Cancer Chemother Pharmacol (1992) 30: 281–285

Cancer Chemotherapy and Pharmacology

Neoadjuvant chemotherapy with cisplatin, vincristine, and bleomycin and radical surgery in early-stage bulky cervical carcinoma

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Received 14 September 1991/Accepted 16 March 1992

Summary. Neoadjuvant chemotherapy consisting of 2–3 courses of cisplatin, vincristine, and bleomycin was used in the primary treatment of 36 consecutive patients with locally advanced early-stage cervical carcinoma [International Federation of Gynecology and Obstetrics (FIGO) stages Ib or IIa; tumor size, ≥4 cm]. The effectiveness of the preoperative chemotherapy was evaluated in the surgical specimens. Among the 33 evaluable patients, the overall clinical response rate was 84.8%, which included a complete response in 8 patients (24.2%) and a partial response in 20 subjects (60.6%). No residual tumor was found in the surgical specimens obtained from 2 complete responders. This therapy induced varying degrees of tumor shrinkage and rendered radical surgery feasible in all evaluable cases despite the initial bulky size of the lesions. No significant difference was observed in the response rate according to age and disease stage. Lymph-node metastases were found after chemotherapy in 18.2% (6/33) of the patients. Grade II and III hematological toxicities occurred in 23.3% of the 90 chemotherapy cycles completed. Nausea and vomiting occurred to a mild to moderate degree in 75 (83.3%) cycles. These preliminary results suggest that the administration of induction chemotherapy involving two to three courses of cisplatin, vincristine, and bleomycin prior to surgery is effective in reducing the tumor volume and in providing better circumstances for surgical removal of the early yet bulky cervical tumors and results in tolerable toxicity. This protocol is now undergoing prospective randomized trials to test its impact on long-term survival.

Introduction

Although effective cytological screening has markedly decreased the overall mortality from cervical carcinoma through early detection, the 5-year survival for each stage has not improved significantly over the past 25 years [20]. Although primary treatment is quite successful for the early stages, nearly 45% of all patients afflicted with this malignancy eventually die due to either local cancer progression or metastases [2]. Up to 60% of patients with nodal metastases and more locally advanced tumors undergo relapse [11].

Two new therapeutic concepts, neoadjuvant and adjuvant chemotherapy, are evolving to improve tumor control and ultimate survival in patients with unfavorable cervical cancers [2]. Neoadjuvant chemotherapy is given prior to surgery or radiation, whereas adjuvant chemotherapy is usually given either simultaneously with radiotherapy to augment the response or after the primary treatment due to the discovery of high-risk factors such as nodal metastases. Both of these treatment modalities are designed to enhance local tumor control and eliminate micrometastases.

Most investigators agree that larger lesions respond poorly to treatment. The size of the primary cervical tumor correlated inversely with both survival and time to recurrence in the series of Fuller et al. [7]. Chung et al. [3] note that patients with bulky primary tumors (≥4 cm) show a significantly higher incidence of nodal metastases than do those bearing smaller tumors (80% vs 16%). The high relapse rates emphasize the need to develop other sources of therapy for these lesions.

Chemotherapy has traditionally been reserved as last-line treatment, in particular for individuals with metastases or disease recurrence. Previous studies have indicated that cervical carcinoma is a chemoresponsive tumor, and the addition of chemotherapy as part of the treatment strategy represents a new trend [4–6, 8–10, 12–19]. Clinical trials using neoadjuvant chemotherapy followed by surgery have demonstrated that a reduction in the tumor bulk can make radical surgery possible in a high percentage of cases that have previously been considered to be inoperable [4, 9, 13, 16]. Preoperative chemotherapy did not seem to increase surgery-related complications. Moreover, the preliminary 2- or 3-year survival periods resulting from these studies appear to be encouraging [10, 14]. The incidence of lymph-

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node metastases seems to be reduced by the addition of neoadjuvant chemotherapy [9, 13, 14].

These encouraging results stimulated us to initiate the present study to assess the feasibility of combined induction chemotherapy followed by radical surgery in the treatment of bulky cervical carcinoma in our institution. The aim of this pilot study was to assess the response rate and the toxicities associated with this particular three-drug combination protocol.

Patients and methods

Between April 1989 and January 1991, 36 consecutive patients with previously untreated cervical carcinoma were entered into this study as part of our clinical investigations. Patient eligibility criteria included the following: the presence of bulky cervical lesions (tumor size, ≥ 4 cm) of stages Ib and IIa; a Zubrod's performance status of 0–1; a histological diagnosis of squamous, adenosquamous, or adenocarcinoma; an age of ≤ 70 years; written informed consent of the patient (and her family) to participate in this study; and no history of either other cancer or prior curative-intent therapy. Adequate hepatic, renal, and cardiopulmonary functions were also required. In addition, a hemoglobin level of ≥ 10.0 g/l, a total WBC of $\geq 3000/cm^3$, and a platelet count of $\geq 1 \times 10^5/cm^3$ were mandatory. Patients presenting with medical complications that would contraindicate the administration of chemotherapy were excluded. Other exclusion criteria included an undifferentiated small-cell type and any distant metastasis documented in oncological surveys.

The initial oncological investigation prior to the administration of chemotherapy included a complete blood count, liver- and kidney-function tests, an electrocardiogram, a chest X-ray, i.v. pyelography, and computerized axial tomography (CT scan) using enhancement. Tumor markers included squamous-cell carcinoma antigen (SCC) and carcinoembryonic antigen (CEA). The tumor size was estimated by pelvic examination and CT scan.

After the initial assessment, the first course of combination chemotherapy was given. Subjects were scheduled to receive three courses at intervals of 7 days. Patients were checked for response and toxicity, and precise records were kept for every admission. After the cessation of chemotherapy, subjects were admitted for clinical response evaluation and for surgery consisting of a type III radical abdominal hysterectomy plus systemic para-aortic and bilateral pelvic lymphadenectomy. Tumor response was evaluated according to the International Union Against Cancer (IUCC) definition of an objective response. A complete response (CR) was defined as the disappearance of all measurable disease. A partial response (PR) was defined as a decrease of at least 50% in the product of the two maximal tumor diameters. Stable disease (SD) represented a regression of <50% of the tumor, and progressive disease (PD) was defined as an increase of >25% in the size of the tumor and/or the appearance of new lesions. The duration of survival and the time to recurrence were measured from the commencement of chemotherapy. Toxicity was assessed according to WHO criteria [21]. The end points of the study were local tumor response, acute toxicity, and disease-free survival.

The chemotherapy regimen consisted of 50 mg/m^2 cisplatin given as an i.v. infusion on day 1, 1 mg/m^2 vincristine given as an i.v. bolus on day 2, and 25 mg/m^2 bleomycin given as a 24-h i.v. infusion on days 2–4. During the treatment, patients received high-dose antiemetics, including 3 mg/kg metoclopramide given by i.v. infusion, and 50 mg diphenhydramine and 20 mg dexamethasone given as an i.v. bolus.

Results

Patients' characteristics and clinical response

A total of 36 consecutive eligible patients were accured into this study. Three patients refused further treatment after one cycle of chemotherapy and were therefore removed from evaluation. The clinical characteristics of the 33 evaluable patients who completed at least 2 courses of chemotherapy and underwent surgery are shown in Table 1. The median age was 45 years (range, 25–62 years). In all, 21 subjects had stage Ib disease and 12 had stage IIa carcinoma of the cervix; in 29 of the patients, the cell type was squamous, whereas 3 cases were adenosquamous and 1 was adenocarcinomatous (Table 2).

The overall rate of clinical response for the primary tumor was 84.8%, including 8 CRs (24.2%) and 20 PRs (60.6%). In all, 5 patients had SD including 3 cases of distinctive tumor regression that amounted to a reduction of <50% in the primary tumor mass; the size of the lesions in the other 2 subjects remained the same as that measured pretreatment. None of our patients developed PD during chemotherapy. No difference in the response rate was found when patients were grouped according to age and disease stage. On the other hand, the tumor size correlated significantly with the subsequent response to chemotherapy. Apart from the subject bearing a primary tumor measuring 7 cm, who achieved a PR, the response of patients with larger tumors was poorer (94.1% for lesions measur-

Table 1. Chemotherapeutic response according to clinical variables

Characteristics	Total responses	CR	PR	SD	CR+PR	%
Age (years):						
<35	7	1	4	2	5	71.4
36–45	10	1	7	2	8	80
46–55	11	4	6	1	10	90.9
>55	5	2	3	0	5	100
Stage:						
Ib	21	5	13	3	18	85.7
IIa	12	3	7	2	10	83.3
Primary tumor size:						
4 cm	17	6	10	1	16	94.1
5 cm	11	2	7	2	9	81.8
6 cm	4	0	2	2	2	50
7 cm	1	0	1	0	1	100
Courses (*n*):						
2	9	3	6	0	9	100
3	24	5	14	5	19	79.2

Table 2. Tumor response according to surgicopathological findings

Characteristics	Total responses	CR	PR	SD	CR+PR	%
Cell differentiation:						
Good	–	–	–	–	–	
Moderate	13	5	7	1	12	92.3
Poor	20	3	13	4	16	80
Lymph-node metastasis:						
Negative	27	8	16	3	24	88.9
Positive	6	0	4	2	4	66.7
Cell type:						
Squamous	29	7	17	5	24	82.8
Adenosquamous	3	0	3	0	3	100
Adenocarcinoma	1	1	0	0	1	100

Table 3. Incidence of lymph-node metastasis according to various prognostic factors

Characteristics	Patients (*n*)	Positive lymph-node metastasis	
		n	%
Age (years):			
≤35	7	2	28.6
36–45	10	2	20
46–55	11	2	18.2
>55	5	0	–
Stage:			
Ib	21	3	14
IIa	12	3	25
Clinical response:			
CR	8	0	–
PR	20	4	20
SD	5	2	40

Table 4. Hematological toxicities[a]

Toxicity	WHO grade	Number[b]	%
WBC:			
2000–2999	2	18	20
1000–1999	3	3	3.3
Platelet count (× 1000):			
50–99	2	15	16.7
25–49	3	2	2.2

[a] Overall incidence, 23.3% (21/90)
[b] Total of 90 chemotherapy cycles

ing 4 cm; 81.8% for those measuring 5 cm; and 50% for those measuring 6 cm). The reason for the paradoxical response rates obtained during the different chemotherapy courses was that all patients who had completed two cycles achieved at least a PR and were thus not encouraged to undergo another cycle of chemotherapy.

Another clinical parameter that was significantly associated with chemoresponsiveness was the tumor grade (Table 2). The 13 patients with moderately differentiated lesions achieved a 92.3% (12/13) response rate in contrast to 80% (16/20) of those bearing poorly differentiated tumors. As the number of cases involving with adenosquamous and adenocarcinomatous lesions were limited, the impact of the histological type on the tumor response could not be determined. Another interesting finding was that for the 27 patients who tested negative for lymph-node metastasis, the response rate was 88.9% as compared with the 66.7% response rate obtained for those with positive nodes.

Surgicopathological findings after chemotherapy

Lymph-node metastases were found in the surgical specimens obtained from 6 patients (18.2%). When the incidence of lymph-node metastases was correlated with the chemotherapeutic response, we found that all nodal metastases had developed in patients who achieved a PR (4/20, or 20%) or those who had SD (2/5, or 40%; Table 3). All 8 patients who achieved a clinical CR showed no evidence of lymph-node involvement; in 2 cases, no residual tumor was detected in the entire surgical specimen (complete pathological response), including the lymph nodes. The lymph nodes of 3 of the 21 patients (14%) with stage Ib disease tested positive for metastasis, as did those of 3 of the 12 subjects (25%) with stage IIa disease. The age of the patient apparently had no influence on the lymph-node status.

Table 5. Nonhematological toxicities

Toxicity	Grade	Number	%
Nausea/vomiting[a]:			
Mild	1	51	56.7
Moderate	2	24	26.7
Severe	3,4	0	–
Diarrhea[a]		10	11
Hepatic (SGOT, >50 U/L)[a]		8	9
Drug fever[a]:			
38°–38.5° C	2	35	38.9
38.6°–39° C	3	14	15.6
>39° C	4	8	9
Significant hair loss[b]		27	81.8
General malaise[b]		25	75.8

[a] Total of 90 chemotherapy cycles
[b] Total of 33 patients

Toxicities

No treatment-related death occurred during the 90 chemotherapy courses delivered. Grade 2 and 3 hematological toxicities occurred during 21 cycles (23.3%; Table 4), which necessitated a delay in treatment for 1–7 days. Mild to moderate nausea and vomiting occurred during 75 (83.4%) chemotherapy cycles despite the administration of high-dose antiemetics (Table 5). Transient drug fever was frequently observed (63.5%) after the administration of bleomycin, but it responded rapidly to simple measures such as an icepillow, rectal aspirin suppositories, antihistamines, and steroids. Significant hair loss (alopecia) occurred in 27 patients (81.8%) after the completion of chemotherapy. General malaise during the administration of chemotherapeutic agents occurred in 75.8% of our subjects. Mild impairment of hepatic function developed during 8 cycles (9%). No neuro-, cardiac, pulmonary, or renal toxicity occurred in any case. Two patients experienced antiemetic-related extrapyramidal symptoms, which resolved soon after antidote injection. Chemotherapy did not seem to complicate the surgical procedures. We encountered no major postoperative complication. Prolonged bladder training was required for >1 month in three patients who had undergone adjuvant whole pelvic radiation postoperatively. Thus, toxicity hindered neither the administration of chemotherapy nor the ensuing surgical procedures.

Protocol design and patients' status during follow-up

Our protocol for early-stage bulky cervical cancer was designed to evaluate the clinical response after three courses of neoadjuvant chemotherapy. If a CR or a PR has been achieved, a radical hysterectomy is then performed. If SD is found, it is up to the physician to decide whether radiotherapy or surgery should be undertaken. Lymph-node status is evaluated postoperatively. If all lymph nodes are negative, the tumor is confined to the cervix, and no other risk factors are found, then no adjuvant therapy is given. If the tumor is found to extend beyond the cervix or if full-thickness cervical invasion is evident, additional radiotherapy is given. If pelvic lymph nodes are found to be positive for metastases, adjuvant radiation or combined chemo- and radiotherapy are indicated.

Of the six patients with positive nodes, two received additional radiation therapy. Two patients received two further courses of chemotherapy because of common-iliac-node involvement. The other two subjects refused further treatment. Adjuvant irradiation was carried out in another four patients who showed full-thickness cervical involvement but no lymph-node metastasis.

Four patients experienced disease recurrence during a median follow-up period of 18 months (range, 6–31 months); three of them were in the SD group, and the other one showed an initial PR but developed lymph-node metastases. All recurrent patients had distant metastases (two in the lung, one in bone, and one in Virchow's node), and one also experienced central recurrence. All but one of these recurrent patients are currently on salvage chemotherapy and are alive but not free of disease. The patient who developed extensive lung metastases died of pulmonary failure at 12 months after the initial diagnosis despite aggressive management.

Discussion

This pilot study was undertaken to assess the utility of preoperative induction chemotherapy in reducing the primary tumor size to facilitate surgical removal of locally advanced cervical cancer. The use of neoadjuvant chemotherapy as part of multimodality treatment offers some theoretical advantages in the treatment of advanced disease. Chemotherapy may shrink bulky tumors prior to surgical and radiation treatment and may also reduce the incidence of lymph-node metastases [10, 14]. Following induction chemotherapy, radical surgery may be performed to remove residual central disease, to evaluate lymph-node status, and, presumably, to improve the rate of cure [4].

During the past few decades, the overall survival of patients with cervical cancer has improved, mainly due to earlier detection via increased cytological screening and to better surgical and radiotherapeutic techniques. Chemotherapy has played a minor role [2]. On the basis of the promising results reported by Friedlander et al. [5, 6], Kim et al. [8–10], Panici et al. [12–14], Park et al. [15], Sardi et al. [16, 17], and Tobias et al. [18], a new role may be emerging for chemotherapy in the primary treatment of individuals at high risk for relapse, especially those with bulky disease. Tumor size has been demonstrated to give a better indication of tumor behavior than does the clinical tumor stage [1].

Table 6. Review of the literature on neoadjuvant chemotherapy in the treatment of cervical cancer

Reference	Case (*n*)	Regimen	Total response (%)	CR (%)
Friedlander et al. [5]	33	PVB	66	18
Sardi et al. [16]	8	POB, 21 days[a]	62.5	25
	25	POB, 10 days[a]	92	44
Kim et al. [9]	35	PVB	89	46
Panici et al. [13]	3	PMB	75.7	12.1
Tobias et al. [18]	32	PIB	69	7
Dottino et al. [4]	28	POMiB	100	35
Panici et al. [14]	5	PMB	83	15
Present study	33	POB, 7 days[a]	84.8	24.2

P, Cisplatin; B, bleomycin; M, methotrexate; V, vinblastine; O, oncovin (vincristine); I, ifosfamide; Mi, mitomycin C

[a] Course intervals

The overall response rate obtained in the present study using two to three courses of cisplatin, vincristine, and bleomycin is comparable with those previously reported for other cisplatin-containing combinations, as can be seen in Table 6. The acceptable toxicity and the low incidence of prolonged delays in treatment demonstrate the feasibility of using an intensive scheme with short intervals between courses, which theoretically has the therapeutic advantage of enhancing responsiveness. As also observed by Panici et al. [14], the initial tumor size significantly affected the subsequent response to chemotherapy in our study.

It is noteworthy that the lymph-node positivity (18.2%) was surprisingly lower than expected in view of the bulky size of the primary tumors. Remarkably, no lymph-node involvement was found in any of the eight patients who achieved a clinical CR. The incidence of lymph-node metastasis was lower in partial responders (20%) than in patients who had SD (40%). These findings suggest that the effects of chemotherapy on lymph nodes are more marked in individuals who demonstrate more favorable responses and that chemotherapy might thus eliminate disease in lymph nodes. That no residual tumor was detected in the final surgical specimens obtained from two patients further indicates that some cervical cancer is definitively chemosensitive. This may lead to a new trend of exploring the role of neoadjuvant chemotherapy in the management of unfavorable cervical carcinoma in the near future.

In conclusion, our preliminary results suggest that the administration of initial chemotherapy involving two to three courses of cisplatin, vincristine, and bleomycin prior to surgery is effective in reducing the primary tumor size in early-stage bulky cervical cancer, results in acceptable toxicities, provides better circumstances for subsequent surgery, and may be capable of eliminating lymph-node disease and micrometastases. This regimen is currently undergoing prospective randomized trials to assess its impact on long-term disease-free survival.

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