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ORIGINAL ARTICLE

Mitomycin-C versus oxaliplatin during cytoreductive surgery and HIPEC for peritoneal metastases secondary to colorectal carcinoma: a retrospective analysis

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Summary

Purpose: *Combining cytoreductive surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) can benefit patients with peritoneal metastasis from colorectal cancer, however the optimal choice of the HIPEC chemotherapy is still under debate. The present study compares the clinical outcome in patients with peritoneal metastases treated with CRS and HIPEC using Mitomycin – C versus Oxaliplatin.*

Methods: *We retrospectively analyzed patients that underwent CRS and HIPEC for recurrent colorectal cancer with peritoneal metastases. Patient characteristics, procedure details, and clinical outcomes were evaluated.*

Results: *114 consecutive patients were included in the analysis (62 males – 52 females, mean age 58,3 years). The mean intraoperative PCI-score was 15.3 (range: 3 – 36). The mean follow–up period was 28.2 months. Patients receiving MMC – based HIPEC had significantly higher mean overall survival compared to oxaliplatin (54 versus 26 months), translated to a hazard ratio of 0.26 (95% CI 0.128 – 0.529, p<0.01). The HIPEC regimen as well as the completeness of cytoreduction were the only independent prognostic factors of survival in our sample.*

Conclusion: *Our results imply that the use of MMC offers a survival advantage over oxaliplatin when used for HIPEC in CRC PC. A randomised trial comparing oxaliplatin and MMC would enhance decision-making in such patients.*

Key words: *HIPEC, colorectal cancer, mitomycin, oxaliplatin, cytoreductive surgery, peritoneal malignancy.*

Introduction

Colorectal cancer is currently the third most common cancer worldwide, and represents a significant burden [1]. Peritoneal dissemination is the second most frequent site of metastatic disease in these patients, affecting approximately up to 7% of the newly diagnosed patients – despite the advances that facilitate early detection of the disease [2,3] – and up to 30% of patients with recurrent or metastatic colorectal cancer. [4]PC from colorectal cancer origin has been associated with poor prognosis as well as poor quality of life [2,5], as chemotherapy – based treatments usually do not affect the natural course of the disease and yield disappointing outcomes [6] with disease progression in the majority of patients [7].

Over the last three decades, a novel approach in the management of Peritoneal Carcinomatosis (PC) from colorectal cancer origin that involves extensive surgery (Cytoreductive Surgery, CRS) as well as Hyperthermic Intraperitoneal Chemotherapy (HIPEC) has been developed. This multimodal approach includes surgical procedures aiming

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to remove all macroscopic disease using certain standardized surgical techniques, with the addition of HIPEC in order to eradicate any residual tumor burden by direct local administration of chemotherapy to the peritoneal cavity, at an increased temperature that enhances cytotoxicity [8]. The use of CRS and HIPEC in such patients has been shown to have promising results, conferring significant survival benefit in selected patients [9-11].

During the evolution and dissemination of the technique of CRS and HIPEC, several different chemotherapy regimens have been used, including platinum – based regimens, mitomycin-C, fluouracil, and irinotecan, either in combination or as single-agent regimens [12]. To date, no consensus has been reached in this field, and not only the choice of HIPEC drugs, but also the temperature, dose and duration of the administration of the chemotherapy solution remain under debate [13].

Mitomycin-C (MMC) and Oxaliplatin are currently the most frequently administered chemotherapy drugs being used in HIPEC. They are both high molecular weight substances, allowing exposure of tumor cells to high intraperitoneal concentration, with limited systemic toxicity, and have been established as effective drugs in the adjuvant treatment of colorectal cancer [14]. However, data comparing MMC and Oxaliplatin when used in CRS and HIPEC is still scarce, and the studies conducted so far cannot lead to definite conclusions [7,14]. The present study compares the clinical outcome in patients with peritoneal metastases treated with CRS and HIPEC using MMC versus Oxaliplatin.

Methods

The present study is a retrospective analysis of prospectively maintained data from patients that underwent cytoreductive surgery followed by HIPEC for resectable peritoneal carcinomatosis from colorectal cancer in the participating institutes between 2010 and 2018. The study was approved by both institutional ethics and research boards.

Patient selection

All patients underwent detailed preoperative assessment including radiological and/or laparoscopic staging to estimate the extent of peritoneal dissemination and resectability of the disease. Radiological staging included thoracic, abdominal and pelvic computed tomography with oral and intravenous contrast. The patient's performance status was assessed based on the Eastern Cooperative Oncology Group (ECOG) scale [15]. All cases were discussed in a dedicated Multi–Disciplinary Team (MDT) meeting, in which treatment options were discussed, and the MDT results were available to the patients before surgery.

Procedure details

In all cases, a laparotomy was performed and the extent of peritoneal disease was calculated using the PCI score, as described by Sugarbaker et al [16]. In case the tumor burden was deemed to be resectable, cytoreduction was performed using tumor removal, organ resections and peritonectomy techniques as described by Sugarbaker et al [16]. After the surgical procedure, the completeness of cytoreduction (CC) was evaluated for each patient as follows: a CC-0 score indicated no visible tumor in the peritoneal cavity; a CC-1 score indicated residual tumor <2.5mm; a CC-2 score indicated residual tumor 2.5mm-2.5cm; a CC-3 score indicated a residual tumor >2.5cm [16]. Patients with CC-0/CC-1 scores were considered to have undergone complete cytoreduction.

Following cytoreduction, patients underwent HIPEC using the closed abdomen technique. During the closed abdomen technique, all intestinal reconstructions are performed before closure of the abdomen, four tubes (two for inflow of the chemotherapy solution and two for outflow) are inserted and the abdomen was closed with standard abdominal closure techniques. After testing for possible leaks with Normal Saline 0.9%, MMC or Oxaliplatin was administered in the abdominal cavity at an intraperitoneal temperature of 42 degrees Celcius at a dose of 15mg/m^2 (MMC) or 360mg/m^2 (Oxaliplatin) for 60-90 min.

Parameters evaluated

For each patient, demographic data (age, sex, ECOG status), details of the course of the disease (site of primary tumor, previous chemotherapy), and procedural details (PCI score, CC score, HIPEC regimen) were recorded. Overall survival was defined from the time of the surgical procedure to the date of reported death.

Statistics

Overall survival was used as the primary endpoint of this study. For categorical variables, the chi-square and Fisher's exact test were used as appropriate. Survival analysis was performed using the Kaplan-Meier

Table 1. Patient sample characteristics (numbers)

Characteristics	*n*
Sex	
Males	62
Females	52
Mean age, years	58.3 (33-77)
Mean PCI score	15.3 (3-36)
Time from initial surgery	13 months (4-30)
Neoadjuvant chemotherapy	
Yes	63
No	51
HIPEC regimen	
MMC	58
Oxaliplatin	56

Table 2. Comparison of patient group characteristics (numbers)

	MMC (n=58)	*Oxaliplatin (n=56)*	*p*
Sex			
Male	27	35	NS
Female	31	21	
Mean age, years	58.3	58.4	NS
Mean PCI score	14.6	16	NS
Time from initial Sx	13.9 months	12.2 months	NS
NACT			
Yes	28	35	NS
No	30	21	
CC-score			
CC-0/1	48	44	NS
CC-2	10	12	

NS: not significant

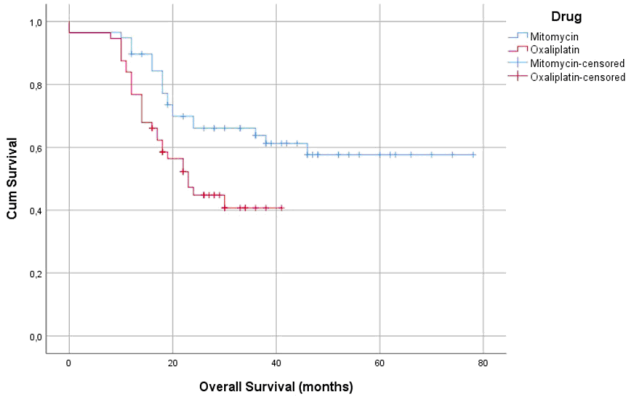

Figure 1. Kaplan – Meier curves for overall survival.

method, and compared using the log-rank test. Multivariate analyses using Cox-regression models (Forward LR and Backward LR) were performed in order to identify independent prognostic factors of survival.

A p value of less than 0.05 was considered statistically significant and the analysis was performed using SPSS v 25 for Windows (SPSS, Chicago, Illinois, USA).

Results

114 consecutive patients were included in the analysis (62 males-52 females, mean age 58.3 years). The mean intraoperative PCI-score was 15.3 (range: 3-36) and the mean follow–up period was 28.2 months. 44.5% of the patients received neoadjuvant chemotherapy prior to the surgical procedure. The patient sample demographics are summarized in Table 1.

58 patients received CRS and HIPEC with MMC whereas 56 patients received CRS and HIPEC with Oxaliplatin, in the dose regimens reported above. There was no significant difference between the two patient groups in terms of age and sex distribution, intraoperative PCI score, time from initial surgery, administration of chemotherapy prior to the surgical procedure or the completeness of cytoreduction (CC-score) (Table 2).

Table 3. Case-processing summary of the patients included in the study

Drug	*Total N*	*N of Events*	*Censored n (%)*
Mitomycin	58	22	36 (62.1)
Oxaliplatin	56	30	26 (46.4)
Overall	114	52	62 (54.4)

62% of the patients receiving MMC-based HIPEC were alive at the end of the follow-up period, compared to 46% of the patients in the Oxaliplatin group (Table 3). Descriptive statistics of survival in both groups are summarized in Table 4. Patients receiving MMC-based HIPEC had significantly higher mean overall survival compared to oxaliplatin (54 versus 26 months), and statistical analysis confirmed that patients receiving MMC-based HIPEC had significantly better overall survival compared to those receiving Oxaliplatin (Log-rank=6.384, p=0.012) (Figure 1).

In a multivariate regression model, statistical analysis identified the HIPEC regimen as well as the completeness of cytoreduction as the only independent prognostic factors of survival in our sample (Table 5).

Discussion

The introduction of cytoreductive surgery with the addition of HIPEC in order to eradicate any residual tumor burden, has changed the management of patients with peritoneal carcinomatosis second-

Table 4. Means and medians for survival time

Drug	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			*LowerBound*	*UpperBound*
Mitomycin	53.669	4.063	45.706	61.632	.	.	.	.
Oxaliplatin	25.937	1.897	22.219	29.655	23.000	3.021	17.078	28.922
Overall	47.086	3.142	40.927	53.245	46.000	.	.	.

[a]Estimation is limited to the largest survival time if it is censored

Table 5. Multivariate analysis of factors affecting overall survival

	B	*SE*	*Wald*	*df*	*Sig.*	*Exp(B)*
Gender	-0.152	0.319	0.229	1	0.632	0.859
Age	0.021	0.016	1.662	1	0.197	1.021
Stage	0.130	0.334	0.152	1	0.696	1.139
Peritoneal cancer index	0.045	0.041	1.193	1	0.275	1.046
Time from initial operation	-0.027	0.048	0.307	1	0.580	0.974
Completeness of cytoreduction score	1.391	0.387	12.952	1	0.000	4.020
Neoadjuvant chemotherapy	-0.775	0.646	1.441	1	0.230	0.461
Drug	-1.347	0.362	13.845	1	0.000	0.260
Progression free survival (months)	0.009	0.031	0.076	1	0.782	1.009

ary to colorectal cancer. As the evidence on the use of CRS and HIPEC in such patients grow, there is increasing interest in fine-tuning the method in terms of choice of the chemotherapeutic agents used.

Oxaliplatin, being the standard of care in the adjuvant and palliative treatment of colorectal cancer patients, has been considered the appropriate HIPEC drug of choice treatment by many groups [17]. Likewise, MMC is also considered a suitable option, as it also has several favourable pharmacokinetic characteristics [18]. Both drugs allow high intraperitoneal concentrations due to their large molecular weight, with minimal systemic absorption [19] and both have been reported to have increased efficacy with hyperthermia [20,21].

The present retrospective cohort study reports a significantly increased overall survival in patients receiving CRS and HIPEC with MMC compared to oxaliplatin. However, results of similar studies have so far been controversial. Ceelen et al [22] reported no significant difference in survival in patients undergoing CRS and HIPEC with MMC versus oxaliplatin, while another retrospective study also showed similar survival rates regardless the chemotherapeutic agent used [23]. Also, neither a Dutch study could demonstrate any difference in overall survival between oxaliplatin and MMC, despite its limitations in terms of the baseline characteristics of the patient sample [24]. On the other hand, in contrast to our results, Leung et al [14]. demonstrated a significant survival benefit in patients treated with HIPEC using oxaliplatin (56 versus 29 months). Finally, most recently, the Prodige 7 trial failed to demonstrate any survival benefit in patients undergoing CRS and HIPEC using oxaliplatin compared to patients receiving CRS alone [25], with an additional burden in terms of increased complication rates, putting skepticism in the concept of HIPEC itself and its use in the treatment of PC secondary to colorectal cancer.

Complication rates and mortality is another important factor that needs to be taken into consideration for the choice of the optimal HIPEC chemotherapy agent. Although the present study did not investigate this parameter, there is evidence that the use oxaliplatin in HIPEC is associated with increased complication rates [26], as also demonstrated in the recently published Prodige 7 study [27], with reported morbidity rates up to 40% [28]. This is a possible reason that many groups opt to use oxaliplatin in lower doses or reduce the HIPEC time, raising questions about the efficacy of the method when used with altered dosimetry and duration [14]. However, the increased complication rates associated with the use of oxaliplatin has not been confirmed in a retrospective cohort study by van Eden et al [29], who report similar outcomes in patients receiving HIPEC with either MMC or oxaliplatin for PC secondary to colorectal cancer.

The present study was carried out in order to investigate a possible difference in survival of patients undergoing CRS and HIPEC for PC secondary to colorectal cancer depending on the chemotherapy regimen used. The study benefits from the fact that the data come from a prospectively maintained database, and the high standardization of the surgical technique and clinical practice between the two centers that contributed to the study. Still, there are several limitations that need to be taken into account: First, some possibly important parameters (e.g ECOG status) and tumor (e.g. initial tumor TNM staging, histology) are missing from our database, and therefore could not be included in the analysis. Secondly, our patient sample is relatively small, and our results ought to be confirmed in larger prospective randomized studies. Nevertheless, our relatively homogeneous patient sample with similar baseline characterestics is reassuring.

In conclusion, our results indicate that the use of MMC offers a survival advantage over oxaliplatin when used for HIPEC in PC secondary to colorectal cancer. It becomes evident that a prospective randomised trial with an adequate patient sample comparing directly oxaliplatin and MMC would enhance decision-making in such patients.

Conflict of interests

The authors declare no conflict of interests.

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