Morbidity associated with the use of oxaliplatin versus mitomycin C in hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal carcinomatosis of colorectal or appendiceal origin: a multi-institutional comparative study

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Background: The raw costs of mitomycin C (MMC) and oxaliplatin for hyperthermic intraperitoneal chemotherapy (HIPEC) differ substantially. We sought to compare the morbidity and toxicity profiles associated with the use of oxaliplatin and MMC in patients undergoing cytoreductive surgery (CRS) and HIPEC for peritoneal carcinomatosis (PC) of colorectal or appendiceal origin, to evaluate whether the cost-effectiveness of these 2 agents should dictate drug choice.

Methods: We conducted a retrospective multi-institutional study of all patients with PC of colorectal or appendiceal origin treated with CRS-HIPEC using MMC or oxaliplatin from 2010 to 2015. Demographic, perioperative, morbidity, toxicity and cost data were compared between the 2 treatment groups and between cancer-origin subgroups.

Results: Forty-two patients treated with MMC and 76 treated with oxaliplatin were included in the study. Baseline demographic and tumour characteristics were comparable in the 2 groups, except that the patients treated with MMC had higher Charlson Comorbidity Index scores. The MMC group had a higher rate of cancer of colorectal origin (76.2% v. 57.9%, $p = 0.047$) and longer operative times (553 v. 320 min, $p < 0.001$). In the subgroup of patients whose cancer was of colorectal origin, patients treated with MMC had a higher transfusion rate (50.0% v. 28.6%, $p = 0.023$) and lower postoperative baseline hemoglobin level (100 v. 119 g/L, $p = 0.002$) than those treated with oxaliplatin. There was no difference in hematologic toxicity scores after controlling for postoperative anemia. There was no difference in the rates of major complications and 90-day mortality. However, MMC was less costly than oxaliplatin ($724 v. $8928).

Conclusion: MMC and oxaliplatin are both suitable agents for HIPEC and are associated with comparable morbidity and toxicity profiles, regardless of cancer origin. Thus, we propose that cost-effectiveness should ultimately dictate drug selection.

Contexte : Les coûts bruts de la mitomycine C (MMC) et de l'oxaliplatine pour la chimiothérapie hyperthermique intrapéritonéale (CHIP) sont très différents. Nous avons voulu comparer la morbidité et la toxicité associées à l'oxaliplatine et à la MMC chez les patients subissant une chirurgie de réduction tumorale (CRT) et une CHIP pour une carcinomatose péritonéale (CP) d'origine colorectale ou appendiculaire afin d'évaluer si le choix des professionnels de la santé devrait reposer sur le rapport coût–efficacité de ces médicaments.

Méthodes : Nous avons mené une étude multicentrique rétrospective sur tous les patients qui, entre 2010 et 2015, présentaient une CP d'origine colorectale ou appendiculaire et ont subi une CRT ainsi qu'une CHIP à la MMC ou à l'oxaliplatine. Les données relatives aux caractéristiques démographiques, aux résultats périopératoires, à la morbidité, à la toxicité et aux coûts ont été comparées entre les 2 groupes de traitement et entre les sous-groupes formés en fonction de l'origine du cancer.

Résultats : Au total, 42 patients traités à la MMC et 76 patients traités à l'oxaliplatine ont été inclus dans l'étude. Les caractéristiques démographiques et tumorales des 2 groupes avant le traitement étaient semblables, à l'exception de l'indice de comorbidité de Charlson, qui était plus élevé dans le groupe MMC. Le groupe MMC présentait un taux plus important de cancer d'origine colorectale (76,2 % c. 57,9 %; $p = 0,047$), de même qu'un temps opératoire plus long (553 min

c. 320 min; $p < 0{,}001$). En ce qui concerne le sous-groupe de patients atteints d'un cancer d'origine colorectale, les personnes traitées à la MMC affichaient un taux de transfusion plus élevé (50,0 % c. 28,6 %; $p = 0{,}023$) et un taux d'hémoglobine postopératoire de référence plus bas (100 g/L c. 119 g/L; $p = 0{,}002$) que celles traitées à l'oxaliplatine. Une fois l'anémie postopératoire prise en compte, aucune différence n'a été observée quant à la toxicité hématologique. Les taux de complications majeures et de mortalité à 90 jours étaient aussi comparables. La MMC coûtait toutefois moins cher que l'oxaliplatine (724 $ c. 8928 $).

Conclusion : La MMC et l'oxaliplatine conviennent à la CHIP, et la morbidité et la toxicité qui y sont associées sont comparables, quelle que soit l'origine du cancer. Nous proposons donc que le choix du médicament à utiliser repose sur le rapport coût–efficacité.

Peritoneal carcinomatosis (PC) of colorectal or appendiceal origin is associated with a dismal 6-month prognosis if left untreated.[1,2] Despite substantial improvements in chemotherapeutic regimens, fewer than 10% of patients treated with systemic chemotherapy alone survive beyond 5 years.[3]

Cytoreductive surgery (CRS) with complete resection of macroscopic disease, followed by hyperthermic intraperitoneal chemotherapy (HIPEC), is widely used. Combined with systemic chemotherapy, CRS-HIPEC with complete cytoreduction increases the 5-year survival rate to 25%–47% for patients with PC with colorectal primaries.[2–4] For patients with PC arising from the appendix, the 5-year overall survival increases to 40%–62%.[5–8] However, CRS-HIPEC is associated with considerable postoperative morbidity risks. Thirty percent complication rates have been reported in the past and are mainly attributable to perioperative morbidity and bone marrow toxicity.

Although the effectiveness of CRS-HIPEC is well documented, few studies have examined the selection of chemotherapeutic agent, which remains largely institution dependent. Mitomycin C (MMC) and oxaliplatin both have large molecular weights and can achieve high intraperitoneal concentrations with limited systemic absorption, rendering them ideal agents for HIPEC. In a systematic review of the literature, Wisselink and colleagues reported that complication rates were lower when oxaliplatin was used as the chemotherapeutic agent in CRS-HIPEC of colorectal origins than when MMC was used.[9] Tan and colleagues found higher rates of postoperative bleeding when oxaliplatin was used for HIPEC, but they noted no other significant difference in the morbidity or mortality outcomes when the 2 chemotherapeutic agents were compared.[10] One study found a higher survival rate for a subgroup of patients treated with oxaliplatin, including female patients, patients with a peritoneal cancer index (PCI) score of 10–15, patients with tumours presenting without signet ring pathology and patients with moderately to well-differentiated tumours.[11] However, the authors of this study did not conduct a morbidity comparison between the 2 chemotherapeutic agents. A recent prospective randomized trial of 121 patients found relatively small hematologic toxicity rates for both MMC and oxaliplatin. The patients who received oxaliplatin reported a marginally higher quality of life and had slightly lower toxicity rates.[12] The literature suggests that the 2 agents are associated with similar overall survival benefits.[12–14]

Although Van Eden and colleagues suggest using oxaliplatin as the preferred CRS-HIPEC agent on the basis of its shorter infusion times,[15] in this study we aim to assess the financial implications of drug choice, given the limited difference in survival outcomes between the 2 drugs. This study was conducted in a publicly funded health care system, where cost is an important consideration for drug choice when mortality, morbidity and toxicity profiles are comparable. This concept is part of value-based medicine.[16] Value-based medicine is a framework for medical decisions wherein both the clinical effects and the costs of the treatment are evaluated. Combining these variables creates a quantifiable metric called value, which is calculated as benefit divided by cost.[17] Treatments that are beneficial to the patient as well as society at large are considered to be of high value. With the ever-increasing costs of public health care, resource allocation and cost analyses are becoming more important. Given that the survival outcomes associated with MMC and oxaliplatin are comparable, we sought to evaluate the comparative morbidity and toxicity of these 2 drugs in adults undergoing CRS-HIPEC for PC originating from colorectal or appendiceal neoplasms. The values of these 2 chemotherapeutic agents can inform the choice of chemotherapeutic agent.

Methods

Patient selection

Patients with PC of colorectal or appendiceal origin who underwent CRS-HIPEC at 2 Canadian tertiary care centres in Montreal (Maisonneuve-Rosemont Hospital and Jewish General Hospital) between January 2010 and June 2015 were eligible for inclusion. Exclusion criteria included re-do surgery, elective palliative HIPEC, age younger than 18 years, cases with a breach in protocol, and completeness of cytoreduction (CCR) scores higher than 2. All surgeries were performed by experienced surgical oncologists (T.V., L.S., P.D.). The research ethics committees of the 2 institutions

(the Research Ethics Committee of the Jewish General Hospital and Comite d'éthique de la recherche de l'hôpital Maisonneuve-Rosemont) approved the study.

Data collection and outcomes

Baseline demographic data including age, sex, body mass index (BMI) and Charlson Comorbidity Index (CCI)[18] were analyzed. Oncologic data, including the location of the primary cancer and histopathologic characteristics, were evaluated. Intraoperatively, the extent of peritoneal carcinomatosis was evaluated using the PCI. Following cytoreduction, the CCR score was assessed to determine whether complete (CCR-0, CCR-1) or incomplete cytoreduction (CCR-2, CCR-3) had been achieved.[19] Perioperative outcomes, including operative times, estimated blood loss and rate of blood transfusions, were recorded. Postoperatively, toxicity was evaluated on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) for oncology and hematology trials.[20] Toxicity scores were based on cut-off values for each criterion that contribute to the overall score (see Appendix 1, available at canjsurg.ca/001619-a1). Anemia, neutropenia, thrombocytopenia, increases in creatinine concentration, fever, infections and infusions are criteria that contribute to the NCI-CTCAE grading system. The incidence of 30-day complications was analyzed using the Clavien–Dindo grading system.[21] Length of stay and 90-day mortality were also assessed.

Surgical procedure

The HIPEC procedure begins following macroscopically complete cytoreduction (CCR-0, CCR-1). Once the hyperthermic perfusion reaches a temperature of 41°C to 42°C, the intraperitoneal chemotherapeutic agent is added. At the Jewish General Hospital, MMC is instilled at a fixed dose of 40 mg over 90 minutes. At the Maisonneuve-Rosemont Hospital, HIPEC is performed using oxaliplatin at a dose of 460 mg/m^2 over 30 minutes.

Before undergoing their surgery, patients received neoadjuvant systemic chemotherapy treatment for approximately 3–6 months, usually with FOLFOX with or without bevacizumab, which was stopped approximately 6 weeks before surgery. These treatments, although fairly standard between the 2 groups, were tailored to each patient. We were unable to collect these preoperative data because some patients received their chemotherapy treatment in a community hospital before being admitted to 1 of the study hospitals.

Statistical analysis

Continuous variables, expressed as medians (ranges), were compared using the Mann–Whitney *U* test. Categorical variables were compared using the Fisher exact test. A subgroup analysis was performed comparing MMC and oxaliplatin on the basis of cancer origin using all the above-mentioned outcomes. For the entire cohort, an analysis was also performed to compare the resulsts for patients whose cancer was of appendiceal versus colorectal origin, irrespective of the treatment drug received. No surgeon-specific subgroup analysis was performed given that only 1 surgeon performs this surgery at the Jewish General Hospital using solely MMC, and at the Maisonneuve-Rosemont Hospital the 2 surgeons who perform this procedure collaborate on most cases using solely oxaliplatin. A multivariate analysis was used to clarify the effect of tumour origin on the difference in transfusion rates and toxicity scores between the 2 drug groups. A 2-tailed p value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 17.0 statistical software (IBM).

Results

Of 392 patients reviewed, who underwent or planned to undergo CRS-HIPEC for PC of colorectal or appendiceal origin, 118 patients met the inclusion criteria and were included in the study. Seventy-six patients received oxaliplatin at the Maisonneuve-Rosemont Hospital, and 42 patients were treated with MMC at the Jewish General Hospital (Figure 1).

Baseline demographic characteristics were similar between the 2 treatment groups (Table 1). However, the MMC group had significantly higher CCI scores than the oxaliplatin group (9 v. 9, $p = 0.003$). There were significantly more tumours of colorectal origin in the MMC group (76.2% v. 57.9%, $p = 0.047$), but there were no significant differences in the histopathologic characteristics of the tumour between the 2 groups (Table 2).

Perioperative outcomes are shown in Table 3. The PCI scores were similar between the 2 groups. However, higher rates of complete cytoreduction (CCR-0) were achieved among the subgroup of patients with PC of colorectal origin who received oxaliplatin than among those who received MMC (97.6% v. 84.4%, $p = 0.039$). In the entire cohort, the MMC group had significantly longer operative times than the oxaliplatin group (553 v. 320 min, $p < 0.001$). Figure 2 depicts the hemoglobin trends throughout the 30-day postoperative period. Although the MMC group started at a lower hemoglobin level, the overall postoperative trend was similar for the 2 groups. The cumulative transfusion rate was significantly higher for the MMC group than for the oxaliplatin group (50.0% v. 28.6%, $p = 0.023$). This difference can be attributed to the higher rates of blood transfusion among patients in the colorectal subgroup, the majority of whom received their tranfusions postoperatively (50.0% v. 24.4%, $p = 0.023$).

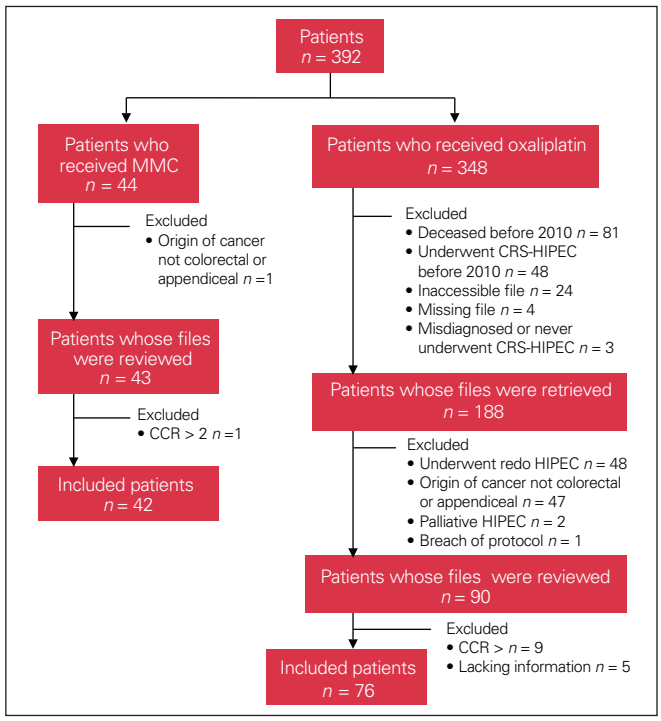

Fig. 1. Flow diagram of the selection process used to identify patients for inclusion in the study. CCR = completeness of cytoreduction; CRS = cytoreductive surgery; HIPEC = hyperthermic intraperitoneal chemotherapy; MMC = mitomycin C.

Table 1. Demographic characteristics of study patients

Characteristic	Treatment group		*p* value
	Mitomycin C	Oxaliplatin	
Age, yr, median (range)	59 (35–76)	57 (35–72)	0.17
Sex, male, %	54.8	36.8	0.06
Height, cm, median (range)	172 (156–183)	165 (105–189)	0.10
Weight, kg, median (range)	76 (48–103)	71 (50–125)	0.77
Body mass index, median (range)	25.1 (18.8–33.6)	25.7 (16.5–56.2)	0.22
CCI score, median (range)	9 (6–14)	9 (1–11)	0.003
CCI median score below relative median value	42.86	21.05	0.012

CCI = Charlson Comorbidity Index.

Table 2. Tumour characteristics of study patients

Characteristic	% of patients; treatment group		*p* value
	Mitomycin C	Oxaliplatin	
Appendiceal origin	23.8	40.8	0.06
Colorectal origin	76.2	57.9	0.047
Unknown origin	0	1.3	—
Cancer grade			
Low	33.3	47.4	0.14
Moderate	11.9	17.1	0.45
High	19.0	14.5	0.52
Unknown	35.7	21.1	0.08
Mucinous cancer	42.9	57.9	0.08
Adenocarcinoma	85.7	89.0	0.60

As shown in Table 4, a significant difference was noted in the toxicity grades between the MMC and oxaliplatin groups. Further analysis showed that this difference can be attributed to the higher toxicity found in the colorectal subgroup that received MMC. Notably, the postoperative hemoglobin levels were significantly lower in the colorectal subgroup that received MMC (100.0 v. 118.5, $p = 0.002$). In addition, there was no correlation between higher CCI scores and greater postoperative toxicity (Figure 3). The incidence of postoperative complications was similar between the 2 groups in the entire cohort (59.5% v. 69.7%, $p = 0.262$), even when complications were subdivided into minor (Clavien–Dindo grades I and II) and major (Clavien–Dindo grades III and IV) ones (major: 40% v. 41.5%; minor: 60.0% v. 58.5%, $p = 0.90$) (Appendix 1).

No statistically significant differences were noted in 90-day mortality rates between the 2 groups (Table 5). One patient in the MMC group died within 90 days postoperatively because of a biliary leak associated with microangiopathic hemolytic anemia and pleural effusions secondary to metastatic disease.

When we combined the MMC and the oxaliplatin groups and stratified them solely on the basis of whether their cancer was of appendiceal or colorectal origin, no statistical differences were found in the baseline demographic characteristics or in the perioperative, toxicity and mortality outcomes between the 2 groups. Patients with PC of appendiceal origin were found to have significantly lower cancer grades and lower recurrence rates than patients with colorectal primaries. There was a predominance of adenocarcinomas in the colorectal subgroup and a predominance of mucinous cancers in the appendiceal subgroup. PCI scores were significantly higher in the appendiceal group, although this did not translate to differences in CCR scores, operating times or morbidity outcomes.

The raw cost of each drug was obtained through the hospital's pharmacy in Canadian dollars per milligram, from which the estimated raw cost of each drug was determined. The raw cost of MMC was $724 and that of oxaliplatin was $8928 at the institutions at which they were used. At the time of this study, oxaliplatin was not available through generic branding; however, costs remained similar once the generic option became available.

Discussion

During the last 2 decades, an increasing body of evidence has been published in support of CRS-HIPEC for PC of appendiceal and colorectal origin. The overall survival rates have increased to 25%–47% and 40%–62% for PC of appendiceal and colorectal origin, respectively.[2–8] MMC and oxaliplatin are commonly used agents, which confer a comparable survival benefit.[14] However, analyzing the overall morbidity associated with a combined treatment,

Table 3. Perioperative outcomes of study patients

	All patients			Patients with PC of colorectal origin		
Outcome	Mitomycin C	Oxaliplatin	*p* value	Mitomycin C	Oxaliplatin	*p* value
PCI score, median (range)	9 (0–26)	8 (0–28)	0.67	7 (0–22)	6 (0–28)	0.30
CCR score of 0, %	83.3	88.2	0.25	84.4	97.6	0.039
OR time, min	553 (275–936)	320 (130–767)	< 0.001	549.5 (275–936)	318 (130–767)	< 0.001
Total OR time minus HIPEC time	462 (185–846)	290 (100–737)	< 0.001	459.5 (185–846)	288 (100–737)	< 0.001
Estimated blood loss, mL, median (range)	500 (0–3000)	500 (100–5400)	0.81	520 (0–3000)	500 (100–5400)	1.0
Blood transfusion, no. (%)	21/42 (50.0)	20/70 (28.6)	0.023	16/32 (50.0)	10/31 (24.4)	0.023
Transfusion of pRBC, no. (%)						
Intraoperative	8/21 (38.1)	4/20 (20.0)	0.20	6/16 (37.5)	4/10 (40.0)	0.90
Postoperative	18/21 (85.7)	18/20 (90.0)	0.68	14/16 (87.5)	8/10 (80.0)	0.61

CCR = completeness of cytoreduction; HIPEC = hyperthermic intraperitoneal chemotherapy; OR = operating room; PC = peritoneal carcinomatosis; PCI = peritoneal cancer index; pRBC = packed red blood cells.

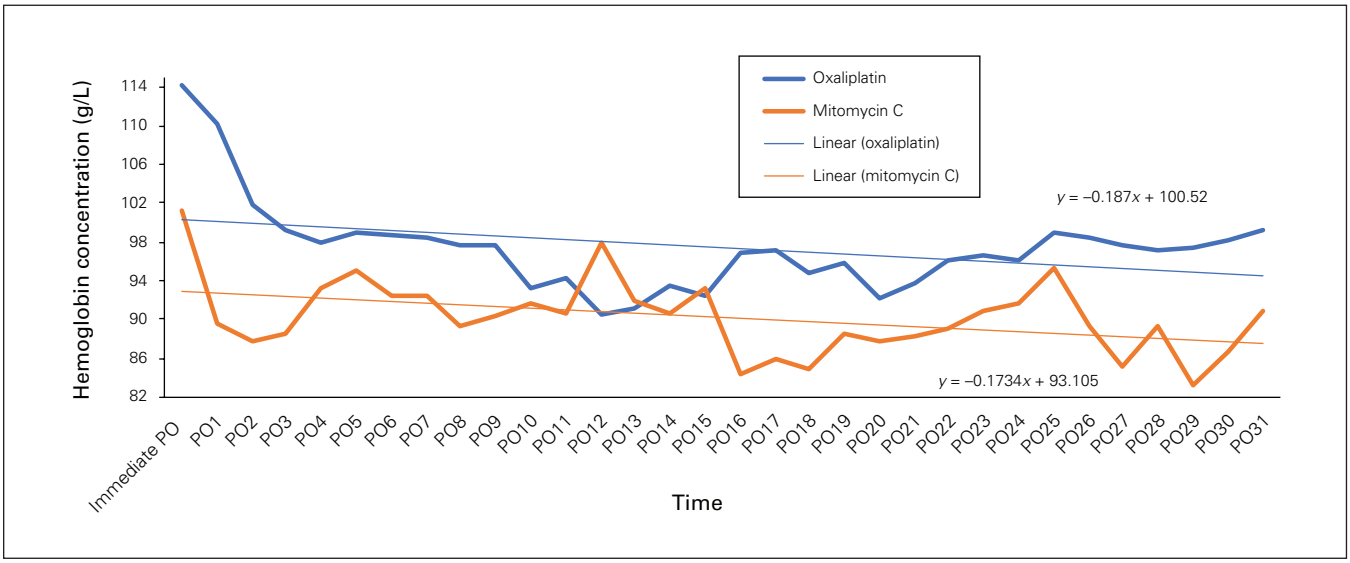

Fig. 2. One-month postoperative hemoglobin levels of patients who underwent hyperthermic intraperitoneal chemotherapy with mytomycin C or oxaliplatin. PO = postoperative.

Table 4. Postoperative toxicity and morbidity of study patients

	All patients			Patients with PC of colorectal origin		
Characteristic	Mitomycin C	Oxaliplatin	*p* value	Mitomycin C	Oxaliplatin	*p* value
Fever, %	47.6	40.7	0.47	37.5	38.6	0.92
National Cancer Institute Common Toxicity Criteria for Adverse Events, median (range)	3 (1–4)	2 (0–4)	0.002	3 (1–4)	2 (1–4)	0.010
National Cancer Institute Common Toxicity Criteria for Adverse Events (high), %	61.9	38.2	0.013	59.4	38.6	0.07
Immediate postoperative hemoglobin level (RBC), g/L, median (range)	100 (70–140)	117 (73–142)	0.001	100 (70–137)	118 (76–142)	0.002
Postoperative complication occurrence, no. (%)*	25/42 (59.5)	53/76 (69.7)	0.26	18/32 (56.3)	29/44 (65.9)	0.39
Clavien–Dindo grade (high), no. (%)	10/25 (40.0)	22/53 (41.5)	0.90	5/18 (27.8)	9/29 (31.0)	0.81
Length of stay , d	12 (6–76)	14.5 (7–64)	0.95	12 (6–76)	14 (7–64)	0.88

PC = peritoneal carcinomatosis; RBC = red blood cells.

*See Table S9 in Appendix 1 (canjsurg.ca/001619-a1) for a classification of the complications experienced by patients in this study and a breakdown of their frequency in the study groups.

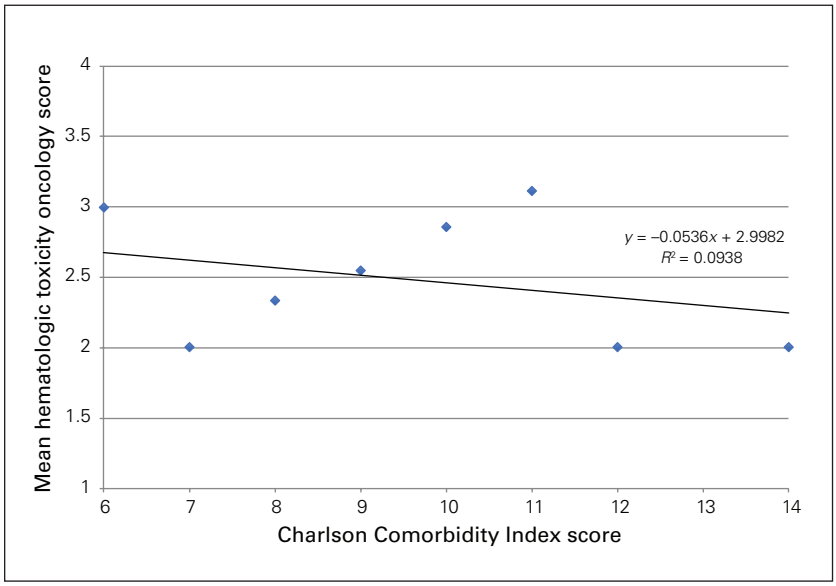

Fig. 3. Mean hematologic toxicity oncology score per Charlson Comorbidity Index score of the 42 patients who received mytomycin C.

Table 5. Long-term outcomes of study patients

Outcome	Treatment group		*p* value
	Mitomycin C	Oxaliplatin	
Disease-free interval, d, median (range)	350 (71–766)	246 (84–1327)	0.84
Disease recurrence, %	45.2	37.3	0.46
90-day mortality, %	2.9	0	0.16

such as cytoreduction and HIPEC, is a complex undertaking. The NCI-CTCAE grading system reflects toxicity from the chemotherapy, whereas surgical complications from cytoreduction are captured in the Clavien–Dindo classification system. In this multi-institutional study, we used these parameters to compare the morbidity associated with MMC and oxaliplatin.

Although the 2 groups of patients underwent CRS-HIPEC at different institutions, they were highly comparable with respect to tumour characteristics. In addition, the same 3 surgeons performed all of the procedures, thus minimizing interoperator variability in surgical technique.

Although some differences were found in histopathologic characteristics between the appendiceal and colorectal groups, they were consistent with the known behaviours of these cancers.[22] The lower cancerous grade and recurrence rate of appendiceal cancer and the predominance of nonmucinous adenocarcinomas in the patients with cancer of colorectal origin are consistent with the current literature. The PCI score was significantly higher in the appendiceal group, which is consistent with the results of the study by Son and colleagues that demonstrated higher rates of peritoneal seeding in appendiceal cancers and higher rates of metastatic invasion in perforated cancers, which were predominantly of appendiceal origin.[22] However, this difference in tumour characteristic between the cancers of appendiceal and colorectal origin did not affect the perioperative variables or the primary outcomes.

The overall toxicity was high in both groups, but it was comparable to standards reported in the literature.[14] A total 61.9% of patients who received MMC and 38.2% of patients who received oxaliplatin experienced at least a grade 3 hematologic toxicity. The higher toxicity grades in the MMC colorectal subgroup probably reflect the relative postoperative anemia of these patients and differences in institutional practices for transfusion, rather than actual increased toxicity of the chemotherapeutic agent. We confirmed on multivariate analysis that even after we adjusted for tumour origin, MMC remained associated with higher transfusion rates and higher toxicity rates. Of note, the patients who received MMC had significantly higher CCI scores than those who received oxaliplatin. Although a higher comorbidity score could theoretically potentiate chemotherapy-related toxicity, no clear correlation could be found between higher CCI scores and greater postoperative toxicity in our study.

One parameter assessed by the NCI-CTCAE toxicity criteria in oncology and hematology is postoperative anemia, with increasing severity of postoperative anemia corresponding to higher grades of toxicity. Interestingly, in the subgroup of patients with cancer of colorectal origin, the immediate postoperative hemoglobin value was significantly lower in patients who received MMC than in those who received oxaliplatin, even though they had comparable estimated blood loss. Unsurprisingly, a trend toward increased rates of postoperative transfusions was noted in the MMC group, but it did not achieve statistical significance. Therefore, the higher toxicity grades in the MMC group may reflect the relative anemia of these patients rather than a true increase in the toxicity of the agent. There were no differences in the incidence of Clavien–Dindo grade I and II and Clavien–Dindo grade III and IV complications between the 2 groups. Ninety-day mortality rates were similar for patients receiving MMC and oxaliplatin and in keeping with previously reported data.[13]

Overall, our study highlights that these 2 chemotherapeutic agents are associated with comparable operative morbidity and toxicity. In addition, all patients receive neoadjuvant chemotherapy, usually on a backbone of FOLFOX, ending approximately 4–6 weeks before surgical intervention. Thus, it appears unlikely that differences in preoperative systemic chemotherapy treatment may be influencing the immediate postoperative

hemoglobin levels. To better understand the difference in baseline hemoglobin levels between the 2 groups, the preoperative systemic chemotherapy treatments would need to be analyzed, as it is known that chemotherapy-induced anemia peaks within the first 6 weeks following treatment.[23]

The MMC group had significantly longer operative times than the oxaliplatin group. Of note, MMC was instilled in the peritoneal cavity for 90 minutes compared with 30 minutes for oxaliplatin. However, even when the operative times were adjusted to account for this difference, it remained statistically significant. Therefore, this discrepancy is probably attributable to variations in institutional practices and surgical teams.

The results of this study are in agreement with those obtained in a prospective multicentre randomized trial by Levine and colleagues published in 2018.[12] In their study, the authors sought to compare levels of hematologic toxicities in 121 patients who survived appendiceal cancer who underwent CRS-HIPEC. After intraperitoneal treatment injection of oxaliplatin or MMC, the 2 groups shared similar PCI scores, mortality rates, morbidity rates and 30-day Clavien–Dindo scores. The overall and disease-free survival rates were comparable for the oxaliplatin and MMC groups. However, owing to slight differences in hematologic toxicity, Levine and colleagues suggested that oxaliplatin was the preferred treatment for patients with leukopenia, whereas MMC was the preferred treatment for patients with thrombocytopenia.[12] This is consistent with the toxicity results of our study when we controlled for postoperative anemia.

Wisselink and colleagues conducted a systematic literature review that compared the use of MMC and oxaliplatin for CRC-HIPEC in patients with cancer of colorectal origin and found comparable results to our study concerning toxicity and mortality between the 2 groups.[9] Their study found significant heterogeneity in severe postoperative complications between the 2 groups whereas our study found no significant difference in the postoperative complication rate between the groups. Although we found no statistically significant difference in the disease-free interval, recurrence rate and 90-day mortality rate between the groups, Wisselink and colleagues reported that no meaningful comparison could be drawn for overall survival and disease-free survival for the 2 groups. They found that the major differences between MMC and oxaliplatin treatment included duration of HIPEC and completeness of cytoreduction. We concur that there is a significant difference in operative times and duration of HIPEC between the 2 groups. However, we were only able to find a difference in the completeness of cytoreduction rates when we analyzed the results for the colorectal subgroup alone. They also identified important differences in baseline demographics between the MMC and oxaliplatin groups including the synchronous and metachronous presentation and differences in neoadjuvant systemic chemotherapy regimen, both of which, as discussed above, are potential influencers of outcome, particularly the postoperative hemoglobin toxicity levels.

Given their similar toxicity, morbidity and mortality profiles, MMC and oxaliplatin are both suitable agents for intraperitoneal chemotherapy, and the choice can be based on surgeon and institutional preference. In the context of the Canadian health care system, in which fiscal pressures are increasing, cost-effectiveness and value are increasingly important drivers of patient care. Assuming all other clinical outcomes are comparable, cost-effectiveness should guide the choice of chemotherapeutic agent. Using the value-based approach, since there is no statistically significant difference in outcomes, the cost-effectiveness becomes a deciding factor in drug choice.

The preliminary cost comparison revealed that the difference in costs between the drugs was significant. However, there is a cost associated with the 60-minute additional infusion time with MMC. Paci and colleagues calculated the average cost per minute of operating room time in Canada to be $21.86 for patients undergoing elective thoracic surgery. Using this estimate, which was obtained in a sister tertiary care institution at McGill University, the difference in drug costs after correcting for the added duration of the MMC infusion was $6892 ($2036 for MMC versus $8928 for oxaliplatin), which is substantial.[24]

Limitations

This study is a retrospective study, and the files from the Maisonneuve-Rosemont Hospital were paper files at the time of data collection; some data were irretrievable as a result. Further complicating the collection of data on the preoperative chemotherapy treatments, not all patients at Maisonneuve-Rosemont Hospital received their treatment at the same hospital at which they underwent surgery. Given that all of the patients who received MMC were treated at a single hospital (Jewish General Hospital) and all of the patients who received oxaliplatin were treated at a different hospital (Maisonneuve-Rosemont Hospital), it is difficult to differentiate between institutional differences and differences in surgical practices or even mortality outcome. In addition, there were a limited number of cases of appendiceal origin (10 patients received MMC and 13 received oxaliplatin), limiting the statistical power of the subgroup analyses.

Conclusion

For patients with PC of colorectal and appendiceal origin who undergo CRS-HIPEC, the use of oxaliplatin and MMC is associated with comparable toxicity and morbidity outcomes. With all outcome parameters being equal, differences in cost-effectiveness may drive the selection of 1 agent over the other.

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