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ORIGINAL ARTICLE

Capped-dose mitomycin C: a pooled safety analysis from three prospective clinical trials

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Abstract
Background Mitomycin C (MMC) up-regulates topoisomerase-I and thymidine phosphorylase making it ideal to combine with irinotecan or capecitabine. One of the most devastating toxicities MMC has been associated with is thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) in 4–15% of patients, especially when receiving cumulative doses higher than 60 mg/m^2.
Methods We conducted a pooled safety analysis of 140 patients enrolled in three prospective clinical trials at our institution from 2001 to 2008. MMC on all our studies was capped to a cumulative dose of 36 mg/m^2 to limit toxicity while retaining efficacy. We reviewed our electronic medical records and clinical trial database for individual patient data on these studies with a specific intent to identify patients meeting criteria for TTP/HUS.
Results In combination with irinotecan or capecitabine, MMC was associated with manageable toxicities. We found no cases of MMC-associated TTP/HUS. There were no reported cardiac or pulmonary toxicities in our analysis. Most common grade 3/4 toxicities were diarrhea (19%), neutropenia (17%) and dehydration (12%) predominantly when MMC was combined with irinotecan.
Conclusions In this large pooled analysis, we found MMC, when capped at a cumulative dose of 36 mg/m^2, to be safe and tolerable in combination with capecitabine or irinotecan with no reportable cases of TTP/HUS.

Keywords Mitomycin C · Thrombotic thrombocytopenic purpura · HUS · Dose

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Introduction

Over the last decade, survival rates have improved for many patients with solid tumor malignancies [1–3]. As a consequence, many patients are surviving frontline regimens and remain in good functional status for either entering clinical trials or receiving salvage regimens at the time of disease progression.

Mitomycin C (MMC) is a classic bioreductive compound with activation to super-oxide radicals resulting in inhibition of DNA synthesis and function [4]. MMC causes DNA strand breakage and therefore cytotoxicity. This effect is not limited to cancer cells, thus explaining the toxicity of MMC to normal cells. The formation of free radicals is believed to be responsible for the cardiac and pulmonary toxicities that are sometimes seen with the use of cytotoxic agents such as MMC and bleomycin [5].

MMC is an alkylating agent that has been approved for clinical use in pancreas and gastric cancer by the United States Drug and Food Administration (FDA) in 1974 [6]. In addition, MMC has been widely used in many solid tumors including bladder, breast, cervical and colorectal cancers [7]. Currently, there are few frontline treatments that still utilize MMC in North America. MMC is used for intravesical application in various stages of transitional cell cancer of the bladder [8] where it has been shown to be equivalent

or perhaps superior to bacillus Calmette-Guerin (BCG) in in situ transitional cell carcinoma [9]. It is also widely used in combination with 5-fluorouracil and radiation therapy in patients with locally advanced squamous cell carcinomas of the anal canal. A phase III trial conducted by Flam et al. [10] demonstrated lower colostomy rates and improved disease free survival with the combination of radiation and MMC and 5-FU when compared with 5-FU alone. The addition of MMC was however, associated with greater toxicity. More recently, a published intergroup chemoradiation study has confirmed the superiority of a MMC-based regimen over a cisplatin-based combination therapy in the treatment of anal cancer [11]. MMC has also shown clinical activity in combination with a number of other cytotoxic agents [12–15] and some of the clinical combinations and use of MMC in solid tumor malignancies have been reviewed in details elsewhere [6]. Such combinations include the use of MMC with ifosfamide and 5-FU [16] in advanced breast cancer although the availability of many active agents in metastatic breast cancer limit such combinations today. In both untreated and refractory metastatic colorectal cancer, MMC has shown very interesting activity when combined with various fluoropyrimidines [17–20].

Currently, the clinical use of MMC outside of intravesical instillation in transitional bladder cancer and in anal cancers has declined significantly in the United States. This decline in the use of MMC can be traced to the availability of modern chemotherapeutic drugs as well as concerns by treating oncologists regarding the toxicity of MMC [21]. Typical toxicities include nausea, vomiting and diarrhea as well as skin ulceration in the event of extravasations [22]. Myelosupression is often the dose limiting toxicity and can sometimes be prolonged with thrombocytopenia which may limit further therapeutic options. However, one of the most concerning toxicities associated with MMC is the rare but often fatal thrombotic thrombocytopenia purpura/hemolytic uremia syndrome (TTP/HUS) [23–26]. This syndrome does not seem to be isolated to MMC and has been reported in association with other chemotherapeutic agents such as the widely used agent gemcitabine [27, 28].

In a series by Lesesne and colleagues [23] from a cancer registry of 85 cases of cancer associated TTP/HUS, 84 of the patients had received MMC as part of their therapy. The reported cumulative dose was more than 60 mg/m^2 in all patients except nine in the cohort. There is evidence to suggest that the toxicities of MMC with the exception of pulmonary toxicity may be related to cumulative dose [5]. In our studies, we have chosen lower doses of MMC (6 mg/m^2) as in vitro data suggest that MMC may be more toxic to hypoxic tumor cells at low concentrations compared to well oxygenated normal tissues [29].

For the last few years, we initiated a series of clinical trials utilizing MMC in combination with capecitabine or irinotecan in patients with various solid tumors. We hypothesized that by capping the cumulative dose of MMC to 36 mg/m^2, we would improve the toxicity profile, specifically the risk of HUS/TTP. Herein, we report the results of a pooled analysis we performed on a large cohort of patients from three clinical trials conducted over a 7-year period (2001–2008), looking at the safety of capped-dose MMC in patients with various solid tumors. We paid particular attention to the occurrence of TTP/HUS in order to identify patients who meet the criteria for this syndrome and attempted to assign causality.

Methods

Subjects and study design

Subjects in this pooled analysis were enrollees in three prospective (one phase I and two phase II) clinical trials conducted at The Ohio State University between the years 2001 and 2008 utilizing MMC in combination with irinotecan or capecitabine in various advanced solid tumors (OSU 0151, 0155 and 0330 described below). We reviewed our electronic medical records and clinical trial database for individual patient data on these studies with a specific intent to identify patients meeting criteria for TTP/HUS. All 140 patients from the three studies mentioned above were found to be evaluable for toxicity and included in this pooled analysis. This study describes the safety and toxicity profile of mitomycin-C used in a modified dose schedule, a maximal cumulative dose of 36 mg/m^2 and in combination with irinotecan or capecitabine in patients with advanced gastrointestinal or breast cancers. In one phase one study (OSU 0330), 28 patients with refractory gastrointestinal malignancies received MMC at a dose of 6 mg/m^2 every four weeks while the dose of capecitabine was administered on days 8–21 on a 28-day schedule. Capecitabine dose (1,000–2,000 mg/m^2/day in split doses) was escalated in cohorts using standard 3 by three phase I trial design. Two phase II studies (OSU 0151 and OSU 0155) combined irinotecan with MMC in patients with untreated advanced esophageal (and gastroesophageal) cancer or refractory breast cancer respectively. OSU 0151 ($n = 80$) utilized a randomized phase II design such that irinotecan was given at a dose of 125 mg/m^2 on days 2 and 9 following MMC at 6 mg/m^2 on day 1 (Arm A) or 3 mg/m^2 on days 1 and 8 (Arm B). Both schedules were repeated every 28 days. OSU 0155 ($n = 32$) utilized the combination of MMC at 6 mg/m^2 on day 1 with irinotecan at 125 mg/m^2 on days 2 and 9 every 28 days (Fig. 1). We have previously reported in details on the methods as well as preliminary safety and efficacy [30–33] data of the trials included in this cohort of patients. In all three studies, patients were allowed to

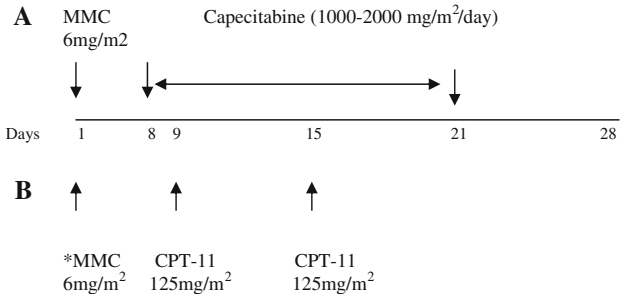

Fig. 1 Schedule of drug administration. **a** Shows the schema of the combination of capecitabine with mitomycin C (OSU 0330) where MMC was given on days 1 with capecitabine from days 8 to 21 every 28 days. **b** Shows the combination of mitomycin C with irinotecan in two studies (OSU 0151 and OSU 0155) and MMC was given on days 1 while CPT-11 was given on days 2 and 9. 0151 had an additional arm with MMC given at 3 mg/m^2 on days 1 and 8 of the same cycle (not shown in this figure). **MMC* mitomycin C, *CPT-11* irinotecan

continue on capecitabine or irinotecan once they capped on MMC in the presence of continued benefit.

With regards to TTP/HUS, we conducted a thorough review of individual patient data as described above using criteria published by Lesesne et al. [23]. Patients had to have four definitive findings to meet criteria for TTP/HUS: 1—renal dysfunction (creatinine > 1.6), 2—anemia (hematocrit < 25), 3—thrombocytopenia (platelets < 100 K) and 4-microangiopathic hemolysis on peripherial blood smear.

In all three prospective studies included in this pooled analysis, patients were followed up very closely for signs or symptoms of cardiopulmonary dysfunction. We had previously decided not to perform serial echocardiograms and/or pulmonary function tests given the lack of certainty about their significance in the absence of symptoms.

This study is a pooled analysis of individual patient toxicity data from all three prospective clinical trials. Statistics were therefore descriptive in this retrospective study and no statistical inferences or comparisons were made. All studies were approved by the Institutional Review Board of The Ohio State University and in accordance with the ethical standards of the Helsinki Declarations.

Results

Patients characteristics

The baseline characteristics of the 140 subjects who formed the cohort for this study is presented on Table 1. This cohort comprised mostly Caucasian (94%) and male (65%) patients. The majority of the patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (96%). The mean age was 58 with a range of 27–84 (Table 1). Overall, patients included in this analysis received a median of two cycles of MMC (range 1–6), with a cumulative median dosage of 12 mg/m^2 (range 6–36 mg/m^2). 20% of all patients on this analysis had at least four cycles of MMC.

Table 1 Characteristics of patients in the pooled analysis

Age: mean(range)	58 (27–84)[b]
Race/ethnicity[a]	
African Americans: *N* (%)	4 (3)
Caucasians: *N* (%)	122 (95)
Others: *N* (%)	3 (2)
Sex	
Males: *N* (%)	85 (66)
Females: *N* (%)	44 (34)
Performance status	
PS 0	62 (48)
PS 1	61 (47)
PS 2	6 (5)
Median # of cycles of MMC	2 (range 1–6)
Median cumulative dose of MMC	12 mg/m^2 (range 6–36 mg/m^2)
Receiving ≥4 cycles (%)	20%
Prior therapy on every study	
OSU 0151 (%)[c]	0
OSU 0155 (%)[d]	100
OSU 0330 (%)[e]	93

PS Eastern Cooperative Oncology Group performance status

[a] Others comprise 1 patient of Hispanic and 2 of Asian ancestry

[b] Mean age and range is shown

[c] In combination with irinotecan in esophageal cancer

[d] In combination with irinotecan in breast cancer

[e] In combination with escalating doses of capecitabine in gastrointestinal malignancies

Toxicities

MMC was well tolerated in combination with partner chemotherapeutic agents in our study populations. In our analysis, MMC was found to be associated with manageable and reversible grade 3 and 4 hematologic and non-hematologic toxicities. Notably, grade 3/4 hematologic toxicities and febrile neutropenia were only observed when MMC was combined with irinotecan and not with capecitabine. Dehydration associated with gastrointestinal toxicities was observed in 21% of patients including 12% with grade 3 or 4 toxicity. This toxicity was noted again when MMC was combined with irinotecan and not with capecitabine. None of the 140 patients included in this analysis met the criteria for TTP or HUS. There were no symptomatic cardiac or pulmonary toxicities.

Discussion

The incidence of TTP/HUS has been estimated at about 4–15% in cancer patients treated with MMC and in some randomized studies, the syndrome has only been seen in the arm containing MMC [23, 28, 34]. In our pooled toxicity analysis, we found that when treatment with MMC with a cumulative capped dose of 36 m/m^2 is safe, tolerable and does not seem to be associated with a verifiable episode of TTP/HUS. Our findings are consistent with evidence that has linked the cumulative dose of MMC to the risk of TTP/HUS. In one series of 85 cases of cancer-associated TTP/HUS, 84 of the patients had received MMC as part of their therapy [23]. The reported cumulative dose was more than 60 mg/m^2 in all patients except nine in the cohort [23]. Another study suggested that only cumulative doses of more than 40 mg/m^2 of MMC resulted in reported cases of HUS/TTP [18]. In addition, one other study suggested that a cumulative dose of MMC less than 50 mg/m^2 was associated with the least incidence of TTP/HUS [35].

The pathogenesis of MMC-associated TTP/HUS is not completely understood but the syndrome is best characterized by the clinico-pathological findings of microangiopathy. It has been suggested that direct endothelial damage may be central to its pathogenesis and unusually large Von Willebrand factor multimers from damaged endothelial cells may cause intravascular platelet clumping and microangiopathy [24]. Ultralarge Von Willebrand factor multimers are now recognized to be involved in the pathogenesis of idiopathic relapsing TTP and a metalloprotease for Von Willebrand factor, the ADAMTS13 has been associated with the majority of cases of idiopathic TTP [36–38]. In our review, we adopted validated published criteria [23] to capture a larger number of possible/probable/definite cases of TTP/HUS since many challenges exist in recognizing the syndrome.

Hematologic toxicities tended to be mostly mild, manageable and reversible. Grade 3/4 hematologic toxicities, febrile neutropenia were seen only when MMC was combined with irinotecan but not with capecitabine. The most significant non-hematologic toxicities were gastrointestinal, including grade 3/4 diarrhea and vomiting with eventual dehydration and occasional hospitalizations. Once again, these toxicities were seen exclusively when MMC was combined with irinotecan .Finally, we found no evidence of symptomatic cardiac or pulmonary toxicity likely attributed to the fact that we used a lower dose of MMC (6 mg/m^2) in addition to capping the cumulative dose.

MMC has shown activity in a number of solid tumor malignancies [5]. In all three studies included in this pooled analysis, we chose a dose/schedule aimed to limit toxicity while retaining efficacy. MMC was given at a dose 6 mg/m^2 every 4 weeks (except for arm B of OSU 0151 where 3 mg/m^2 given on days 1 and 8 of a 28-day cycle) that was capped at 36 mg/m^2 [30, 32, 33]. In all three studies, there were some noticeable responses in patients with untreated esophageal cancer [32], in patients with refractory breast cancer [30] and patients with refractory gastrointestinal malignancies [33]. Given these preliminary results, further randomized studies are required to confirm that synergy of this dose/schedule of MMC with other chemotherapeutics is maintained.

As mentioned previously, the outcome for patients with advanced malignancies has improved over the last several decades. This improvement is associated with rapidly rising costs with more patients are being treated with complex chemotherapy regimens, molecularly targeted agents and other modalities [39]. Because of the advances in cancer therapy, many patients are surviving frontline therapies and remain in good functional status for further treatment. Unfortunately, for many of these patients with a good functional status, there may be no standard options available if they do not meet eligibility criteria or decline clinical trials. One prominent example is metastatic colorectal cancer (MCRC) where recent evidence [40, 41] suggests that patients with a *KRAS* mutation in their tumors will not benefit from anti-epidermal growth factor receptor inhibitors, leaving around 45% of them with no options beyond the second line. As such, there is renewed interest in utilizing MMC in the salvage setting based on established clinical activity of the drug in combination with fluoropyrimidines in MCRC. More recently, multiple studies showed very interesting responses when MMC was combined with fluoropyrimidines including capecitabine, UFT/Leucovorin or tegafur-uracil in patients with MCRC across lines of therapy [19, 20, 42, 43].

In conclusion, lower dose MMC when used with a maximal cumulative dose of 36 mg/m^2 was tolerable with little hematologic toxicity and no proven cases of TTP/HUS in this series of 140 patients. To our knowledge, this pooled analysis represents one of the largest ever reported safety experience with MMC. There are however, a number of limitations to our study. The median dose of MMC was 12 mg/m^2 although the range was wide (6–36 mg/m^2) and 20% of all patients received an actual cumulative dose of at least 24 mg/m^2. The study is retrospective in nature with all the limitations that accompany this type of analysis, although noteworthy that the data was extracted from individual patient medical and research records (unlike the case with meta-analyses) included on three prospective studies from one single institution. Our findings therefore, should be interpreted with these limitations in mind. Moreover, TTP/HUS is a rare syndrome and as such may not have occurred in our limited cohort of patients. Despite these limitations, we believe our findings are valid and capped cumulative doses of MMC may be associated with a

decreased risk of TTP/HUS. Capped dose MMC should be incorporated into combination trials with modern (and perhaps some older) therapies and should be considered in salvage regimens for patients with certain refractory malignancies such as MCRC given its relative low cost, acceptable toxicity profile and potential activity especially in combination with irinotecan or capecitabine.

Conflict of interest statement Tanios Bekaii-Saab: Reasearch Funding (Roche, Genentech and Pfizer), Remuneration (Genentech). Gregory Otterson: Research funding (Genentech, Pfizer, Abraxis).

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