease, amenable to cure; however, developments in systemic chemotherapy for cervical cancer have been rather slow.

Recurrences following primary treatment of carcinoma cervix may occur either in the pelvis alone or may be disseminated. In the former situation, if it follows previous surgery the modalities available are radiotherapy, exenteration and chemotherapy; if it follows previous radiotherapy the options available are pelvic exenteration or chemotherapy. In disseminated disease, the use of cytotoxic drugs would appear logical. Whilst pelvic exenteration has a place in the treatment of pelvic recurrence, its role is limited by the high degree surgical expertise necessary, the rather high operative mortality and morbidity and the low 5-year survival rate (Table 1).

Table 1
RESULTS OF PELVIC EXENTERATION IN CERVICAL CANCER

Authors	Patients	Operative Mortality %	5-year Survivors %
Douglas & Sweeney [1]	23	4	22
Brunschwig [2]	535	16	20
Symmonds et al [3]	198	8	32
Morley and Lindenauer [4]	34	3	62
Rutledge et al [5]	296	14	33
Average	1086	13	27

What Is The Role Of Chemotherapy In Cervical Cancer?

Chemotherapy can be expected to provide palliation in advanced disease or have a curative role in disseminated disease or local recurrence following initial surgery or radiotherapy. A third possible role is as an adjunct prior to operative or radiotherapy treatment and post-operatively.

Chemotherapy In Recurrent Or Advanced Cervical Cancer

1. Single agent chemotherapy

   Over the years various single agents have been used (Table 2). With the exception of hydroxyurea, the overall response rates range from 6 to 25%, the average median response being 4 to 6 months. Results show no long term benefits, with little effect on survival. Our recent experience with the new analogue of doxorubicin (Adriamycin), epirubicin, has been disappointing in the treatment of recurrent cervical cancer following primary surgery or irradiation.[10] In 17 evaluable patients, although a less than 20% partial response was seen, this was not sustained, suggesting that the drug, epirubicin, is of little value in these advanced cases when used alone; such poor response was observed even when the recurrence occurred at sites outside the irradiated field, such as lungs and bone.

   Of all drugs used as a single agent, cisplatinum appears to be the most active with response rates reported as high as 50%.[11] In a very large series of 418 patients, Bonomi et al[12] found no difference in the progression-free interval or duration of response in a randomised 3-arm study of cisplatinum given at 20 mgm/m^2 daily for 5 days, and 50 mgm/m^2 given on day 1 only.

2. Use of combination chemotherapy in advanced or recurrent cervical cancer

   Attempts to prolong and increase survival rates have prompted the use of various combination of drugs (Table 3). Such multiple-agent chemotherapy allows mechanism of action of the various drugs to be combined and thus

Dept of Obstetrics and Gynaecology
Faculty of Medicine
University of Malaya
59100 Kuala Lumpur, Malaysia

V Sivanesaratnam AM, MBBS (S'pore), FRCOG, FICS, FACS
Professor and Head

Table 2
SINGLE AGENT CHEMOTHERAPY IN CERVICAL CANCER
(modified from Thigpen[6], 1981)

	Drugs	No. of patients	Overall response %
Alkylating agents	Cyclophosphamide	188	15
	Chlorambucil	44	25
Anti-metabolites	5-FU	140	21
	MTX	77	16
Mitotic Inhibitors	Vincristine	44	23
Antibiotics	Adriamycin	28	18
	Bleomycin	172	10
	Mitomycin C	18	22
Other Agents	Hexamethyl-melamine	49	22
	Hydroxyurea	14	0
	6-MP	18	6
		792	16.7%
+ Recent Study[10]	Epirubicin	17	20 (partial response only)

together might be expected to yield higher response rates with minimum toxicity. Miyamoto et al,[13] using a combination of bleomycin 5 mgm i.v. daily for 7 days and Mitomycin C 10 mgm on day 8 and repeating the therapy on day 16, reported a remarkably high response rate of 93 per cent (80% complete response). However, this has not been duplicated by others; Boyce et al[14] used a similar regime in 23 patients and obtained complete and partial responses of only 9 and 17 per cent respectively. Our own experience using a similar regime in 8 patients with recurrence following primary surgery or irradiation for carcinoma of the cervix showed no responses.[15] The mitomycin C/bleomycin combinations are unfortunately toxic as well. Miyamoto reported one death from lung fibrosis secondary to bleomycin; Krebs et al[16] using doses similar to those of Miyamoto's had approximately 10 per cent mortality as a result of this complication.

Combinations using cisplatinum appear promising. Friedlander et al[17] using cisplatinum, bleomycin and vinblastine in 33 patients achieved an overall response rate of 67 per cent with median survivals of 40 and 44 weeks respectively in the complete and partial remission groups respectively. A recent AOFOG Cervical Cancer Study[18] using a similar regime in 161 patients with advanced or recurrent cervical cancer an overall response of 55 per cent with complete response in 15 per cent of patients. In our limited experience with this combination therapy in 9 patients[15] with recurrent disease we obtained a complete response lasting 48 months in one patient after surgical excision of a recurrence in the anterior rectal wall following Wertheim's radical hysterectomy for Stage 1B carcinoma of the cervix, and she remains well. This suggests that tumour debulking where possible will help response to chemotherapy. There were no responses observed in our 8 other patients.

Table 3
COMBINATION CHEMOTHERAPY IN PATIENTS WITH ADVANCED OR RECURRENT CERVICAL CANCER

Drugs	n	CR (%)	PR (%)	Reference
ADR + CCNU	31	9(29)	5(16)	Day et al[7]
ADR + MTX	59	12(22)	26(44)	Guthrie and Wau[8]
ADR + Cyclo	20	1(5)	5(21)	Trope et al[9]
Mito C + Bleo	15	12(80)	2(13)	Miyamoto et al[13]
Mit C + Bleo	23	2(9)	4(17)	Boyce et al[14]
Mit C + Bleo	8	0	0	Sivanesaratnam and Sen[15]
Cis P + Bleo + Vin	9	1(10)	0	Sivanesaratnam and Sen[15]
Cis P + Bleo + Vin	33	6(18)	16(48)	Friedlander et al[17]
Cis P + Vin + Bleo	161	23(15)	64(40)	AOFOG Cervical Cancer Study[18]
Cis P + Bleo + VCN + Mito C	24	5(21)	8(33)	Surwit et al[19]
Cis P + Bleo + VCN + Mito C	13	3(23)	7(54)	Vogl et al[20]

ADR = Adriamycin; MTX = Methotrexate; Cyclo = cyclophosphamide;
VCN = Vincristine; MITO C = Mitomycin C; Bleo = bleomycin;
Cis P = cisplatinum; Vin = Vinblastine; CR = complete response;
PR = partial response

Combinations of cisplatinum, bleomycin, vincristine and mitomycin C have been used by Surwit et al[19] in 24 patients and obtained complete remissions lasting 5 to 46 months. Bogl et al[20] on the other hand, using a similar combination of drugs obtained an overall 77% response with a median survival of only 4 months.

Although a high percentage of response may be seen with such cisplatinum combination regime, the duration of response continues to be disappointing.

3. Intraarterial chemotherapy

Intra-arterial chemotherapy for advanced gynaecologic cancer began in the 1950s.[21] However, its role in the treatment of locally advanced tumours has not yet been proven. The theoretical advantages of achieving higher concentrations of drugs to perfuse the tumour, decreased drug delivery to systemic tissue and prolonged tumour cell exposure to anti-cancer drugs during continuous infusion, if administered intra-arterially, makes this route of administration a useful modality where standard treatment does not obtain successful local tumour control.

Intraarterial monochemotherapy have been used previously for the management of cervical cancer. Using bleomycin, Morrow et al[22] obtained an objective response of only 10 per cent in 20 patients, with survival in these two patients of 5 and 8 months respectively. Severe toxic effects were observed in 10 patients — renal failure in 4, pulmonary fibrosis in 4 one death, and septic embolisation from the catheter in one. Carlson et al[23] using cisplatinum as a single agent obtained a 33 per cent response rate. Using peptichemio, a multipeptide complex of m-di-2-dichloroethylamino-L phenylalanine (M-L-phenylalanine mustard) with alkylating and anti-metabolic properties, Scarabelli et al[24] noted a 53 per cent response rate.

Kavanagh et al[25] reported a 48 per cent response rate using a combination of cisplatinum, bleomycin, vincristine and mitomycin C. Swenerton et al[26] employing an intermittent infusion of the non-cisplatinum combination of vincristine, bleomycin and mitomycin C in 20 patients, obtained no complete response and only 3 partial responses lasting 27 to 28 weeks. Complications of Staphylococcus aureus sepsis, distal arterial embolisation and fatal pulmonary fibrosis noted in each of 3 patients, makes such a regime prohibitive. Major catheter complications were also observed by Lifshitz et al[27] using methotrexate alone or in combination with vincristine. Whilst overall response was poor, he obtained pain relief in 11 out of 14 patients. Scarabelli et al[28] treated 25 patients with locally advanced or recurrent cervical carcinoma using a bilateral sequential infusion of peptichemio 20 mgm, doxorubicin 10 mgm and cisplatinum 20 mgm in a 6-hour period via an external infusion pump, restarting treatment after a rest period of 4 days until maximum response or toxicity was noted. An overall objective response rate of 84% was achieved and a complete response, was comfirmed in 2 patients with Stage 2B and 3 disease, respectively. Catheter related toxicity was noted in four patients causing femoral thrombosis in two.

Marked relief of pelvic pain in 74 per cent of patients with minimal toxicity has been reported by Lathrop and Frates[29] in 62 patients with advanced pelvic malignancies using nitrogen mustard. This effect was felt to be the result of toxic effects of nitrogen mustard on finely myelinated and non-myelinated nerve fibres. Except for control of pain, where other measures have failed, this modality of treatment at present appears limited.

4. Reasons for the poor response to chemotherapy in recurrent cervical cancer

There are several reasons for the poor response to chemotherapy observed in these cases. Previous pelvic irradiation causes pelvic fibrosis making assessment of response difficult; diminished blood supply reduces tumour perfusion; diminished bone marrow reserve limits dose of drugs; and urethral obstruction if present impairs renal function and limits the choice and dose of drugs that can be used. Further, squamous cell carcinoma which comprises 95% of all cervical cancers is the least responsive to most chemotherapeutic agents.

Chemotherapy Prior To Radiotherapy In Cervical Cancer

Recent emphasis has been on the use of chemotherapy prior to radiotherapy; this would have the theoretical advantage of destroying micrometastases elsewhere and also reduce the primary tunour bulk, features advantageous from a radiobiological view point.

Sinclair[30] noted that the G_1 and G_2 phases of cell cycle of Chinese hamster lung cells grown in culture were more sensitive to radiotherapy than was the S phase. He later showed the latter phase to be most sensitive to hydroxyurea, which also blocked cycling cells at the G_1-S interphase, thereby maintaining the cells in a relatively sensitive phase of the cell cycle. In a randomised study using hydroxyurea or placebo followed by radiotherapy for Stage 2B to 4A cervical cancer,[31] response rates of 68.1 and 48.8 per cent were deserved in the hydroxyurea and placebo groups respectively. A recent study by Piver et al[32] reviewed 40 patients with Stage 2B carcinoma of the cervix, who underwent pretreatment staging laparotomy and pelvic node sampling. The patients were then given either hydroxyurea or placebo followed by radiotherapy. A 94 per cent 5-year survival rate was observed in the hydroxyurea group compared with 53 per cent in the placebo group. Apart from an increased incidence of leucopenia in the hydroxyurea group, there was no significant increase in morbidity.

Kavanagh et al[25] obtained a partial remission in 12 out of 25 patients with advanced cervical cancer after intra-arterial chemotherapy with cisplatinum, bleomycin, vincristine and Mitomycin C. Ten of the these partial responders became tumour free following subsequent radiotherapy. No significant myelosuppression was observed. Using a similar combination of drugs prior to radiotherapy the EORTC study group[33] in their preliminary study, report a complete remission in 14 out of 37 patients with advanced disease.

The above studies appear encouraging. The Asian Oceanian Clinical Oncology Association (AOCOA) is about to embark on a study using cisplatinum and epirubicin in combination prior to radiotherapy in locally advanced cervical cancer.

Chemotherapy As An Adjuvant To Radical Surgery For Cervical Cancer

Some form of adjuvant therapy becomes necessary in a group of high risk patients following surgery for cervical cancer. These include metastases to pelvic nodes, lymphatic and vascular channel permeation by tumour cells, microscopic parametrial extension, tumour infiltrating the full thickness of the cervical wall and positive peritoneal washings. The presence of pelvic node metastases reduces 5-year survivals to 19 to 48%[34] from overall 75 to 85%.[35, 36] The presence of lympathic and vascular channel permeation reduces 5-year survivals to 60 to 70%.[37, 38] Although adjuvant radiotherapy decreases the incidence of local recurrences, the overall survival is not improved because of the subsequent development of distant metastases.[39]

Whilst adjuvant chemotherapy is today an accepted modality of treatment in management of ovarian cancer, its use in the management of those patients undergoing radical hysterectomy for early cervical cancer has not been established yet. The use of such agents as adjuvant would appear more logical to improve survival than pelvic irradiation, as the

latter cannot be expected to prevent the development of distant metastases. Recent reports using Cisplatinum in combination with other drugs have shown short duration, high response rates of 55 to 80% for recurrent cervical cancer.[17, 40, 41] The use of cisplatinum and bleomycin as adjuvant to radical Wertheim's hysterectomy has been reported recently to result in a survival of 91% in those high risk group of cases.[42] Our own preliminary experience using the PVB regime (Cisplatinum, bleomycin and vinblastine) on 22 high risk cases following radical surgery showed a disease free survival rate of 86.4% at a median follow up of 23 months.[43]

CONCLUSION

Metastatic carcinoma of the uterine cervix and unresectable pelvic recurrences do show some objective tumour response to cytotoxic drugs in a high proportion of cases. The average duration of tumour response is, however, relatively short. The necessity to improve local treatment modalities is, therefore, important. The use of cytotoxic drugs as radiosensitisers and intraarterial chemotherapy as part of a multimodality treatment in advanced carcinoma of the cervix needs further active investigation. The use of these drugs as an adjuvant in selected high risk patients following radical surgery has been shown in preliminary studies to improve survival[27, 28] and would need further evaluation.

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