

Avoidance of Early Post-Operative Intraperitoneal Chemotherapy (EPIC) Following Peritonectomy with Heated Intraperitoneal Chemotherapy (HIPEC) Significantly Reduces Cost and Hospital Stay

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Abstract: *Aims:* Peritoneal carcinomatosis is treated with Cytoreductive surgery (CRS) and Heated Intraperitoneal Chemotherapy (HIPEC) with or without Early Postoperative Intraperitoneal Chemotherapy (EPIC) depending on the pathology involved. Since 2010 heated intraperitoneal oxaliplatin has been utilised in our institution. Our aim was to determine if there was a significant cost difference between patients receiving oxaliplatin and those requiring five additional days of EPIC.

Methods: We retrospectively analysed 30 patients from our database. 15 patients underwent cytoreductive surgery, heated intraperitoneal oxaliplatin (350mg/m²) and 5-fluorouracil (FU) intravenously administered intraoperatively. We compared those patients with 15 patients who underwent CRS, heated intraperitoneal mitomycin C (10-25mg/m²) as well as EPIC with 5-FU (600-800mg/m²) on postoperative days 1 to 5. Patients were matched for age, gender, pathology and peritoneal carcinomatosis index (PCI).

Results: There was no significant difference between radiology (p=0.6) and transfusion costs (p=0.4). The chemotherapy costs in the oxaliplatin group were significantly higher (p=0.001) however overall bed costs including ward, HDU and ICU were significantly lower in the oxaliplatin group (p 0.029). There was a higher percentage of patients in the EPIC group that had postoperative ileus (p 0.4), rate of infection (p 0.1), fistula formation (p 0.03), return to theatre (p 0.2) and collection formation (p 0.07) compared to the oxaliplatin group. The overall cost was significantly lower in the oxaliplatin group (p 0.038). There was no significant survival benefit between both groups (p 0.3).

Conclusion: In colorectal cancer the cost and complications of EPIC following HIPEC are unjustified. We now use oxaliplatin HIPEC as our standard regimen in colorectal cancer and appendiceal adenocarcinoma.

Keywords: Cost analysis, cytoreductive surgery, peritonectomy.

INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is now a common treatment for pseudomyxoma peritonei (PMP), malignant mesothelioma, peritoneal carcinomatosis (PC) from colorectal cancer (CRC) and appendiceal carcinoma, currently supported by survival, morbidity and mortality data [1-5].

HIPEC with mitomycin C followed by early postoperative intraperitoneal chemotherapy (EPIC) with 5-fluorouracil (FU) was the first regimen widely utilised based on Sugarbaker's work [6].

More recent data predominantly from France has shown that oxaliplatin has achieved good results and may have some advantage because of the avoidance of EPIC [7, 8].

In a study by Elias *et al.*, CRS and HIPEC with oxaliplatin, a median survival of 63 months was achieved and 51% 5 year survival [9].

Patients with PC with a peritoneal carcinomatosis index (PCI) score less than 19 have a 5 year survival of 29% and if the score is greater than 19 have a five year survival of 7% following CRS and HIPEC [10].

Since 2010 we have changed our protocol for colorectal cancer peritonectomy and omitted the five days of EPIC with 5-FU which was our previous standard with MMC HIPEC.

There is currently no randomised controlled trial of these two regimens.

There is limited data on the cost of cytoreductive surgery and there are no comparable studies of the cost of oxaliplatin versus mitomycin C intraperitoneal treatment. Our aim was to determine if there was a significant cost difference between patients receiving oxaliplatin and those requiring five additional days of early postoperative intraperitoneal chemotherapy (EPIC).

METHODS

We retrospectively analysed 30 patients from a prospective database of 677 patients who have undergone peritonectomy at our institution including 190 cases of colorectal cancer.

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15 consecutive patients underwent cytoreductive surgery, heated intraperitoneal oxaliplatin (350 mg/m²) at 41.5° for 30 minutes at a flow rate of 1 L/min and 5-fluorouracil (FU) intravenously (600-800 mg) administered intraoperatively from the beginning of 2010 to our most recent.

We compared those patients with 15 matched patients who underwent CRS, heated intraperitoneal mitomycin C (10-25 mg/m²) at 41.5° for 90 minutes at flow rate of 1L/min as well as EPIC with 5-FU (600-800 mg/m²) on postoperative days 1 to 5.

Patients were randomly selected from our database but matched for age, gender and peritoneal carcinomatosis index (PCI). A cost analysis was performed comparing groups with regard to cost of chemotherapy, length of stay in HDU/ICU and on the ward, radiology and transfusions requirements. We also analysed our most recent survival statistics for colorectal cancer as well as mesothelioma, Peritoneal Mucinous Carcinomatosis (PMCA) and Disseminated Peritoneal Adenocarcinoma (DPAM). Groups were analysed using paired two tailed t-test where appropriate. Results were deemed statistically significant with a p value < 0.05.

RESULTS

There was no significant difference between the two groups with regard to gender (10 female, 5 male) age (p=0.6) and PCI (p=0.8) as illustrated in Table 1.

The mean operative time was 9 hours in the oxaliplatin group and 7.7 hrs in the HIPEC/EPIC group (0.1).

There was no significant difference between radiology (p=0.6) and transfusion costs (p=0.4). The chemotherapy

costs in the oxaliplatin group were significantly higher (p=0.001) however overall bed costs including ward, HDU and ICU were significantly lower in the oxaliplatin group (p=0.029). Details are outlined in Table 2 and Graph 1.

Postoperative complications are outlined in Table 3. There was a higher percentage of patients in the HIPEC/EPIC group that had a postoperative ileus (p 0.4), rate of infection (p 0.1), fistula formation (p 0.03), return to theatre (p 0.2) and collection formation (p 0.07) compared to the oxaliplatin group. We had no reported anastomotic leaks in our reported thirty patients.

The HIPEC (mitomycin C) and EPIC group had a higher percentage of patients with grade 4 morbidity (three cases versus seven). There was no significant difference between both groups with regard to survival. In the oxaliplatin group the mean mortality time from surgery was 13 months compared to 22 months (p 0.3) in the HIPEC/EPIC group. The St. George Hospital's survival data is outlined in Table 4. The five year survival for colorectal cancer in our institute is twenty percent with a mean PCI of 19.

DISCUSSION

Cytoreductive surgery and HIPEC provides an important chance of long term survival in patients with peritoneal spread of colorectal cancer [1, 11].

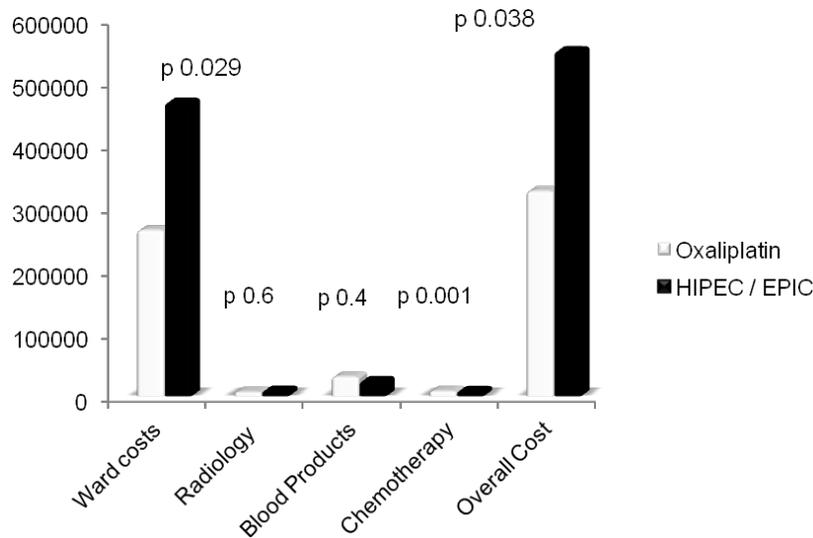
Peritoneal spread of colorectal cancer was associated with death in all patients and a limited and often symptomatic survival until the advent of peritonectomy. The incidence of peritoneal spread of colorectal cancer at the time of presentation has been well described by a number of groups.

Table 1. Comparison of outcome following surgery and heated intraperitoneal chemotherapy (HIPEC) with oxaliplatin versus surgery and HIPEC (mitomycin C) and early postoperative intraperitoneal chemotherapy (EPIC).

	HIPEC Oxaliplatin	Standard Deviation	HIPEC Mitomycin/EPIC	Standard Deviation	p Value	Standard Deviation
Gender (Male:Female)	4:11		4:11			
Age (mean)	55	11	55.5	11	0.6	11
PCI (mean)	13	9.7	12.9	6.4	0.95	8
LOS (days)						
ICU	3	2.3	4.5	6.8	0.3	5
HDU	2.4	2	5	3	0.006	3
Ward	12	8.7	22	11	0.02	11
Total	17	10	34	12	0.0005	13

Table 2. Comparison of cost in patients following surgery and heated intraperitoneal chemotherapy (HIPEC) with oxaliplatin versus surgery and HIPEC (mitomycin C) and early postoperative intraperitoneal chemotherapy (EPIC).

Mean Cost (Aust Dollars)	HIPEC Oxaliplatin	Standard Deviation	HIPEC Mitomycin/EPIC	Standard Deviation	p Value
Ward Costs	6162	6058	11144	15059	0.029
Radiology	496	503	595	486	0.6
Blood Products	2218	1875	3217	1541	0.4
Chemotherapy	552	52	501	6	0.001
Overall Cost	3591	4970	6040	11601	0.038



Graph 1. Cost Analysis: heated intraperitoneal chemotherapy (HIPEC) with oxaliplatin versus HIPEC with mitomycin C and early postoperative intraperitoneal chemotherapy (EPIC). (Australian Dollars).

Peritonectomy has however been associated with significant morbidity and mortality associated with a learning curve outlined by several institutions that have identified improved results but do not identify the factors which have created this improvement [12-15].

Table 3. Comparison of complications in patients following surgery and HIPEC (oxaliplatin) versus surgery and HIPEC (mitomycin C) and EPIC.

Complications	HIPEC Oxaliplatin	HIPEC/EPIC	p Value
	Number (%)	Number (%)	
Infection	4(27)	8(53)	0.1
Fistula	0	4 (27)	0.03
Ileus	3 (20)	5(33)	0.4
Collection	4(27)	9(60)	0.07
Return to Theatre	2(13)	5(33)	0.2

214 (8%) patients were diagnosed with synchronous peritoneal carcinomatosis in a study that included 2756 patients with colorectal cancer [16].

Recently, two population-based studies reported the incidence of synchronous peritoneal carcinomatosis in the Netherlands (4.8%) and in Sweden (4.3%) [17, 18].

A further proportion of patients will develop peritoneal carcinomatosis in their follow up.

Following curative resection for colon cancer metachronous peritoneal carcinomatosis is reported in 4% to 12% of patients in 2% to 19% of patients following curative resection for rectal cancer [19].

Following primary curative resection and undergoing repeat procedures for colorectal cancer, 21% to 44% of patients are diagnosed with peritoneal tumour deposits [20].

The evidence base for peritonectomy/HIPEC in colorectal cancer is now very strong in appropriately selected patients with a randomized trial demonstrating a survival benefit of cytoreductive surgery and intraperitoneal chemotherapy over systemic chemotherapy alone [5, 9, 10, 21-23]. Elias *et al.* have demonstrated a cure rate (16%) after complete CRS of colorectal peritoneal carcinomatosis, followed by intraperitoneal chemotherapy in selected patients is close to that obtained after resection of colorectal liver metastases [1].

It is also true however that selection of patients is critically important both in terms of excluding patients with other untreatable metastatic disease or a PCI of greater than 20.

The five year survival for colorectal cancer in our institute is twenty percent with a mean PCI of 19. Currently in our institution patients with colorectal cancer are considered for peritonectomy with a PCI less than 15 with no

Table 4. St. George Hospital results for peritonectomy for Peritoneal Mucinous Carcinomatosis (PMCA), Disseminated Peritoneal Adenomucinosis (DPAM), mesothelioma and colorectal cancer.

Pathology	Procedure Number	PCI (Mean)	Mean Survival (Months)	5 Year Survival (%)
PMCA	118	20	65	43
DPAM	218	23	133	77
Mesothelioma	55	19	63	53
Colorectal Cancer	190	10	39	20

liver metastases or less than 10 with three or less resectable liver metastases.

The two peritonectomy regimens for intraperitoneal chemotherapy following complete cytoreduction is one of the original regimens of Sugarbaker, HIPEC with mitomycin C and EPIC with 5-Fluorouracil and the more recent French regimens of HIEC with oxaliplatin.

Mitomycin C is the most frequently used intraperitoneal chemotherapy agent for peritoneal carcinomatosis of colorectal and appendiceal origin [24].

Mitomycin C is not without complications such as renal toxicity, haemolytic uremic syndrome, impaired wound healing that can contribute to bowel perforation or anastomotic leak or fistula formation. It has been suggested that 5-Fluorouracil used in conjunction with mitomycin C for five consecutive days of EPIC may be important for long term survival particularly in disseminated peritoneal adenomucinosis (DPAM), however EPIC has its own consequences and is thought to be associated with prolonged ileus and anastomotic failure but has not been previously been compared as in our study [25, 26].

There are side effects which are associated with intraperitoneal oxaliplatin as with all chemotherapeutic agents. The use of 5% dextrose in the chemoperfusion can lead to solute and electrolyte shifts across the mesothelial barrier as well as elevated blood glucose levels. This can be combatted with careful intraoperative intravenous supplementation and continuous insulin infusion.

Our study clearly shows that cost is significantly reduced (p 0.038) by the avoidance of EPIC, this is not a trivial cost in our study as the ward costs were halved. The reason for the cost saving is because of shorter hospital stay and we found that the fistula rate was significantly lower (p 0.03) in the HIPEC alone group. This again is not of trivial importance in the post op recovery in a peritonectomy patient. We presume that the higher fistula rate in the EPIC group is due to the effects of 5-FU on anastomotic healing [27].

We conclude that in CRC the cost and complications of EPIC following HIPEC are unjustified. Whether there is any good reason to continue EPIC 5-FU in DPAM should also be addressed. We now use oxaliplatin HIPEC as our standard regimen in colorectal cancer and appendiceal adenocarcinoma.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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