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Gastrointestinal Oncology

Impact of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy on Systemic Toxicity

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Introduction: The purpose of this study was to analyze the postoperative systemic toxicity and procedure-related mortality (PRM) of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of peritoneal surface malignancies (PSMs).

Patients and methods: A total of 242 (84 males/158 females) patients with PSM underwent 247 consecutive procedures. The mean age was 52 years (range 22–79). CRS was performed using peritonectomy procedures. The HIPEC technique through the closed abdomen was conducted with cisplatin (CDDP 25 mg/m^2/l of perfusate) + mitomycin C (MMC 3.3 mg/m^2/l perfusate) or CDDP (43 mg/l perfusate) + doxorubicin (Dx 15.25 mg/l perfusate) at 42.5°C. These dosages were reduced by 30% when the patient had received systemic chemotherapy before the CRS + HIPEC. Systemic toxicities were graded according to the NCI CTCAE v3 criteria.

Results: G3-5 systemic toxicity rate was 11.7 % and adverse events were bone marrow suppression, 13; nephrotoxicity, 14; neutropenic infection, 2 and pulmonary toxicity, 1. Independent risk factors for G3-5 systemic toxicity after multivariate analysis were a dose of CDDP for HIPEC of 240 mg or more (OR 2.78, CI 95% 1.20–6.45) and CDDP + Dx schedule for HIPEC (OR 2.36, CI 95% 1.02–5.45). PRM was 1.2%.

Conclusions: CRS + HIPEC presented acceptable systemic toxicity and PRM rates. Independent risk factors for systemic toxicity were the CDDP + Dx schedule and CDDP dose for HIPEC.

Key Words: Peritonectomy—Hyperthermic Intraperitoneal Chemotherapy—Toxicity.

The comprehensive treatment of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been proven to be beneficial in the management of some peritoneal surface malignancies (PSMs) according to several phase-II studies.[1,2,3,4] Moreover, results of a phase-III trial have confirmed the superiority of CRS + HIPEC in the treatment of patients with carcinomatosis from colon cancer relative to other standard palliative surgical therapies associated with systemic chemotherapy.[5]

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The methodology regarding the technique of CRS + HIPEC was discussed extensively during a Consensus Statement conducted throughout the year 2006. The results of this debate were presented at the 5th International Workshop on Peritoneal Surface Malignancy held in Milan in December 2006.[6] An agreement was achieved in several aspects among the local-regional experts. Obviously there are several other issues to be resolved by future prospective trials regarding, for example, the best drug combination for HIPEC for each clinical situation.

Studies of the side effects related to the CRS + HIPEC have mainly focused on the morbidity attributable to the surgical aspect of the local-regional procedure. The systemic toxicity related to HIPEC has not been investigated in great detail by the experts in the management of PSM.

The aim of this study was to analyze the systemic toxicity and procedure-related mortality (PRM) of CRS followed by HIPEC (closed abdominal technique) using the cisplatin + doxorubicin (CDDP + Dx) and cisplatin + mitomycin-C (CDDP + MMC) combinations in the treatment of patients affected by PSM.

PATIENTS AND METHODS

Patients' Characteristics

All patients included in this study were treated under an institutionally approved protocol and with written informed consent. The eligibility requirements for treatment were as follows: histologically confirmed diagnosis of peritoneal carcinomatosis or sarcomatosis, age under 75 years, no distant metastasis, and adequate renal, hematopoietic and liver functions and performance status (ECOG) 0, 1 or 2.

A total of 242 patients with PSM underwent 247 consecutive procedures from February 1995 to July 2006. Due to disease relapse, 5 underwent the intervention twice. Further data on patients' characteristics are summarized in Table 1.

TABLE 1. *Patients' characteristics*

Characteristic	n
Total number of patients (procedures)	242 (247)
Mean age (range)	52 years (range 22–79)
Male/female	84/158
Body mass index (kg/m^2)	25 (range 15.9–40)
Histological type distribution	
-Peritoneal mesothelioma	62
-Pseudomyxoma peritonei	74
-Ovarian cancer	40
-Abdominal sarcomatosis	33
-Adenocarcinoma of the colon	14
-Gastric cancer	10
-Carcinomatosis from other origins	9
Performance status(ECOG)	
0	200
>1	47
Previous chemotherapy	126 (51%)
Carcinomatosis extension: mean PCI (range)	20 (range 6–39)

PCI: peritoneal cancer index

Cytoreductive Surgery

The technique of cytoreductive surgery has been described elsewhere.[7] Briefly, the surgical procedure was carried out with one or more of the following steps, depending on disease extension: (1) greater omentectomy, right parietal peritonectomy ± right colon resection; (2) pelvic peritonectomy ± sigmoid colon resection ± hystero-adnexectomy; (3) lesser omentectomy and dissection of the duodenal-hepatic ligament ± antrectomy ± cholecystectomy; (4) right upper quadrant peritonectomy ± Glisson's capsule; (5) left upper quadrant peritonectomy ± splenectomy; and (6) other intestinal resection and/or abdominal mass resection. A ball-tip electrosurgical hand piece was used to dissect the tumor on peritoneal surfaces from normal tissue.[8] The electrosurgery was used on pure cut at high voltage. The 2-mm ball-tip electrode was used for dissecting on visceral surfaces, including stomach, small bowel, and colon. When more rapid tumor destruction was required, the 5-mm ball-tip was used.

A more detailed description of the surgical technique regarding gastrointestinal resection procedures, anastomotic technique, and policy for ostomy performance can be found elsewhere.[9,10]

Peritoneal carcinomatosis was quantified according to the Peritoneal Cancer Index (PCI).[11] The mean PCI was 20 (range 6–39). Cytoreduction was classified into three levels according to the number of procedures performed: level I, 1–2 steps; level II, 3–4 steps; and level III, 5 steps or more. Residual disease after surgery was classified according to Sugarbaker criteria:[11] CC-0, no residual disease; CC-1, minimal residual disease of 0–2.5 mm; CC-2, residual disease of 2.5 mm–2.5 cm; and CC-3, residual disease >2.5 cm.

HIPEC Technique

After cytoreduction, four silicone catheters were placed in the abdominal cavity—one in the right subphrenic cavity, one in the deep pelvis, one in the

left subphrenic cavity, and one in the superficial pelvic site cavity. In order to continuously monitor peritoneal temperature during HIPEC, thermocouples were placed in the abdominal cavity. Following the closed abdomen technique, the skin was closed with a running suture. The catheters were then connected to the extra-corporeal circuit Performer LRT, RAND, Medolla (MO), Italy. Intraperitoneal chemotherapy regimens used were as follows: CDDP (25 mg/m^2/l) and MMC (3.3 mg/m^2/l)[12] for pseudomyxoma peritonei, colorectal and gastric carcinomatosis; and CDDP (43 mg/l of perfusate) and Dx (15.25 mg/l of perfusate)[13] for peritoneal mesothelioma, ovarian carcinomatosis and abdominal sarcomatosis. Patients over 70 years of age and those who had undergone previous chemotherapy received a 30% dose reduction of both drugs, whatever the combination was. A heat exchanger kept the perfusate at 44° C as it was being administered, so that the intracavitary perfusate temperature was maintained at 42–43° C. The HIPEC lasted 60–90 min, depending on the drug schedule. Following perfusion, the perfusate was quickly drained and the abdomen closed after careful intracavitary inspection.

Postoperative Work-up

During the postoperative period, patients were admitted to the Intensive Care Unit, where they were evaluated daily by means of laboratory and/or radiological exams. They were then discharged to the surgical ward for recovery. The laboratory exams [complete blood cell count, serum creatinine, and blood urea nitrogen (BUN)] were performed every other day during the first postoperative week and every 3 days during the second week until discharge. If there was postoperative renal failure, the following measurements were made: creatinine clearance, concentration of sodium in the urine, and urinalysis every other day.

Study Parameters

Systemic toxicities were graded according to the NCI CTCAE v3 criteria. We defined the following dependent variables: combined G3-5 systemic toxicity, combined G3-5 serum creatinine alteration, and combined G3-5 hematological toxicity. The PRM was defined as death occurring during the in-hospital stay after CRS and HIPEC.

The following independent variables were taken into consideration for potential association with G3-5 systemic toxicity and liver/pancreatic trauma: sex, age (<70 years vs. >70 years), performance status (WHO: 0 vs. 1/2), previous systemic chemotherapy, extension of carcinomatosis, duration of the cytoreduction (<540 min vs. ≥ 540 min), extent of cytoreduction (level 1/2 vs. 3), completeness of cytoreduction (CC0/1 vs. 2/3), HIPEC drug schedule (CDDP + MMC vs. CDDP + Dx) and CDDP dose for HIPEC (<240 mg vs. ≥ 240 mg). Continuous variables were categorized into two classes using their mean value as cut-off.

TABLE 2. *Description of peritonectomy and HIPEC procedures*

Surgical procedures and results	n
Peritonectomy	
Diaphragmatic (left + right)	277
Glissonian capsule	91
Lesser omentum	130
Pelvic peritoneum	162
Greater omentum	177
Other surgical procedures	
Gastrointestinal resections	313
-Gastrointestinal anastomosis	241
Splenectomy	71
Hysterectomy +/− bilateral salpingo-oophorectomy	31
Other resections	52
Mean no. of peritonectomy procedures per patient	6.0
Mean duration of the cytoreduction (min)	483 (range 160–1260)
Mean no. of blood units transfused	2.6 (range 0–37)
Level of peritonectomy procedure	
I	40 (16.2%)
II	100 (40.5%)
III	107 (43.3%)
No. of optimally cytoreduced cases (CC0/1)	217 (87.8%)
HIPEC drug schedule	
-CDDP + Dx	98 (39.7%)
-CDDP + MMC	146 (60.3%)
Dose of the drugs (mean, range)	
-CDDP	204 mg (100–300)
-MMC	30 mg (15–50)
-Dx	65 mg (25–90)
The mean length in the intensive care unit stay	3 days
The mean length of in-hospital stay	23 days (range 7–101)

Statistical Analysis

A univariate analysis of each clinical variable was performed using the Fisher's exact test or chi square test to determine a probability of association with each morbidity variable. A logistic regression model was used in a multivariate analysis to determine a correlation between clinical variables and morbidity variables. All clinical variables resulting in a P value less than 0.15 on univariate analysis were included in the logistic regression model. The backward elimi-

nation method was used to determine which clinical variables best predicted the presence of G3-5 systemic toxicity and G3-5 serum creatinine alteration. All statistical analyses were conducted using SPSS for Windows Version 8.0.0.

RESULTS

Intraoperative and postoperative details of CRS + HIPEC are outlined in Table 2. Accordingly, 217 (87.9%) cases were optimally cytoreduced (CC-0/1).

Systemic Toxicity

In 29 patients, 34 G3-5 systemic toxicity events occurred, accounting for a systemic toxicity rate of 11.7%. The adverse events were: bone marrow suppression, 13; nephrotoxicity, 14; febrile neutropenia, 2; gastrointestinal events, 4 and pulmonary toxicity, 1.

Hematological Toxicity

There were 6 cases of leukopenia (5 G3 and 1 G4). The nadir was reached at a mean of 12.7 days postoperatively (range 1–26) and the mean duration was 4.7 days (range 2–10).

Severe neutropenia was observed in 9 cases (6 G3 and 3 G4). The nadir was reached at a mean of 13.4 days postoperatively (1–30) and the mean duration was 2.9 days (1–6). Only one patient received granulocyte-colony stimulating factor (G-CSF, Neupogen), for 3 days at a dose of 300 μg/day. One patient with G4 neutropenia and concomitant sepsis died on postoperative day 26.

There were 4 cases of thrombocytopenia (3 G3 and 1 G4). The mean day of nadir was 3.3 (1–6) and mean duration was 4 days (1–6). Only one patient required platelet concentrate transfusion. A detailed description of the hematological adverse events is outlined in Table 3.

Renal Toxicity

Regarding nephrotoxicity there were 10 cases of G3 and 4 cases of G4 serum creatinine alteration in the immediate postoperative period. The mean day of onset, peak serum creatinine and mean values of the clearance of creatinine and blood urea nitrogen are outlined in Table 4. Of 11 cases, 10 demonstrated no granular casts in the urinalysis (this information not available in 3 cases) and 10 of 11 presented microscopic hematuria. After a mean period of 16 days (range 7–42) from surgery, at the time of hospital discharge, 5 patients had completely normalized renal function, 5 patients had up to G2 serum creatinine alteration, and 4 patients still presented G3-5 alteration. Three patients (2 peritoneal mesothelioma and 1 peritoneal sarcomatosis) required hemodialysis during the immediate postoperative period and evolved with chronic renal failure; 2 of them are currently on chronic hemodialysis.

Risk Factors for G3-5 Systemic Toxicity, and Renal and Hematological Toxicities

After univariate analysis, the following variables were proven to be correlated with G3-5 systemic toxicity: male sex ($P = 0.036$) and CDDP dose for HIPEC ≥240 mg ($P = 0.045$). Independent risk factors for G3-5 systemic toxicity after multivariate analysis were a CDDP dose for HIPEC of 240 mg or more (OR 2.78, CI 95% 1.20–6.45; P value = 0.017) and CDDP + Dx schedule for HIPEC (OR 2.36, CI 95% 1.02–5.45; P value = 0.042) (Table 5).

The assessment of risk factors for renal toxicity identified the CDDP dose for HIPEC of 240 mg or more as having a significant correlation with G3-5 serum creatinine alteration during the postoperative period, after univariate analysis. A multivariate analysis was conducted using a logistic regression model including those variables associated with G3-5 serum creatinine alteration during the postoperative period with a P value less than 0.15 in the univariate analysis. No independent risk factor for the emergence of G3-5 serum creatinine alteration during the postoperative period was identified. The CDDP dose for HIPEC of 240 mg or more presented a correlation with G3-5 serum creatinine alteration of borderline significance (OR 3.021, CI 95% 0.981–9.304; P value 0.054).

The assessment of risk factors for hematological toxicity revealed only the sex of the patients (univariate analysis, P value 0.041) as a variable significantly correlated with the emergence of such adverse events. Male patients presented a threefold higher risk of developing myelotoxicity after the procedure.

Procedure-Related Mortality

The PRM rate was 1.2%.Three patients died during the early postoperative period. The first died on the 21st day after the procedure due to a duodenal perforation associated with abdominal bleeding. The second died on the 26th day due to microangiopathic hemolytic anemia syndrome, colic perforation,

TABLE 3. *Detailed description of G3-5 hematological adverse events*

	Bone marrow adverse events		
	Leukopenia	Neutropenia	Thrombocytopenia
PO day of G1 alteration onset (mean, range)	10.5 (1–23)	12.8 (1–30)	1.7 (1–3)
PO day of nadir (mean, range)	12.7 (1–26)	13.4 (1–30)	3.3 (1–6)
Duration of adverse event (mean, range)	4.7 (2–10)	2.9 days (1–6)	4 (1–6)
Number of cases			
Grade 3	5 ($< 2.0 - 1.0 \times 10^9$ /L)	6 ($< 1.0 - 0.5 \times 10^9$ /L)	3 ($< 50.0 - 25.0 \times 10^9$ /L)
Grade 4	1 ($< 1.0 \times 10^9$ /L)	3 ($< 0.5 \times 10^9$ /L)	1 ($< 25.0 \times 10^9$ /L)
Grade 5	0 (Death)	0 (Death)	0 (Death)

TABLE 4. *Detailed description of alterations of renal function parameters and renal toxicity*

Postoperative serum creatinine alteration	Grade 3 (> 3.0–$6.0 \times$ ULN)	Grade 4 ($> 6.0 \times$ ULN)	Grade 5 (Death)
Number of cases	10 cases	4 cases	0
Serum creatinine g/dl (mean, range)	3.8 (2.7–5.0)	7.3 (6.6–7.8)	-
BUN g/dl (mean, range)	162 (82–239)	160 (114–229)	-
Creatinine clearance (mean, range)	23 (11–54)	9 (3–20)	-
PO day of onset of renal function alteration (mean, range)	3 (1–6)	3 (1-6)	-
PO day of maximum alteration (mean, range)	8 (3–15)	8 (3–15)	-
	Evolution in the late postoperative period with renal failure		
	Grade 3	Grade 4	Grade 5
	Not requiring chronicdialysis	Requiring chronic dialysis	Death
Number of patients	12	2	0

bronchial bleeding and sepsis. The third patient died on the 27th postoperative day due to generalized sepsis and respiratory failure.

DISCUSSION

Only a few authors have conducted a comprehensive study of systemic toxicity associated with CRS + HIPEC, attempting to identify high-risk groups for the development of such adverse events, outside the context of a dose-finding study. As outlined in Table 5, the CDDP + Dx drug schedule for HIPEC and the CDDP dose for HIPEC were found to be the best predictors of G3-5 systemic toxicity related to CRS + HIPEC.

The CDDP dose for HIPEC was proven to be independently correlated with systemic toxicity. As already outlined in Patients and Methods, two HIPEC drug schedules were used, according to the tumor type, namely CDDP (25 mg/m^2/l of perfusate) + MMC (3.3 mg/m^2/l of perfusate) and CDDP (43 mg/l of perfusate) + Dx (15.25 mg/l of perfusate). The CDDP dose for HIPEC in each of the combinations is calculated in different ways and in our study ranged from 100 to 300 mg. We chose 240 mg as a cut off value as it represents the theoretical maximum tolerable dose, in our series, according to the schedule proposed by Rossi et al. It is the approximate result of the product 43 mg by 6 l (maximum volume of perfusate used in our series). Patients receiving a CDDP dose for HIPEC of 240 mg or more presented a significantly higher rate of combined G3-5 systemic toxicity. They had 2.78 times higher risk of developing a G3-5 postoperative systemic toxicity than those who received a lower dose, when adjusted for the other variables. The CDDP dose for HIPEC of 240 mg or more was proven to be an independent risk factor for the emergence of major surgical morbidity, according to a previous study.[10] Following CDDP dose for HIPEC of 240 mg or more, the second major risk factor for systemic toxicity in the present study was the HIPEC drug schedule.

Patients receiving CDDP + Dx showed a higher rate of combined G3-5 systemic toxicity (15.3%) than those receiving CDDP + MMC (9.4%). When adjusted for the other variables, the former group presented a 2.36 times higher risk than the CDDP + MMC group. One could raise the hypothe-

TABLE 5. *Univariate and multivariate analysis of clinical risk factors for G3-5 systemic toxicity, postoperative serum creatinine alteration and hematological toxicity*

	G3-5 Systemic toxicity			G3-5 Serum creatinine alteration	G3-5 Hematological toxicity
Dependent variables	Univariate*	Multivariate**		Univariate*	Univariate*
Independent variables	P value	OR (adjusted) CI 95%	P value	P value	P value
1. Male sex	0.036			NS	0.041
2. Age >70 years	NS			NS	NS
3. Performance Status (ECOG) >1	NS			NS	NS
4. Previous systemic CHT	NS			NS	NS
5. Previous systemic CDDP	NS			NS	NS
6. Carcinomatosis extension (PCI > 20)	NS			NS	NS
7. Duration of the CRS > 540 min	NS			NS	NS
8. Extent of cytoreduction: levels 1/2 vs. level 3***	NS			NS	NS
9. Transfusion of >2 blood cell units	NS			NS	NS
10. Completeness of cytoreduction: cc0/1 vs. cc2/3	NS			NS	NS
11. HIPEC drug schedule (CDDP + Dx vs. CDDP + MMC)	0.114	2.36 (1.02–5.45)	0.042	NS	NS
12. CDDP HIPEC dose >240 mg	0.045	2.78 (1.20–6.45)	0.017	0.044	NS

OR: odds ratio; CI: confidence interval; CHT: chemotherapy; CDDP: Cisplatin; DX: Doxorubicin; MMC: Mitomycin-C; PCI: Peritoneal Cancer Index; CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy; * Chi square test or Fisher's exact test; ** logistic regression model with backward elimination method. ***Cytoreduction classified into 3 levels according to the number of procedures performed: level I - 1- 2 procedures; level II - 3 or 4 procedures; level III – more than 5 procedures.

sis that this difference in toxicity profiles is due to the low dose of mitomycin-C. In fact, we used 3.3 mg/m^2/l of perfusate, which is fairly inferior to those used in other studies: 10 mg/l, 10–12.5 mg/m^2, 25–40 mg/m^2.[14,15,16] One could justify the lower quantity of MMC in the present study because it was in combination with CDDP; other investigators used MMC as a single agent.

A subset analysis of patients receiving CDDP + MMC, demonstrated that the CDDP dose for HIPEC of 240 mg or more still remained the main risk factor for the emergence of systemic toxicity, after logistic regression (OR: 4,19; CI95%: 1,12–15,70). In other words, the most prominent contributor for systemic toxicity in the combination CDDP + MMC was CDDP. These data raise concerns about the possible suboptimal dose of MMC in this combination, the schedule of which, in contrast to that of the combination CDDP + Dx, has not yet been formally set by a phase-I dose-finding study.

Several drug schedules have been used in the last two decades for hyperthermic intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies. Usually the scientific pathway expected to be followed before the introduction of an antiblastic drug (alone or in combination) in the routine clinical practice includes the following steps: experimental studies (preclinical), dose-finding studies (phase I), antitumor activity assessment (phase II), and comparative trials (phase III).[17]

However, such a pathway has not been strictly respected in the local-regional therapy scenario. As an example, some drugs have been tested in phase-II studies without having been adequately tested in phase-I trials, such as for CDDP + MMC.[18,19] Fortunately such situations have resulted in procedures with acceptable morbidity, which is in agreement with the conceptual goal of local-regional therapy of minimal systemic antiblastic side effects. The disadvantage of such an introduction policy is that the drug (alone or combination) could be adopted by the local-regional therapist with an ill-defined suboptimal dose that does not exploit the whole antiblastic potential of the chemotherapy. In summary, although the schedule CDDP (25 mg/m^2/l) + MMC (3.3 mg/m^2/l) has been largely employed by local-regional therapists, it should probably be reviewed with conduction of a formal dose-finding phase-I study.

The most frequent systemic toxicity observed in our study was renal (5.7%). During the postoperative period, 14 patients demonstrated progressive elevation of serum creatinine up to G3 level. Most of these recovered their normal renal function within the period of in-hospital stay. However, 3 patients evolved with permanent deficit and 2 became chronically hemodialysis dependent.

No independent risk factor for renal failure was identified. Only a CDDP dose for HIPEC of 240 mg or more presented a positive correlation with postoperative serum creatinine G3-5 alteration after univariate analysis. Counter-intuitively, variables such as age over 70 years, previous systemic chemotherapy, previous treatment with CDDP, and quantity of blood transfusion (an indirect measure of intraoperative loss) were not proven to be associated with nephrotoxicity.

CDDP is known to be the most nephrotoxic agent among the chemotherapies used in the present study. The mechanisms underlying the emergence of such an adverse event is related to (1) decreased mitochondrial function;[20,21] (2) decreased ATPase activity;[22] (3) altered cell cation content;[23] (4) altered solute transport;[24] (5) decreased blood renal flow; (6) decreased glomerular filtration rate; (7) increased serum creatinine; and (8) increased blood urea nitrogen.[25,26]

Mitomycin-C has been reported to be potentially nephrotoxic when used systemically. It causes renal lesions characterized by arteriolar fibrin thrombi, expanded subendothelial membranes, ischemic wrinkling of glomerular basement membranes, and mesangiolysis. The mechanism of action is postulated to be endothelial cell damage. MMC is known to be correlated with microangiopathic hemolytic anemia syndrome,[27] an uncommon condition that was recognized in one of the patients of the present series. He died on the 27th postoperative day after CRS + HIPEC due to G4 neutropenic sepsis and massive bronchial bleeding.

According to Table 6, there are only 2 of 7 published studies that have reported on renal toxicity after CRS + HIPEC, which reflects the rarity of this side effect related to the procedure. Verwaal et al. reported on 102 patients submitted to CRS + HIPEC with MMC 25–40 mg/m^2 and observed renal failure in 4.9% of cases.[16] Glehen et al., in a phase-II study on PSM of various origins, analyzed the morbidity related to the procedure. They performed the HIPEC with MMC 0.7 mg/kg or CDDP 1 mg/kg or CDDP 0.5 mg/kg + MMC 0.7 mg/kg and observed a postoperative renal failure rate of 1.3%.[28]

The second most frequent systemic toxicity was bone marrow suppression (5.3%). These data seem to be in line with those from the literature. Hematological toxicity rates according to most of the authors range from 2.5 to 19% (Table 6).[14,15,16,28,29,30,31] Only one study presented an outlier value of 48%.[29] In the present study, the assessment of risk factors for hematological toxicity revealed that only male patients presented a threefold higher risk of developing myelotoxicity after the procedure (univariate analysis, P value: 0.041). (Table 5)

Elias et al.[32] conducted a study of 83 patients who were submitted to CRS + HIPEC with intraperitoneal oxaliplatin (360 mg/m^2) and irinotecan (360 mg/m^2), in 2 l/m^2 of dextrose over 30 min at 42–45°C, using the Coliseum technique. At 60 min prior to HIPEC, patients also received an intravenous perfusion of leucovorin (20 mg/m^2) and 5-fluorouracyl (400 mg/m^2). The incidence of severe bone marrow aplasia was 48% and was associated with the duration of surgery and extent of the peritoneal disease.

There are two main differences between our results and those of Elias' study. First, we observed a significantly lower incidence of bone marrow suppression. Second, neither of the variables in our study (duration of the surgery and extent of the peritoneal disease) was proven to be associated with systemic toxicity or bone marrow suppression (Table 5). These disagreements could be accounted for by the differences in the drug schedules and HIPEC techniques used in each study. Moreover, in the Elias study, the positive correlation between the variables was found only on univariate analysis. Finally, we did not include anemia as a parameter in the assessment of myelotoxicity.

Rather than being secondary to bone marrow suppression, the decrease in the hemoglobin level after CRS + HIPEC could be, in most of the cases, a result of bleeding secondary to surgery. The presence of eventual blood loss could constitute a bias to assess the bone marrow suppression. One way to accurately identify the compromise of the red cell stem is by measuring the level of reticulocytes instead of hemoglobin. The reticulocytes are immature erythrocytes that are expected to increase in case of anemia due to bleeding and decreased in case of bone marrow suppression. Unfortunately, the number of reticulocytes was not measured in our patients, the reason for which we decided not to include anemia as a parameter of bone marrow suppression.

Comparison of our results with those of other investigators is hampered by several factors. First, there are different conceptions and definitions of toxicity adopted by the published studies. Some groups adopt a broad definition of toxicity that includes complications attributable to the surgical aspect of the local-regional therapy. There has been little attempt to report accurately and specifically the systemic adverse events secondary to drugs. Second, different grading scales have been used to classify this side effect. Third, there is a broad range of variation in the adopted drug schedules and technical aspects of HIPEC among the authors.

TABLE 6. *Overview of operative complications associated with CRS + HIPEC (series with more than 50 patients)*

Author/year	Number of Procedure	Previous systemic CHT (%)	HIPEC Drug schedule	EPIC	Severe hematological toxicity (%)	Renal toxicity (%)	Mortality (%)	Risk factor for systemic toxicity
Jacquet et al.[14] 96	60	NA	MMC 10 mg/l	60	7	-	5	Not identified
Schnake et al.[15] 99	242	Yes	MMC /CDDP	yes	2.5	-	4	Not identified
Stephens et al.[30] 99	200	NA	MMC 10–12.5 mg/m^2	145	4	-	1.5	Not identified
Glehen et al.[28] 03	216	NA	MMC 0.7 mg/kg or CDDP 1 mg/kg or CDDP 0.5 mg/kg + MMC 0.7 mg/kg	-	4.6	1.3	3.2	NA
Verwaal et al.[16] 04	102	NA	MMC 25–40 mg/m^2	-	18.6	4.9	8	NA
Shen et al.[31] 04	77	NA	MMC 30–40 mg/3l of perfusate	-	19	-	4	NA
Smeenk et al.[29] 06	103	NA	MMC 35 mg/m^2	-	10.6	-	11	NA
Elias et al.[32] 05	83	NA	Ox 360 mg/m^2 + CPT11 360 mg/m^2 + Leucovorin 20 mg/m^2 iv + 5FU 400 mg/m^2 iv	-	48	-	4.8	Duration of proc and PCI
Present series 07	247	51	CDDP 25 mg/m^2/l + MMC 3.3 mg/m^2/l or CDDP 43 mg/l + Dx 15.25 mg/l	-	5.3	5.7	1.2	CDDP dose >240 mg and CDDP + Dx schedule for HIPEC

CHT: chemotherapy; NA: not available; HIPEC: hyperthermic intraperitoneal chemotherapy; EPIC: Early postoperative intraperitoneal chemotherapy; MMC: mitomycin-C; Ox: oxaliplatin; CDDP: Cisplatin; CPT11: irinotecan; 5FU: 5Fluorouracil; Dx: Doxorubicin; PCI: peritoneal cancer index.

While CDDP and MMC are phase non-specific, doxorubicin is a phase-specific agent. The former drugs have a greater delay in causing myelosuppression than the latter. CDDP is a platinum complex with moderate toxic effects on bone marrow, characterized by mild leukopenia with a nadir in the 4th week after the infusion. Doxorubicin is an S-phase-dependent antibiotic agent and is characterized by a dose-limiting myelotoxicity, which nadirs on the 10th to 15th day after the infusion. Usually the hematological alteration normalizes after the 3rd week. MMC produces a less predictable neutropenia and thrombocytopenia. Usually the nadir myelosuppression is seen between the 4th and 6th weeks after the last dose, with a recovery 2–3 weeks later.[33]

The descriptive analysis of the cases presenting myelotoxicity in the present study demonstrates that all the patients, except for 2, presented the nadir within the 2 weeks after the procedure. Thus, the kinetics of the myelosuppression in these cases showed a pattern suggesting neutropenia secondary to a phase-specific agent (doxorubicin) rather than CDDP or MMC.

Aspects representing methodological weaknesses of the present study relate to the retrospective nature of the data and the absence of a control group. Another factor that limits the external validity of our results is related to the inheriting differences in the pharmacokinetics of the drugs according to the modality of perfusion. For example, our conclusions should not be arbitrarily extrapolated to cases treated with the Coliseum technique of HIPEC, and not even to cases treated with Early postoperative intraperitoneal chemotherapy. Further studies should be conducted to find common denominators for pharmacokinetic aspects, irrespective of the variation of the intraperitoneal chemotherapy technology.

In conclusion, the systemic toxicity and the PRM rate following CRS + HIPEC were both acceptable. The HIPEC drug schedule and CDDP dose for HIPEC independently influenced the emergence of systemic toxicity. The combination of CDDP + MMC may require a revision with a formal phase-I trial, because the MMC dose of 3.3 mg/m^2/l seems to be suboptimal.

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