Mitomycin-C and Capecitabine (MIXE) as Salvage Treatment in Patients with Refractory Metastatic Colorectal Cancer: A Retrospective Study

MUHAMMAD WASIF SAIF[1], KRISTIN KALEY[2], MARIANNE BRENNAN[2], MARIE CARMEL GARCON[3] and GLADYS RODRIGUEZ[3]

[1]*Section of GI Cancers and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, U.S.A.;*
[2]*Yale School of Medicine, New Haven, CT, U.S.A.;*
[3]*Columbia University Medical Center, New York, NY, U.S.A.*

Abstract. *Aim: To report on the efficacy and safety of mitomycin-C-capecitabine (MIXE) regimen as salvage chemotherapy regimen for patients with refractory metastatic colorectal cancer. Patients and Methods: We retrospectively reviewed patients who were treated with mitomycin-C (7 mg/m^2) every three weeks in combination with capecitabine (1,000 mg) twice daily (2,000 mg per day) days 1 to 14 every three weeks. All patients had previously received at least three chemotherapy regimens including biological agents, such as a monoclonal antibody either against vascular endothelial growth factor receptor or epidermal growth factor receptor (only if wild-type KRAS). Laboratory tests including complete blood count were checked weekly, while chemistries, liver function tests and carcinoembryogenic antigen levels were determined every three weeks. Radiological assessment of their disease with computed tomography scans was performed every nine weeks. Results: Fifteen patients were included: Male:female ratio, 9:6; age ranged from 52-70 years; Eastern Cooperative Oncologic Group performance status 1 in 5 patients and 2 in the remaining 10 patients. Seven patients demonstrated a clinical benefit (one partial response, two minor responses, five stable disease), disease in six patients progressed and one patient participated in a phase I clinical study and hence was not evaluable. No grade 3 or 4 hematological toxicities were noticed; the most common toxicities included grade 2 hand-foot syndrome (HFS), grade 1 fatigue and grade 2 diarrhea. Conclusion: The MIXE regimen showed a modest efficacy in heavily pre-treated patients with mCRC. The MIXE regimen may be considered for patients with mCRC who are refractory to primary treatment and are without other options or who are not eligible for clinical studies.*

Correspondence to: M. Wasif Saif, MD, MBBS, Director, Section of GI Cancers and Experimental Therapeutics, Tufts University School of Medicine, 800 Washington Street, Boston, MA 02111, U.S.A. Tel: +1 6176365627, Fax: +1 6176368535, e-mail: wsaif@tuftsmedicalcenter.org

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Colorectal cancer (CRC) is the third most common cancer diagnosed in both men and women in the USA. It is estimated that approximately 102,480 new cases of colon cancer and 40,340 new cases of rectal cancer will be diagnosed in 2013. CRC will lead to about 50,830 deaths during 2013, making it the second leading cause when both sexes are combined (1). Advances in the treatment of CRC have achieved a 5-year survival rate of 6% of patients in U.S.A (1). Current treatment options include chemotherapeutic agents [5-fluorouracil (5-FU), irinotecan, oxaliplatin and capecitabine] and biological agents [bevacizumab, cetuximab, ablibercept, regorafenib] (2). New treatment options have improved prognosis but at the cost of increased toxicity and expense. Ultimately, most patients with metastatic disease will eventually become refractory to the available drugs (3). The development of new effective and less toxic regimens has, therefore, become a necessity (4).

Mitomycin-C belongs to a family of aziridine-containing natural products isolated from *Streptomyces caespitosus* or *Streptomyces lavendulae* (4). Mitomycin-C is a natural antibiotic that has demonstrated antitumor activity, has already been used for a variety of solid tumors, including gastrointestinal tumors (anal, upper gastrointestinal), breast, lung and bladder cancer, while capecitabine is useful in treating patients with colorectal, gastric, breast and pancreatic malignancies (5-9). Mitomycin-C is usually considered an old drug and is not often used, partly due to associated delayed bone marrow toxicity. The most common schedule is 6-weekly administration. Prolonged use may

result in permanent bone marrow damage. In addition, hemolytic uremic syndrome (HUS), lung fibrosis and renal damage may also occur (10, 11).

Pre-clinical data suggested that mitomycin-C enhances capecitabine conversion to 5-FU in tumors by increasing the level of thymidine phosphorylase (TP), a critical enzyme for the conversion. Tumor necrosis factor-alpha (TNFα) was found to raise the level of TP and treatment of human cancer xenografts with mitomycin-C leads to increase in TNFα, suggesting a possible mechanism of TP enhancement (12). Moreover, there is some evidence to suggest that the combination of 5-FU plus mitomycin-C is more active *in vitro* than each compound alone against CRC (13).

We present a retrospective study of mitomycin-C and capecitabine (MIXE) regimen used in patients with refractory mCRC.

Patients and Methods

We retrospectively reviewed efficacy, safety and toxicity data on patients at our institution diagnosed with cytologically- or histologically-proven mCRC who were treated with MIXE salvage chemotherapy. According to institutional standards, all of these patient had satisfactory bone marrow function (hemoglobin >9 g/dl; absolute neutrophil count >1,500 cells/mm^3 and platelet count >100 cells/mm^3); renal (serum creatine <1.5 mg/dl) and liver function (serum total bilirubin <1.5 mg/dl and serum transaminases <2.5 times the upper limit of laboratory normal if no liver metastases or <5-times the upper limit if liver metastases were present) before administration of MIXE chemotherapy. Treatment regimen consisted of mitomycin-C at 7 mg/m^2 intravenously every three weeks in combination with capecitabine at 1,000 mg twice daily (2,000 mg per day) days 1 to 14 every three weeks. All patients had previously received at least 3 chemotherapy regimens including biological agents, such as a monoclonal antibody either against vascular endothelial growth factor receptor (VEGFR) or epidermal growth factor receptor (EGFR) [only if wild-type KRAS]. Laboratory tests including complete blood count were checked weekly, while chemistries, liver function tests and carcinoembryogenic antigen (CEA) levelswere determined every three weeks. The radiological assessment of their disease with computed tomography (CT) scans was performed every 9 weeks. Toxicity was documented and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 (14). Staging and radiological evaluation was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) (15). Reference range for CEA in our institution was <3 μg/L in non-smokers and <5 μg/L in smokers. Patients continued to receive MIXE chemotherapy until disease progression or unacceptable toxicity. Pre-emptive anti-emetics included ordansetron 8 mg *i.v.* and dexamethasone 10 mg *i.v.* prior to administration of mitomycin-C according to the institutional guidelines. Furthermore, pegfilgrastim support was given prophylactically for patients who were above 65 years of age or had history of previous grade 4 neutropenia or neutropenic fever with the most recent chemotherapy regimen.

We obtained data from Electronic Patients Records including age, gender, Eastern Cooperative Oncologic Group performance Status (ECOG), type of previous chemotherapy regimens, doses of MIXE regimen, and previous biological regimens.

Results

Between July 2007 and February 2013, we treated 15 patients with mCRC. The demographics included: Male:female ratio, 9:6; age ranged from 52-70 years (median age=59 years); ECOG PS was 1 in 5 patients and 2 in the remaining 10 patients. All patients had previously received at least three chemotherapy lines (FOLFOX: oxaliplatin, 5-FU and leucovorin; FOLFIRI: irinotecan, 5-FU and leucovorin; XELOX: oxaliplatin and capecitabine) and biological agents (bevacizumab in 15/15, cetuximab in 9/15 patients and panitumumab in 1/15 patient).

The median number of treatment cycles was six (range: 3-9). No grade 3 or 4 hematological toxicities were noticed. Six out of 15 patients received prophylactic pegfilgrastim on day 2. Two patients developed grade 2 thrombocytopenia and three patients developed grade 2 anemia. The most common non-hematological toxicities included grade 2 hand-foot syndrome (HFS) (three patients), grade 1 fatigue (four patients) and grade 2 diarrhea (three patients).

One patient achieved a partial response (PR) (35% tumor shrinkage), two had minor response (<30%) and five patients had stable disease as their best response. In total, seven patients demonstrated a disease control rate (DCR) of 46% (7/15). Of the remaining patients, disease progressed at the first staging CT scan in six patients and one patient was not evaluable as he was included in a phase I clinical study. The duration of response (DoR) for the one patient with PR was nine cycles (27 weeks), whereas it was 18 weeks for both patients with minor response. The DoR for patients with stable disease ranged from 9 to 18 weeks. The CEA level dropped by more than 25% in three patients, more than 10% in one patient, and was stable in seven patients. The CEA level was not elevated in one patient.

Discussion

For patients with mCRC whose disease has progressed upon the available modern chemotherapeutic and biological agents, treatment options outside the context of a clinical trial are limited and they, therefore, pose a major therapeutic challenge for the medical oncologists (16-21). Mitomycin-C is an old regimen that has been used for a variety of solid tumor types in the past and has also been tested in several phase I, II and III clinical trials in patients with CRC in various settings. There are data to support the synergism of mitomycin-C with capecitabine, as mentioned earlier. Our retrospective study demonstrates that the combination of mitomycin-C with capecitabine has a modest efficacy and favorable toxicity profile in pre-treated patients with mCRC.

A review of the medical literature revealed a total of seven studies with a total of 747 patients: 27 patients in a phase I study, 223 patients in four phase II studies, and 471 patients in

a phase III study (16-21). Capecitabine plus mitomycin-C was used as first-line therapy in three studies (610 patients), as third line treatment in two studies (57 patients) and as fourth-line therapy in two studies (16-21). One study evaluated the MAX regimen (mitomycin-C + bevacizumab + capecitabine) in the first line setting for mCRC (22). In the phase I study, the recommended dose of mitomycin-C was 10 mg/m^2 on the first day of three week cycles in combination with capecitabine at 1,000 mg/m^2 twice daily on days 1-14. In the phase II studies, capecitabine at 1,000-1,250 mg/m^2 twice daily on days 1-14 of three week cycles and mitomycin-C at 7 mg/m^2 on the first day every six weeks was administered. In the phase III study, mitomycin-C was administered at 7 mg/m^2, along with bevacizumab at 7.5 mg/m^2 and capecitabine at 2,000-2,500 mg/m^2 on days 1-14 every three weeks. In these clinical studies, the reported response rate, including PR and complete responses (CR), ranged from 10 to 45.4%, the median time-to-progression was 2.6 to 7.6 months and median survival was 6.8 to 9.3 months. In the phase III trial, the addition of bevacizumab to the combination of mitomycin-C with capecitabine resulted in an objective response rate of 45%, overall survival of 16.5 months and progression-free survival of 8.4 months. The most commonly reported grade 3 or 4 toxicities were neutropenia, thrombocytopenia, anemia, nausea, diarrhea and HFS (16-22). Our study used a more conservative dose of mitomycin-C and capecitabine (MIXE) and hence resulted in a very favorable toxicity profile. One can also argue that the MIXE regimen offers a therapeutic option at a low cost, which provides a well-tolerated alternative, with acceptable efficacy. However, others may regard the MIXE regimen an unacceptable alternative offering no benefits to the patient over best supportive care (23). The MIXE regimen has also shown promise in other types of malignancies, such as breast cancer (24, 25). The convenience of the regimen and toxicity of MIXE are more favorable to historical comparison to either bolus or infusional 5-FU (26-27).

We believe that the MIXE regimen can be considered as a palliative treatment regimen for patients with mCRC that is refractory to standard treatment and who are not eligible for enrollment in a clinical trial, but have a good ECOG PS and wish to receive therapy. Further prospective phase III studies with these combinations in the second- or third-line treatment of mCRC are warranted.

Conflicts of Interest

The Authors state no conflicts of interest and have received no payment in preparation of this manuscript or conduct of the study.

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