

Hyperthermic Intraoperative Intraperitoneal Chemotherapy with Cisplatin and Doxorubicin in Patients Who Undergo Cytoreductive Surgery for Peritoneal Carcinomatosis and Sarcomatosis

Phase I Study

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BACKGROUND. Hyperthermic intraperitoneal intraoperative chemotherapy (HIIC) combined with cytoreductive surgery (CS) has been proposed as a new multimodal treatment mainly for carcinomatosis of gastrointestinal origin. To evaluate whether this regimen could be used for other tumor types, the authors conducted a Phase I study on HIIC with doxorubicin and cisplatin in patients with peritoneal carcinomatosis or sarcomatosis.

PATIENTS AND METHODS. Thirty-one patients with peritoneal carcinomatosis or sarcomatosis (PCS) were enrolled for the study. After completion of CS, HIIC was administered with drug doses that were increased for each consecutive cohort following a three-patient cohort scheme. Thereafter, the accrual was stopped when Grade 4 locoregional or systemic toxicity was observed. The maximum tolerated dose (MTD) was considered the dose in the previous triplet. Drug pharmacokinetics and procedure costs also were analyzed.

RESULTS. After CS, residual tumors were not present or measured less than or equal to 3 mm (in dimension) in all cases. Maximum tolerated dose was 15.25 and 43.00 mg L⁻¹ for doxorubicin and cisplatin, respectively. The perfusate/plasma area under the curve ratios were favorable for both drugs, at 162 ± 113 and 20.6 ± 6.0, respectively, for doxorubicin and cisplatin. Doxorubicin levels in the peritoneum were higher than in tumor or normal tissue samples. There were no postoperative deaths. Surgery-related complications were observed in 25% of cases. Findings at cost analysis showed that the length of stay in the operation room and intensive care unit were the major cost drivers.

CONCLUSIONS. Cytoreductive surgery combined with HIIC is an expensive but feasible therapeutic approach for locally advanced abdominal tumors. Because our preliminary findings for local disease control are encouraging, a Phase II study is now advisable to verify the activity of this promising treatment. *Cancer* 2002;94:492-9. © 2002 American Cancer Society.

KEYWORDS: peritoneal carcinomatosis, peritoneal sarcomatosis, cytoreductive surgery, doxorubicin, cisplatin, hyperthermia.

Patients with peritoneal carcinomatosis and sarcomatosis (PCS) have an extremely poor prognosis,¹⁻³ even when the disease is confined within the abdominal cavity, and no standard treatment has been found to increase the survival rate. Systemic chemotherapy, which is followed by different response rates depending on the tumor histologic type, does not affect the natural course of PCS,⁴ whereas

systemic toxicity, the main limitation of this approach occurs before satisfactory intraperitoneal drug concentrations can be achieved. Even when cytoreduction is macroscopically complete, it is hardly ever successful because microscopic residues together with malignant cells spillage during surgical manipulation cause tumor recurrence in almost all patients.⁵

In theory, locoregional chemotherapy has the advantage of enabling high intraperitoneal drug concentrations to be achieved while keeping systemic drug levels low, thus minimizing systemic toxicity.⁶ However, as the intraperitoneal route cannot guarantee adequate drug penetration into large tumors,^{7,8} cytoreductive surgery is the main prerequisite for intraperitoneal chemotherapy. However, this combined treatment has not been found to significantly improve the clinical outcome.^{9–11} As some antineoplastic drugs act synergistically with heat, hyperthermic intraperitoneal antineoplastic perfusion (HIIC) after cytoreductive surgery (CS) has been proposed to maximize antitumor cytotoxic effects. Although the results of some pilot studies on CS combined with HIIC have been encouraging,^{12–17} no reliable conclusions can be drawn because few formal clinical trials have been conducted and the clinical series reported in literature are heterogeneous for histologic type, peritoneal involvement by the disease, extent of CS, drug regimen, HIIC duration, and temperature achieved during perfusion.

Doxorubicin, considered one of the most active antineoplastic drugs available, is widely used for locoregional chemotherapy of various tumor types.^{18,19} As a single drug regimen, it has been administered intraperitoneally in patients with advanced ovarian carcinoma, with a good tumor response but a high local toxicity.²⁰ There is also *in vitro* evidence that its activity is enhanced by the association with cisplatin²¹ and under conditions of hyperthermia.^{22,23} This potential synergism might be exploited to enhance the therapeutic activity of HIIC and to widen the spectrum of tumor types treatable with it.

The current article first reports on the results of our Phase I study on CS combined with HIIC administered doxorubicin-cisplatin in the treatment of patients with PCS from various tumor types potentially sensitive to this treatment. Our main objective was to establish the maximum tolerable dose (MTD) of doxorubicin and cisplatin administered during HIIC in patients with peritoneal carcinomatosis/sarcomatosis who had undergone CS. A further objective was to evaluate the pharmacokinetics of doxorubicin and cisplatin during HIIC, and its costs.

PATIENTS AND METHODS

Patient Selection

Patients were considered eligible for HIIC if they met the following criteria:

1. Histologically confirmed PCS originating from: ovarian carcinoma (not pretreated with anthracyclins), peritoneal mesothelioma, and multiple or recurrent visceral/retroperitoneal sarcoma;
2. After CS residual disease absent or less than or equal to 3 mm
3. Age between 18 and 72 years
4. Satisfactory cardiovascular, respiratory, hepatic and renal functions (ASA score 1–2)
5. Leukocyte greater than or equal to 4000 mm³, platelet count normal
6. Eastern Cooperative Oncology Group performance status 0, 1, or 2.
7. Patient's fully informed consent obtained.

Study Design

On completion of CS, HIIC was performed with doxorubicin and cisplatin for 90 minutes, at a mean intraperitoneal temperature of 42.5 °C. The drugs were administered to triplets of patients in escalating doses, starting with 5 and 20 mg per liter of perfusate for doxorubicin and cisplatin, respectively, with a 25% dose increase for each subsequent triplet. Accrual was stopped when Grade IV locoregional toxicity was observed in one patient: MTD, considered that of the previous triplet, was confirmed after three more patients had been treated uneventfully with the putative MTD. Patients were followed up every 3 months for the first year and then twice a year, a thoracoabdominal computed tomography scan being included each time.

Toxicity Evaluation

Locoregional and systemic toxicity were graded using modified Ozols' criteria²⁰ (Table 1) and the World Health Organization classification, respectively. Toxicity that occurred within 30 days from CS and HIIC was considered treatment-related.

Cytoreductive Surgery

Cytoreductive surgery consisted of tumor bulk resection and peritonectomy procedures together with resection of contiguous structures with tumor spread, such as the gallbladder, the spleen, the stomach, segments of the small or the large bowel, kidney, and uterus. Six different peritonectomy procedures, as described by Sugarbaker,²⁴ were used to treat tumor spread involving visceral or parietal peritoneum.

TABLE 1
Locoregional Toxicity Grading System, Modified from Ozols et al.²⁰

Grade I	Abdominal pain after the third postoperative day requiring analgesic drug administration (NSAID)
	Ileus time on or after third but before fifth postoperative day
Grade II	Abdominal pain after third postoperative day requiring major analgesic drug administration (morphine)
	Ileus time on or after 6th but before 10th postoperative day
Grade III	Abdominal pain resistant to major analgesic drugs
	Ileus time on or after 11th but before 15th postoperative day
Grade IV	Bowel leakage/perforation or persistent ileus requiring reoperation

Adapted from Ozols et al.²⁰

NSAID: nonsteroidal antiinflammatory drug.

HIIC Technique

HIIC was performed after tumor resection but before gastrointestinal tract reconstruction. Two pairs of Jackson Pratt silicon catheters were placed through the abdominal wall in the peritoneal cavity, one above and one below the transverse mesocolon. A Y-shaped joint connected the catheters to each other and to the circuit pump. The perfusate (4–5 L of normal saline solution or peritoneal dialysis solution) was forced through the catheters by a peristaltic roller pump, to obtain a flow rate of 500–1000 mL/minute. A heat exchanger warmed the perfusate to 43–46 °C. Thermal probes were placed intraperitoneally and along the circuit to monitor perfusate temperature during the procedure. We performed HIIC according to either the “closed”²⁵ or the “open” technique, the latter using a peritoneal cavity expander as reported by Fujimura et al.,²⁶ that allows the surgeon to gently but continuously manipulate the viscera to enhance drug diffusion within the abdominal cavity. Drugs were bolus-injected into the circuit once an intraperitoneal temperature of 41.5 °C had been reached. A temperature of from 41 and 42.5 °C was maintained throughout perfusion, after which the perfusate was drained from the abdomen.

Pharmacokinetic Study

Samples of perfusate and blood for pharmacokinetic analysis were obtained at 0, 15, 30, 45, 60, 75, and 90 minutes. The data were modeled by using the Graph-Pad Prism (version 2.0) software. In all cases, the best fit was obtained using a biexponential equation. Areas under the concentration time curves from 0 to 90 min (AUC_{0-90}) were calculated from the coefficients and exponents of the best fitting equations. Drug clearance from the perfusion fluid was calculated as the ratio of the amount of drug eliminated from the perfusate during the 90 minutes HIIC to the corresponding AUC. Terminal half-life ($t_{1/2}$) was calculated as

$0.693/\beta$, where β is the rate constant of the terminal decay phase. The peak concentration (C_{max}) and the time of its occurrence (t_{max}) were the observed values. Student two-tailed t test was used for comparison of pharmacokinetic parameters, with the exception of t_{max} , for which the nonparametric Kruskal–Wallis test was used. Probability values of less than 0.05 were considered statistically significant.

Samples of normal and pathologic tissues were obtained before and after perfusion. Plasma, perfusate, and tissue doxorubicin concentrations were assessed by means of high performance liquid chromatography performed by a reverse-phase C-18 DB column (Beckman Instruments), whereas cisplatin plasma and perfusate levels were assayed using the Atomic Absorption technique (Perkin-Elmer, Oak Brook, IL).

The limits of detection and coefficients of variation of the above assays were previously reported.^{27,28}

Cost Analysis

Cost analysis was assessed according to the Activity Based Costing system, a widely used methodology that measures cost and performance of activities, resources, and cost objects, assigns resources to activities and activities to cost objects based on their use and recognizes causal relations between of cost drivers and activities. This system processes financial and operating data on the basis of resources, activities, cost objects, cost drivers, and activity performance measures and assigns cost to activities and cost objects.²⁹

RESULTS

From June 1997 through December 1999, 31 patients (15 females, 16 males) who met the above eligibility criteria were enrolled and submitted to CS and HIIC with doxorubicin and cisplatin. The mean age was 50.1 years (range, 21–74). Tumor histology was liposarcoma ($n = 9$), leiomyosarcoma ($n = 6$), other soft tissue sarcomas ($n = 4$), ovarian carcinoma ($n = 6$), and malignant mesothelioma ($n = 6$).

Before surgery, six patients underwent systemic chemotherapy, three radiotherapy, two radiotherapy and chemotherapy, whereas the other 20 had no preoperative therapy. Cytoreductive surgery consisted of total ($n = 2$) and partial ($n = 9$) peritonectomy, bowel resection ($n = 14$), splenectomy ($n = 3$), and nephrectomy ($n = 5$). In all cases, HIIC was performed for 90 minutes, the intraperitoneal mean temperature being 41.7 °C (range, 39.8–42.6).

Grade I locoregional toxicity was observed in five cases, and Grades II and III in three cases, respectively. One patient treated with 19 mg L⁻¹ of doxorubicin

TABLE 2
Study Design and Acute Locoregional and Systemic Toxicity Observed

Triplet ^a	DXR ^b	CDDP ^b	Toxicity ^a (grade)
I	5	20	1 anemia (I) 1 ileus (I)
II	6.25	20	—
III	6.25	25	1 anemia (I)
IV	7.81	25	1 anemia (I) 1 ileus (I)
V	7.81	31.25	—
VI	9.76	31.25	2 fever (2)
VIII	12.2	39.10	1 anemia (2) 1 fever 1 ileus (II)
IX	15.25	39.10	—
X	15.25	43	2 ileus (I)
XI	19	43	1 ileus (IV)
XII	15.25 ^c	43 ^c	2 ileus (II)

DXR: doxorubicin; CDDP: cisplatin.

^a Acute toxicity was considered that occurring within 30 days from hyperthermic intraoperative intraperitoneal chemotherapy. Locoregional and systemic toxicity were graded according to the modified Ozols system (Table 1) and the World Health Organization criteria, respectively.^b Milligram per liter of perfusate.^c Maximum tolerated drug dose.

bicin and 43 mg L⁻¹ of cisplatin experienced Grade IV locoregional toxicity (persistent ileus) and required reoperation and adhesiolysis. To confirm that MTD had been reached, we treated three more patients with the previous triplet drug dosages. Because no significant locoregional toxicity was observed, MTD was established at 15.25 mg L⁻¹ of doxorubicin and 43 mg L⁻¹ of cisplatin.

Regarding systemic toxicity, Grades 1 and 2 hematologic toxicity (anemia) and persistent fever were recorded in four and three patients, respectively (Table 2). There were no postoperative deaths. Postoperative complications consisted of septicemia ($n = 3$), anastomotic fistula ($n = 2$), segmental bowel infarction that required reoperation ($n = 2$), and pneumothorax ($n = 1$).

The average intensive care unit stay was 5.5 days (range, 3–12), whereas the average overall hospital stay was 17.8 days (range, 12–45).

After a median follow-up of 19.2 months (range, 13–31), 9 (29%) patients died of disease and 3 (10%) of other causes (1 of myocardial infarction, 1 of pulmonary embolism, and 1 of multiple injuries reported in a car accident). Eleven (35%) patients were disease free at the time of writing this article, whereas 8 (26%) were alive with disease. Eight (26%) patients developed local recurrence. Four (13%) patients developed distant metastasis, two liver metastasis, one cerebral metastasis, and one pulmonary metastasis. In one pa-

TABLE 3
Mean \pm Standard Deviation Values of Pharmacokinetic Parameters of DXR and CDDP

Parameter	DXR		CDDP	
	Perfusate	Plasma	Perfusate	Plasma
AUC ₀₋₉₀ ($\mu\text{g mL}^{-1} \text{min}^{-1}$)	372 \pm 260	4.1 \pm 6.0	1581 \pm 425	76.8 \pm 7.5
AUC _{perf} /AUC _{pl}		162 \pm 113		20 \pm 6
C _{max} ($\mu\text{g mL}^{-1}$)	8.8 \pm 4.0	0.17 \pm 0.30	38.3 \pm 5.2	1.0 \pm 0.1
C _{max perf} /C _{max pl}		249 \pm 147		36 \pm 5 ^a
t _{max} (min)	0 (0–0) ^b	45 (15–60) ^b	0 (0–0) ^b	60 (30–60) ^b
t 1/2 (min)		87 \pm 48		80 \pm 26
Cl (mL/min^{-1})		111 \pm 87		99 \pm 42

AUC₀₋₉₀: area under the plasma concentration time curve between 0 and 90 min in perfusate (AUC_{perf}) or plasma (AUC_{pl}); C_{max}: peak concentration; t_{max}: time at which C_{max} was reached; t 1/2: half-life of the terminal decay phase; Cl: clearance from the perfusion fluid; DXR: doxorubicin; CDDP: cisplatin.^a $P < 0.05$ vs. the corresponding value for DXR.^b Median value (range).

tient, liver metastases were detected during follow-up, and radical resection was performed. Sixteen months after metastasectomy, this patient was disease free.

The findings for pharmacokinetics are reported in Table 3. Data for doxorubicin were obtained from 13 patients treated with 5–19 mg L⁻¹ doxorubicin, whereas data for cisplatin were obtained from 4 patients treated with 31–44 mg L⁻¹ cisplatin. As shown in Table 3, it was evident that the ratio between AUC₀₋₉₀ values in perfusate and plasma was one order magnitude greater for doxorubicin. In particular, apart from one case in which AUC₀₋₉₀ perfusate/plasma ratio was 37, the value of this parameter for doxorubicin was always greater than 100. Conversely, the same ratio calculated for cisplatin ranged from 13 to 25, in agreement with the results previously obtained by Cho et al.³⁰ Quite analogous considerations can be made on C_{max}. No significant differences were observed between the two drugs as far as other pharmacokinetics parameters were concerned. These results are illustrated in Figure 1, which clearly shows how similar perfusate concentrations of doxorubicin and cisplatin gave very different plasma concentrations, doxorubicin levels being roughly 50-fold lower.

The mean doxorubicin tissue concentration was 6.01 \pm 1.89 μgg^{-1} in tumor samples, 23.11 \pm 11.62 μgg^{-1} in peritoneum, 6.21 \pm 6.04 μgg^{-1} in muscle, and 9.75 \pm 7.34 μgg^{-1} in fat tissue.

Cost analysis results are reported in Table 4. The estimated cost of the entire procedure was 17,550 Euros. The costs were almost totally attributable to the operating room costs (5000 Euros) and the stay in the intensive care unit (10,000 Euros).

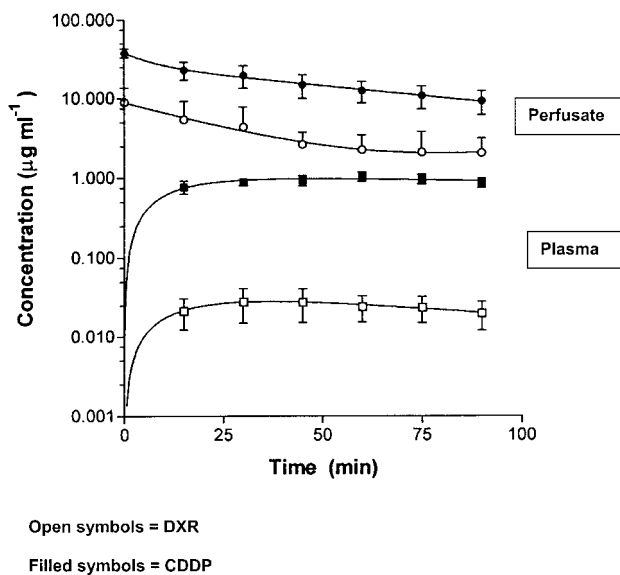


FIGURE 1. Time courses of the mean concentrations of doxorubicin and cisplatin in perfusate and plasma. Solid lines obtained by nonlinear least squares regression analysis of data. Open symbols, doxorubicin (DXR); filled symbols, cisplatin (CDDP).

TABLE 4
Cost Analysis

Phase	Cost (Euros)	Percentage
Diagnosis	500	3
Preoperative hospital stay	250	1.4
Operating room	5000	29
Intensive care unit	10,000	56
Postoperative hospital stay	1700	10
Follow-up (first month)	100	0.6
Totals	17,550	100

DISCUSSION

Abdominal adenocarcinomas and soft tissue sarcomas have a high incidence of peritoneal seeding, during their natural history, which may be because of cell exfoliation from the primary tumor and/or malignant cell spillage during surgery,³¹ leading to PCS, the most frequent cause of death in patients with abdominal tumors.^{32,33} The overall prognosis of PCS is extremely poor, the median survival ranging from 2.3 to 8.8 months.¹⁻³

The growth of some of the tumors is confined to the peritoneal cavity without there being a tendency to develop distant metastases. The "metastatic inefficiency" of these tumors therefore might be exploited for treatment.³⁴ In fact, the clinical outcome of a subset of these patients has been shown to be mainly related to local disease control.³

Surgery alone for PCS can never be assumed ad-

equate, because it can only reduce the tumor mass. Effective complementary treatment therefore is required to eliminate minimal tumor residues. However, as yet none of complementary treatments proposed, such as systemic or intraperitoneal chemotherapy, has been found to significantly improve the results of CS results.³⁵⁻³⁷

Because it is well known that heat synergistically enhances the antitumor effects of several antitumor agents,³⁸⁻⁴⁷ HIIC has been proposed to implement and improve the therapeutic advantage of locoregional chemotherapy, allowing high drug concentrations to be reached at the tumor site while maintaining low systemic toxicity. Various tumor types (gastrointestinal tract tumors) and various drugs (mainly mitomycin C and cisplatin) have been tested with this approach.⁴⁸⁻⁵⁶ Although the results have been encouraging, several technical aspects are still controversial, and consensus as to clinical outcome has not yet been achieved.

To standardize the HIIC technique and to extend its use to tumor types other than those of gastrointestinal origin, we conducted a Phase I study using doxorubicin and cisplatin.

Doxorubicin has several properties making it, in theory, suitable for intraperitoneal administration, including 1) the clinically proved activity against several tumor types which commonly spread to the peritoneum (e.g., ovarian carcinoma, mesothelioma, and soft tissue sarcoma)^{57,58}; 2) a favorable plasma/peritoneal ratio³⁷; 3) a high molecular weight, which allows clearance to be more rapid through normal tissue than through tumor capillary vessels.^{20,59}

The activity of doxorubicin is also synergistically enhanced by heat and cisplatin, thus favoring its use in combination drug regimen under hyperthermic conditions. Our working hypothesis therefore was to administer combined doxorubicin-cisplatin through HIIC to achieve the same antitumor effect at lower doxorubicin dosages, thus reducing the locoregional toxicity typical of this anthracycline.

As we expected in view of Ozols' experience,²⁰ MTD was determined by the locoregional toxicity leading to a chemical peritonitis complication (ileus from adhesions) requiring reoperation 1 month after HIIC. In other Phase I trials dealing with cisplatin based HIIC,⁶⁰ MTD was determined by systemic toxicity. Because we stopped patient accrual before observing significant systemic side effects, we believe that in our study the MTD for cisplatin was not reached. However, the cisplatin perfusate peak concentration ($38 \mu\text{g mL}^{-1}$) reached at the MTD defined is comparable to that considered effective *in vitro*,⁶⁰ thus

indicating the potential cytotoxicity of this drug regimen.

The low incidence of systemic toxicity observed by us is consistent with the low plasma concentrations of both doxorubicin and cisplatin during HIIC. The locoregional administration appears particularly advantageous for doxorubicin, plasma concentrations being 200 times lower than in perfusate. Plasmatic doxorubicin levels were also much lower than those in tumor and peritoneal samples. This pharmacokinetic behavior may be explained on the basis of the high molecular weight (580) and low lipophilic characteristics of doxorubicin, which prevent it from crossing the peritoneal–plasma barrier, as postulated by Jacquet and Sugarbaker.⁶¹

These conclusions also are supported by the results obtained by Nicoletto et al.⁶² with mitoxantrone, an antiproliferative agent structurally related to doxorubicin, but much more lipophilic. Using a similar HIIC technique, these authors obtained mean perfusate/plasma AUC ratio five times lower than that here observed with doxorubicin.

The amount of drug cleared from the perfusion fluid during 90 HIIC was $73 \pm 20\%$ and $76 \pm 7\%$ for doxorubicin and cisplatin, respectively. Thus, considering the length of the terminal half-lives of the two drugs in the perfusion fluid (Table 3), it can be concluded that prolonging the perfusion time would produce a small increase of the amount of the drug cleared and, as a consequence, a modest gain in drug uptake by tissues.

With respect to results reported by authors after HIIC,^{12,13} our results are encouraging, with no deaths and a 25% incidence of surgery-related complications, thus confirming the feasibility of this complex treatment.

At costs analysis, the procedure was found to be costly. The greatest burden, however, was linked to the length of stay in the intensive care unit (56%) and operating room costs (29%). Although it is difficult to reduce the latter, the former might be curtailed by means of improving patient selection. This could be achieved by excluding patients who have undergone multiple cycles of chemotherapy.

Although this is only a Phase I study, our findings for local disease control, with a 35% of disease free rate, are encouraging. However, the short-term follow-up and the heterogeneity of drug dosages and tumor types preclude definitive conclusions. However, the findings made in our pharmacokinetic study confirm the potential efficacy of the treatment as the doxorubicin perfusate concentration reached with the MTD (15.25 mg L^{-1}) was 1.5-fold that considered active in vitro under normothermic conditions and with-

out the addition of cisplatin.⁶³ Furthermore, the doxorubicin concentration reached during HIIC was higher in the peritoneum, which can be contaminated by microscopic disease, than in tumor and normal tissue samples. These findings confirm that there is a peritoneal–plasma barrier and that doxorubicin can be delivered favorably within the peritoneum, with a low systemic toxicity.

Hyperthermic intraperitoneal intraoperative chemotherapy after CS seems a feasible multimodal approach for patients with PCS, which is fatal in the short-term. Further contributions are required in the attempt to standardize this complex procedure, thus allowing the assessment of its potential activity. Now that the MTD of doxorubicin combined with cisplatin has been determined, a Phase II trial is warranted to evaluate the activity of HIIC in a homogeneous and selected group of patients.

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