ONLINE FIRST

Initial Experience With Hyperthermic Intraperitoneal Chemotherapy

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Background: Until 2004, we treated peritoneal carcinomatosis with cytoreductive surgery accompanied by perioperative systemic chemotherapy. From October 2004, we decided to initiate a hyperthermic intraperitoneal chemotherapy (HIPEC) program for this condition.

Objective: To determine the effect of HIPEC on postoperative outcomes at a single institution performing a high volume of cancer operations.

Method: Sixty consecutive patients underwent cytoreductive surgery plus HIPEC (oxaliplatin; 460 mg/m^2 in 2 L/m^2) from October 1, 2004, through December 31, 2010. Usual perioperative factors were studied for 3 groups of patients who underwent HIPEC: 0 to 20 HIPEC procedures (period 1), 21 to 40 HIPEC procedures (period 2), and 41 to 60 HIPEC procedures (period 3).

Results: The mean peritoneal carcinomatosis index was 9.6, the mean duration of surgery was 410.7 minutes, and the mean blood loss was 450.2 mL/L. Mortality and morbidity were 0% and 33%, respectively. Grade III/IV morbidity ($P=.02$), transfusion ($P<.01$), and reintervention rate ($P=.04$) significantly decreased during the 3 periods. No difference was seen between the 3 periods with regard to mean peritoneal carcinomatosis index, operative duration, blood loss, mortality, overall morbidity, length of hospital stay, and readmission. The overall 1-, 3-, and 5-year survival rates of 26 patients with peritoneal carcinomatosis originating from colorectal cancer were 100%, 51%, and 37%, respectively. The overall median survival was 39 months.

Conclusions: We observed a significant reduction of grade III/IV morbidity, perioperative transfusion, and reintervention rate after 20 procedures. The introduction of the HIPEC program was successful because of the surgical team's prior experience in cytoreductive and cancer operations.

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PERITONEAL CARCINOMATOSIS (PC) originating from digestive or ovarian malignant tumors is ideally treated by cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC). Several studies[1-11] have demonstrated that this is an effective and safe technique that has been used in numerous cancer centers. However, HIPEC is a complex procedure with directly related morbidity and mortality.[12] Thus, many institutions are hesitant to initiate the HIPEC program because of the need of specific instrumentation,[13] such as a heating circuit that requires a specific pump and close monitoring of intra-abdominal temperatures, and the likelihood of a poor postoperative course.

See Invited Critique at end of article

Our institute is a comprehensive cancer center that performs a high volume of oncologic operations. Until 2004, PC originating from colorectal or ovarian cancer was treated with cytoreductive surgery, according to the guidelines by Sugarbaker,[14] accompanied by perioperative systemic chemotherapy. According to indisputable reports of the positive effect of HIPEC on survival,[1-11] we decided to initiate a HIPEC program in 2004. However, combining a well-controlled cytoreductive surgery with the newest HIPEC might impair the postoperative course of patients undergoing laparotomy for PC. The aim of this study was to determine the effect of the HIPEC program on postoperative clinical outcomes in patients undergoing cytoreductive surgery at a single medical institution performing a high volume of oncologic surgical procedures.

METHODS

Seventy-eight consecutive patients underwent explorative laparotomy for PC at the Institut Paoli-Calmettes from October 1, 2004,

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Table 1. Characteristics of 60 Patients Who Underwent Cytoreduction Surgery Plus HIPEC

Characteristic	Value
Age, mean (SD), y	52.1 (11.6)
Sex, No.	
Male	20
Female	40
Primary tumor site, No. (%)	
Colorectal	26 (43)
Ovary	12 (20)
Appendix	10 (17)
Pseudomyxoma/mesothelioma	10 (17)
Other	2 (3)
No. of lines of chemotherapy before HIPEC	
Mean (SD)	1.5 (0.9)
No. (%)	
0	7 (13)
1	22 (37)
2	23 (38)
≥3	8 (13)
No. of cycles of chemotherapy before HIPEC, mean (SD)	7.6 (4.9)
Adjuvant chemotherapy, No. (%)	37 (62)

Abbreviation: HIPEC, hyperthermic intraperitoneal chemotherapy.

through December 31, 2010. According to the intraperitoneal findings, 60 patients (77%) underwent cytoreductive surgery followed by HIPEC. All patient data were prospectively entered into a clinical database approved by the institutional review board. All patients had asymptomatic PC, no extra-abdominal malignancy, an Eastern Cooperative Oncology Group performance status of 0 or 1, age younger than 70 years, no malnutrition (ie, <10% weight loss 3 months before surgery), and serum albumin level greater than 20.0 g/dL (to convert to grams per liter, multiply by 10).

SURGERY AND HIPEC

Surgery was performed through a median incision. Careful examination of the peritoneal cavity was possible after complete liberation of the digestive tract. The PC index (PCI) was used to classify the extension of PC. Resection of PC was achieved according to the guidelines by Sugarbaker.[14] Completeness of cancer resection (CCR) by cytoreductive surgery was assessed by the surgeon at the end of the procedure and classified into 3 categories: CCR-0, no macroscopic residual cancer; CCR-1, no residual nodule greater than 5 mm in diameter; and CCR-2, every residual nodule greater than 5 mm in diameter. The consensus statement issued by the Peritoneal Surface Oncology Group International after the 2006 meeting in Milan concluded that the debate on the best method to deliver HIPEC is still open, and there is no sufficient evidence in the literature confirming the superiority of one technique or drug over the other in terms of outcome, morbidity, and safety to the personnel in the operating room.[13] Thus, after cytoreduction surgery, at a mean temperature of 43°C for 30 minutes, an "open" HIPEC technique (the Coliseum technique) was performed intraperitoneally with administration of oxaliplatin (460 mg/m^2 in 2 L/m^2 of dextrose). Before the initiation of HIPEC, all patients were given a 1-hour infusion of intravenous fluorouracil (400 mg/m^2) and leucovorin calcium (20 mg/m^2) to potentiate oxaliplatin activity. In case of digestive resection, anastomosis was performed after evacuation of intraperitoneal chemotherapy. A nonaspirative drain was placed in the pelvic cavity.

STUDY VARIABLES

The evaluated variables included age, sex, primary tumor site, perioperative chemotherapy, PCI, digestive resection, associated resection (spleen, liver, and urinary tract), operative duration (in minutes), intraoperative blood loss (in milliliters), morbidity according to the Clavien-Dindo classification,[15] mortality (30 days after surgery or before hospital discharge), length of hospital stay (in days), and readmission 30 days after hospital discharge. We separately evaluated the intraoperative criteria and postoperative course for the 3 groups of patients who underwent HIPEC: 0 to 20 HIPEC procedures (period 1), 21 to 40 HIPEC procedures (period 2), and 41 to 60 HIPEC procedures (period 3). The thoroughness or quality of resection for PC is difficult to analyze. As a surrogate marker, quality was assessed by evaluating the survival of patients who received HIPEC for PC originating from colorectal cancer.

STATISTICAL ANALYSIS

Data analysis was conducted with GraphPad Prism 5.0d (GraphPad Software, Inc) and Excel 2008 (Microsoft) software. Survival was measured from the time of HIPEC until death or the last known follow-up (censor date was October 1, 2011). Significant associations between categorical factors were assessed using the Fisher exact test. Categorical variables are described in terms of frequency and percentage. The distribution of continuous variables is described as mean (SD). The association of categorical factors with survival was assessed using the Kaplan-Meier method and was tested using the log-rank test. Statistical significance was set at $P<.05$.

RESULTS

PATIENT CHARACTERISTICS

Patient characteristics are detailed in **Table 1**. No patients were lost to follow-up. Median (SD) follow-up was 41 (22) months (range, 10-83 months). The Eastern Cooperative Oncology Group performance status was 0 or 1 for all patients. Peritoneal carcinomatosis originated from colorectal cancer in 26 patients (43%), from ovarian cancer in 12 (20%), from appendix cancer in 10 (17%), from pseudomyxoma/mesothelioma in 10 (17%), from pancreatic cancer in 1 (2%), and from small-bowel cancer in 1 (2%). Fifty-three patients (88%) had previously been treated with systemic chemotherapy with a mean (SD) of 7.6 (4.9) cycles. Thirty-seven patients (62%) received systemic chemotherapy after HIPEC.

SURGERY

The mean (SD) PCI was 9.6 (4.2). Excision of PC was synchronous with resection of the primary tumor in 13 patients (22%). A CCR-0 resection was achieved in 55 patients (92%). The mean (SD) duration of surgery was 410.7 (145.4) minutes (range, 130-680 minutes). The mean (SD) blood loss was 450.2 (291.2) mL/L. Three patients (5%) had minor hepatectomy for synchronous liver metastasis.

POSTOPERATIVE COURSES

Postoperative courses are summarized in **Table 2**. Mortality and morbidity were 0% and 33%, respectively. He-

Table 2. Perioperative Outcomes of 60 Patients Who Underwent Cytoreduction Surgery Plus HIPEC[a]

Outcome	Value
PCI, mean (SD)	9.6 (4.2)
Synchronous resection of primary tumor	13 (22)
Digestive resection	
Small bowel	17 (28)
Colon	14 (23)
Stomach	3 (5)
Duodenum	1 (2)
Associated resection	
Splenectomy	7 (12)
Hepatectomy	3 (5)
Others	2 (3)
CCR	
0	55 (92)
1	3 (5)
2	2 (3)
Operative duration, mean (SD), min	410.7 (145.4)
Intraoperative blood loss, mean (SD), mL/L	450.2 (291.2)
Patients receiving red cell transfusion	17 (28.3)
Red cell transfused, range, U[b]	0-18
Mortality	0
Morbidity	20 (33)
Hematologic toxicity	8 (13)
Digestive fistula	6 (10)
Gastric emptying	6 (10)
Others	4 (7)
Grade I/II[c]	9 (15)
Grade III/IV[c]	10 (17)
Reintervention	11 (18)
Length of hospital stay, mean (SD), d	23 (13)
Readmission	3 (5)

Abbreviations: CCR, completeness of cancer resection; HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal carcinomatosis index.
[a] Data are given as number (percentage) unless otherwise indicated.
[b] Range is given (vs mean [SD]) due to a nonnormal variation of the value.
[c] According to Clavien-Dindo classification.

matologic toxicities (13.3%) and digestive fistula (10%) represented the more common complications after HIPEC. Major complications (Clavien-Dindo grade III/IV complications) occurred in 10 patients (17%). A second operation was necessary in 11 patients (18%) because of digestive fistula (n=7), intra-abdominal hematoma (n=3), and bladder fistula (n=1). The mean (SD) length of hospital stay was 23 (13) days (range, 7-62 days). Readmission was needed for 3 patients (5%).

LEARNING CURVE

Table 3 shows the evolution of perioperative courses according to the 3 periods. Perioperative red cell transfusion ($P<.01$), grade III/IV morbidity ($P=.02$), and reintervention rate ($P=.04$) significantly decreased during the 3 periods. No difference was observed between the 3 periods with regard to mean PCI, operative duration, blood loss, mortality, overall morbidity, length of hospital stay, and readmission.

SURVIVAL

The overall 1-, 3-, and 5-year survival rates of 26 patients with PC originating from colorectal cancer were 100%, 51%, and 37%, respectively; the corresponding disease-free survival rates were 42%, 25%, and 20%, respectively (**Figure**). The overall median survival was 39 months.

COMMENT

In this series, we examined the administration of the first 60 HIPEC procedures performed in a comprehensive cancer center. Our institution performs a high volume of oncologic operations: all surgeons who participated in the HIPEC program are experienced and skilled in oncologic surgery. Until 2005, patients with PC were treated

Table 3. Perioperative Outcomes of Patients Who Underwent Cytoreduction Surgery Plus HIPEC According to Period of Achievement[a]

	Period (No. of HIPEC Procedures)		
Outcome	1 (0-20)	2 (21-40)	3 (41-60)
PCI, mean (SD)	9.5 (5.6)	9.5 (3.6)	9.8 (3.4)
Operative duration, mean (SD), min	409.5 (157.4)	398.5 (135.2)	424 (149.2)
Intraoperative blood loss, mean (SD), mL/L	544 (344)	402.5 (273.6)	403.5 (264)
Patients receiving red cell transfusion	11 (55)	4 (20)	2 (10)
Red cell transfused, mean (SD), U	7.2 (11)	1.7 (4.1)	0.5 (1.8)
Morbidity	8 (40)	6 (30)	5 (25)
Digestive fistula	3 (15)	2 (10)	1 (5)
Hematologic toxicity	4 (20)	2 (10)	2 (10)
Gastric emptying	2 (10)	2 (10)	2 (10)
Others	1 (5)	2 (10)	1 (5)
Grade I/II[b]	1 (5)	4 (20)	4 (20)
Grade III/IV[b]	7 (35)	2 (10)	1 (5)
Reintervention	7 (35)	3 (15)	1 (5)
Length of hospital stay, mean (SD), d	27 (16)	21 (10)	20 (10)
Readmission	2 (10)	1 (5)	0

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; PCI, peritoneal carcinomatosis index.
[a] Data are given as number (percentage) unless otherwise indicated. No patients died.
[b] According to Clavien-Dindo classification.

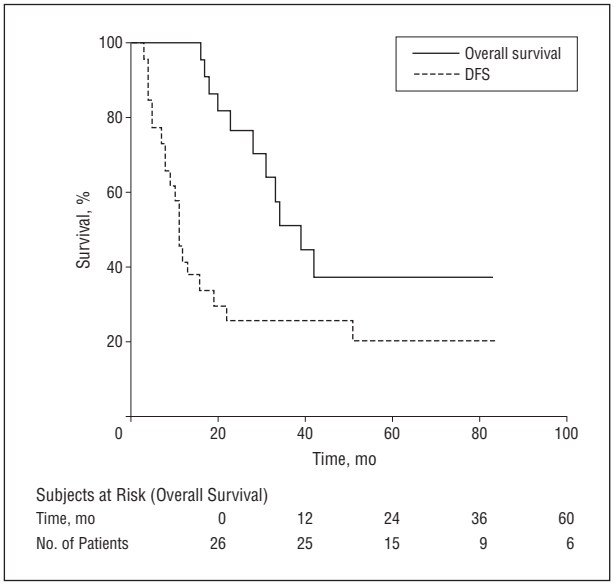

Figure. Overall and disease-free survival (DFS) of patients who underwent cytoreduction plus hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis arising from colorectal cancer.

with aggressive cytoreductive surgery[14] and perioperative systemic chemotherapy. In 2003, Verwaal et al[1] published a randomized trial showing the indisputable effect of HIPEC in selected patients (≤65 years old, with an Eastern Cooperative Oncology Group performance status of 0-1, asymptomatic PC, and completeness of cytoreductive surgery). Thus, when we started our HIPEC program in 2004, we opted for an open technique with intraperitoneal administration of oxaliplatin as described by Elias et al.[16-19] Because of our experience with cytoreduction, the only learning curve that we experienced was with the introduction of HIPEC itself. Three major results have been obtained from our study.

IMPORTANCE OF ABIDING BY THE ELIGIBILITY CRITERIA

Our patients were subject to strict eligibility criteria that had been previously established: all patients had good clinical status, had no symptomatic disease, and were younger than 70 years.[20] During the initiation of this new procedure, we strongly supported the criteria that had been previously established by an experienced surgical team. It was necessary to have favorable postoperative courses in the initial patients so that the medical and paramedical teams did not experience discouragement with biased, poor results. Conversely, we could not justify performing HIPEC in patients with limited PC: the mean PCI was 9.6, and our patients required multiple digestive and associated resection (hepatectomy and splenectomy), which confirmed that we achieved extended peritonectomies usually associated with a high morbidity rate.

PERIOPERATIVE OUTCOMES

We reported zero mortality and acceptable morbidity rates (33%), which have been previously reported by other experienced centers.[1-12] We also showed that accumulating cases of HIPEC did not affect the operative duration, mortality and morbidity rates, length of hospital stay (despite a tendency of decrease during the 3 periods), and readmission rate. We noted that digestive fistula and hematologic toxicities were the more common morbidities that have already been reported with the use of intraperitoneal oxaliplatin.[21] Thus, the mean reintervention rate was 18%, but it decreased to 5% for the last 20 HIPEC procedures.

We did not observe a significant difference in intraoperative blood loss between the first and last 20 procedures. However, there was a trend in decreased bleeding (544 mL/L vs 403.5 mL/L; $P=.06$). Because patient characteristics (notably the PCI) and cytoreductive surgery did not differ between the 3 periods, it was necessary to examine other factors that could explain the decrease in bleeding and the reduction in perioperative transfusion, grade III/IV morbidity, and reintervention rates. During the first 20 procedures, we did not observe any specific delay between the last chemotherapy cycle and HIPEC and drug dilution (Elias et al[16,17] recommended a dilution of 2 L/m^2). It is likely that a delay of less than 1 month between the chemotherapy cycle and surgery could increase the hematologic toxicity of both systemic and intraperitoneal chemotherapy, leading to related complications. Two factors, delay of less than 1 month and administration of intraperitoneal oxaliplatin (and not mitomycin C[22]), probably led to an accumulation of systemic oxaliplatin that is frequently used in digestive PC. Insufficient drug dilution similarly increased the concentration of intraperitoneal oxaliplatin with corresponding morbidity as reported by Elias et al.[16,17] After correction of these 2 crucial points, the grade III/IV morbidity ($P=.02$) and perioperative red cell transfusion ($P<.01$) significantly decreased and the reintervention rate ($P=.04$) decreased from 35% to 5%.

ONCOLOGIC RESULTS

The quality of resection was excellent with a CCR-0 resection rate of 91.7%. This result was not surprising with our extensive experience with cytoreduction in patients with PC. This highlighted our capacity to evaluate the resectability of PC. For HIPEC treatment administered to patients whose PC originated from colorectal cancer, we observed a median survival of 39 months and a 5-year overall survival of 37%, similar to a recently reported large series.[23] The median disease-free survival (11 months) was similarly consistent with the literature.

If eligibility criteria and pharmaceutical drug recommendations are strictly observed, we supposed that center volume and surgeons with sufficient experience treating cancer and with previous experience with PC resection would improve the patient's postoperative courses. In 2007, Smeenk et al[24] published their series of PC treatment with HIPEC and affirmed that a minimum of 130 procedures was required to reach acceptable postoperative outcomes. Paradoxically, our findings are reinforced by this publication. Smeenk et al[24] initially accumulated their surgical experience while performing both cytoreductive surgery and HIPEC in 1996. In that era, proper peritonectomy technique, patient selection, phar-

macology of HIPEC, and perioperative care were not well established. Thus, a long learning curve was needed to control each part of the procedure and consequently improve perioperative courses.

In conclusion, our initial program with HIPEC was safe (no perioperative deaths occurred) and provided survival benefits comparable with HIPEC performed in an experienced center. We observed a significant reduction in grade III/IV morbidity and reintervention rate after 20 procedures. Our encouraging results have to be moderated by the previous experience of our team in aggressive cytoreductive surgery, the high volume of cancer operations performed in our center, and the cancer treatment experience of the surgeons who initiated and developed the HIPEC program.

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