The THAI Journal of SURGERY 2007; 28:73-75.
Official Publication of the Royal College of Surgeons of Thailand

Toxicity of Mitomycin C and 5-FU Regimen: Experience at Srinagarind Hospital, Khon Kaen University, Thailand

Nedtra Nedphokaew, MD
Potchavit Aphinives, MD, FICS
Vajarabhongsa Bhudhisawasdi, MD, FRCS (Ed)
Otur Sae-seow, MD
Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Abstract

Objective: **To evaluate the toxicities in patients receiving Mitomycin C (MMC) and 5-FU regimen.**

Materials and Methods: **Between October 2001 and September 2005, 199 medical records of patients treated with MMC and 5-FU regimen were reviewed. The regimen consisted of a bolus of MMC (10 mg/m^2) on the first day and 5-FU (600 mg/m^2/day) given as a continuous infusion for 5 days; these were repeated every 4 weeks for 6 cycles. Responses and toxicities were analyzed according to WHO criteria.**

Results: **The study population included a total of 199 patients; 122 males (61%) and 77 females (39%). Residents of Khon Kaen province comprised 21% of the study population, while those who lived outside the province constituted 79%. The age ranged from 15-70 years old (mean 52). Body surface area (BSA) averaged 1.51 m^2. Only one-third of patients received a complete course of chemotherapy. There was no significant difference in the occurrence of toxicity between patients who received complete course of chemotherapy compared to those received incomplete course. Patients residing in Khon Kaen province were twice as likely to receive a complete course of chemotherapy as patients from outside (p = 0.04). Seventy-five percent of treated patients (150/199) developed toxicities during the courses of chemotherapy. Of these, gastrointestinal toxicities predominated (81%, 122/150) with nausea being the most common subtype, WHO severity grade II (56%, 68/122), followed by bone marrow suppression (43%, 65/150) with anemia being the most common subtype, WHO severity grade II (75%, 49/65).**

Conclusions: **The MMC and 5-FU regimen produced high toxicities. Most patients could not complete the regimen. Furthermore, economic constraints and difficulties in getting access to treatment facilities in this impoverished region also reduced compliance.**

Key words: **Mitomycin C, Toxicity**

Correspondence address : *Potchavit Aphinives, MD, FICS, Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. E-mail: potchavit@thaimail.com*

Introduction

For over 30 years, the Mitomycin C (MMC) and 5-FU regimen has been used in treating many types of cancer,[1-6] but newer drugs with lower toxicities are taking its place. However, this older regimen is still one of the most potent and affordable regimens for treating advanced cancers in developing countries.

Since 1993, the 5-FU and MMC regimen has been used as a standard regimen for GI and hepatobiliary cancers, i.e. gastric cancer, colon cancer, rectal cancer, pancreatic cancer, cholangiocarcinoma (CHCA) and cancer of the gall bladder. However, some patients did not complete the course of treatment and the high toxicity of these drugs might be the main reason. So we designed this study to determine why the patients failed to complete MMC and 5-FU treatment regimen.

Materials and Methods

Between October 2001 and September 2005, 339 patients received MMC and 5-FU treatment regimen at Khon Kaen University Hospital. However, only 199 patients met the eligibility criteria which included age range from 15-70 years old, no underlying diseases, no drug allergy and no usage of any modulators for 5-FU. This research proposal was approved by the ethical committee of the Faculty of Medicine, Khon Kaen University. Toxicities were classified according to World Health Organization (WHO) criteria into grades 1-4.[7] Statistical analysis included mean, percent and Chi-square; p-value <0.05 is considered statistically significant.

Results

The study population included 199 patients, 122 males (61%) and 77 females (39%) with age ranged from 15 to 70 years (mean 52). BSA averaged 1.51 m^2. Of all cancers in these patients, cholangiocarcinoma (CHCA) was the most common (Table 1).

About one-third (76/199) of patients received a complete course of chemotherapy. Patients residing in Khon Kaen province were twice as likely to receive a complete course of chemotherapy as compared to patients living outside (Table 2).

Seventy-five percent of treated patients (150/199) developed toxicities during the chemotherapy.

Table 1 Distribution of cancers

Cancer	Amount	Percentage
1. Cholangiocarcinoma	125	62.80
2. Colon	23	11.56
3. Stomach	16	8.04
4. Pancreas	7	3.52
5. Gall bladder	2	1.01
6. Others	26	13.07
Total	**199**	**100**

Table 2 Complete VS incomplete course of chemotherapy in patients living in Khon Kaen province comparing to patients from other provinces

Treatment	Residing in Khon Kaen	From other provinces
Complete (6 cycles)*	23/43 (53.49%)	53/156 (33.97%)
Incomplete (< 6 cycles)	20/43 (46.51%)	103/156 (66.03%)

*p = 0.04

Table 3 Toxicities

Toxicity	Grade 1-2	Grade 3-4
GI tract		
- Nausea	68	-
- Vomiting	29	-
- Diarrhea	33	-
Bone marrow		
- Leucopenia	20	18
- Anemia	49	11
- Thrombocytopenia	29	-
Infection	52	1
Alopecia	1	-

The occurrence of toxicity in patients receiving complete course of chemotherapy (92/150) compared to those receiving incomplete course (58/150) was not significantly different (p = 0.99). Of these, gastrointestinal toxicities predominated (81%, 122/150) with nausea of WHO grade II severity being the most common subtype, (56%, 68/122); followed by bone marrow suppression (43%, 65/150) with anemia of WHO grade II severity being the most common subtype (75%, 49/65) (Table 3). There was no treatment-related death.

Discussion

The Mitomycin C (MMC) and 5-FU regimen has been used in treating many types of cancer with various degrees of toxicity that affects 2-50% of patients.[3,5,8,9] Most patients develop non-hematological toxicity, such as skin lesions and diarrhea, with 12-28% of patients develop toxicity of grade 3-4 severity. The hematological toxicity is also common, esp. leucopenia, but only 2-10% of patients develop this toxicity with grade 3-4 severity.[5,6] However, few cases resulted in toxic death which is the most serious side effect.

In this study, gastrointestinal toxicities occurred in 81% and were limited only to grade 2 severity. We were concerned about the hematological toxicities, which involved 43% of the patients. Unfortunately, one-fourth of them developed toxicity of grade 3-4 severity. So the incidence of grade 3-4 leucopenia in this study (12%) is higher than the incidence reported by others.[5,6] Because of the low economic status of the patients, we managed the toxicity by delaying the chemotherapeutic cycle rather than administering G-CSF drug.

Besides toxicities, the patients' habitat also affected the success of treatment. Patients living in Khon Kaen province had significantly more chance to complete the treatment course than patients living outside. Poverty, long distance and difficult transportation might be the causes. The patients and their relatives need to be emphasized on the importance of the completeness of treatment that affects their prognosis. It is useless to treat the patient with chemotherapy, if we cannot support two-third of patients to complete their treatment.

Conclusion

Cancer patients receiving MMC and 5-FU regimen develop high incidence of toxicity. Most patients cannot complete the treatment regimen. Furthermore, economic constraints and difficulties in gaining the access to treatment facilities in this impoverished region also reduce compliance.

REFERENCES

1. Ross P, Norman A, Cunningham D, et al. A prospective randomized trial of protracted venous infusion 5-fluorouracil with or without mitomycin C in advanced colorectal cancer. Ann Oncol 1997; 8: 995-1001.
2. Chen JS, Lin YC, Jan YY, Liau CT. Mitomycin C with weekly 24-h infusion of high-dose 5-fluorouracil and leucovorin in patients with biliary tract and periampullar carcinomas. Anticancer Drugs 2001; 12: 339-43.
3. Takada T, Amano H, Yasuda H, et al. Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. Cancer 2002 Oct 15; 95: 1685-95.
4. Liu LX, Zhang WH, Jiang HC, et al. Arterial chemotherapy of 5-fluorouracil and mitomycin C in the treatment of liver metastases of colorectal cancer. World J Gastroenterol 2002; 8: 663-7.
5. Bosset JF, Roelofsen F, Morgan DA, et al. Shortened irradiation scheme, continuous infusion of 5-fluorouracil and fractionation of mitomycin C in locally advanced anal carcinomas. Results of a phase II study of the European Organization for Research and Treatment of Cancer. Radiotherapy and Gastrointestinal Cooperative Groups. Eur J Cancer 2003; 39: 45-51.
6. Rudi J, Werle S, Bergtholdt D, Hofheinz RD. Infusional 5-fluorouracil and mitomycin C: an effective regimen in the treatment of advanced gastric cancer. Onkologie 2005; 28: 128-32.
7. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-14.
8. Chester JD, Dent JT, Wilson G, Ride E, Seymour MT. Protracted infusional 5- fluorouracil (5-FU) with bolus mitomycin in 5-FU-resistant colorectal cancer. Ann Oncol 2000; 11: 235-7.
9. Sawada T, Hojo K, Moriya Y. Results of intra-arterial infusion chemotherapy in colorectal cancer patients with metastatic liver cancer. Gan To Kagaku Ryoho 1988; 15(8 Pt 2): 2437-42.