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A multicenter, multinational analysis of mitomycin C in refractory metastatic colorectal cancer

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Mitomycin C
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Abstract *Background*: A considerable number of metastatic colorectal cancer (mCRC) patients who progress on standard treatment with 5-fluorouracil (5FU), oxaliplatin, irinotecan and monoclonal antibodies, still have adequate performance status and desire further treatment. Mitomycin C (MMC) has been widely used in this context, and despite good tolerability, there are doubts regarding its true benefit.
Methods: In order to assess the activity of MMC in the refractory mCRC setting, we retrospectively evaluated 109 heavily pre-treated patients who received MMC as single agent or in combination for mCRC at three different institutions in two countries.
Results: Median patient's age was 54 years old, 57% were male and 94% had performance status ECOG 0 or 1. MMC was used in second line in 11%, third line in 38% and fourth line or beyond in 51% of patients. 58% received MMC combinations, mainly with capecitabine. Grade 3 or 4 toxicity was observed in 5% of patients and 6% required dose reductions. Median time to treatment failure (TTF) was 1.7 months with MMC and 3.6 months on the regimen prior to MMC, with a ratio between these TTF below 1 in 82% of patients. Median survival was only 4.5 months (95% confidence interval (CI) of 3.48–5.56).

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Conclusions: This retrospective data represent the largest reported series of unselected refractory mCRC patients treated with MMC. The median survival of 4.5 months is similar to the survival expected for best supportive care. This lack of activity strongly suggests that MMC should not be routinely used in refractory mCRC.

1. Introduction

Colorectal cancer is the second most common neoplasm and the third leading cause of cancer-related mortality in the United States (US) according to data from the National Cancer Institute. Worldwide, over 1 million patients are diagnosed annually and 50% of these will develop metastatic disease.[1] Since the introduction of oxaliplatin and irinotecan, the combination of these drugs with 5-fluorouracil (5FU) and leucovorin (LV) is considered standard chemotherapy for metastatic colorectal cancer (mCRC).[2–4] More recently, the addition of target therapy such as bevacizumab, cetuximab, and panitumumab have improved outcomes, but advanced disease remains mostly incurable.[5–7] Third and fourth line treatments are often offered to patients whose disease progressed after exposure to the most active regimens and still have a good performance status. Since 1968, mitomycin C (MMC), an antitumour antibiotic, has been widely evaluated in the mCRC scenario.[8] Due to in vitro data showing synergistic effects of MMC and 5FU, this combination has been preferred by oncologists.[9]

To better evaluate the role of MMC in the treatment of mCRC, we conducted a large retrospective study including 109 patients from three different institutions in two countries.

2. Patients and methods

2.1. Patients

The data presented in this retrospective analysis was obtained from the tumour registry of three institutions: Hospital Sírio Libanês (HSL); M. D. Anderson Cancer Center (MDACC); and Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo (ICESP). HSL and MDACC are reference cancer centres that treat mainly private and insured patients. ICESP is a recently open public teaching hospital that provides evidence-based care considering cost-effectiveness for patients with no insurance and has more rigid protocols and limited access to the new monoclonal antibodies.

Patients were eligible if they had proven metastatic colorectal adenocarcinoma, defined by biopsy and imaging studies, and received at least one cycle of intravenous MMC based regimen. Patients who received intraperitoneal or intra-arterial MMC or had predominantly neuroendocrine differentiation as the histology were excluded. All patients had progressed on previous chemotherapy regimens for metastatic disease based in 5FU, irinotecan and/or oxaliplatin. Progressive disease (PD) was confirmed by imaging studies in the majority of patients, but in some instances, patients who had clinical deterioration associated with increased tumour marker were considered to have PD.

2.2. Chemotherapy

The administered dose of MMC varied between 6 to 10 mg/m^2 every 4–6 weeks. Treatment was continued until PD or significant toxicity was observed. Dose reductions were made according to side-effects. Tumour assessment was performed every two or three cycles and toxicity was evaluated at each cycle as part of standard-of-care. If the patients had clear clinical signs of progression or increasing tumour marker, the evaluation of response by image was performed earlier or they were considered to have PD. Response to therapy by image was retrospectively assessed through the radiologist report. If the report considered stable disease or response, the images were reviewed by a neutral radiologist and response rate was re-accessed according to Response Evaluation Criteria in Solid Tumors (RECIST). Toxicity information was collected from the medical notes and classified according to the National Cancer Institute Common Toxicity Criteria Version 4.0. Grade 3 or higher toxicity reported in the patient chart was considered for analysis.

2.3. Statistical analysis

Due to the differences between the institutions in evaluating response to MMC therapy in heavily pre-treated mCRC patients, the primary goal of our analysis was to determine the overall survival (OS), defined as the time from the beginning of therapy with MMC until death from any cause. As time to treatment failure (TTF) can be a function of both chemotherapy benefit and the underlying rate of tumour progression, we also attempted to assess the rate of tumour progression in patients prior to initiating treatment with MMC. The ratio of TTF on the prior regimen to the TTF of the current regimen for each patient is one method to control for the under rate of tumour progression.[10] Considering that, secondary objectives included TTF, defined as time from beginning of therapy with MMC until clinical or radiologic progression and TTF ratio between MMC and previous therapy. Possible prognostic factors were analysed by log-rank test. A p

value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patient's characteristics

A total of 109 patients received MMC for mCRC: 55 (50.5%) were treated at HSL; 30 (27.5%) at MDACC; and 24 (22%) at ICESP. Patients from HSL were included since 7/1/2003; from MDACC since 1/1/2000; and ICESP since 1/1/2009. The cut-off date for analysis was 11/14/2010. Patients' characteristics are shown in Table 1.

Patients' median age was 54 years old (range 25–88), 57% were male, 43% female and 94% Zubrod performance status 0 or 1 at diagnosis of metastatic disease. Colon was the primary tumour site in 73% of the cases and 58% patients were diagnosed at stage IV, while 42% had recurrence disease. Thirty-two patients (29%) received adjuvant chemotherapy (16% fluoropyrimidine and 13% oxaliplatin based) and 84% (91 patients) had surgery for resection of the primary site. The most common site of metastasis was the liver (66%), followed by

Table 1
Patient's characteristics.

Variable	HSL		MDACC		ICESP		All institutions	
	N or ys	% or range	*N* or ys	% or range	*N* or ys	% or range	*N* or ys	% or range
Age (median in years)	57	25–88	53	25–72	53	27–78	54	25–88
Sex								
Male	35	64%	19	63%	8	33%	62	57%
Female	20	36%	11	37%	16	67%	47	43%
Zubrod PS at diagnosis								
0 or 1	54	98%	30	100%	18	75%	102	94%
$\geqslant 2$	1	2%	0	0%	2	8%	3	3%
Unknown	0	0%	0	0%	4	17%	4	4%
Primary site								
Colon	42	76%	21	70%	17	71%	80	73%
Rectum	13	24%	9	30%	7	29%	29	27%
Stage at diagnosis								
II or III	19	35%	15	50%	12	50%	46	42%
IV	36	66%	15	50%	12	50%	63	58%
Adjuvant chemotherapy	16	29%	12	40%	4	17%	32	29%
Site of metastases								
Liver	35	64%	20	67%	17	71%	72	66%
Peritoneum	9	16%	10	33%	7	29%	26	24%
Lung	19	35%	7	23%	12	50%	38	35%
Lymph nodes	10	18%	10	33%	3	13%	23	21%
Others	8	15%	8	27%	4	17%	20	18%
Previous surgery (primary)								
Yes	49	89%	22	73%	20	83%	91	84%
No	6	11%	8	27%	4	17%	18	17%
1st line treatment								
Oxaliplatin based	33	60%	6	20%	20	83%	59	54%
Irinotecan based	14	25%	12	40%	3	13%	29	27%
Oxaliplatin and Irinotecan based	5	9%	3	10%	0	0%	8	7%
Floropyrimidine based	3	5%	8	27%	1	4%	12	11%
Others	0	0%	1	3%	0	0%	1	1%
2nd line treatment								
Oxaliplatin based	11	20%	4	13%	3	13%	18	17%
Irinotecan based	36	65%	10	33%	17	71%	63	58%
Oxaliplatin and Irinotecan based	1	2%	2	7%	0	0%	3	3%
Floropyrimidine based	2	4%	6	20%	0	0%	8	7%
Others	1	2%	2	7%	2	8%	5	5%
Biologics[a]	47	85%	7	23%	7	29%	61	56%

N, number; ys, years; HSL, Hospital Sírio Libanês; MDACC, M. D. Anderson Cancer Center; ICESP, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo.

[a] Bevacizumab and/or cetuximab.

lung (35%), peritoneum (24%) and lymph nodes (21%). Ninety-six (88%) and 84 (78%) patients received oxaliplatin and/or irinotecan in first or second line of treatment, respectively, and 56% were exposed to biologic agents. KRAS status was available for 49 patients (45%), 26 were wild type (24%) and 23 were mutated (21%). Cetuximab was used as single agent or combined with chemotherapy in 47% of patients.

3.2. Treatment characteristics

The vast majority of patients (89%) received MMC in 3rd line or beyond, after progression with oxaliplatin and irinotecan based chemotherapies. The median number of lines of chemotherapy was 4, with a range from 2 to 6 lines. Thirty-five out of 109 patients received additional line of chemotherapy after exposure to MMC. Patients that received MMC in 2nd line (11%) were treated before oxaliplatin was approved for use in mCRC, had some contraindication to irinotecan or oxaliplatin, or had progressed during adjuvant therapy with oxaliplatin and received irinotecan in first line. The median number of cycles of MMC was two, with a range from 1 to 5. Only one patient received five cycles. As the dose and schedule of MMC varied, we calculated the median dose of MMC evaluable for 85 patients obtaining a total of 27 mg (range 8.9–65.5 mg). Out of the 58% of patients that were treated with MMC combination, 86% received capecitabine. Overall, MMC was well tolerated. Grade 3 or 4 adverse events, as assessed by chart review, were observed in 5% of patients, mainly haematologic toxicity. Other side-effects attributable to MMC included fatigue and nausea. Only one patient had haemolytic uremic syndrome and recovered. There was no pneumonitis reported. MMC treatment related data are available in Table 2.

Table 2
Mitomycin treatment characteristics.

Variable	HSL		MDACC		ICESP		All institutions	
	N	% or range	*N*	% or range	*N*	% or range	*N*	% or range
Line of treatment								
2nd	4	7%	6	20%	2	8%	12	11%
3rd	15	27%	9	30%	17	71%	41	38%
⩾4th	36	65%	15	50%	5	21%	56	51%
Median cycles	2	1–5	1.5	1–3	1.5	1–3	2	1–5
Concurrent agent								
Capecitabine	37	67%	17	57%	0	0%	54	50%
Other	7	13%	2	7%	0	0%	9	8%
Dose reduction	2	4%	0	0%	5	21%	7	6%
Grade 3/4 toxicity	2	4%	2	7%	1	4%	5	5%

N, number; HSL, Hospital Sírio Libanês; MDACC, M. D. Anderson Cancer Center; ICESP, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo.

4. Outcome measures

The results demonstrated a median TTF on line prior to MMC of 3.6 months and median TTF to MMC of 1.7 months. (Figs. 1 and 2, Table 3) The ratio of TTF on the MMC regimen to TTF on previous line of treatment was below 1 in 82% of patients, meaning that the majority of patients had a longer progression free survival on line prior to MMC, which suggests MMC did not add a significant benefit (Fig. 3). Out of the 55 patients available for response by tomography (50% of patients), there was no partial response by RECIST criteria in the re-evaluation of the selected images. The only patient who received five cycles of MMC had a 21% reduction in tumour size. This specific patient received FOLFOX and bevacizumab in first line; FOLFIRI and bevacizumab in second line and MMC with capecitabine in 3rd line.

The overall survival since initiation of MMC, the primary end-point of the study, was 4.5 months (Table 3,

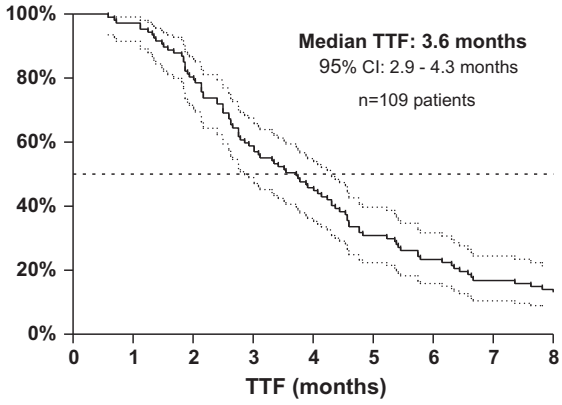

Fig. 1. Time to treatment failure on line prior to mitomycin C (MMC).

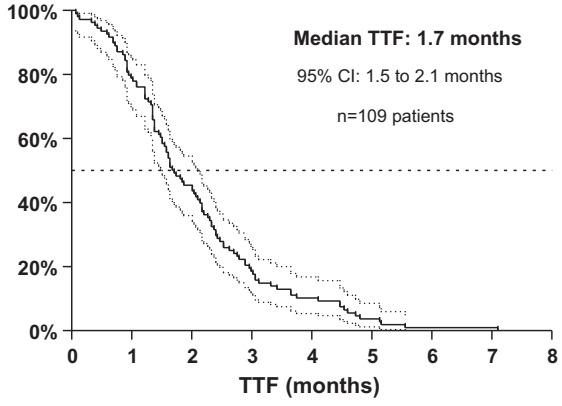

Fig. 2. Time to treatment failure with mitomycin C (MMC).

Table 3
Results.

Variable	HSL		MDACC		ICESP		All institutions	
	Months	95% CI	Months	95% CI	Months	95% CI	Months	95% CI
TTF on line prior to MMC	4.1	2.7–4.6	3.4	2.2–5.2	3	2.6–3.9	3.6	2.9–4.3
TTF with MMC	1.6	1.4–2.1	1.8	1.4–2.4	1.6	1.2–2.4	1.7	1.5–2.1
Overall survival	4.8	3.5–6.0	4.5	3.0–7.0	3.7	2.0–6.0	4.5	3.5–5.6

HSL, Hospital Sírio Libanês; MDACC, M. D. Anderson Cancer Center; ICESP, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina, Universidade de São Paulo; CI, confidence interval; TTF, time to treatment failure; MMC, mitomycin C.

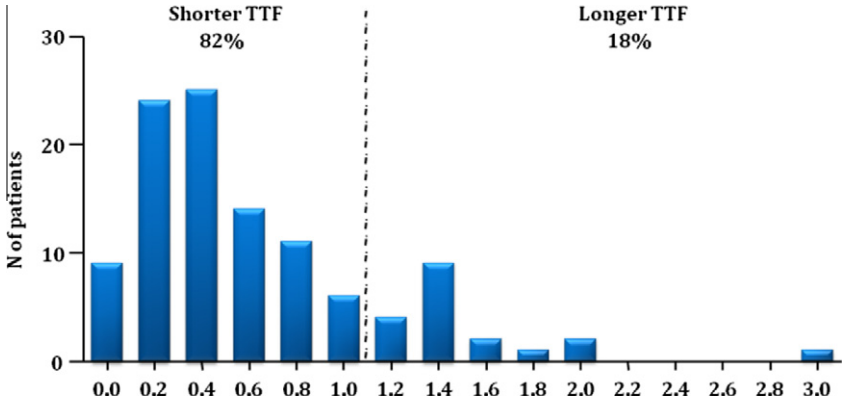

Fig. 3. Ratio of mitomycin C (MMC) time to treatment failure (TTF) to prior line of treatment. *X* axis represents ratio of MMC TTF to prior line of treatment. *Y* axis represents number of patients.

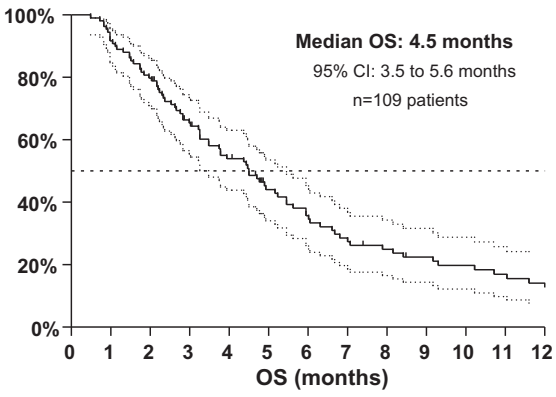

Fig. 4. Overall survival with mitomycin C (MMC).

Fig. 4). In a multivariate analysis considering stage of disease at diagnosis (stage I-III versus stage IV); site of metastases (liver, peritoneal, lung or nodal); resection of the primary tumour; primary radiotherapy and line of MMC treatment (1st or 2nd versus 3rd or beyond), lymph node metastasis was significantly associated with a shorter OS while prior locoregional therapy like surgery or radiotherapy for the primary tumour was associated with an increased OS. Patients with liver and/or lymph nodes metastasis had a significantly shorter TTF.

5. Discussion

MMC has been used as a salvage treatment in patients with mCRC in many institutions around the world, based mostly in small studies published in an era when oxaliplatin, irinotecan and target therapies were not routinely used. Most are phase II studies, with heterogeneous populations and combination regimens. A summary is presented in Table 4.

In first line, a randomised trial evaluating protracted 5-FU infusion with or without MMC in 200 patients with advanced colorectal cancer, demonstrated an increased response rate (RR) with the combination therapy but a lack of survival advantage with the addition of MMC (14 months versus 15 months).[11] The association of Tegafur-Uracil (UFT) with MMC was also evaluated in patients that had not been previously treated for mCRC[12] demonstrating a median progression free survival (PFS) of 5 months and median OS of 13 months, which compares similarly to activity of 5FU monotherapy.[13] Recently, MMC was evaluated in first line associated with capecitabine and bevacizumab. The addition of MMC to the capecitabine and bevacizumab combination did not add a PFS or OS benefit.[14]

MMC was also evaluated in second line, after patients had progressed to 5-FU alone or combined with LV. A retrospective analysis of 24 patients demonstrated a median PFS of 3.5 months, with an OS of 9 months. In this cohort, 50% of patients received irinotecan or oxaliplatin based regimens in further lines of treatment.[15] Besides fluoropyrimidines, MMC had been studied in association with irinotecan or oxaliplatin. The median OS for the irinotecan and oxaliplatin MMC combinations was 12 and 11.2 months, respectively[16,17]; which is similar to the OS with irinotecan monotherapy

Table 4
Studies with regimens containing MMC.

Author	Type	*N*	Drug(s) combined with MMC	RR	Survival
First line					
Ross et al. (1997)[11]	Phase III	200	5FU	54%	FFS 7.9 months OS 14 months[a]
Gyldenkerne et al. (2004)[12]	Phase II	97	UFT/LV	23%	TTP 5 months OS 13 months
Price et al. (2004)[22]	Phase III	320	5FU protracted (A) versus circadian-timed (B)	38% (A) 30.3% (B)	FFS 8.0 versus 9.9 months OS 15.8 versus 16.3 months[a]
Rao et al. (2004)[23]	Phase II	84	Capecitabine	38%	FFS 7.11 months OS 14.3 months
Tebbutt et al. (2010)[14]	Phase III	471	Capecitabine and bevacizumab	45%	PFS 8.4 months OS 16.4 months[a]
Second line					
Chester et al. (2000)[15]	Phase II	24	5FU	12.5%	FFS 15 weeks OS 9 months
Scheithauer et al. (2002)[16]	Randomized phase II	64	Irinotecan (A) or oxaliplatin (B)	21.2% (A) 16.1% (B)	TTP 7.0 (A) versus 5.2 months (B) OS 12 (A) versus 11.2 months(B)[a]
Yamada et al. (2003)[17]	Phase II	41	Irinotecan	34%	TTP 4.2 months OS 11.9 months
Rimassa et al. (2006)[9,b]	Retrospective analysis	28	Capecitabine	4%	TTP 2 months OS 6 months
Third line					
Rosati et al. (2003)[20]	Phase II	21	Raltitrexed	0%	TTP 2.3 months OS 5 months
Chong et al. (2005)[19]	Phase II	36	Capecitabine	15.2%	FFS 5.4 months OS 9.3 months
Lim et al. (2005)[21]	Phase II	21	Capecitabine	4.8%	TTP 2.6 months OS 6.8 months
Ferrarotto et al. (2011)[c]	Retrospective analysis	109	Single use and multiple agents	NA	TTP 1.7 months OS 4.5 months

MMC, mitomycin C; RR, response rate; 5FU, 5-fluorouracil; FFS: failure free survival; TTP, Time to Progression; LV, leucovorin; OS, overall survival; NA: not available.
[a] No statically significant difference between control arm.
[b] Following oxaliplatin and irinotecan.
[c] Second line and beyond.

or oxaliplatin combined with 5FU after progression to fluoropyrimidine (range 10.8–12.2 months), making it questionable the utility of MMC in this context.[2,18]

A phase II study that gave support to the inclusion of MMC in the armamentarium of mCRC was published by Chong et al., who evaluated the combination of MMC and capecitabine as third line therapy in 36 patients with mCRC who progressed during or within 6 months following treatment with 5FU and irinotecan. The authors reported an objective RR of 15.2% and a median TTF of 5.4 months. The median OS was 9.3 months, however, the patients included in this study had not received oxaliplatin in previous line and 22% received oxaliplatin after MMC failure.[19]

In a more usual scenario, small retrospective studies have evaluated MMC after progression to 5FU, irinotecan and oxaliplatin based regimens. A retrospective analysis of 28 patients in this context demonstrated a median PFS of 2 months and OS of 6 months.[9] A phase II Italian study evaluating a combination of raltitrexed and MMC in 21 refractory patients demonstrated a median PFS and OS of 2.3 and 5 months, respectively.[20] Another phase II study evaluating 21 Korean patients with refractory mCRC reported similar results.[21]

The natural history of mCRC patients who exhausted the main chemotherapy options can be appreciated in recent trials. Jonker et al. randomized 572 patients with mCRC refractory to fluoropyrimidine, oxaliplatin and irinotecan to receive cetuximab or best supportive care. The median PFS and OS for the best supportive care group were 1.8 and 4.6 months, respectively.[24]

When the results from these studies are compared with ours, it becomes evident that MMC has minimum, if any, activity after progression is documented with the use of the most modern and active agents. New and more active salvage drugs are needed, and participation in phase I trials is a reasonable option. A retrospective analysis of 78 patients with mCRC who progressed after 5FU, oxaliplatin and irinotecan and participated in phase I trials, demonstrated a PFS of 2.2 months and OS of 7.3 months.[25]

Aside from the Chong study, which was small and limited by subsequent use of oxaliplatin, there is no clear evidence of activity of MMC in the mCRC scenario. The recently divulged Australian MAX study evaluating MMC in first line of treatment for mCRC corroborate our findings, showing no benefit when MMC was added to capecitabine and bevacizumab combination.[14,19]

6. Conclusion

Although commonly used, the available data evaluating the efficacy of MMC based chemotherapy in third line and beyond is not encouraging, particularly since the introduction of newer and more effective therapeutic agents in previous lines. In spite of being retrospective in nature, our review represents the largest reported series of heavily pre-treated mCRC patients treated with MMC in the literature thus far. Our data do not encourage nor support the use of MMC as single agent or in combination in patients previously exposed to 5-FU, irinotecan and oxaliplatin, associated or not with biologic agents. The OS of 4.5 months is not consistent with an active regimen. Supportive care or participation in a clinical trial should be the recommendation for patients who have progressed after the standard therapies.

Conflict of interest statement

None declared.

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