

## Mitomycin-C and Capecitabine (MIXE) Regimen as Salvage Therapy for Advanced Pancreatic Cancer

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### ABSTRACT

#### BACKGROUND

The prognosis of patients with advanced pancreatic cancer (APC) is dismal. Following nab-paclitaxel plus gemcitabine (AG) and FOLFIRINOX, there is no recommended third-line chemotherapy. There is in vivo evidence of mitomycin-C induced upregulation of tumor thymidine phosphorylase (TP) for the conversion of capecitabine to 5-fluorouracil, the active chemotherapeutic agent. This could translate clinically to synergistic effects of mitomycin-C and capecitabine (MIXE). We report here the efficacy and safety of the MIXE regimen as salvage chemotherapy regimen for patients with refractory APC.

#### METHODS

We retrospectively reviewed patients who were treated with mitomycin-C ( $7 \text{ mg/m}^2$ ) every three weeks in combination with capecitabine (1000 mg) twice daily (2000 mg/day) on days 1 to 14 every three weeks. All patients had previously received at least two chemotherapy regimens including AG, FOLFIRINOX or irinotecan liposome injection. Laboratory tests including complete blood count were checked weekly, while chemistries, liver function tests and CA19-9 were determined every three weeks. Radiological assessment of their disease with computed tomography scans was performed every nine weeks.

#### RESULTS

A total of 27 patients (16 males), aged 51-79, ECOG<2, who had received either two prior regimens (13), three prior regimens (8) or four prior regimens (6), or prior radiation (7) were included. Stable disease was seen in 12 patients (44%) and partial response in 2 patients (7%), while disease progression was seen in 12 patients (44%). Duration of response ranged from 9 to 24 weeks. No patient demonstrated complete response. One patient was not evaluable. The most common toxicities included grade 2 hand-foot syndrome (HFS), grade 1 fatigue and grade 2 diarrhea. Due to multiple prior regimens and/or history of grade 4 neutropenia or neutropenic fever, 80% of patients received peg-filgrastim upfront as primary prevention. No grade 3 or 4 hematological toxicities were noted.

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## **CONCLUSIONS**

The MIXE regimen showed a modest efficacy in heavily pre-treated patients with APC. Given the in vivo evidence of mitomycin-C-induced upregulation of TP, this efficacy could be the result of the synergy between mitomycin-C and capecitabine and should be further evaluated. The MIXE regimen may be considered for patients with APC who are refractory to primary treatment and are without other options or who are not eligible for clinical studies.

## **KEYWORDS**

Pancreatic cancer; Capecitabine; Fluoropyrimidines; Mitomycin

## **INTRODUCTION**

Pancreatic ductal adenocarcinoma is an aggressive malignancy and one of the leading causes of cancer-related death in the United States. The most effective treatment is surgical resection, however only 15%-20% of patients are candidates as most patients are diagnosed with locally advanced or metastatic disease. The five-year overall survival for patients with pancreatic cancer is 9% [1]. The treatment of patients with advanced pancreatic cancer (APC) focuses on disease control, prolonging survival, and palliation of symptoms.

For patients with good performance status (PS), Eastern Cooperative Oncology Group (ECOG) 0 or 1, limited comorbidities and normal serum bilirubin, initial treatment should be with FOLFIRINOX (5-fluorouracil (5-FU), leucovorin, irinotecan and oxaliplatin). An alternate, less intensive regimen is nab-paclitaxel and gemcitabine (AG). If patients are not likely to tolerate an intensive regimen, treatment with gemcitabine alone or with the addition of capecitabine or erlotinib is an option, for ECOG PS 2 [2].

Beyond first-line therapy there are options for patients with genetic germline mutations, such as NTRK (larotrectinib, entrectinib), BRCA1/BRCA2 (PARP inhibitor olaparib), and PD-1/MSI-H/dMMR (pembrolizumab). However, if patients do not have any favorable mutations, there is no standardized third-line regimen beyond 5-FU and gemcitabine-based regimens.

Review of medical literature revealed that there have been several clinical trials using mitomycin-C (MMC) combined with various agents, including capecitabine, to treat different stages of pancreatic cancer. Table 1 outlines some of these studies from 1980 to 2019. Given the diverse nature of the studies included in the table, for example published year, trial goals, single center vs multicenter, and patient populations, the common parameters may not be available for comparison. Some trials included gallbladder and bile duct cancers along with pancreatic cancer (the table includes numbers specifically for pancreatic cancer patients).

There is in vivo evidence of MMC-induced upregulation of tumor thymidine phosphorylase (TP) for the conversion of capecitabine to 5-FU, the active chemotherapeutic agent [3]. This could translate clinically to synergistic effects of mitomycin-C and capecitabine (MIXE) regimen.

Here we examine the MIXE regimen which combines MMC and capecitabine, a chemotherapy combination that capitalizes on the synergistic effects of these two agents.

## **PATIENTS AND METHODS**

We retrospectively reviewed efficacy, safety and toxicity data on patients at our institution diagnosed with APC who were treated with the MIXE regimen. Data from electronic

patient records was collected including age, gender, diagnosis, stage, ECOG status, previous chemotherapy regimens, doses of MIXE regimen, toxicities and outcome including RR, CA 19-9 and survival when available.

According to institutional standards, all these patients had satisfactory bone marrow function (hemoglobin >9 g/dl); absolute neutrophil count >1,500 cells/mm<sup>3</sup> and platelet count >100 cell/mm<sup>3</sup>; renal (serum creatinine <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 MMC (7 mg/m<sup>2</sup>) every three weeks in combination with capecitabine (1000 mg) twice daily (2000 mg/day) on days 1 to 14 every three weeks. All patients had previously received at least two chemotherapy regimens including AG, FOLFIRINOX or irinotecan liposome injection. Laboratory tests including complete blood count were checked weekly, while chemistries, liver function tests and CA 19-9 were determined every three weeks. Radiological assessment of their disease with computed tomography scans was performed every nine weeks.

Pre-emptive antiemetics included ondansetron 8mg intravenously and dexamethasone 10 mg intravenously. Prior to the administration of mitomycin-C according to the institutional guidelines. Furthermore, peg-filgrastim 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.

Toxicity was documented and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [4].

Staging and radiological evaluation was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [5]. Patients continued to receive MIXE chemotherapy until disease progression or unacceptable toxicity.

## **RESULTS**

### ***Demographic Characteristics***

Between 2013 and 2020 we treated 27 patients with APC were treated with the MIXE regimen. Demographic features showed male:female ratio of 16:11, aged 51-79 (mean: 63), with ECOG PS <2. Number of prior chemotherapy regimens included: two prior regimens in 13 patients, three prior regimens in 8 patients, four regimens in 6 patients, while 7 patients had radiation before receiving MIXE. Baseline patient characteristics are summarized in Table 2.

### ***Toxicities***

The median number of treatment cycles was 5 (range: 2 - 17). No grade 3 or 4 hematologic toxicities were noted. Due to multiple prior regimens and/or history of grade 4 neutropenia or neutropenic fever, 80% of patients received peg-filgrastim upfront as primary prevention. The most common non-hematological toxicities included grade 2 hand-foot syndrome, grade 1 fatigue, and grade 2 diarrhea.

### ***Efficacy***

Overall disease control was seen in 52% patients including partial response (PR) in 2 patients (7%) and stable disease in 12 patients (44%). Disease progression was seen in 12 patients (44%) and one patient was not evaluable. Duration of response ranged from 9 weeks to 24 weeks (median: 9).

Regimen	Dose	# Of Pts	Stage	Outcome	Reference
5-FU, mitomycin, streptozotocin	NA	22	Unresectable	ORR 32% mOS 6 m	Burkowski RM, et al., Cancer Clinical trials, 1980 [34]
FEMII	5-FU, dose escalated 4-epidoxorubicin, MMC	12	Advanced	ORR 25% SD 30% mOS 3.4 m	Verhees S, et al.; Onkologie 1990 [39]
5-FU vs. Mallinson regimen (combined/ sequential 5-FU, cyclophosphamide, methotrexate, vincristine, and MMC) vs. Combined 5-FU, doxorubicin, and cisplatin	NA	41	Advanced	ORR 7% vs. 21% vs. 15% mOS 4.5 m vs. 4.5 m vs. 3.5 m	Cullinan S, et al., Cancer 1990 [33]
Streptozotocin, MMC and 5-FU vs. cisplatin, cytosine arabinoside, and caffeine	NA	82	Advanced	ORR 10% vs. 5.5% mOS 10 m vs. 5 m	Kelsen D, et al., Cancer 1991 [40]
5-FU, leucovorin, MMC, dipyridamole	5-FU 200 mg/m <sup>2</sup> /day by continuous infusion, leucovorin 30 mg/m <sup>2</sup> IV weekly, MMC 10 mg/m <sup>2</sup> day 1, and dipyridamole 75 mg PO four times daily × 5 weeks on and 1 week off	46	Advanced	ORR 22% CR 2%	Burch PA, et al., Am J Clin Oncol., 2000 [41]
PVI 5-FU vs. PVI 5-FU + MMC	PVI 5-FU (300 mg/m <sup>2</sup> /day for maximum of 24 weeks) or PVI 5-FU plus MMC (7 mg/m <sup>2</sup> every 6 weeks for four courses)	280	Advanced (65% metastatic)	ORR 8.4% vs. 17.6% mPFS 2.8 m vs. 3.8 m mOS 5.1m vs. 6.5m	Maisey N, et al., JCO 2002 [35]
Gemcitabine + MMC	Gemcitabine 800 mg/m <sup>2</sup> IV on days 1, 8 and 15, and MMC 8 mg/m <sup>2</sup> IV on day 1, every 4 weeks	55	II (2%) III (18%) IV (80%)	ORR 29% SD 33% mPFS 4.7 m mOS 7.25 m	Tuinmann G, et al.; Anticancer drugs. 2004 [22]
MDI regimen	MMC 6 mg/m <sup>2</sup> day 1, docetaxel and irinotecan on days 2 and 8 with escalating doses every 4 weeks.	15	Metastatic, pretreated	ORR 0% SD 20% mPFS 1.7 m mOS 6.1 m	Reni M, et al., Cancer Invest. 2004 [23]
SWOG S9700	5-FU 200 mg/m <sup>2</sup> /day continuous IV for 4 weeks then 1 week off; leucovorin 30 mg/m <sup>2</sup> IV on days 1, 8, 15, and 22, then 1 week off; MMC 10 mg/m <sup>2</sup> IV every 6 weeks for 4 doses; Dipyridamole PO 75 mg three times daily during 5-FU administration	50	Stage II or III unresectable	ORR 26% CR 4% Underwent resection 12%	Isakoff WH, et al., JCO 2007 [12]
DocMitoCape Regimen	Capecitabine 2000 mg/m <sup>2</sup> on days 1-14; docetaxel 40 mg/m <sup>2</sup> on day 1; MMC 4 mg/m <sup>2</sup> on day 1, every 21 days	16	Advanced, pretreated	PR 25% SD 25% Minor remission: 31% (shrinkage not fulfilling RECIST criteria for PR)	Kruth J, et al., J Cancer Res Clin Oncol. 2010 [19]
Infusional 5-FU, doxorubicin, and MMC (iFAM)	5-FU 800 mg/m <sup>2</sup> infusion on days 1-5; doxorubicin 30 mg/m <sup>2</sup> on day 1; MMC 8 mg/m <sup>2</sup> on day 1, every 4 weeks	60	Gemcitabine pretreated	ORR 10% SD 13% mPFS 2.4 m mOS 6.1 m	Lim KH, et al., Cancer Chemother Pharmacol. 2011 [15]
MMC and ifosfamide	MMC 8 mg/m <sup>2</sup> on day 1; ifosfamide 2,500 mg/m <sup>2</sup> and mesna 3,000 mg/m <sup>2</sup> on days 1-3, every 28 days	21	Metastatic (gemcitabine resistant)	PR 5% SD 10% mOS 3.7 m	Cereda S, et al., Chemotherapy 2011 [42]
Intra-arterial gemcitabine and MMC	1 cycle of MMC 8.5 mg/m <sup>2</sup> and gemcitabine 500 mg/m <sup>2</sup> on days 1 and 22 through an angiographic catheter into the celiac artery and IV infusions of 500 mg/m <sup>2</sup> gemcitabine on days 8 and 15	17		ORR 24% mPFS 4.6 m mOS 9.1 m	Heinrich S, et al., Hepatogastroenterology. 2013 [16]
Adjuvant four drug chemotherapy regimen: 5-FU, leucovorin, MMC, and dipyridamole with chemoradiation (chemoRT) Trials A and B	Trial A: Upfront chemoRT (50 Gy split-course, 2.5 Gy/fraction) followed by four drug chemotherapy with bolus 5-FU for 4 cycles Trial B: Four drug chemotherapy with continuous infusion 5-FU for 1 cycle followed by continuous chemoradiation (45-54 Gy, 1.8 Gy/fraction) and 2 additional cycles of chemotherapy	Trial A- 62 Trial B 57	Localized, post-surgery T3 (66%) T4 (21%)  T3 (86%) T4 (4%)	3 yr. OS 48% 5 yr. OS S31% 10 yr. OS 26%  3 yr. OS 32% 5 yr. OS 23% 10 yr. OS 9%	Schunke KJ, et al., Adv Radiat Oncol. 2017 [10]
Neoadjuvant radiation with four cycles of 5-FU continuous infusion and cisplatin on day 5, 12, 19, and 26; MMC on day 6, 13, 20, and 27; and heparin infusion	NA	25	T3/T4 (7 <sup>th</sup> edition)	Treatment completion 92% Resection rates: 68% Pathological response according to Evans' classification: Grade IIA: 58.8% IIB: 29.4% IV: 11.8%	Endo Y, et al., World J Surg Oncology, 2019 [9]

**Table 1:** Summary of clinical trials using mitomycin-C (MMC) combined with various agents to treat different stages of pancreatic cancer.

<b>Patients Enrolled</b>	27
<b>Age</b>	
Mean	63
Range	51 - 79
<b>Gender</b>	
Male	16
Female	11
ECOG	1
	2
<b>Prior Regimens</b>	
Two	13
Three	8
Four	6
Radiation	7

**Table 2:** Patient characteristics at baseline.

## **DISCUSSION**

In patients with APC who have progressed following first-line and second-line therapy, there is a relative paucity of published studies evaluating the safety and effectiveness of chemotherapy regimens in this population, except for phase I studies. This might largely be due to the fact that such patients have a declining performance status and are no longer eligible to receive further systemic therapy. Treatment options for this group outside of a clinical trial are limited. MMC has been part of treatment regimens for pancreatic cancer for decades and recent data supports the synergistic effect of MMC with capecitabine. Our retrospective study illustrates that the combination of MMC with capecitabine achieves efficacy in heavily pre-treated patients with very limited remaining treatment options.

A review of the medical literature revealed numerous studies, including Phase I, II and III studies, as well as retrospective studies, chronically the use of MMC and capecitabine [6-33]. Some of the most important studies are listed in Table 1. In these clinical studies the reported response rate (RR), PR and complete response ranged from 4% to 32%, and mOS was 3.4 months to 10 months. The most reported toxicities were neutropenia, thrombocytopenia, anemia, nausea, diarrhea and hand-foot syndrome.

Some of the earliest data from 1980 showed a response rate (RR) of 32% and a median overall survival (mOS) of 6 months with a combination of 5-FU, MMC, and streptozotocin in unrespectable pancreatic cancer [34]. One of the largest multicenter, prospectively randomized studies, randomized 280 patients to protracted venous infusion (PVI) 5-FU (300 mg/m<sup>2</sup>/day for a maximum of 24 weeks) or PVI 5-FU plus MMC (7 mg/m<sup>2</sup> every 6 weeks for four courses) [35]. PVI 5-FU plus MMC resulted in a superior RR in comparison with PVI 5-FU alone (overall RR 8.4% vs. 17.6% (P = 0.04) in APC. The median OS was numerically better but not statistically significant (mOS 5.1 months vs. 6.5 months (p = 0.34). The DocMitoCape regimen (docetaxel, MMC, capecitabine) was studied in 28 patients with a median age of 59 suffering from pancreatic, gallbladder, intra or extrahepatic bile duct carcinoma [19]. There were 16 patients with pancreatic cancer in the trial. The regimen was well tolerated with the most common grade 3 adverse events (AE) being anemia (14%) and leukopenia/thrombocytopenia (<10%). Partial response was 25% and stable disease was seen in 25% patients. In all, the DocMitoCape regimen exhibited a favorable safety profile and a high rate of tumor stabilization in patients with pre-treated gallbladder, bile duct and pancreatic carcinoma.

Germline BRCA (gBRCA) mutations have become a new promising target in treating APC, as supported by a recent success of POLO trial demonstrating improved progression free survival in a gBRCA-mutated APC population [36]. As a tumor suppressor gene, BRCA 1/2 are mainly involved in DNA damage repair process and having mutations in these genes is associated with increased risk of various types of malignancy. Compared to BRCA1 carriers, BRCA2 carriers have higher odds of pancreatic cancer (2.58 and 6.20, respectively) [37] and with a relative risk of 3.51, having BRCA2 mutation is associated with

increased lifetime risk of developing pancreatic cancer [38]. BRCA2 protein repairs double-strand DNA breaks via homologous recombination, and this supports rationale of using DNA-damaging chemotherapeutic agents against tumors harboring BRCA2 mutation [38]. In line with this, MMC demonstrated treatment response in BRCA2-mutated APC, either alone or in combination with capecitabine [20,38]. Notably, the response was seen in the third-line setting. One patient achieved partial response for 6 months with MIXE regimen, until she developed grade 3 thrombocytopenia that led to discontinuation of MMC [20]. Although this was only observed in a small patient population, it is reasonable to consider using MMC based regimen in BRCA2-mutated APC patients, especially when they exhaust other treatment options.

Our study used a more conservative dose of MIXE and hence resulted in a very favorable toxicity profile. One can 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. The MIXE regimen has also shown promise in other types of malignancies, such as colorectal and breast cancer. The convenience of the regimen and toxicity of MIXE are more favorable to historical comparison to either bolus or in fusional 5-FU.

Our study had several limitations. Most notably, the small sample size did not allow for adequate capture of the most clinically significant endpoints. We did not observe any episodes of Grade 3-4 toxicities. There were also not enough intra-cycle blood draws to allow for reliable trending of the absolute neutrophil count nadir and recovery time. Additionally, this was a tertiary care institution retrospective analysis which may limit the extrapolation of results to a more diverse patient population.

### **CONCLUSIONS**

We believe that the MIXE regimen can be considered as a palliative treatment regimen for patients with APC 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. Review of the literature has shown the use of MMC in chemotherapy regimens dating back to 1980. While cross trial comparisons are difficult, MMC-containing regimens and specifically MMC and capecitabine combinations, have evidence of PR, CR, and stable disease responses. These data are valuable as salvage treatment options for heavily pretreated patients with APC. Further prospective studies including combination with novel agents in this setting are warranted.

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