Chemotherapy for Lymphatic Metastatic Gynecologic Cancer via Pelvic Retroperitoneal Cannulation: A Preliminary Report

CAO ZEYI, M.D., YOU ZONGBING, M.D., ZHOU SHIYING, M.D., PENG ZHILAN, M.D., WANG JINGHUA, M.D., AND LI PEIYI, M.D.

Department of Obstetrics and Gynecology, Second Affiliated Hospital, West-China University of Medical Sciences, Chengdu, Sichuan 610044, People’s Republic of China

Received April 25, 1995

INTRODUCTION

The high incidence of metastasis via lymphatic passage is a chief factor affecting the postoperative recurrence and prognosis of gynecologic cancers. Despite improvements in operative procedures as well as radiochemotherapies, the treatment of lymphatic metastasis of gynecologic malignancies is still the major concern of gynecologists worldwide [1, 2]. In this paper we present the preliminary results of clinical study on the feasibility of chemotherapy via pelvic retroperitoneal route and its efficacy on lymphatic metastatic gynecologic malignancies. This protocol was evaluated and approved by the Institutional Review Board of West-China University of Medical Sciences.

SUBJECTS AND METHODS

Subjects of study. Twenty-five patients with malignant tumor were admitted to our department from April 1993 to March 1994. They were 28–67 years of age (average 50), and their body weight varied from 40 to 79 kg (mean 55 kg). Of the 25 patients, 4 had cervical carcinoma, 13 endometrial carcinoma, 6 ovarian carcinoma, 1 vulval carcinoma, and 1 cervical squamous cell carcinoma associated with highly differentiated endometrial adenocarcinoma. All had been confirmed pathologically and had not received any form of radio- or chemotherapy. Blood and urine analyses, liver and kidney tests, EKG, and chest X-ray examinations revealed nothing abnormal. All patients signed informed consent prior to being included in this study.

Procedure of pelvic retroperitoneal infusion. The patient lying flat received a puncture perpendicularly at 1.5 to 2.0 cm, under local anesthesia, inside the superoanterior iliac spine, with an extradural cannula (No. 18), going through the skin, subepidermis, the muscular layer and between it, and the abdominal fascia transversalis, toward the retroperitoneal space, where a sudden feeling of loss was felt. The stylet was taken out and 5 ml of saline was injected to separate the fasia transversalis from the peritoneum, allowing further advance of the cannula. The stylet was reinserted and the cannula was turned slightly toward the caudal end and pushed in at an angle parallel to the iliac fossa plane, for another 8 cm, adjacent to the upper external iliac artery. If no blood came out on withdrawal of the stylet, and the position of the puncture proved correct, the cannula was advanced to the 10- to 12-cm mark and its patency was tested by the injection 2 ml of saline. Then the stylet was taken away, leaving the cannula in place by suturing it to the skin (Fig. 1).

Seven of the 25 patients had bilateral cannulations, each infused with 10 ml Isovist-300 plus 40 ml of saline to demonstrate the extent of drug distribution. Seventeen had unilateral cannulation with infusion of 500 mg 5-FU in 20 ml mixed with 10 ml Isovist-300 and 20 ml saline (infusion side, N = 17), while the contralateral side without infusion...
served as control (control side, \( N = 17 \)). Another patient who had had no infusion was used as control. Five patients had cannula retained for further infusion. 5-FU is a product of Haipu Pharmaceutical Factory, Shanghai, China. Isovist-300 is a radiopaque contrast medium from Shering Co., Germany.

Ascertainment by regional X-ray films. Anterior pelvic X-ray films were taken immediately after each infusion to verify the exact extent of distribution and to compare the difference between the first infusion and the subsequent infusions through the retained cannulae.

Pathologic examination of lymph nodes. Extirpation of the pelvic lymph nodes was performed in the 25 patients respectively 1, 2, 4, 6, 8, 12, 34, 36, 48, and 72 hr after the infusion of drugs, starting from the paraaortic and then the common iliac, external iliac, internal iliac, and deep inguinal up to the obturator foramen groups on both sides. The surrounding tissues were carefully trimmed off and the nodes were bisected along the efferent lymphoduct. Half of each node was fixed with Formalin. Metastasized cancer cells were searched for microscopically in the lymph nodes, and the effects of the chemicals were evaluated.

5-FU concentration assay in lymph nodes. The remaining half of the lymph node was dried with blotting paper, weighed, and pounded into a homogenate for volume measurement. Five milliliters of each lymph homogenate was stored in a test tube for assay. Three milliliters of peripheral venous blood was drawn from each of six patients in 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hr after drug administration. Following centrifugation, 1.5 ml of the plasm was kept under −32°C for assay.

High-performance liquid chromatography was employed to measure the concentration of 5-FU in the lymphatic homogenate and plasma. Homogenate (0.2 ml) or plasma was mixed with 0.1 ml redistilled water and 2 ml ethyl acetate, whirled and quenched for 10 min, and then centrifuged at 2800 rpm for 10 min. The supernatant was drawn at desired amounts into test tubes with a V-shaped bottom and desiccated by evaporation under air current in a 50°C water bath. The residue was dissolved at 30 µl flowing phase. Twenty microliters was taken as sample. The peak-height chromatographic peak height, which was analyzed by linear regression against the drug concentration. A standard curve was thus drawn.

\[
C \text{(5-FU concentration)} = \frac{C \text{(sample concentration of 5-FU)}}{G \text{(weight of lymph node)}} \times V \text{(volume of homogenate)}
\]

Formation of standard curve. Standard 5-FU (0.1 ml) and 0.1 ml quantitated water solvent were added into nonmediated human lymphatic homogenate in 8 standard concentrations ranging from 0.06 to 7.68 µg/ml. An additional 2 ml ethyl acetate was given as stated above. Twenty microliters was taken from each sample for reading of the chromatographic peak height, which was analyzed by linear regression against the drug concentration. A standard curve was thus drawn.

Statistical analysis. Normal distribution, Student’s \( t \) test, correlation \( t \) test, and Wilcoxon paired signal test were used to check the results between the experimental and control groups.

RESULTS

Extent of drug distribution. X-ray film was taken right after drug infusion to determine the extent of drug dissolution. The results exhibited that the external iliac, internal iliac,
obturateur, and deep inguinal and most of the common iliac group of lymph nodes were all within the field of drug distribution (Fig. 2). The extent of drug distribution following repeated drug infusions through the cannulae was the same as that of the first infusion.

5-FU concentration in lymph nodes and blood plasma. The average 5-FU concentrations in the submerged side in comparison to the control side are shown in the Table 1. The paired data t test showed that the concentration in the drug-submerged side 48 hr later was higher than that in the control side \( P < 0.01 \). The 5-FU concentration in the paraaortic lymph nodes was between the submerged and the control sides. Seventy-two hours after the infusion, there was no significant difference between the two sides.

The 5-FU concentration in blood plasma was 0.3 \( \mu g/g \) after 0.5 hr and was undetectable 12 hr after drug infusion.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>After drug infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Infusion side</td>
<td>17.3</td>
</tr>
<tr>
<td>Control side</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Pathological findings in lymph nodes. No metastasis in
the paraaortic lymph nodes was seen in the 25 patients but
positive cancer cells were noted in the pelvic lymph nodes
of 7 patients (28%), of whom 3 had bilateral metastasis. Of
the patients with one side submerged in drug, 4 had most
metastatic cells showing evident degeneration and necrosis
within the lymph nodes (except the case having lymphade-
nectomy 1 hr after infusion) (Fig. 3). Neither evident degen-
eration nor necrosis was seen in the metastatic cancer cells
in the lymph nodes in the controls.

Complications and systemic toxic effect. No serious dis-
comfort and complication occurred except for mild dis-
tending pain at the site of the drug infusion. GOG criteria
[3] were employed to assess the presence of systemic toxic
effect but no untoward reaction from the gastrointestinal
tract, skin, and other systems was noted in patients receiving
the pelvic retroperitoneal drug infusion. Blood counts before
and 7–10 days after drug administration gave no significant
difference among hemoglobin, WBC, and platelet counts
(Table 2).

DISCUSSION

We have injected drug through the lymphoduct by opening
up the tissues on the inner aspect of the thigh to improve
the result of chemotherapy of gynecologic tumors, but were
forced to stop owing to a high failure rate caused by the
difficulty in penetrating and fixing the needle to the lymph
nodes deep in these locations. We also failed to inject emulsi-
fied chemicals through the lymphoduct on the dorsum of
foot because the emulsion was too thick to overcome the

| TABLE 2 | Blood Counts before and 7-10 Days after 5-FU Administration (N = 17) |
|----------------|------------------|------------------|------------------|------------------|
|               | Before           | After            | P                |
| Hemoglobin (g/liter) | 107.1 ± 0.2      | 105.2 ± 0.2      | >0.05            |
| WBC (10⁹ liter)     | 5.7 ± 0.2        | 6.6 ± 0.1        | >0.05            |
| Platelet (10⁹/liter)| 106.6 ± 4.0      | 111.1 ± 4.6      | >0.05            |
resistance of the lymph duct in diameter of 0.5–0.75 mm, resulting in lymphogenous embolism, disrupting, and inflammatory reaction. Hence, we selected the retroperitoneal space for drug infusion by inserting a cannula.

Cannulation through puncturing into the pelvic retroperitoneal space. A point 1.5–2.0 cm inside the superoanterior iliac spine was chosen for puncturing. The reasons for this are as follows: first, there is a clear landmark—superoanterior iliac spine; second, there is a potential cleavage in between the anterobdominal peritoneum reverting posteriorly to the obturator peritoneum and the fascia transversalis turning onto the fascia iliaeca, allowing the needle to go into the iliac fossa without intruding the abdominal cavity; and third, there is no large blood vessel and important organ involved in the penetration route; thus safety is secured. The course of the cannulation from the puncturing point inside the superoanterior iliac spine goes through the skin, subepidermal tissue, muscular wall, along the fascia transversalis up to the iliac fossa, and then along the retroperitoneal cleavage to the lateral edge of the true pelvic inlet, where the upper external iliac artery branches from the common iliac. The 25 patients received 31 cannulations without complications such as hematoma formation, penetration into the peritoneal cavity, or injury of the abdominal organs. Instrumentations for this procedure are simple (extradural needle and cannula) and the technique is easily managed. For 7 of our patients it took on the average 31 min to finish the bilateral cannulation and for 17 it took 12 min to insert one cannula. The cannula was retained for reinfusion in 5 patients, and there was no shifting of position or obliteration of the lumen. One cannula was retained for as long as 5 days before its removal for operation. Our clinical experience suggested that it was it retainable for about 2 months or more, just as the intraperitoneal cannulation.

Choice of chemicals. The chemicals suitable for tissue injection are 5-FU, MTX, TSPA, etc., of which 5-FU seems to be commonly used and its concentration is easily determined. Isovist-300 is a contrast medium that can be injected into tissues with ideal image density and the lowest toxicity. We mixed the two in animal experiments and found that the mixture infused into the retroperitoneal space without causing degeneration and necrosis of the normal tissue cells in the submerged field, except for slight lymphocytic and neutrophilic infiltration possibly due to operative irritation (data not published).

Extent of drug distribution. X-ray films after drug infusion proved that anticarcinogens infused through pelvic retroperitoneal cannulation were distributed in the external iliac, internal iliac, obturator, and deep inguinal and most of the common iliac lymph nodes, and submerged in chemicals. Although the retroperitoneal space was a potentially distensible space, drug distribution within delimited dosage was fairly even. When 50 ml was used, the extent of distribution was satisfactory and was almost unchanged in the repeated infusions through the retained cannula. It is a way for repeating chemotherapy.

Chemical concentration within the lymph nodes. The concentration of 5-FU in the lymph nodes on the infused side was 2–10 times that on the control side. The half-life of 5-FU was 21.5 hr which favors the destruction of the metastatic cells inside the lymph nodes [4, 5]. Some 5-FU in the lymph nodes on the control side probably came from the lymphatic drainage of the drug infused on the opposite side, since communicating branches existed in front of the sacrum. The 5-FU concentration in the paraaortic lymph nodes was between the concentration of the infused side and that of the control side, likely due to upward dispersion of the chemicals infused. The concentration would further increase if both sides were infused.

The plasma 5-FU concentration–time curve after pelvic retroperitoneal infusion corresponded well with that of the biventricular open model and was similar to that of the intravenous medication reported. This fulfilled the expectation of high efficacy and low toxicity from chemotherapy [6].

Pathologic changes in lymph node metastatic cells after drug infusion. It is difficult and costly to ascertain the presence or the side of metastasis in lymph nodes. We randomly divided the trial and control groups. In our series, three of four patients with unilateral metastasis had been grouped as controls and did not show degenerative change and necrosis in the metastatic cells of the lymph node. Another three patients with bilateral metastasis to the lymph nodes presented marked degeneration and necrosis of metastatic cells of the nodes. No such phenomenon in the controls indicated the direct effect of the chemical on the metastatic cells of the regional nodes after pelvic retroperitoneal infusion [7–10]. No degeneration or necrosis in the normal tissues around the lymph nodes with or without metastasis of cancer cells suggested a good tolerance of the normal tissue to the given drug.

Complication and systemic toxic effect. In this series no patient had bleeding, infection, or inflammatory adhesion at the infusion site. 5-FU via pelvic retroperitoneal infusion went slowly into the bloodstream and a small amount was eliminated rapidly ($t_{1/2}$ = $0.27$ hr). Systemic toxic reaction was mild.

Pelvic retroperitoneal chemotherapy is safe and easy to manage; its effectiveness is under evaluation. Whether it is feasible to put in the cannula during operation and retain it for chemotherapy instead of extirpation of lymph nodes or postoperative radiation and at the same time to elevate the survival rate of patients with gynecologic malignancies, already metastasized to the lymphatic system, awaits further research.
REFERENCES


