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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy for Colorectal Peritoneal Carcinomatosis : Higher Complication Rate for Oxaliplatin Compared to Mitomycin C

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Key words. Cytoreductive surgery ; hyperthermic intraperitoneal chemotherapy ; peritoneal carcinomatosis ; colorectal cancer ; oxaliplatin ; mitomycin C.

Abstract. *Background :* Peritoneal carcinomatosis (PC) from colo-rectal cancer carries a very poor prognosis with a mean and median overall survival times of 6.9 and 5.2 months. It has been proved that a locoregional therapeutic approach of this disease with cytoreduction followed by hyperthermic intraperitoneal chemotherapy (HIPEC) improved survival of these patients. However, this combined treatment presents a high complication rate.
Methods : 21 patients with PC of colorectal origin underwent complete cytoreduction followed by HIPEC using Mitomycin-C (13 patients) or oxaliplatin (8 patients) and the open coliseum technique. For each case the medical datas were retrospectively analysed to determine feasibility, morbidity, mortality, survival time and prognostic factors.
Results : All patients presented a Sugarbaker's Peritoneal Cancer index inferior to 15. The mean operating time was 453 minutes. After a median follow-up of 24.9 months, actuarial disease-free survival was 36.6% at 5 years. The median survival time was 34 months. The morbidity rate was 33.3% with a significant higher complication rate in the oxaliplatin group (5/8) than in the Mytomycin-C (MMC) group (2/13). One patient (4.7%) died two months after treatment with MMC (endocarditis).
Conclusions : This series confirm positive impact of cytoreduction and HIPEC on PC. We obtained a moderated complications rate thanks to a high degree of selection of the patient. Oxaliplatin scheme is responsible of a higher morbidity than in MMC group. Phase III trial comparing these two drugs is needed.

Introduction

Colorectal cancer is the fourth commonest worldwide form of cancer with more than 700.000 individuals each year (1), representing an incidence of 40 per 100.000 patients in Belgium. Regional recurrence of colorectal cancer in the peritoneal cavity carries a very poor prognosis (2) with a mean and median overall survival times of 6.9 and 5.2 months (3).

The predominant patterns of peritoneal spread, concerning 20 to 50% of colorectal cancer recurrences, has provided the impetus for a locoregional approach employing intraperitoneal perfusion of cytotoxic agents (4).

Hyperthermic intraperitoneal chemotherapy (HIPEC) has the advantages of bathing the entire cavity and permitting very high local drug concentration to be reached (5). However, it is ineffective when used without maximal cytoreduction because cytotoxic agents only penetrate tumour nodule superficially to a depth of less than 2 mm (6). Theoretically, HIPEC can increase local drug exposure with less systemic toxicity when compared with conventional chemotherapy. Hyperthermia has a direct cytotoxic effect and enhances the activity and the penetration depth of many cytotoxic drugs.

Although MMC is still considered as the gold standard in HIPEC since this is the only regimen that has proven its efficacy in a phase III trial, oxaliplatin is considered as an alternative of choice in HIPEC for its significant activity in advanced colorectal cancer, despite a grade 3-4 haematological toxicity rate of 58% (7).

We report a retrospective study on 21 consecutive patients treated by complete cytoreduction and HIPEC for colorectal peritoneal carcinomatosis (PC). We first used MMC scheme, then we switched for oxaliplatin HIPEC. We propose to compare complications rate of these two groups.

Material and methods

From February 1998 to February 2004, 21 patients with colorectal PC were treated curatively in our centre. There were 11 males and 10 females, with a mean age of 56.5 years (range 33-79 years). The PC arose from adenocarcinoma of colon in 17 patients and from rectum in 4 patients. PC was diagnosed as recurrence in 14 patients (66%) while in 7 cases (33%) it was found during treatment of the primary tumour.

The abdomen was approached trough a xyphopubic incision. The extent of the PC was scored using peritoneal index described by SUGARBAKER (8).

Complete resection (or electrocauterisation) of all macroscopically visible lesions of PC was required before HIPEC. If complete resection (residual tumour < 1 mm in diameter) was not possible, the procedure was contraindicated and the laparotomy was closed.

In 5 patients (23%), we performed resection of synchronous liver metastases with one right hepatectomy, one segmentectomy III and three localised tumorectomies. No patients presented indications of radiofrequence resection.

HIPEC was performed intra operatively. A continuous closed circuit was used with three thermal probes placed inside the peritoneal cavity. The skin surrounded the laparotomy was sutured to a retractor placed above the anterior surface of the abdomen, causing an elevated "coliseum" rim around.

The first 13 patients were treated with MMC alone (10 mg/m^2) and other 8 received 460 mg/m^2 of oxaliplatin in 2 l/m^2 of dextrose at 5% for the HIPEC associated to a systemic chemotherapy of 5-FU (400 mg/m^2) and folic acid (20 mg/m^2) given one hour prior the HIPEC infusion. HIPEC lasted 90 minutes in the first group and 30 minutes in the second group, at a peritoneal temperature of between 41 and 42.5°C.

Radiotherapy was proposed before intervention in 2 of 4 cases of rectal adenocarcinoma and 16 patients of the entire population received chemotherapy after HIPEC.

We used a Kaplan-Meier method for the establishment of overall and disease free survival of all patients. However, the comparison of complications due to MMC or Oxaliplatin HIPEC was feasible and powered by a Chi-square test.

Results

All patients presented a PC index < 15 and the mean peritoneal index was 8.28 (range 3-15). HIPEC with MMC or Oxaliplatin were realised only if the cytoreduction was complete. No patient presented ascitis or bowel obstruction. The MMC group and the Oxaliplatin group were comparable in term of metastases, Karnofsky performance status and peritoneal cancer index (Table I).

Table I

Comparison of both groups

	MMC	Oxaliplatin	
Number of patients	13	8	p
Karnofsky performance status			
100%	1/13	2/8	NS
90%	7/13	5/8	NS
80%	2/13	0/8	NS
70%	2/13	1/8	NS
Ascitis	0/13	0/8	NS
Obstruction	0/13	0/8	NS
Cytoreduction			
RO	13/13	8/8	NS
R1	0/13	0/8	NS
R2	0/13	0/8	NS
Metastases	7/13	3/8	NS
Peritoneal cancer index			
< 10	10/13	4/8	NS
> 10	3/13	4/8	NS

Pathological examination of the resected tumours revealed a UICC staging of II in 4 patients, III in 7 patients and IV in 10. The mean number of resected organs was 2. The treatment of primary tumour needed one total colectomy, two ileo-caecal resections, two anterior rectal resections and two left hemi-colectomies. For the cytoreduction of PC and recurrences, we performed one ileo-caecal resection, one anterior rectal resection, two left hemi-colectomies, nine small bowel resection, five total hysterectomies, one bladder resection, four omentectomies, two caudal pancreatectomies and two splenectomies.

The mean operating time was 453 minutes (range 315 to 750 min).

Overall and disease free survival rates among the entire population were respectively 88.7% and 72.6% at 1 year, 72.9% and 37.1% at 2 years, 45.5% and 36.6% at 3 years, 36.6% both at 4 and 5 years. The median survival time was 34 months (Fig. 1 and 2). After a median follow-up of 24.9 months (range 2 to 80 months), cancer recurrence was detected in 8 patients (38.0%). MMC and oxaliplatin groups were not comparable in term of survival because of the low follow-up of the oxaliplatin group (Fig. 3).

One patient died during post operative period, 2 months after HIPEC. Minor and major complications occurred in 7 (33.3%) patients with reoperation in 5. Anastomotic leakage represented the most current complications in the post operative period, without significative difference between MMC and Oxaliplatin groups. However, we noticed a significative difference of total morbidity in term of number of complicated patients ($p < 0.05$) with 5 patients attached to the oxaliplatin group (5/8) and 2 to the MMC group (2/13). Number of complications were also different ($p < 0.001$) with a higher morbidity of the oxaliplatin group (Table II).

Even though the smal number of patients included in our study doesn't permit to obtain significative results, we noticed several factors influencing survival (9).

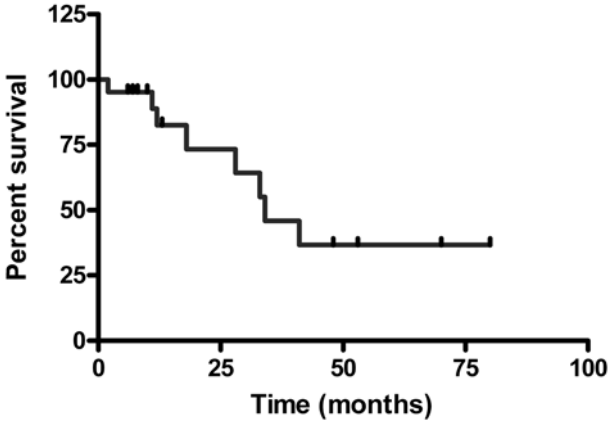

Fig. 1
Overall survival

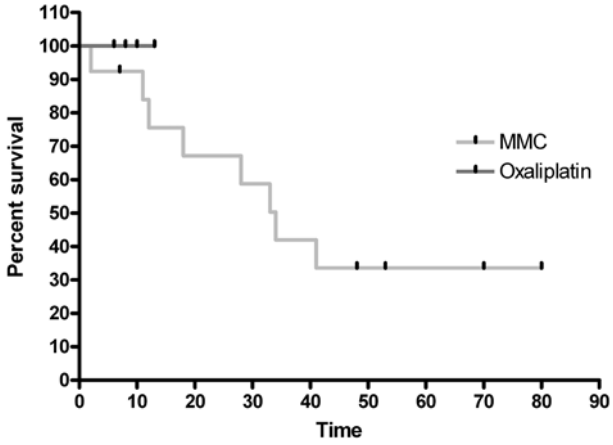

Fig. 3
Survival by drugs

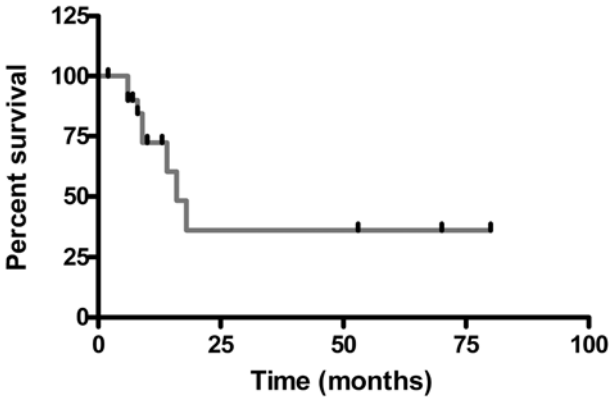

Fig. 2
Disease free survival

The presence of associated metastases seems to have a negative impact with 4-year overall survival rates of 17.5% and 58% without metastases ($p < 0.28$) (Fig. 4).

Our study doesn't confirm the negative impact on survival of the peritoneal cancer index ($p < 0.34$).

Discussion

Complete treatment of PC by cytoreduction and HIPEC has positive impact on survival (10). Several other trials of HIPEC without preliminary maximal cytoreduction surgery described a 5-year survival rate of 0 % (11). However, a complete stripping of all the peritoneum including normal tissue is unnecessary and can result in a high incidence of post operative complications (10).

Table II
Complications

	MMC	Oxaliplatin	
Number of interventions	13	8	p
Complicated patients	2/13	5/8	p < 0,05
Complications (22)			
Grade II (pharmacological treatment)			
Ascitis infection		1	NS
Grade IIIa (radiological intervention under local anesthesia)			
Sub-liver abcess		1	NS
Anastomotic leakage		1	NS
Grade IIIb (surgical reintervention under general anesthesia)			
Anastomotic leakage	2	2	NS
Bowel leakage		1	NS
Ureteral injury		1	NS
Hemothorax		1	NS
Grade V			
Post operative death	1		NS
Total complications	3	8	p < 0,001

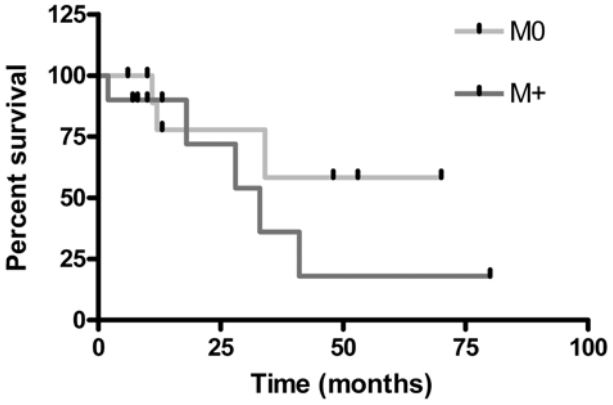

Fig. 4
Survival by metastase staging

We applied this consideration and we could obtain a moderated morbidity and mortality rates (Table III).

The peritoneal carcinomatosis index (PCI), based on a cut off of 16 for ELIAS *et al* (5) or 10 and 20 for SUGARBAKER *et al* (10), has shown a major impact on survival. The encouraging results of our serie could also be attributed to patients who presented a peritoneal carcinomatosis index (PCI) lower than 15, allowing a moderated cytoreduction surgery.

Many authors have proved that non peritoneal metastases have a negative impact on survival after HIPEC (5, 10). In our serie, patients with liver metastases seem to have a worth overall and disease free survival. In fact, we do not recommand synchronous resection of liver metastases. This technic must be reserved for exceptionnal case of alone and unifocal tumor. HIPEC procedure must be valided before to be associated with liver resection.

The study by EILBER *et al.* showed that post operative adhesions prevented complete bathing of the peritoneal cavity and that recurrent peritoneal disease was located in drug "no go" areas (12). It's the reason why we chose HIPEC over early postoperative intraperitoneal chemotherapy (EPIC). The coliseum technique permits a high control of full peritoneal bathing and the surgeon, with the thermal probes monitoring, regularise with precision the 41 to 42.5°C temperature of drug solution.

In HIPEC procedures, a direct activing cell cycle independent cytotoxic agent is needed. We preferred HIPEC over EPIC to avoid the "no go areas" where drugs can not act because of post-operative adherences (5) and because of the potentialisation of the cytotoxic action.

We first chose MMC as chemotherapic agent because of its known activity in colorectal cancer (13), its direct cytotoxic effect, the thermal enhancement of its activity (14), and penetration depth. However, clinical trials and phase III MOSAIC study (15) have proved the high Oxaliplatin efficacity on overall and disease free survival in colorectal cancer. Preclinical study demonstrated that the exposure of peritoneal surfaces to oxaliplatin was significantly increased by intraperitoneal administration than with systemic treatment and hyperthermia showed a trend toward the enhancement of tissue absorption of oxaliplatin (16). In phase I clinical trial (17), oxaliplatin HIPEC showed a high tumour penetration and a limited systemic absorption with a peritoneal absorption 25-fold than in plasma and no haematological, renal nor hepatic toxicity. Ended, given the potentiating effect of 5-FU on oxaliplatin (17) and the impossibility of intraperitoneal administration, a perfusion of 5-FU and folic acid has been proposed before HIPEC. For these reasons, we have changed our MMC protocol since 2001 for oxaliplatin HIPEC associated with systemic 5-FU chemotherapy.

The follow-up of the oxaliplatin group is still too short to estimate differences on survival impact with HIPEC with MMC. However, we noticed a morbidity rate higher in the oxaliplatin group whereas the bathing time is shorter (30') than in MMC HIPEC (90') and the bathing temperature is the same in both group. Only one phase II study of oxaliplatin HIPEC has been reported in literature and no increased morbidity has been described (18). These data must be confirmed with randomised study.

Table III
Review of HIPEC series

	MMC			Oxaliplatin		
	Patients Nb	Morbidity	Mortality	Patients Nb	Morbidity	Mortality
ROUERS A. *et al.*	*13*	*23%*	*7,60%*	*8*	*62,50%*	*0%*
(19)	102	65%	7,80%			
(23)	506	22,40%	4%			
(5)	64	66%	9,30%			
(18)				24	41,60%	8%

As many series (19), important part of our morbidity is represented by leakages. It has been proved that the use of heated chemotherapy has a detrimental effect on the strength of colonic anastomosis, especially during the early postoperative period (until day 10) (20, 21). This may cause anastomotic failure and postoperative morbidity. Therefore, careful selection and avoidance of unnecessary anastomoses are mandatory.

Conclusion

As described in literature, we confirm the high morbidity in patients treated by HIPEC. However, median survival of our serie is very encouraging. Complication rate with MMC, wich is considered as the gold standard in HIPEC since this is the only regimen that has proven its efficacy in a Phase III trial, seems to be lower than with Oxaliplatin. Till a comparative study is realised, we recommand to be cautious with the use of Oxaliplatin in HIPEC.

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