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ORIGINAL ARTICLE

# A phase I dose escalation study of a pharmacobiologically based scheduling of capecitabine and mitomycin C in patients with gastrointestinal malignancies

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**Abstract**
*Background* Mitomycin C (MMC) produces significant upregulation of thymidine phosphorylase, a principal determinant of the therapeutic index of capecitabine-based treatment, starting 4–6 days after treatment. On the basis of the time-dependency of this upregulation, we performed a phase I dose escalation study of capecitabine and MMC in patients with gastrointestinal malignancies.
*Methods* A total of 29 patients with advanced gastrointestinal malignancies received MMC at 6 mg/m$^2$ on day 1 and capecitabine escalated in four successive patient cohorts of doses 500–1,000 mg/m$^2$/day twice daily on days 8–21, every 28 days. MMC was capped at 36 mg/m$^2$.
*Results* A total of 29 patients were enrolled and 90% had at least one prior treatment in the metastatic setting. There was one DLT, grade 3 hand and foot syndrome, at dose level four. The most common toxicity was fatigue (61%). No patients experienced grade 4 toxicities. Nine patients experienced prolonged stability of disease.
*Conclusion* Capecitabine in combination with MMC in the proposed schedule is well-tolerated with evidence of preliminary activity. The recommended dose for phase II studies are MMC at 6 mg/m$^2$ on day 1 of a 28-day cycle with the dose capped at 36 mg/m$^2$, in combination with capecitabine at 1,000 mg/m$^2$ twice daily on days 8–21.

**Keywords** Capecitabine · Mitomycin C · Gastrointestinal malignancies

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## Introduction

The American Cancer Society (ACS) estimated that there were 1,444,920 new cases of cancers in 2007, out of which 271,250 (19%) were gastrointestinal (GI) cancers [1]. Additionally, there were 559,650 deaths from cancer in 2007, with 134,710 (24%) disproportionately from GI cancers [1]. Two of the four most common cancer killers are GI cancers including colorectal and pancreas cancers [1]. Moreover, three of the four most lethal cancers (with 5-year survival rate <20%) are GI cancers including pancreas, liver, and esophageal cancers [1, 2]. As such, GI cancers remain some of the most difficult cancers to treat, with limited treatment options, very few salvage regimens, and a relatively poor outcome [1, 2].

Mitomycin C (MMC) is a classic bioreductive compound with production of superoxide radicals resulting in inhibition of DNA synthesis and function [3]. MMC was first approved for clinical use in pancreas and gastric cancer by the United States Food and Drug Administration (FDA) in 1974 [4]. MMC is an effective anticancer agents used for the treatment of a broad variety of gastrointestinal tumors including gastric, pancreatic, biliary tract, colorectal, and anal cancer [5]. Significant concerns have been raised about the cumulative dose (>50 mg/m$^2$) related toxicity produced by MMC [6]. By capping its total dose and limiting the individual dose, this toxicity may be markedly reduced. In our experience, we found that when MMC is given at an

individual dose of 6 mg/m$^2$ and capped at a cumulative dose of 36 mg/m$^2$, it is safe and tolerable with no reportable cases of TTP/HUS [7]. In various combination studies conducted by our group, this dose/schedule was also found to be associated with noticeable activity in patients with various solid tumor malignancies [8–11].

Capecitabine was designed as an orally administered, tumor selective fluoropyrimidine, preferentially converted to 5-fluorouracil (5FU) at the tumor site by the higher levels of thymidine phosphorylase (TP) in tumor tissues compared to normal tissues [12]. Due to the preferential expression in tumor tissues of the rate-limiting enzyme TP in converting capecitabine to 5-FU, capecitabine has been shown to have a superior therapeutic index to 5-FU in preclinical studies [13]. Capecitabine has widespread activity in most if not all GI malignancies as shown by multiple studies using it either as a single agent or in combination with other agents [14].

Since a principal determinant of the therapeutic index with capecitabine-based treatment is the level of TP activity in malignant tissues, therapeutic strategies which maximize TP activity can result in higher antineoplastic efficacy after administration of capecitabine. Indeed, transfection of the TP gene into the DLD-1 human colon cancer cell line, which is TP-deficient and highly resistant to 5′-deoxyfluorouracil (5′-DFUR), has been shown to increase TP activity by 1,068-fold and sensitivity to 5′-DFUR by 1,070-fold [15]. MMC produces significant upregulation of the TP starting 4–6 days after treatment persisting for at least 10 days [16]. There is also evidence for upregulation of TP by MMC in human subjects with colorectal cancer. In one study, biopsy specimens were obtained preoperatively through colonoscopy and then patients received neoadjuvant therapy with MMC followed by surgery after 1–12 days [17]. TP was shown to be upregulated in the group of patients with operations over 6 days after MMC, in contrast to patients with operations less than 6 days after MMC [17].

On the basis of the time-dependency and transience of this upregulation, we performed a phase I study of a pharmacobiologically based scheduling of escalating doses of capecitabine in combination with MMC at a dose of 6 mg/m$^2$ and capped at a cumulative dose of 36 mg/m$^2$. The aim of this study was to determine the maximally tolerated dose (MTD) of this combination in patients with GI malignancies.

## Patients and methods

This was a dose escalation phase I study searching for the MTD of capecitabine in combination with MMC. The study was conducted at the Ohio State University and approved by the Ohio State University institutional review board (IRB).

### Eligibility

Patients were required to have histologically confirmed gastrointestinal solid tumor malignancy (with the exclusion of lymphomas and sarcomas). Up to two prior chemotherapy regimens in the metastatic setting were allowed. At least 4 weeks from the end of any chemo- or radiotherapy to the start of the study was required. Exclusion criteria included the following: age less than 18 years and pregnant or lactating women; psychiatric disorders that would interfere with consent of follow up; uncontrolled intercurrent illness including, but not limited to, clinically significant cardiac disease not well-controlled with medication (e.g., congestive heart failure, symptomatic coronary artery disease, and cardiac arrhythmias) or myocardial infarction within the last 12 months, and serious concurrent infections; patients being anticoagulated with warfarin-based medications; patient with a known history of severe hypersensitivity reaction to fluoropyrimidines; and patients with previous exposure to MMC or capecitabine. All women of childbearing capacity were required to have a negative pregnancy test prior to study entry, and both men and women of childbearing capacity were required to utilize an effective contraceptive method, while on the study and for 3 months thereafter, if applicable. Patients were required to have an ECOG performance status of 0–2, as well as a life expectancy of at least 12 weeks. Patients were required to have adequate organ function defined as follows: absolute neutrophil count (ANC) greater than 1,500/mm$^3$; hemoglobin >9 g/dl; platelet count $\geq$1,00,000/mm$^3$; creatinine <1.5 upper limit normal (ULN); serum bilirubin $\leq$ULN; and AST/ALT $\leq$2.5 ULN (<5 ULN if due to liver metastases). Patients were to have no evidence of any active serious infection, and they were to be free of other malignancies for $\geq$5 years (except basal and squamous cell skin cancers and carcinoma in situ of the cervix). Other exclusionary criteria included lack of physical integrity of the upper gastrointestinal tract, inability to swallow tablets or malabsorption syndrome, and patients who have an organ allograft.

### Treatment plan

Treatment was administered on an outpatient basis. Four dose levels were planned, with the dosage and dose escalation detailed in Table 1. Each cycle was defined as 28 days. Essentially, MMC was given at a dose of 6 mg/m$^2$ over 30 min through a central venous access catheter on day 1. The cumulative dose of MMC was set at 36 mg/m$^2$ (6 cycles), with patients having the option of continuing on the same dose/schedule of capecitabine alone after the MMC cap is reached. As shown in Table 1, capecitabine was given orally, twice daily, on days 8–21 with doses escalated in successive patient cohorts with a target maximal

**Table 1** Dose escalation schema ($N = 29$)

| | Dose level[a] | No. of patients | No. with DLTs | No. with DR or DD[b] |
|---|---|---|---|---|
| 1 | MMC 6 mg/m$^2$ C 1,000 mg/m$^2$ | 4[c] | 0 | 0 |
| 2 | MMC 6 mg/m$^2$ C 1,250 mg/m$^2$ | 5[d] | 0 | 1 |
| 3 | MMC 6 mg/m$^2$ C 1,500 mg/m$^2$ | 4[e] | 0 | 1 |
| 4 | MMC 6 mg/m$^2$ C 2,000 mg/m$^2$ | 7[f] + 9[g] | 1[h] | 9 |

[a] Mitomycin C (MMC) i.v. on day 1 with cumulative cap dose of 36 mg/m$^2$; (C)apecitabine p.o. in split doses bid on days 8–21 every 28 days

[b] DR = Dose reduction; DD = Dose Delay. Please refer to text for more details

[c] One patient was non-evaluable for DLT only

[d] Two patients were non-evaluable for DLT or response

[e] One patient was non-evaluable for DLT only

[f] One patient was non-evaluable for DLT only

[g] Nine patients were enrolled at the MTD to further define toxicities and preliminary activity. One patient was lost to follow up and was non-evaluable for response and toxicities

[h] DLT was grade 3 Hand and Foot Syndrome

daily dose of 2,000 mg/m$^2$ as is standard of practice in the United States [18].

Dose-limiting toxicity (DLT) in the first two cycles of therapy was defined as follows: any grade 4 neutropenia lasting more than 5 days or accompanied by ≥grade 2 fever, or any grade 4 thrombocytopenia; grade 3 or 4 non-hematologic toxicity that results in an interruption of capecitabine for more than 5 days; grade 3 or 4 non-hematologic toxicity (except for alopecia or nausea and vomiting not appropriately controlled by medication); clinical inability (due to toxicity) to start the next cycle of treatment within 2 weeks of planned start date. Toxicities should be considered drug-related by the investigator to be designated as DLT. Three patients were initially entered at Dose level 1. In the absence of a DLT in the first 2 cycles in any of these three patients, the next patient was entered at Dose level 2. The same principle was exercised for escalation to dose level 3. When MTD was determined, 9 additional patients were planned to be enrolled at this level to better define toxicity and efficacy. At any given dose level, if 1 of 3 patients had a DLT, 3 additional patients were entered at that dose level. The maximum-tolerated dose (MTD) was the highest dose level at which 3 of 3 or 5 of 6 patients tolerated the dose without DLT. Prophylactic use of colony-stimulating factors or erythropoietin was not permitted in the first two cycles, in order to better define DLTs.

### Dose modifications

Separate criteria for dose reductions were followed for MMC and capecitabine, depending upon the type of toxicity observed and whether it was observed within a treatment cycle or at the beginning of a subsequent treatment cycle. During the first two cycles of treatment only, dose modifications were limited to the occurrence of dose limiting toxicities only. During the dose escalation period, patients experiencing a DLT were allowed to continue receiving treatment as outlined at the dose level previously found to be safe. Dose adjustments during a course of therapy were based on toxicity observed the day of treatment. Dose adjustments for hematological toxicity during a course of therapy were based on the blood counts obtained in preparation for that day of treatment. All subsequent dose adjustments were relative to the dose given at a previous week of that cycle. In general, grade 3 and 4 toxicities (grade 2–4 for diarrhea and grade 2–3 for hand and foot syndrome; with the exception of grade 3 neutropenia, grade 3–4 anemia and lymphopenia) required dose omission for capecitabine, with resumption at the original dose within a course when the toxicity had resolved to ≤grade 2. Dose modifications of capecitabine were based on the total daily dose administered. Capecitabine treatment interruptions were considered as lost treatment days, missed doses were not to be replaced, and the planned treatment schedule was maintained.

Dose adjustments for MMC and capecitabine at the start of a new cycle of therapy (excluding cycle #1 and #2) were based on the worst toxicity observed during the previous cycle of therapy and were relative to the starting doses of each drug received in the previous cycle. A new course of therapy was to begin when the granulocyte count was ≥1,500/mm$^3$, the platelet count was ≥1,00,000/mm$^3$, and any other treatment-related toxicities were ≤grade 1; otherwise, treatment was to be withheld and the patient re-evaluated 1 week later. If the treatment was held for more than 3 weeks, then the patient was removed from the study.

### Evaluation

Radiological assessment was done by CT or MRI (as long as the same consistent measure was used serially) every 8 weeks and responses were measured according to the RECIST criteria [19]. This study utilized the CTC version 3.0 for toxicity evaluation (http://ctep.info.nih.gov/CTC3/ctc_ind_term.htm).

## Results

### Demographics (Table 2)

A total of 29 patients with various gastrointestinal malignancies and a majority of colorectal, esophageal, and

**Table 2** Patient characteristics

| Characteristics | Number of patients |
|---|---|
| Total number of patients enrolled | 29 |
| Median age (range) in years | 61 (27–78) |
| Sex | |
| Female | 16 |
| Male | 13 |
| Race | |
| Caucasian | 24 |
| African–American | 3 |
| Asian | 3 |
| ECOG performance status | |
| 0 | 6 |
| 1 | 21 |
| 2 | 2 |
| Disease Sites | |
| Colorectal | 10 |
| Esophageal (including GE) | 8 |
| Pancreas | 7 |
| Hepatiobiliary Tract | 3 |
| Stomach | 1 |
| Prior chemotherapy | |
| 0 | 3 |
| 1 | 11 |
| 2 | 15 |
| Prior 5-fluorouracil | 19 |
| Other prior therapy | |
| Surgery | 16 |
| Radiotherapy | 8 |
| Cycles of therapy administered | |
| Median | 2 |
| Range | (1–13) |

pancreas cancer were enrolled into the study at The Ohio State University between 9/30/2004 and 1/3/2008. One patient is currently still being treated on study. The demographics of the patients are summarized in Table 2. The median age was 61, and 72% of the patients had a performance status of 1. Twenty-Six patients had undergone more than one prior therapy including 19 with prior exposure to 5FU. A median of two cycles was administered per patient (range, 1–13+ cycles).

Adverse events and DLTs (Tables 1, 3)

Four patients were enrolled at treatment dose level one, five at level two, four at level three, and 16 at level four (Table 1). Five patients were considered not evaluable for DLT for the following reasons: three patients were not compliant with the instructions on capecitabine administration missing some of their planned doses during their first cycle with no significant toxicities noted. Two more patients were taken off the study before completing two cycles due to complications clearly unrelated to therapy and likely related to their cancer progression (such as obstruction of biliary stent). All five patients were replaced in their respective cohort (see Table 1). We observed one DLT, grade 3 hand and foot syndrome, at level four. No further DLTs were observed. All patients were evaluable for toxicity except one who was lost to follow up. Thirty-eight percent of patients required dose reductions and/or delays (DR/DD) after a median of three cycles (range 1–6 cycles). Toxicities leading to DR/DD included thrombocytopenia (6), hand and foot syndrome (3), and fatigue (2). The most common toxicities of any grade were fatigue (61%) and anemia (43%). The most commonly experienced grade 3 toxicity was lymphopenia (14%). There were no grade 4 toxicities. All toxicities were manageable and reversible.

**Table 3** Toxicity assessment ($N = 28$)[a]

| | % grade 1/2 | % grade 3[b] |
|---|---|---|
| Hematologic toxicities | | |
| Anemia | 43 | 0 |
| Thrombocytopenia | 39 | 0 |
| Leukopenia | 36 | 0 |
| Lymphopenia | 18 | 14 |
| Neutropenia | 18 | 0 |
| Non-hematologic toxicities[a] | | |
| Fatigue | 57 | 4 |
| Nausea | 32 | 4 |
| Hand–foot syndrome | 29 | 7 |
| Diarrhea | 32 | 0 |
| Parasthesias | 21 | 0 |
| Vomiting | 11 | 4 |
| Mucositis | 11 | 0 |
| Dehydration | 4 | 4 |
| Dry Skin | 7 | 0 |
| Rash | 7 | 0 |
| Dysgeusia | 7 | 0 |

[a] Additionally, there were 4% of patients who had each grade 1 alopecia or gum bleeding, or grade 2 DVT

[b] There were no grade 4 Toxicities

Preliminary antitumor activity (Table 4)

A total of 29 patients were enrolled on this study with 3 non-evaluable for response as they were removed from the study before restaging scans were done. Reasons for removal from study were rapid symptomatic progression (2) and loss to follow up (1). Additionally, one patient was non-evaluable for time to tumor progression as he was withdrawn due to

**Table 4** Preliminary efficacy results and prior therapy

| Disease site | Prior therapy | Dose level | Best response | TTP (months) |
|---|---|---|---|---|
| Colorectal | | | | |
| 1 | 1-FO 2-FIB | 2 | SD | 6.1 |
| 2 | 1-FOB 2-ICe | 3 | PD | 2 |
| 3 | 1-FOB 2-ICe | 3 | PD | 1.8 |
| 4 | 1-FO | 4 | SD | NE |
| 5 | 1-FOB 2- ICeB | 4 | PD | 1.9 |
| 6 | 1-FI 2-FOB | 4 | SD | 7 |
| 7 | 1-FOB 2-FIB | 4 | SD | 3.6 |
| 8 | 1-FOC 2-FIB | 4 | PD | 2.1 |
| 9 | 1-FOB 2-ICe | 4 | PD | 2.0 |
| 10 | 1-FOB 2-ICe | 4 | SD | 13+ |
| Esophageal | | | | |
| 1 | 1-PTIl 2-FI | 1 | PD | 1.7 |
| 2 | None | 1 | PD | 1.7 |
| 3 | 1-CF | 1 | PD | 1.2 |
| 4 | 1-FI | 3 | PD | 1.8 |
| 5 | 1-CF 2-FI | 4 | SD | 4.8 |
| 6 | 1-CF | 4 | SD | 12.5 |
| 7 | 1-ECF 2-CaP | 4 | PD | 1 |
| 8 | 1-CF | 4 | SD | 4.7 |
| Pancreas | | | | |
| 1 | 1-G 2-IC | 2 | NE | NE |
| 2 | 1-G | 3 | PD | 1.8 |
| 3 | 1-GO 2-t | 4 | SD | 4.6 |
| 4 | 1-GF | 4 | SD | 4.8 |
| 5 | 1-G | 4 | PD | 1.8 |
| 6 | 1-GOt | 4 | PD | 1.9 |
| 7 | 1-G | 4 | NE | NE |
| Bile duct | | | | |
| 1 | 1-GF | 1 | PD | 1.8 |
| 2 | None | 2 | NE | NE |
| Gastric | 1-PTIl | 2 | SD | 4.1 |
| Hepatocellular | None | 2 | PD | 2.2 |

In the metastatic setting only

Abbreviations: *F* 5-fluorouracil, *O* oxaliplatin *I* irinotecan, *B* bevacizumab, *Ce* cetuximab, *P* paclitaxel, *T* trastuzumab, *Il* interleukin 12, *C* cisplatin, *E* epirubicin, *Ca* carboplatin, *G* gemcitabine, *t* tarceva, *SD* stable disease, *PD* progressive disease, *NE* non-evaluable, *TTP* time to tumor progression

lack of compliance with supportive therapy, and then was switched to an alternative therapy by his treating physician before evidence of progression was documented.

There were no objective responses observed. Nine patients experienced prolonged stabilization of disease (>4 months). The distribution of prolonged stable disease was as follows in evaluable patients: colorectal cancer (3/9), esophageal cancer (3/8), pancreas cancer (2/5), and gastric cancer (1/1). Two patients had disease stabilization that lasted beyond 1 year. The first patient had metastatic colorectal cancer with intrathoracic lymphadenopathy and pulmonary metastasis, and had progressed on FOLFOX/bevacizumab followed by irinotecan/cetuximab before having enrolled on the study. The patient continues to show evidence of stable disease after 13 months on study. He also has had evidence of tumor marker response (best CEA response was a 50% drop from baseline). The other patient had a diagnosis of metastatic esophageal cancer involving the mediastinal and lower abdominal lymph nodes as well the liver and the lungs, and he has had failed cisplatin and 5FU before enrolling on the study. He showed evidence of stable disease that lasted 12.5 months, and had a tumor marker response (Ca 19-9 dropped from 43.64 to <15 U/ml with 35 U/ml being the upper limit of normal).

## Discussion

Mitomycin C (MMC) and capecitabine have shown evidence of activity in a variety of gastrointestinal malignancies [4, 5, 14]. Preclinical as well as clinical studies have suggested that MMC produces significant upregulation of tumor specific levels of TP starting 4–6 days after treatment and persisting for at least 10 days [16, 17]. Since a principal determinant of the therapeutic index with capecitabine-based treatment is the level of TP activity in malignant tissues, therapeutic strategies to maximize TP activity can result in higher antineoplastic efficacy after administration of capecitabine. On that basis, we performed a phase I dose escalation study of pharmacobiologically based scheduling of capecitabine and MMC in patients with various gastrointestinal solid tumor malignancies.

This combination was found to be relatively well-tolerated with no evidence of grade 4 toxicities. Grade 3 hand and foot syndrome was determined to be the DLT in one patient at dose level 4 (MTD) with no further DLTs observed. Higher doses of capecitabine were not tested, given that the dose of 1,000 mg/m$^2$ twice daily for 14 days is commonplace in the US [18]. We found no evidence of MMC-related idiosyncratic or cumulative toxicities with a median cumulative dose of MMC of 12 mg/m$^2$ (Range = 6–36 mg/m$^2$).

Although it is beyond the scope of a phase I study to assess efficacy, we did observe a number of pretreated patients with colorectal, gastroesophageal, and pancreatic cancers experiencing prolonged stabilization of their disease. For example, in metastatic colorectal cancer (MCRC), one-third of the evaluable patients with two prior therapies in our study had prolonged stable disease (6.1, 7, and 13+ months) with 2 of those 3 patients experiencing a 40 and 50% drop in their respective CEA levels. Supporting the

renewed interest in MMC in MCRC are numerous studies combining it with a fluoropyrimidine across lines of therapy. A recent phase II study, combining MMC to capecitabine in first line treatment of patients with MCRC, showed disease control rates similar to those reported with the commonly used oxaliplatin and irinotecan-based regimens [20]. Moreover, a recent phase II study with a higher dose of MMC (7 mg/m$^2$) given over a longer interval (every 6 weeks) in combination with a higher dose of capecitabine (2,500 mg/m$^2$ in split daily doses 2 weeks out of every 3 weeks as standard in Europe [18]) showed an objective response rate of 15.2% in patients with MCRC previously treated with 5FU and irinotecan [21]. More recently, multiple studies showed interesting responses, when MMC was combined with other fluoropyrimidines such as UFT/Leucovorin or tegafur–uracil in pretreated patients with MCRC [22, 23]. In our study, 90% of the patients with MCRC were previously exposed to all 3 available drugs (irinotean, oxaliplatin, and infusional 5FU) in addition to at least one of the standard biologics (bevacizumab and cetuximab) prior to recruitment.

Of course, one can raise the question about the level of contribution of one or the other agent. Single agent MMC [4, 24, 25] and single agent capecitabine have minimal activity in MCRC following documented bolus 5FU failure [26]. In our study, all patients with MCRC and the majority of the ones with esophageal cancer had prior exposure to infusional 5FU. There is also, in MCRC, evidence of improved response rates, when 5FU was combined with MMC when compared to 5FU alone, suggesting some level of synergism between the two [27]. As such, any observed benefit is likely drawn from the combination of the two agents rather from individual activity of one of them.

In conclusion, capecitabine, in combination with MMC in the proposed schedule, is well-tolerated with preliminary evidence of activity in various gastrointestinal malignancies. The recommended doses for phase II studies are MMC at 6 mg/m$^2$ on day 1 of a 28-day cycle, in combination with capecitabine at 1,000 mg/m$^2$ twice daily on days 8–21. The dose of MMC is capped at 36 mg/m$^2$. Future studies utilizing this regimen should be developed in various gastrointestinal malignancies, particularly in MCRC, where recent evidence 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 [28, 29]. Future studies should incorporate correlative work including serial tumor biopsies to validate TP upregulation using this schedule.

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**Conflicts of interest** Tanios Bekaii-Saab: Research Grants (Roche), Consultant and Speaker (Amgen).

## References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ (2007) Cancer statistics, 2007. CA Cancer J Clin 57(1):43–66
2. Edwards BK, Howe HL, Ries LA, Thun MJ, Rosenberg HM, Yancik R, Wingo PA, Jemal A, Feigal EG (2002) Annual report to the nation on the status of cancer, 1973–1999, featuring implications of age and aging on U.S. cancer burden. Cancer 94(10):2766–2792
3. Lown JW, Sim SK, Chen HH (1978) Hydroxyl radical production by free and DNA-bound aminoquinone antibiotics and its role in DNA degradation. Electron spin resonance detection of hydroxyl radicals by spin trapping. Can J Biochem 56(11):1042–1047
4. Bradner WT (2001) Mitomycin C: a clinical update. Cancer Treat Rev 27(1):35–50 Feb
5. Hofheinz RD, Beyer U, Al-Batran SE et al (2008) Mitomycin C in the treatment of gastrointestinal tumours: recent data and perspectives. Onkologie 31:271–281
6. Valavaara R, Nordman E (1985) Renal complications of mitomycin C therapy with special reference to the total dose. Cancer 55(1):47–50 Jan 1
7. Ntukidem N, Arce-Lara C, Otterson GA, Kraut E, Cataland S, Bekaii-Saab T (2009) Capped-dose mitomycin C: a pooled safety analysis from three prospective clinical trials. Cancer Chemother Pharmacol [Epub ahead of print]
8. Xu Y, Kolesar JM, Schaaf LJ, Drengler R, Duan W, Otterson G, Shapiro C, Kuhn J, Villalona-Calero MA (2009) Phase I and pharmacokinetic study of mitomycin C and celecoxib as potential modulators of tumor resistance to irinotecan in patients with solid malignancies. Cancer Chemother Pharmacol 63(6):1073–1082
9. Mrozek E, Kolesar J, Young D, Allen J, Villalona-Calero M, Shapiro CL (2008) Phase II study of sequentially administered low-dose mitomycin-C (MMC) and irinotecan (CPT-11) in women with metastatic breast cancer (MBC). Ann Oncol 19(8):1417–1422
10. Villalona-Calero MA, Kolesar JM (2002) Mitomycin C as a modulator of irinotecan. Anticancer activity. Oncology 16(8 Suppl 7):21–25
11. Villalona MA, Bekaii-Saab T, Burak W, Ross P, Xu Y, Criswell T, Duan W, Young D, Miller J, Kolesar J (2005) Phase II randomized study of mitomycin C (MMC) as a modulator of irinotecan in patients (pts) with esophageal and GE Junction adenocarcinomas. In: 2005 ASCO annual meeting proceedings. J Clin Oncol, vol 23, no. 16S, Part I of II (June 1 Supplement), p 4027
12. Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K (1998) Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 34:1274–1281
13. Ishikawa T, Sekiguchi F, Fukase Y, Sawada N, Ishitsuka H (1998) Positive correlation between the efficacy of capecitabine and doxifluridine and the ratio of thymidine phosphorylase to dihydropyrimidine dehydrogenase activities in tumors in human cancer xenografts. Cancer Res 58:685–690
14. Gennatas C, Michalaki V, Gennatas S (2009) The role of capecitabine in the management of tumors of the digestive system. Rev Recent Clin Trials 4(1):1–11 Jan
15. Eda H, Fujimoto K, Watanabe S, Ishikawa T, Ohiwa T, Tatsuno K et al (1993) Cytokines induce thymidine phosphorylase expression in tumor cells and make them more susceptible to 5′-deoxy-5-fluorouridine. Cancer Chemother Pharmacol 32:333–338
16. Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H (1998) Induction of thymidine phosphorylase activity and

enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. Clin Cancer Res 4:1013–1019
17. Ogata Y, Matono K, Sasatomi T, Ishibashi N, Torigoe S, Fukumitsu T, Mizobe T, Yamashita N, Yanagawa T, Shirouzu K (2006) Upregulation of thymidine phosphorylase in rectal cancer tissues by mitomycin C. J Surg Oncol 93(1):47–55
18. Midgley R, Kerr DJ (2009) Capecitabine: have we got the dose right? Nat Clin Pract Oncol 6(1):17–24
19. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
20. Rao S, Cunningham D, Price T et al (2004) Phase II study of capecitabine and mitomycin C as first-line treatment in patients with advanced colorectal cancer. Br J Cancer 91(5):839–843
21. Scartozzi M, Falcone A, Pucci F et al (2006) Capecitabine and mitomycin C may be an effective treatment option for third-line chemotherapy in advanced colorectal cancer. Tumori 92(5):384–388
22. Francois E, Smith D, Seitz J, Perrier H, Chamorey E, Mari V, Follana P, Dahan L. Oral tegafur–uracil plus leucovorin and mitomycin C (MMC) as salvage treatment in patients with advanced colorectal cancer: a phase II study. ASCO GI 2009; Abs 480
23. Gennatas CG, Michalaki V, Gennatas S. Mitomycin C and UFT/leucovorin as salvage treatment in patients with advanced colorectal cancer. ASCO GI 2009; Abs 486
24. Poplin EA, LoRusso P, Lokich JJ, Gullo JJ, Leming PD, Schulz JJ, Veach SR, McCulloch W, Baker L, Schein P (1994) Randomized clinical trial of mitomycin-C with or without pretreatment with WR-2721 in patients with advanced colorectal cancer. Cancer Chemother Pharmacol 33(5):415–419
25. Anderson N, Lokich J, Moore C, Bern M, Coco F (1999) A dose-escalation phase II clinical trial of infusional mitomycin C for 7 days in patients with advanced measurable colorectal cancer refractory or resistant to 5-fluorouracil. Cancer Invest 17(8):586–593
26. Hoff PM, Pazdur R, Lassere Y, Carter S, Samid D, Polito D, Abbruzzese JL (2004) Phase II study of capecitabine in patients with fluorouracil-resistant metastatic colorectal carcinoma. J Clin Oncol 22(11):2078–2083
27. Ross P, Norman A, Cunningham D, Webb A, Iveson T, Padhani A, Prendiville J, Watson M, Massey A, Popescu R, Oates J (1997) A prospective randomised trial of protracted venous infusion 5-fluorouracil with or without mitomycin C in advanced colorectal cancer. Ann Oncol 8(10):995–1001
28. Van Cutsem E, D'haens G, Moiseyenko V, Zaluski J, Folprecht G, Tejpar S, Kisker O, Stroh C, Rougier P (2008) KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: the CRYSTAL experience. J Clin Oncol 26(15S); Abs 2
29. Amado RG, Wolf M, Peeters M et al (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26(10):1626–1634