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Incidence, Risk Factors, and Impact of Severe Neutropenia After Hyperthermic Intraperitoneal Mitomycin C

Laura A. Lambert, MD[1,7], Terri S. Armstrong, PhD[2], J. Jack Lee, PhD[3], Suyu Liu, MS[3], Matthew H. G. Katz, MD[4], Cathy Eng, MD[5], Robert A. Wolff, MD[4], Melissa L. Tortorice, BS[2], Pier Tansey, MS[1], Santiago Gonzalez-Moreno, MD, PhD[6], Donald H. Lambert, MD, PhD[8], and Paul F. Mansfield, MD[1]

[1]Department of Surgical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; [2]University of Texas–Houston School of Nursing, Houston, TX; [3]Department of Biostatistics, The University of Texas M.D. Anderson Cancer Center, Houston, TX; [4]Department of Surgical Oncology, UC Irvine Medical Center, Orange, CA; [5]Department of GI Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX; [6]Department of Surgical Oncology, Centro Oncológico MD Anderson International España, Madrid, Spain; [7]Division of Surgical Oncology, UMass Memorial Medical Center, Worcester, MA; [8]Department of Anesthesia, Boston Medical Center, Boston, MA

ABSTRACT

Background. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are considered the standard of care for patients with peritoneal dissemination of appendiceal cancer and are increasingly being evaluated for use in patients with carcinomatosis from colon cancer. Mitomycin C (MMC) is one of the most frequently used HIPEC agents in the management of peritoneal-based gastrointestinal malignancies. This study analyzes the incidence and risk factors for developing neutropenia following MMC-HIPEC combined with CRS.

Methods. All patients undergoing CRS and MMC-HIPEC for appendiceal cancer between January 1993 and October 2006 were retrospectively reviewed. Logistic regression was used to identify risk factors for the development of neutropenia, defined as an absolute neutrophil count (ANC) $<1{,}000/mm^3$.

Results. One hundred and twenty MMC-HIPEC were performed in 117 patients with appendiceal cancer. The incidence of neutropenia was 39%. Neutropenia occurred in 57.6% of female and 21.3% of male patients ($p < 0.0001$). Female gender and MMC dose per body surface area (BSA) were independent risk factors for neutropenia on multivariable logistic regression [odds ratio (OR) of neutropenia in females = 3.58 (95% confidence interval, CI: 1.52, 8.43); OR for 5 unit (mg/m^2) increase in MMC dose per BSA = 3.37 (95% CI: 1.72, 6.63)]. Neutropenia did not increase the risk of mortality, postoperative infection or length of hospital stay.

Conclusion. Neutropenia is a frequent complication associated with MMC-HIPEC. Female sex and MMC dose per BSA are independent risk factors for neutropenia. These differences must be considered in the management of patients undergoing MMC-HIPEC to minimize the toxicity of the procedure.

Peritoneal dissemination is a frequent occurrence for mucinous neoplasms of the appendix and it is lethal if untreated. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is considered the standard of care for this disease.[1] In addition CRS with HIPEC is increasingly being used for other peritoneal-based malignancies such as peritoneal mesothelioma and carcinomatosis from colorectal cancer.[2,3] The survival advantage associated with HIPEC has been shown to be dependent upon achieving a complete cytoreduction.[4–6] For this reason CRS and HIPEC often requires a long, morbidity-prone operation, frequently requiring resection of multiple abdominal viscera and stripping of the peritoneum. The extent of the abdominal operation combined with the side-effects of the HIPEC makes this treatment one of the most morbid that cancer patients endure.

Mitomycin C (MMC) is the most frequently used chemotherapy agent in CRS and HIPEC for peritoneal

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L. A. Lambert, MD
e-mail: laura.lambert@umassmemorial.org

dissemination of gastrointestinal malignancies. Systemic administration of MMC is now rare due to its significant cumulative toxicity and the advent of more efficacious and less toxic multi-agent regimens. However, for a number of reasons, MMC is appealing as a HIPEC agent. First, MMC's high molecular weight limits its systemic absorption and toxicity after intraperitoneal (IP) administration. In addition, MMC's pharmacokinetic profile results in rapid tissue concentration in residual tumor deposits and the peritoneum over prolonged periods of time.[7,8] Furthermore, MMC's cytotoxicity is synergistic with hyperthermia.[9]

In spite of these pharmacokinetic advantages, IP MMC is not devoid of systemic toxicity. Cumulative dose-related myelosuppression remains MMC's most common toxicity whether given intravenously or intraperitoneally, with recent reports indicating a 28% incidence of myelosuppression with single-agent IP therapy.[10] Severe myelosuppression in the acute postoperative phase raises many concerns about life-threatening sepsis, poor wound healing, and increased risk of other significant complications. In a previous report, a 66% mortality rate was associated with HIPEC-induced neutropenia in a small group of patients treated with HIPEC followed by early postoperative IP chemotherapy.[11]

This study investigates the incidence and risk factors for developing neutropenia after CRS and HIPEC with MMC. The impact of severe neutropenia upon postoperative recovery and the rate of infectious complications after CRS and HIPEC were also explored.

MATERIALS AND METHODS

This is a retrospective review of 117 consecutive patients with peritoneal dissemination of noncarcinoid appendiceal neoplasms who underwent 120 CRS procedures with MMC-HIPEC between January 1993 and October 2006. The institutional review board approved the retrospective data analysis. At the time of CRS and HIPEC, the following information was collected prospectively for each patient: age, sex, height, weight, body mass index (BMI), body surface area (BSA), history of prior systemic chemotherapy, and baseline laboratory studies. Eligibility for CRS and HIPEC included absolute neutrophil count (ANC) >1,200/mm^3, white blood cell count (WBC) >4,000/mm^3, and platelet count >150,000/mm^3. Additional requirements included international normalized ratio (INR) ≤1.5, adequate hepatic function [total serum bilirubin ≤1.5 mg/dl, alkaline phosphatase <2.5 times the upper limit of normal, and aspartate aminotransferase (AST) <1.5 times upper limit of normal], and blood urea nitrogen (BUN) and creatinine within normal limits. All patients had a complete history and physical examination, electrocardiogram, and chest imaging within 3 months of CRS and HIPEC. Only patients with adequate performance status and computed tomography (CT) imaging that suggested the feasibility of a complete cytoreduction underwent CRS and HIPEC.

CRS included attempted surgical resection of all macroscopic tumor deposits on parietal and visceral peritoneal surfaces, and resection of involved viscera. This was followed by a 90-min closed-abdomen IP perfusion of MMC with target peritoneal surface temperatures over 40°C to eradicate residual disease. The dose of MMC and volume of perfusate were calculated according to a standardized, weight-based algorithm adjusted for any prior chemotherapy (Table 1). This algorithm was constructed to ensure an MMC concentration of 7.5–10 μg/ml. Data recorded at the time of surgery included: total operation time, estimated blood loss, fluid replacement and intraoperative transfusions, viscera and tissues removed (including splenectomy), and volume of perfusate recovered at completion of the HIPEC.

Data recorded postoperatively included: 30-day mortality, the occurrence of neutropenia, length of hospital stay, and development of infectious complications. Post-HIPEC neutropenia was defined according to the National Cancer Institute (NCI) *Common Terminology Criteria for Adverse Events* version 3.0 as grade 3 or 4 (ANC <1,000 cells/ml^3). All patients with neutropenia were placed on standard neutropenic precautions and treated daily with granulocyte-colony stimulating factor (G-CSF) until resolution (ANC >1,000 cell/ml^3). Analysis was then carried out to evaluate factors associated with developing neutropenia.

Statistical Analysis

The incidence of CRS and HIPEC was used as the analysis unit. Chi-square test, Fisher's exact test, and Wilcoxon test were used to compare the demographic and clinical characteristics, such as gender, BMI, and MMC dose, between neutropenic and nonneutropenic patients. After identifying those factors with significant effect on neutropenia, the logistic regression analysis was performed to find the multicovariate independent predictors. The Hosmer–Lemeshow test was employed for checking the goodness of fit of the model. In addition, continuous

TABLE 1 Weight-based intraperitoneal mitomycin C dosing algorithm

Weight (kg)	No prior CTX (mg)	Prior CTX (mg)	Perfusate (L)
<60	50	37.5	5
60–75	55	41.25	5.5
75–90	60	45	6
>90	65	48.75	6.5

variables were evaluated with summary statistics (mean, median, standard deviation). Frequency tables were used to summarize discrete variables. All tests were two-sided. P values ≤ 0.05 were considered statistically significant.

RESULTS

Between January 1993 and October 2006, 117 patients underwent 120 CRS and HIPEC with MMC for peritoneal dissemination of noncarcinoid appendiceal neoplasms. Complete data were available after 119 MMC-HIPEC. Table 2 shows the preoperative and operative demographics. Fifty-one percent of the patients were male. The median age of all patients was 50 years (range 27–71 years). Thirty-six (30%) patients had chemotherapy prior to CRS and HIPEC. The median dose of MMC was 55.0 mg (range 37.5–65.0 mg) and the median MMC dose standardized for BSA (sMMC) was 29.1 mg/m^2 (range 17.6–36.0 mg/m^2). The median proportion of perfusate volume recovered at the completion of HIPEC was 72.7% (range 43.1–94.5%). The median length of surgery was 9.3 h (range 6.0–18.8 h) and the median estimated blood loss was 750 ml (range 150–4,200 ml). Seventy-one (60%) patients received an intraoperative blood transfusion, and 69 (58%) patients underwent splenectomy. The median hospital stay was 22 days (range 8–83 days). There were two perioperative deaths (30-day or same-hospitalization mortality of 1.7%). One had neutropenia, and the other one did not.

Table 3 describes the occurrence of neutropenia and relationship to demographic and clinical variables. The overall incidence of neutropenia was 39% ($n = 47$). The median time to onset of neutropenia was 9 days (range 4–14 days) with a median duration of 2 days (range 1–8 days). The incidence of neutropenia in female patients was 58% ($n = 34$) and 21% ($n = 13$) in males ($P < 0.0001$). There was no difference in the incidence of neutropenia based upon age (above or below 50 years) at time of HIPEC ($P = 0.79$). Patients who developed neutropenia had a significantly lower BMI (median 25.0 kg/m^2, range 19.0–36.2 kg/m^2) than patients who did not develop neutropenia (median 27.0 kg/m^2, range 19.0–42.6 kg/m^2) ($P = 0.02$). Similarly, patients who developed neutropenia had a significantly lower BSA (median 1.77 m^2, range 1.39–2.36 m^2) than patients who did not develop neutropenia (median 2.04 m^2, range 1.41–2.52 m^2) ($P = 0.0001$). There was no significant difference in the MMC dose of patients who developed neutropenia (median 55.0 mg, range 41.3–65.0 mg) and those who did not develop neutropenia (median 55.0 mg, range 37.5–65.0 mg) ($P = 0.95$). However, the median sMMC dose in the patients who developed neutropenia (30.8 mg/m^2, range 20.9–36.0 mg/m^2) was statistically significantly higher compared with those who did not (27.4 mg/m^2, range 17.6–33.2 mg/m^2) ($P < 0.0001$). Of the 36 patients who had received chemotherapy prior to CRS and HIPEC, 8 (22%) developed neutropenia compared with 39 (46%)

TABLE 2 Overall CRS and HIPEC characteristics

Characteristic	Number	%
Total patients	117	
Total CRS and HIPEC	120	
Sex		
Male	60	51
Female	57	49
Age (years)		
Median	50	
Range	27–71	
BMI (kg/m^2)		
Median	26	
Range	19–43	
BSA (m^2)		
Median	1.96	
Range	1.39–2.52	
Splenectomy		
No	51	42
Yes	69	58
Transfusion		
No	48	40
Yes	71	60
Pre-HIPEC chemotherapy		
No	84	70
Yes	36	30
Perfusate recovered (%)		
Median	72.7	
Range	43.1–94.5	
MMC dose (mg)		
Median	55.0	
Range	37.5–65.0	
sMMC (mg/m^2)[a]		
Median	29.1	
Range	17.6–36.0	
Length of surgery (h)		
Median	9.3	
Range	6.0–18.8	
EBL (ml)		
Median	750	
Range	150–4,200	
Length of stay (days)		
Median	22	
Range	8–83	

[a] MMC dose standardized for BSA

TABLE 3 MMC HIPEC-induced neutropenia

Characteristic	Neutropenia		No neutropenia		P^a
	N	(%)	*N*	(%)	
Total	47	(39)	73	(61)	
Gender					
Male	13	(21)	48	(79)	<0.0001
Female	34	(58)	25	(42)	
Age					
>50 years	22	(38)	36	(62)	0.79
≤50 years	25	(40)	37	(60)	
BMI (kg/m^2)					
Median	25.0		27.0		0.02
Range	19.0–36.2		19.0–42.6		
BSA (m^2)					
Median	1.77		2.04		0.0001
Range	1.39–2.36		1.41–2.52		
Splenectomy					
No	18	(35)	33	(65)	0.46
Yes	29	(42)	40	(58)	
Transfusion					
No	20	(42)	28	(58)	0.69
Yes	27	(38)	44	(62)	
Pre-HIPEC chemotherapy					
No	39	(46)	45	(54)	0.01
Yes	8	(22)	28	(78)	
Perfusate recovered (%)					
Median	69.6		74.5		0.07
Range	43.1–90.0		43.3–94.5		
MMC dose (mg)					
Median	55.0		55.0		0.95
Range	41.3–65.0		37.5–65.0		
sMMC (mg/m^2)					
Median	30.8		27.4		<0.0001
Range	20.9–36.0		17.6–33.2		
Length of surgery (h)					
Median	8.9		9.8		0.06
Range	7.3–17.0		6.0–18.8		
EBL (ml)					
Median	650		775		0.59
Range	150–2,500		150–4,200		
Length of stay (days)					
Median	24		19		0.20
Range	10–69		8–83		
Time to neutropenia (days)					
Median	9				
Range	4–14				
Duration of neutropenia (days)					
Median	2				
Range	1–8				

[a] *P*-values were from chi-square test for discrete variables and Wilcoxon test for continuous variables

developing neutropenia among those who did not receive chemotherapy prior to CRS and HIPEC ($P = 0.01$). Neutropenia developed in 29 of the 69 patients who underwent splenectomy (42%) compared with neutropenia developing in 35% of patients who did not undergo splenectomy ($P = 0.46$). Neutropenia developed in 27 of the 71 patients who received an intraoperative blood transfusion (38%) compared with neutropenia developing in 42% of the patients who did not receive an intraoperative blood transfusion ($P = 0.69$). The median length of stay for patients who developed neutropenia was 27 days (range 10–69 days) compared with a median length of stay of 19 days (range 8–83 days) for nonneutropenia patients ($P = 0.20$).

Logistic regression was used to evaluate associations between MMC-HIPEC-induced neutropenia and variables found significant by univariate analysis. After performing the univariate analysis for each potential factor, significant associations with gender, BSA, sMMC, BMI, and prior chemotherapy with neutropenia were identified (Table 3). However, in the multivariate logistic regression analysis, only gender and sMMC were identified as independent risk factors for the development of MMC-HIPEC-induced-neutropenia (Table 4). The Hosmer–Lemeshow test of goodness of fit was performed and indicated the model fitted the data well ($P = 0.78$). The odds ratio of developing neutropenia based upon female gender was 3.58 (95% confidence interval: 1.52, 8.43). The odds ratio of developing neutropenia associated with 5 unit (mg/m^2) increase in sMMC was 3.37 (95% confidence interval: 1.72, 6.63).

Unlike prior reports, neutropenia was not statistically significantly associated with increased risk of perioperative mortality or increased length of stay. However, the overall incidence of postoperative infections was 84 out of 119 (70%) (Table 5). Neutropenia was associated with an increased risk of urinary tract infection ($P = 0.01$) in the univariate analysis. None of the other types of infection were associated with neutropenia.

TABLE 4 Multivariate analysis of predictive factors of MMC HIPEC-induced neutropenia

Characteristic	Multivariate analysis	
	P-value[†]	OR (95% CI)
Sex (female)	0.0035	3.58 (1.52, 8.43)
sMMC dose[a]	0.0004	3.32 (1.67, 6.59)[b]

[†] $P < 0.05$ considered statistically significant

[a] MMC dose standardized for BSA

[b] OR was reported with 5 unit increase in sMMC dose

TABLE 5 Risk of infectious complications from MMC HIPEC-induced neutropenia

Type of infection	Neutropenia			P^a
	No	Yes	Total	
Any infection				
No	24	11	35	0.25
Yes	48	36	84	
Sepsis				
No	59	39	98	0.99
Yes	12	8	20	
Surgical site				
No	59	39	98	0.89
Yes	13	8	21	
Intra-abdomen				
No	68	46	114	1.00
Yes	3	1	4	
Pneumonia				
No	65	42	107	0.87
Yes	7	5	11	
C. difficile colitis				
No	67	46	113	0.65
Yes	4	1	5	
Central venous catheter				
No	64	42	106	0.89
Yes	7	5	12	
Urinary tract				
No	56	27	83	0.01
Yes	15	20	35	

[a] *P*-values were from chi-square tests or Fisher's exact tests for sparse tables with expected count within a cell less than 5

DISCUSSION

CRS and HIPEC is increasingly used for the management of peritoneal surface malignancies of gastrointestinal origin. This combined treatment approach is a complex and demanding surgical procedure which is associated with both significant rates of morbidity (15–70%) and mortality (0–11%).[12–15] MMC combined with hyperthermia is the most commonly used IP agent in the treatment of peritoneal-based malignancies of gastrointestinal origin.[3] Despite an advantageous pharmacokinetic profile, neutropenia has been reported as a frequent side-effect of IP MMC, with an associated 66% mortality rate.[11] Consequently, improved understanding of the incidence, risk factors, and impact of neutropenia following IP MMC is essential to improve the outcome of patients treated with CRS and MMC-HIPEC.

In this study, the incidence of neutropenia after CRS and MMC-HIPEC for peritoneal dissemination of noncarcinoid appendiceal neoplasms was 39%. This is a relatively high incidence of neutropenia after CRS and HIPEC compared with other reports in the literature.[10,15,16] One reason for this relatively high incidence may be that, to our knowledge, this is the only report focused solely on the incidence and risk factors for neutropenia specifically after single-agent MMC-HIPEC for treatment of appendiceal neoplasms. Most other studies reporting rates of neutropenia after IP chemotherapy included treatment with multiple chemotherapy agents with varying toxicity profiles and/or nonhyperthermic IP chemoperfusions. Alternatively, this study also shows that the dose of MMC per BSA is an independent risk factor for developing neutropenia. Therefore another explanation for the high incidence of neutropenia in this study may be the use of a MMC dosing algorithm based upon weight, rather than BSA.

IP MMC is an appealing therapy for a number of reasons. In addition to MMC's high molecular weight, which limits its systemic absorption and toxicity, MMC's pharmacokinetic profile results in rapid tissue penetration with a cytotoxicity that is synergistic with hyperthermia. One recent proposal for controlling IP MMC toxicity is to use a BSA-based algorithm that dictates the MMC dose and the volume of perfusate.[17] Using relatively low, standardized doses of MMC (10 mg/m^2 for female patients and 12.5 mg/m^2 for male patients) and perfusate volumes of 2, 4, or 6 L, Sugarbaker et al showed that increasing volumes of perfusate significantly impacted the MMC IP and plasma concentrations. However, the perfusate volume did not alter the area under the curve ratio of IP MMC to plasma MMC. Adjusting the perfusate volume according to the patient's BSA (1.5 L/m^2) produced a pharmacokinetic profile similar to that achieved with the 4-L perfusate volume. Consequently, Sugarbaker et al. recommend a BSA-based MMC dose and perfusate volume to limit MMC-HIPEC toxicity.

In this study, the prior use of chemotherapy was not associated with an increased risk of neutropenia. It should be noted that patients with a history of prior chemotherapy were treated with a 25% dose reduction (7.5 μg/ml compared with10 μg/ml for chemo-naive patients) due to a theoretical concern for enhanced bone marrow sensitivity. In our study, eight (22%) patients who had prior systemic chemotherapy developed neutropenia after MMC-HIPEC, suggesting that the dose reduction was necessary**.** It is well established that a previous history of chemotherapy-induced neutropenia (CIN) increases the risk of further episodes of CIN, and this is one of the greatest concerns for patients receiving MMC.[10,18] A wide variety of chemotherapies were administered to the patients in our study who received systemic therapy prior to CRS and HIPEC. This was due in part to the length of the time period of the study, the poorly defined management of the primary tumor, and the fact that many patients received their systemic therapy at other institutions prior to presentation at our institution for HIPEC. Due to the potential morbidity

and mortality of severe neutropenia in the immediate postoperative period, any patient who had received prior chemotherapy was considered to be at increased risk for CIN and therefore received a reduced dose of MMC at the time of HIPEC. This is a routine practice in other well-established HIPEC centers as well.[19]

During our analysis of the risk factors for neutropenia, we hypothesized that the incidence of neutropenia would be lower in patients who underwent splenectomy because of a protective effect of the post-splenectomy leukocytosis. In fact, Bidus et al. recently reported findings suggestive of a potentially protective effective of splenectomy on neutropenia in patients receiving adjuvant chemotherapy for gynecologic malignancies.[20] On the contrary, our study demonstrated a higher, although not significant, incidence of neutropenia in the splenectomized patients. One major variable that could explain the different findings between the study by Bidus et al. and our study is the timing of the administration of the chemotherapy. Adjuvant systemic therapy is usually administered following a period of convalescence after major surgery, during which time splenectomized patients could develop a relative leukocytosis. On the other hand, patients receiving HIPEC at the time of splenectomy would not have time to mount a "protective" leukocytosis and therefore would not appreciate any clinical benefit in terms of the incidence of neutropenia.

In our analysis, multivariate logistic regression showed that female sex was an independent risk factor for developing neutropenia. Female sex has previously been reported as a risk factor for CIN, including MMC.[21–23] The reasons for this association between female sex and CIN are unknown.

To our knowledge, this is the first report of an association between neutropenia and female gender for IP MMC. Currently there is no published data to suggest a biological rationale for increased sensitivity of women to MMC toxicity [either intravenous (IV) or IP]. We speculate that the increased risk of neutropenia in women in our study may be due to a pharmacokinetic effect of a relatively larger surface area of the peritoneum combined with a smaller plasma volume in women compared with men of equal weight.[24,25] For example, the plasma volume is roughly calculated to be 8% of an individual's total body water (TBW). TBW in males is approximately 60% of body weight, whereas for females TBW is only 50% of body weight. Therefore a 70-kg man has a TBW of 42 l and a plasma volume of approximately 3.5 L. On the other hand, a 70 kg woman has a TBW of only 35 L and an estimated plasma volume of 2.8 L. Holding both the dose of IP MMC and the single-compartment kinetic model with first-order elimination constant for males and females of equal weight, and given a relatively larger surface area of peritoneum for drug absorption by women, the plasma concentration of MMC could be as much as 1.25 times higher in females than males. This theory could easily be tested by pharmacokinetic (PK) studies. Unfortunately, none of the published PK studies of MMC HIPEC compared serum levels between men and women. Interestingly, despite the lack of published evidence of a gender difference in MMC HIPEC PK, some well-established HIPEC programs use lower doses of chemotherapy in women.[17] Alternatively other surrogate markers of MMC-specific systemic toxicity, such as the incidence and degree of alopecia in men versus women after MMC-HIPEC, could be used to indirectly measure the gender difference in the PK of MMC HIPEC.

Eliminating toxicity owing to IP chemotherapy is integral to improving the risk–benefit ratio of CRS and HIPEC. Management of drug-related toxicity must be carefully balanced with the primary objective of achieving maximal oncologic benefit. The optimal dose of IP MMC which provides maximal tumor cytotoxicity in peritoneally disseminated appendiceal neoplasms is unknown. Because noncarcinoid appendiceal neoplasms are rare and the number of high-volume peritoneal-surface oncology centers limited, CRS-HIPEC clinical trials for determining the best dose of IP MMC are unlikely. Currently each surgeon selects, derived from personal experience, an MMC dosed based upon their estimate of the best benefit–risk ratio. Whether or not higher MMC doses provide better progression-free and overall survival is unknown. Five-year survivals of 22–43% have been reported after complete cytoreduction of colorectal carcinomatosis and MMC-HIPEC. The highest 5-year survival was reported by Verwaal et al., who used an MMC dose of 35 mg/m^2.[26] This series also reported a mortality rate of 6%. On the other hand, Da Silva et al. reported a 32% 5-year survival using a MMC dose of 10 mg/m^2 for female patients and 12 mg/m^2 for male patients.[27] Two additional studies by Glehen et al. and Shen et al. reported 5-year survival of 22% and 35%, respectively, using MMC doses of 40–60 mg.[28,29] The reported morbidity rates in these series were 23% and 30% with mortality rates of 4% and 12%, respectively. Further efforts to optimize the oncologic benefit of IP chemotherapy while minimizing the toxicity are essential to advancing the appropriate use of this combined therapy.

This study did not reveal any increase in perioperative mortality or risk of postoperative infection due to neutropenia. Nonetheless, the impact of HIPEC-induced neutropenia is not insignificant. Patients must be placed under neutropenic precautions, which during a prolonged postoperative recovery can have a negative psychological effect on both the patient and the patient's family. At our institution, neutropenia was aggressively treated with colony-stimulating factors. This may have reduced the length, nadir, and morbidity associated with neutropenia in this sample. Additional consequences of neutropenia include

the cost and discomfort of daily GM-CSF injections until the neutropenia resolves. Because MMC is one of the agents of choice used with CRS-HIPEC for peritoneal carcinomatosis from most gastrointestinal malignancies, our findings may help with developing optimal dosing regimens and provide evidence of the benefit of supportive therapies. Future investigation and cooperative efforts at high-volume peritoneal surface malignancy centers are necessary to determine the optimal dose of IP MMC if a balance of survival versus toxicity is to be realized.

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