THE INFLUENCE OF PRETREATMENT CELIOTOMY AND PARA-AORTIC LYMPHADENECTOMY ON THE MANAGEMENT OF ADVANCED STAGE SQUAMOUS CELL CARCINOMA OF THE CERVIX

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Summary: Thirty patients with advanced stage squamous cell carcinoma of the cervix underwent exploratory celiotomy and para-aortic lymphadenectomy prior to beginning radiation therapy. Para-aortic lymph node metastases were found in 9 patients (30%), and visceral metastases in 2 patients (7%). Findings at celiotomy prior to initiation of therapy allowed patients to be divided into 3 groups: Patients with 1) visceral metastases, 2) para-aortic lymph node metastases but without visceral or scalene lymph node metastases, and 3) patients with disease confined to the pelvis. Therapy was then based on the extent of disease present in each patient. As a result of the surgical findings, 10 of 30 patients (33%) received therapy other than standard pelvic radiation therapy.

The surgical technique, operative morbidity, and prognostic significance of the surgical findings are discussed.

INTRODUCTION

The standard therapy for locally advanced cervical carcinoma is ionizing radiation delivered to the central tumor mass and to the pelvic lymph node bearing areas. It is axiomatic that, in the treatment of cancer, the entire extent of the disease must be treated to achieve a cure. Therefore, patients with metastatic carcinoma in areas outside the pelvic radition field cannot be cured of their disease by standard therapy. The purpose of pretreatment celiotomy and para-aortic lymphadenectomy in the evaluation of patients with advanced stage cervical carcinoma is to determine if there is tumor beyond the pelvis prior to the initiation of therapy. Radiographic techniques, including lymphangiography and computerized tomography, lack both sensitivity and specificity in detecting nodal and visceral metastases.

Cervical carcinoma spreads primarily by local extension and later by tumor embolization to regional lymph nodes. The principal efferent lymphatics of the cervix course laterally through the parametria and drain to the external iliac, hypogastric, obturator, and common iliac lymph nodes (fig. 1). Smaller anterior and posterior lymphatic trunks are also present. The anterior channels pass behind the bladder and terminate primarily in the external iliac lymph nodes. The posterior lymphatic trunks course in the uterosacral ligaments before turning sephalad and terminating in common iliac, superior rectal, and para-aortic lymph nodes. Through the posterior trunks, cervical carcinoma can metastasize directly to the para-aortic lymph nodes, bypassing the pelvic lymph nodes. However, this is thought to be an unusual mechanism for para-aortic metastases from cervical carcinoma.

The common mechanism by which cervical carcinoma reaches the para-aortic lymph nodes is progressive involvement of the pelvic lymph nodes with subsequent tumor embolization to the para-aortic nodes. Efferent lymph flow from the para-aortic nodes is to the cisterna chyli and

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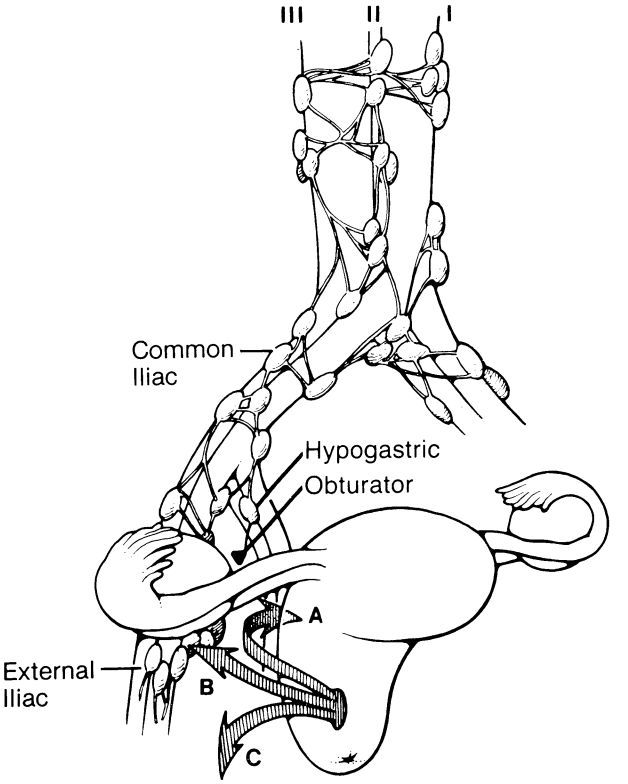

Fig. 1. — The major lymphatic drainage of the cervix is through the lateral channels (B) to the external ilac, hypogastric, obturator, and common iliac lymph nodes. In addition to the lateral lymphatic trunks, smaller but consistent anterior and posterior lymphatic trunks are present. The anterior channels (C) pass behind the bladder and terminate predominantly in the external iliac lymph nodes while the posternor lymphatic channels (A) course posteriorly and common in the uterosacral ligaments before turning cephalad and terminating in the common iliaic, subaortic, para-aortic and superior rectal lymph nodes. The 3 para-aortic lymph node chains are illustrated: The left aortic chain (I) lies to the left of the aorta and the aorto-caval nodes (II) lie between the aorta and vena cava while the caval chain (III) lies to the right of the vena cava. (Reprinted with permission. *Gynecology and Obstetrics*, Vol. 4, Chapter 8, 1986. Lippincott/ Harper & Row).

thoracic duct which ascends into the left thoracic cavity in the posterior mediastinum (fig. 2). The thoracic duct then empties into the venous system at the junction of the left subclavian and internal jugular veins. Prior to emptying into the venous system, the thoracic duct rises above the clavicle and provides afferent lymph flow to the scalene lymph nodes. By this mechanism, tumor emboli from the para-aortic lymph nodes can be deposited in the scalene lymph nodes, as well as disseminated via the venous system.

Hematogenous dissemination of cervircal carcinoma is relatively unusual, occurring in about 5% of cases. Malignant cells can gain entrance to the vasculature via the thoracic duct, or by direct invasion of blood vessels. Liver metastases

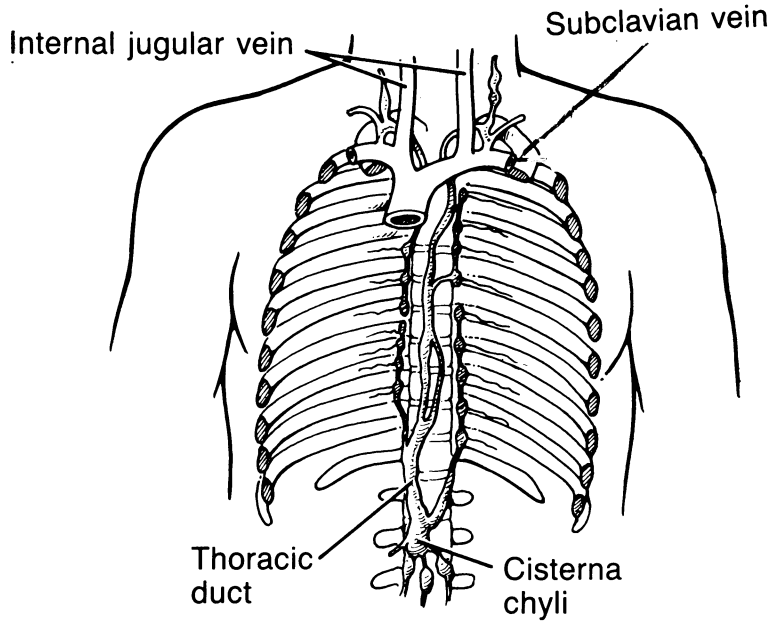

Fig. 2. — Efferent lymph flow from the para-aortic lymph nodes is to the cisterna chyli and subsequently to the thoracic duct. The thoracic duct empties into the venous system at the junction of the left subclavian and internal jugular veins. Prior to emptying into the venous system the thoracic duct arches above the clavicle and incorporates the scalene lymph nodes into the efferent lymph flow. (Reprinted with permission. *Gynecology and Obstetrics*, Vol. 4, Chapter 8, 1986. Lippencott/Harper & Row).

from cervical cancer are thought to occur by hematogenous dissemination of tumor emboli from the cervix, via the hepatic portal system, to the liver. Buchsbaum [1] found liver metastases in 3 of 150 (2%) patients with locally advanced disease. Cervical carcinoma can also spread to the upper abdomen and abdominopelvic viscera by intraperitoneal seeding in a manner analogous to the ovarian carcinomas. Approximately 20% of patients with stage III cervical carcinoma have malignant cells in their peritoneal washings [1].

The incidence of para-aortic lymph node metastases in cervical carcinoma has been well studied and is directly correlated with

Table 1. — *Para-aortic lymph node metastases in cervical carcinoma.*

Author	Stage I		Stage II		Stage III		Stage IV	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Buchsbaum [1] (1979)	4/16	(25.0)	1/19	(5.3)	34/104	(32.7)	4/10	(40.0)
Hughes [2] (1980)	6/140	(4.3)	14/80	(17.5)	23/96	(24.0)	10/23	(43.5)
Chung [3] (1981)	5/110	(4.5)	4/32	(12.5)	6/14	(42.9)	2/3	(66.7)
Welander [4] (1981)	4/14	(28.6)	13/63	(20.6)	10/38	(26.3)	4/12	(33.3)
Twiggs [5] (1984)	5/34	(14.7)	1/21	(4.8)	2/6	(33.3)	———	
Total	24/314	(7.6)	33/125	(15.3)	75/258	(29.1)	20/48	(41.7)

Table 2. — *Visceral metastases in cervical carcinoma.*

Reference	Visceral metastases No.	(%)
Wharton (6) (1977)	11/120	(9.2)
Buchsbaum (1) (1979)	16/150	(10.7)
Hughes (2) (1980)	33/339	(9.7)
Total	60/609	(9.9)

the stage of disease at the time of diagnosis (table 1). The incidence of para-aortic metastases with stage, I, II, III, and IV disease is approximately 7.5%, 15%, 30%, and 40% respectively ([1-5]). About 10% of patients with advanced stage cervical carcinoma have visceral metastases (table 2) ([1, 2, 6]).

In view of the high incidence of extrapelvic metastatic disease in patients with stage III and IV carcinoma, many gynecologic oncologists have advocated pretreatment exploration in the evaluation of patients with advanced disease. This report constitutes our experience utilizing pretreatment celiotomy and para-aortic lymphadenectomy in patients with advanced cervical carcinoma.

METHODS

Between July, 1978 and December, 1983, 30 patients with squamous cell carcinoma of the cerviix underwent pretreatment celiotomy. The celiotomies were performed through a right paramedian incision extending approximately 5 cm above and 5 cm below the umbilicus. After entering the peritoneal cavity, the abdominal and pelvic viscera were examined for evidence of metastatic disease. Suspicious areas were biopsied and the biopsies submitted for frozen section examination. The posterior parietal peritoneum overlying the bifurcation of the aorta was then exposed, and the peritoneum opened from the level of the aortic bifurcation to the duodenum. This allowed a retractor to be placed retroperitoneally, behind the duodenum, and removal of the para-aortic lymph nodes from the level of the aortic bifurcation to approximately the level of the renal arteries. If suspicious nodes were encountered, these were preferentially excised. Radiopaque clips are used to mark the superior and inferior margins of the dissection (fig. 3). In the absence of clinically suspicious nodes, the fat pad overyling the aorta and vena cava was resected. All excised para-aortic lymph nodes were submitted for frozen section examination. If metastatic disease was present in the para-aortic lymph nodes, the patient was further evaluated with a left scalene lymph node excision.

RESULTS

The incidence of para-aortic lymph node metastases was directly related to the clinical stage of disease (table 3). Five patients with clinical stage IIB squamous cell carcinoma of the cervix were explored. This small sub-group of patients with stage II disease were explored before initiation of radiation therapy because they had large, bulky tumor on initial evaluation. Of these 5 patients, 1 (20%) had para-aortic lymph node metastases. Six of 21 patients (29%) with clinical stage IIIB carcinoma had metastatic disease involving the para-aortic lymph nodes. Four patients with stage IVA carcinoma were explored; two (50%) had metastatic disease in the para-aortic lymph nodes.

Of the 30 patients with stage IIB through IVA squamous cell carcinoma of the cervix, 9 (30%) had para-aortic lymph node metastases. In addition, 2 patients (6.7%) were found to have visceral metastases. One patient with clinical stage IVA carcinoma and negative para-aortic lymph nodes was found to have liver metastases. Another patient with clinical

Table 3. — *Incidence of para-aortic lymph node metastases by stage of disease in patients undergoing pretreatment celiotomy.*

Stage	Patients explored	Positive para-aortic nodes	
II B	5	1	(20%)
III B	21	6	(29%)
IV A	4	2	(50%)
	30	9	(30%)

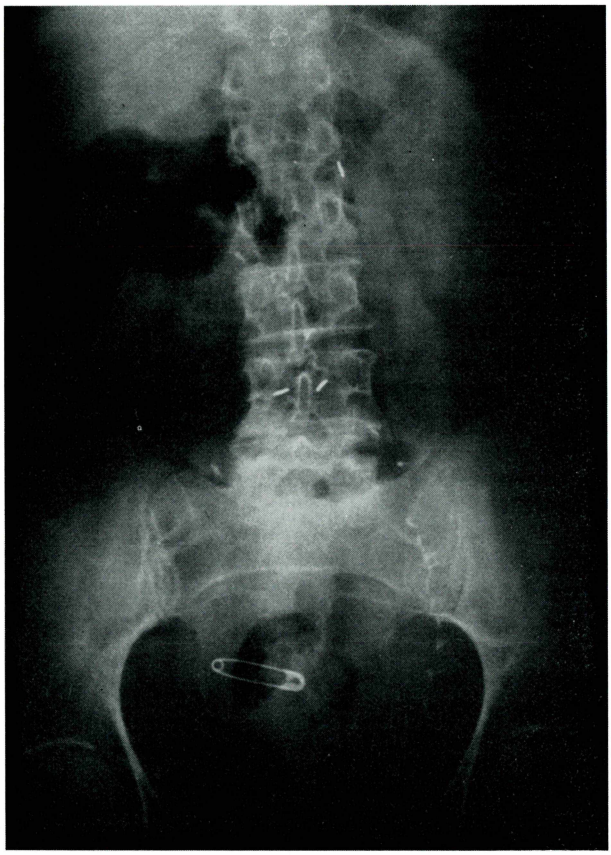

Fig. 3. — Postoperative film of a patient who has undergone a para-aortic lymphadenectomy. Metalic clips (hemoclips) mark the cephalic and caudal margins of the para-aortic lymph node dissection.

stage IIIB carcinoma and positive para-aortic lymph nodes was found to have metastatic disease involving the large bowel serose.

All patients with metastatic disease involving the para-aortic lymph nodes, and without visceral metastases underwent scalene lymph node excisions. No patient had metastatic disease in the scalene lymph nodes.

One patient, with stage IIIB carcinoma and negative para-aortic lymph nodes, was lost to followup and is excluded from further discussion.

Based on the findings at the time of laparotomy, patients were divided into 3 groups: the first group consists of patients with visceral metastases, and was treated with palliative radiation therapy or chemotherapy. The second group contains patients with metastatic disease in the para-aortic lymph nodes, but with no visceral or scalene lymph node involvement. These patients were treated with a standard course of pelvic radiation therapy, plus approximately 4,500 rads of external radiation therapy to the para-aortic lymph node bearing area. The third group con-

Table 4. — *Survival of patients with para-aortic lymph node metastases.*

Stage	No. patients	Alive NED (*)	Dead	Mean survival
II B	1	1	0	——
III B	5	0	5	8.8 mos.
IV A	2	0	2	1.0 mos.

(*) No evidence of disease

sists of patients with disease confined to the pelvis. These patients were treated with a standard course of pelvic radiation therapy consisting of 4,500 to 5,000 rads of external radiation therapy and 1 or 2 radium or cesium applications.

The 2 patients with visceral metastases (group 1) who were treated with palliative radiation therapy to the pelvis both died of disease within 3 months of diagnosis.

There were 9 patients with metastatic disease in the para-aortic lymph nodes. One of these patients had visceral metastases and is discussed above, leaving 8 patients in group 2 (table 4). One patient with stage IIB disease is currently alive and well with no evidence of disease, 24 months following surgery. Five patients with clinical stage IIIB carcinoma had positive para-aortic lymph nodes. All are dead of disease, with a mean survival of 8.8 months following diagnosis. Both patients with clinical stage IVA carcinoma of the cervix and metastatic disease in the para-aortic lymph nodes have died. One patient died of disease approximately 2 months following surgery, and the other patient died on postoperative day 4 of a pulmonary embolus.

Group 3 consists of 19 patients with disease confined to the pelvis (table 5). Two of 4 patients with clinical stage IIB carcinoma are currently alive with no evidence of disease at 30 and 42 months after diagnosis. One patient is alive with disease and receiving chemotherapy and 1 patient is dead of disease. Six of 14 patients with clinical stage IIIB cervical carcinoma and negative para-aortic lymph nodes are alive and well with no evidence of disease from 6 mounths to 4 years (mean 20 months) after diagnosis. Three patients are alive with disease and being treated with chemotherapy; 5 have died of disease. The single patient with stage IVA cervical carcinoma is currently alive and well 48 months after diagnosis.

The morbidity and mortality associated with the surgical procedure were also evaluated. One patient with stage IVA carcinoma and positive para-aortic lymph nodes died on the 4th postoperative day of a pulmonary embolus. Other immediate postoperative morbidity was minimal, consisting of one patient developing pneumonia and 2 developing urinary tract infections, all of which responded promtly to antibiotic therapy. Two patients developed late complications not related to recurrent disease. One patient with para-aortic lymph node metastases treated with pelvic and para-aortic radiation developed radiation proctitis 8 months following her therapy. This was unresponsive to conservative management, and the patient subsequently underwent a sigmoid colostomy. The second patient with late complications had stage III B carcinoma of the cervix with negative para-aortic lymph nodes and was treated with pelvic radiation therapy. She initially developed a small bowel obstruction at the ileocecal junction secondary to radiation fibrosis, treated by resection of the terminal ileum and cecum with ileotransverse colon reanastomosis. She later developed a recto-

Table 5. — *Survival patients without para-aortic or visceral metastases.*

Stage	No. patients	Alive NED (*)	Alive with disease	Dead of disease
II B	4	2 (50%)	1 (25%)	1 (25%)
III B	14	6 (43%)	3 (21%)	5 (36%)
IV A	1	1 (100%)		

(*) No evidence of disease

Table 6. — *Parametrial induration as a prognostic factor in patients with stage III B carcinoma of the cervix.*

Parametrial induration	Patients	Para-aortic lymph node metastasis	Alive and well
Unilateral	9	1 (11%)	3 (33%)
Bilateral	11	5 (45%)	3 (27%)

Table 7. — *Obstructive uropathy as a prognostic factor in patients with stage III B carcinoma of the cervix.*

IVP	No. patients	Para-aortic lymph node metastasis	Alive and well
No obstruction	13	3 (23%)	5 (38%)
Obstruction	7	3 (43%)	1 (14%)

vaginal fistula and bilateral ureteral obstruction secondary to radiation necrosis and fibrosis, necessitating a total pelvic exenteration with fecal and urinary diversion. There was no evidence of carcinoma in the exenteration specimen, but severe radiation reaction was noted. This patient is currently functioning well, with no evidence of recurrent disease.

An attempt was made to identify factors which would predict the occurance of para-aortic lymph node metastases preoperatively, as well as correlate with survival. Two such factors were identified in patients with clinical stage IIIB carcinoma of the cervix. The first was parametrial induration (see table 6). Forty-five percent of patients with bilateral parametrial induration had para-aortic lymph node metastases identified, compared to only 11% of patients with unilateral parametrial induration. The survival rate for patients with bilateral parametrial induration was 27%, compared to 33% for patients with unilateral parametrial induration. The second factor was obstructive uropathy (see table 7). Forty-three percent of patients with obstructive uropathy had para-aortic lymph node metastases, compared to 23% of patients with no obstruction. Fourteen percent of patients with obstructive uropathy are alive and well, compared to 38% of those without obstructive uropathy.

DISCUSSION

The primary value of pretreatment celiotomy in patients with cervical carcinoma is that it enables the physician to individualize the treatment to suit the extent of disease. Postoperatively, patients can be divided into 3 groups:

1) Patients with visceral or scalene lymph node metastases can be treated palliatively or with chemotherapy, and spared the expense and inconvenience of 4 to 5 weeks of daily radiation treatments.

2) Patients with para-aortic lymph node metastases, but without visceral or scalene lymph node metastases, are treated with radiation therapy to the pelvis and para-aortic lymph node bearing areas.

3) Patients with pelvic disease only are treated with standard field pelvic radiation therapy.

Of 30 patients explored, 10 (33%) had their therapy altered on the basis of the surgical findings. The 2 patients with visceral metastases were treated with short courses of pelvic radiation therapy for palliative purposes. We feel these patients were benefited, in that they were spared a full course of pelvic radiation therapy requiring 4 to 5 weeks to complete, as well as 1 or 2 hospital admissions for brachytherapy. A standard course of radiation therapy would not treat the full extent of the disease, and subsequently could not be expected to materially affect the survival of these patients.

Eight patients had para-aortic lymph node metastases without visceral or scalene lymph node metastases. These patients were treated with a full course of pelvic radiation therapy plus external radiation therapy to the para-aortic lymph node bea-

ring area. This group of patients derives the most potential benefit from pretreatment exploration: without benefit of pretreatment laparotomy, these patients would have been treated with pelvic radiation therapy only. In view of the fact that the extent of their disease was clearly beyond the standard pelvic radiation therapy field, there would be no possibility of controlling their disease. Unfortunately, the efficacy of treating patients with positive para-aortic nodes is still low. In our series of patients, one of 8 patients (12.5%) is alive and well 24 months following treatment. The other 7 have all died of disease less than 1 year following initial diagnosis. The group of patients benefiting least from the surgical exploration are those found to have disease confined to the pelvis. This group of patients was treated with a standard course of pelvic radiation therapy. Six of 14 patients (43%) currently are alive and well with no evidence of disease.

There are 2 principal disadvantages to pretreatment celiotomy. The first is operative morbidity and mortality. One patient in our series suffered a fatal pulmonary embolus on postoperative day 4. This patient had clinical stage IVA carcinoma with positive para-aortic lymph nodes. The other postoperative morbidity was minimal, consisting on one pneumonia and 2 urinary tract infections. All responded promptly to antibiotic therapy.

The second potential disadvantage to pretreatment celiotomy is the potential for increased morbidity from radiation therapy following exploratory celiotomy. With any surgical procedure there is the potential for formation of adhesions and the subsequent trapping of small bowel in the radiation therapy field. One patient with clinical stage IIB carcinoma and positive para-aortic lymph nodes developed radiation proctitis requiring a sigmoid colostomy. In view of the fact that the rectosigmoid is relatively fixed in its relationship to the cervix and vagina and therefore to the cervical/vaginal radium or cesium, the development of radiation proctitis cannot be considered a complication of the operative procedure. The second patient with radiation induced morbidity initially had a small bowel obstruction at the ileocecal junction. This portion of the bowel is similarly fixed in position prior to exploratory celiotomy and, in our opinion, this complication cannot be attributed to the pretreatment celiotomy. This same patient went on to develop vaginal vault necrosis with formation of a rectovaginal fistula and bilateral ureteral obstruction, necessitating a total pelvic exenteration. This, again, cannot be attributed to pretreatment celiotomy. Therefore, in our series of patients, we could find no increase in radiation induced morbidity following exploratory celiotomy.

Another potential disadvantage of pretreatment celiotomy is the delay in initiating radiation therapy necessitated by the surgical procedure. In our experience the mean interval from surgery until initiation of radiation therapy was 9 days, an inconsequential delay considering the natural history of the disease.

These data enable us to draw 3 conclusions:

First, therapy will be altered in approximately one-third of patients because of findings at exploratory celiotomy and para-aortic lymphadenectomy. The majority of patients whose therapy is altered will have para-aortic lymph node metastases and will require para-aortic as well as pelvic radiation therapy. A small percentage of patients will be found to have visceral or scalene lymph node metastases and can be spared the usual course of pelvic radiation therapy.

Second, para-aortic lymph node metastases are associated with a high mortality rate (87.5%). However, in the absence of pretreatment celiotomy, metastases at

this site are associated with a mortality rate of 100%.

Third, there was no demonstrable increase in radiation induced morbidity following exploratory celiotomy in our patients. The principal cause of morbidity and mortality was failure to control the primary disease. The radiation induced morbidity that was encountered was confined to 2 patients, and in neither of these patients could the morbidity be attributed to the pretreatment celiotomy.

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ANTIEMETIC COMBINATION FOR PAC (CISPLATIN - ADRIAMYCIN - CYCLOPHOSPHAMIDE) CHEMOTHERAPY-INDUCED EMESIS IN OVARIAN CANCER

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Summary: Twenty-six patients suffering from disseminated epithelial ovarian cancer (FIGO stages III and IV) under treatment with Cisplatin (80-100 mg/m² in 8 hours) in combination on the same day with Cyclophosphamide (500 mg/m² IV) and Adriamycin (50 mg/m²), a severely emetogenic regimen, entered a randomized, double-blind, cross-over trial comparing the antiemetic activity of high-dose IV Metoclopramide (1 mg/kg/dose × 5 doses) with that of a combination of Metoclopramide (same schedule) plus Nortriptyline (50 mg PO × 2 doses) plus Thiethylperazine (10 mg IV × 3 doses). The antiemetic combination was designed in an attempt to act simultaneously on gastrointestinal motility and neuroreceptors at the central emetic pathways (dopamine D-2, histamine H-1 and muscarinic cholinergic). This combination significantly reduced the emesis due to chemotherapy when compared with Metoclopramide alone and was also preferred by a significant number of patients after passing through both the antiemetic arms being compared.

Key words: Chemotherapy - induced emesis. Combination antiemetics.

INTRODUCTION

PAC combination (Cisplatin 80-100 mg/m², Adriamycin 50 mg/m², Cyclophosphamide 500 mg/m², IV), frequently used for the treatment of disseminated epithelial ovarian carcinoma, is probably the most emetogenic regimen among those commonly used for the treatment of solid tumors.

High-dose intravenous Metoclopramide has been shown to be an efficacious antiemetic therapy for Cisplatin-induced vomi-

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