Original Article

Improperness of Hydration for 5-FU Base Chemotherapy for Colorectal Cancer May Induce Hyperammonemic Encephalopathy

Tzung-Ju Lu
Chuang-Wei Chen
Hsueh-Li Yang
Koung-Hung Hsiao
Division of Colon and Rectal Surgery, Department of Surgery, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan

Key Words
Hyperammonemic encephalopathy;
5-fluorouracil;
Chemotherapy

Background and Purpose. 5-fluorouracil (5-FU)-based chemotherapy for colorectal cancer has been used for many years. Complications associated with 5-FU based chemotherapy are not rare, but central neurological effects, including encephalopathy, are unusual. Here, we analyzed our experience with complications associated with chemotherapy of colorectal cancer with the intent of learning how we might decrease the risk of complications.

Methods. We retrospectively reviewed the medical records of patients in our section of Taipei Tzu Chi hospital who had received adjuvant or neoadjuvant chemotherapy from 2010 to 2014 for the treatment of colorectal cancer. We compared and analyzed the patients' clinical characteristics, pre-chemotherapy laboratory data, chemotherapy regimens, and complications.

Results. Eighty patients received the FOLFOX6 regimen; 13 patients received the FOLFIRI regimen together with bevacizumab. Four cases of hyperammonemic encephalopathy occurred. All cases were in patients who had received 5-FU dissolved in a modest volume (500 ml) saline, whereas no cases occurred in patients who received 5-FU in 2000 ml saline. No statically significant differences in pre-chemotherapy laboratory data, body surface area, or chemotherapy dose between patients with encephalopathy and those without encephalopathy were identified. We also analyzed all cases in which the dose of chemotherapy was reduced for any reason. We found a trend towards dose reduction associated with the administration of the chemotherapeutic agents in limited amounts of saline and a BUN/creatinine ratio > 20.

Conclusions. We conclude that the administration of 5-FU in a low volume of fluid increases the risk of hyperammonemic encephalopathy and probably the need to reduce the doses of chemotherapeutic agents. Chemotherapeutic regimens with 5-FU in 500 ml saline should be avoided, especially if the pre-chemotherapy BUN/creatinine ratio is greater than 20.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2015;26:86-92*]

Received: January 22, 2015. Accepted: May 25, 2015.
Correspondence to: Dr. Koung-Hung Hsiao, Division of Colon and Rectal Surgery, Department of Surgery, Taipei Tzu Chi Hospital, No. 289, Jianguo Rd., Xindian Dist., New Taipei City 231, Taiwan. Tel: +886-2-6628-9800; Fax: +886-2-6628-9009; E-mail: a68601@yahoo.com.tw

5-FU-based chemotherapy for colorectal cancer has been used for more than 40 years.[1] More than 20 years ago, irinotecan (CPT-11) and oxaplatin were studied for treatment of colorectal cancer resistant to 5-FU therapy.[2,3] In recent years, increasing numbers of colorectal surgeons have prescribed post-operative chemotherapy according to National Comprehensive Cancer Network guidelines. The regimens have been FOLFOX (folinic acid, fluorouracil, oxaliplatin), FOLFIRI (folinic acid, fluorouracil, irinotecan), infusion 5-FU with leucovorin. Each regimen has suggested doses for achievement of a therapeutic effect.[4] 5-FU still plays an important role in colorectal cancer chemotherapy even though it may induce complications, such as gastrointestinal symptoms (nausea, vomiting, and diarrhea), myelosuppression, cardiotoxicity, photosensitivity, hand-foot syndrome, and headache. Neurological complications are not common in chemotherapy for colorectal cancer; only individual case reports have appeared, one being a case of hyperammonemic encephalopathy associated with dehydration, azotemia, and bacterial infection.[5] Here, we describe our analysis of chemotherapy-treated patients with encephalopathy, with the hope that the analysis will help us reduce the incidence of chemotherapy-related encephalopathy.

Patients and Methods

After obtaining institutional review board approval from the Taipei Tzu Chi Hospital in Taiwan, we retrospectively studied the medical records of 96 consecutive patients who had received chemotherapy between 2010 and 2014 in our division of proctology. All patients received FOLFOX or FOLFIRI regimens. The FOLFOX regimen consisted of a bolus of oxaliplatin, 85 mg/m^2, and folinic acid, 400 mg/m^2, on day 1, followed by 5-FU, 2800 mg/m^2, by continuous infusion. Dexamethasone, 12 mg, and diphenhydramine, 30 mg, were given as pre-medication before chemotherapy. Patients who received FOLFIRI were given a bolus of irinotecan, 85 mg/m^2, and folinic acid, 400 mg/m^2, on day 1, followed by 5-FU, 2800 mg/m^2, by continuous infusion. All patients who received FOLFIRI also received bevacizumab, which is routine in our division. Oxaplatin, irinotican, and leucovorin were dissolved in 250 ml saline, 250 ml; 5-FU was dissolved in 500 ml or 2000 ml of saline. The FOLFOX regimen consisted of pre-medication for 2 h, then oxaplantin for 2 h, leucovorin for 2 h, then continuous 5-FU for 46 h. The FOLFIRI regimen was the same, with the exception of having oxaplantin instead of irinotican. All regimens were given according to our oncology division's guidelines and those of the National Comprehensive Cancer Network.

Results

We reviewed and analyzed data of 93 patients who were treated with chemotherapy between January 2010 and August 2014. Eighty patients received the FOLFOX6 regimen, and 13 received the FOLFIRI regimen together with bevacizumab. Four of the 93 patients developed hyperammonemic encephalopathy during the study period. Patients' characteristics (body surface area; gender; tumor T, N, and M stage; and American Joint Committee on Cancer stage) are presented in Table 1. There were no differences in these characteristic among patients who had encephalopathy and those who did not. Table 2 illustrates that there were no differences either in several laboratory tests between the two patient groups.

Table 1. Characteristics of patients who had hyperammonemic encephalopathy and those who did not

	Encephalopathy	No encephalopathy	
	n = 4 Mean (± SD)	n = 89 Mean (± SD)	*p* value
Body surface area (m^2)	1.54 ± 0.22	1.64 ± 0.18	0.274
Gender (M:F)	3:1	11:78	
T stage (1/2/3/4/unknown)	0/0/3/1	6/4/57/20/2	
N stage (0/1/2/unknown)	0/3/1	15/44/28/2	
M stage (0/1)	2/2	64/25	
AJCC stage (1/2/3/4)	0/0/2/2	1/9/54/25	

Table 2. Pre-chemotherapeutic values in patients with hyperammonemic encephalopathy and those who did not

	Encephalopathy	No encephalopathy	
	n = 4 Mean (± SD)	n = 89 Mean (± SD)	*p* value
WBC (10^3/uL)	6737 ± 4418	5360 ± 1811	0.588
Hb (g/dL)	11.05 ± 2.23	11.95 ± 1.48	0.245
MCV (fL)	90.57 ± 5.56	86.60 ± 8.71	0.370
MCH (pg)	29.87 ± 2.81	28.50 ± 3.62	0.252
GPT (IU/L)	28.5 ± 11.90	32.43 ± 30.10	0.796
BUN (mg/dL)	22.5 ± 3.87	17.54 ± 6.42	0.131
Cr (mg/dL)	1.10 ± 0.29	0.93 ± 0.26	0.077
BUN/Cr	21.85 ± 7.97	19.34 ± 7.66	0.524

The patients who had encephalopathy developed symptoms on day 2 or 3 during receiving chemotherapy. The affected patients received medical treatment, including lactulose several times and hydration; all patients recovered within 1 day. During the encephalopathic period, the patients' blood ammonia levels were average 313 umol/L, white blood cell count 9190* 10^3/uL, average blood urea nitrogen 28 mg/dL, average serum creatinine 1.26 mg/dL, and serum glutamic oxaloacetic transaminase/serum glutamic pyruvate transaminase 31/35 IU/L. The only discernible difference in chemotherapeutic regimen between the 2 groups was in the volume of saline used in the preparation of the 5-FU; encephalopathy occurred only in patients whose 5-FU was dissolved in 500 ml of saline, none occurred among those whose 5-FU was dissolved in 2000 ml. The rate of occurrence of encephalopathy in patients who had received the more concentrated 5-FU was 14.8%.

During the study period, the chemotherapy dose also was reduced in several patients because of neurologic symptoms, such as numbness, nausea, poor appetite, and generalized weakness. Including the 4 cases of encephalopathy (Table 3), 15 patients had their dose of chemotherapy reduced; 9/27 (33%) had received the 5-FU in 500 ml of saline; 6/66 (9%) had received the drug in 2000 ml saline, a statistically significant difference ($p = 0.01$). The laboratory values in patients who had encephalopathy and those who did not are given in Table 4; the only significant differences was higher values for BUN/serum creatinine ratio in the patients with encephalopathy.

When we excluded the 4 patients with encephalopathy, we found that the frequency of dose reduction was 5/23 (21.7%) in patients who had received 5-FU in 500 ml saline and 6/66 (9.0%) in patients who received the 5-FU in 2000 ml saline, not a statistically significant difference ($p = 0.112$). We also found no statistically significant difference in laboratory values for the two patient groups, except for a significantly higher BUN/creatinine ratio among patients who required chemotherapy dose reduction (Table 5).

Discussion

The major finding of our study was that hyperammonemic encephalopathy in patients receiving chemotherapy was specifically associated with the administration of 5-FU in a small (500 ml) volume of saline; encephalopathy did not occur in patients who received the 5-FU dissolved in 2000 ml saline. Because of the small sample size of hyperammonemic encephalopathy cases, we also checked reliability of our data by means of Cronbach's alpha. Although Cronbach's alpha was less than 0.6, we still believe our findings are important, and knowing them may help prevent the serious complication of hyperam-

Table 3. Detail of patients who had hyperammonemic encephalopathy

Case	Regimen	Onset date	Oxaplatin/Irino dose	5FU dose	Treatment	Outcome
1	FOLFOX	3th	85 mg/m^2	2800 mg/m^2	Hydration + Lactual 5 dose	5FU: 75%
2	FOLFOX	3th	85 mg/m^2	2800 mg/m^2	Hydration + Lactual 6 dose + EVAC enema	Stop
3	FOLFOX	3th	85 mg/m^2	2800 mg/m^2	Hydration + Lactual 4 dose	5FU: 90%
4	FOLFIRI	2th	180 mg/m^2	2800 mg/m^2	Hydration + Lactual 7 dose	5FU: 80%

Table 4. Laboratory values in all patients, except those with hyperammonemic encephalopathy, who required dose reduction of chemotherapeutic agents

	Dose reduction	No dose reduction	
	n = 11 Mean (± SD)	n = 78 Mean (± SD)	*p* value
WBC (10^3/uL)	4760 ± 928	5444 ± 1891	0.242
Hb	11.57 ± 1.29	12.01 ± 1.51	0.361
MCV	88.21 ± 7.00	86.37 ± 8.94	0.514
MCH	29.28 ± 2.63	28.39 ± 3.73	0.452
GPT (IU/L)	33.45 ± 20.45	32.29 ± 31.32	0.905
BUN (mg/dL)	20.90 ± 7.13	17.06 ± 6.42	0.063
Cr (mg/dL)	0.96 ± 0.46	0.93 ± 0.22	0.837
BUN/Cr	24.05 ± 11.54	18.67 ± 6.80	0.028*

Table 5. Laboratory values in all patients who required dose reduction of chemotherapeutic agents

	Dose reduction	No dose reduction	
	n = 15 Mean (± SD)	n = 78 Mean (± SD)	*p* value
WBC (10^3/uL)	5287 ± 2370	5444 ± 1891	0.778
Hb (g/dL)	11.43 ± 1.52	12.01 ± 1.51	0.178
MCV (fL)	88.84 ± 6.54	86.37 ± 8.94	0.311
MCH (pg)	29.44 ± 2.59	28.39 ± 3.73	0.305
GPT (IU/L)	32.13 ± 18.28	32.29 ± 31.32	0.984
BUN (mg/dL)	21.33 ± 6.33	17.06 ± 6.42	0.017*
Cr (mg/dL)	1 ± 0.41	0.93 ± 0.22	0.375
BUN/Cr	23.46 ± 10.48	18.67 ± 6.80	0.025*

* $p < 0.05$.

monemic encephalopathy in chemotherapy patients.

Because all our patients had normal renal function, we propose that administration of 5-FU in a larger volume promoted passage of more urine, with excretion of 5-FU catabolic products and less opportunity for hyperammonia to develop. However, our study lacks direct evidence supporting this proposal because patients' urine output and the 5-FU catabolites, F -fluoro -alanine, fluoroacetate, and fluorocitrate, in urine and blood were not measured; we suggest that these measurements be made in future studies. We did, however, find that BUN values and BUN/serum creatinine ratios were significantly higher in patients who had hyperammonemic encephalopathy than in those who did not, which are findings consistent with mild dehydration in the encephalopathic patients.

We also found a trend towards more needed dose reduction of chemotherapeutic agents, because of neurologic symptoms, in patients who received 5-FU in 500 ml saline than in those who received the drug in 2000 ml saline. Also, the BUN/creatinine ratio was significantly higher before the start of chemotherapy in the patients who required dose reduction. We feel that these findings may be further evidence of adverse effects due to 5-FU in the setting of mild hemoconcentration.

5-FU is a pyrimidine analog that irreversibly inhibits thymidylate synthase. Thus, toxic effects on rapidly dividing cells such as those of the gastrointestinal tract and bone marrow are to be expected. 5-FU is broken down by dihydropyrimidine dehydrogenase, and more than 80% is excreted in urine in various forms.[6-8] Dihydropyrimidine dehydrogenase deficiency is not a rare condition, with a prevalence of 3-5%. The deficiency results from a mutation of the DPYD gene, which is located on the short arm of chromosome 1 at position 22. More than 50 mutations in DPYD gene, which can induce a wide range of effects on dihydropyrimidine dehydrogenase activity, have been identified.[9-12] In addition to side effects caused by delayed excretion of 5-FU, catabolism of 5-FU can also induce side effects. 5-FU downstream catabolic products include F -fluoro -alanine, fluoroacetate, and fluorocitrate. 5-FU-induced neurotoxicity, which has been recognized for years, results from blocking of the Krebs cycle by fluoroacetate.[7] alpha-fluoro-beta-alanine and, especially, fluoroacetate have also been shown to induce neuropathological vacuolar changes.[13] Toxicity with fluoroacetate has also occurred when it has been used as a rodenticide. Some of the complications of fluoroacetate are similar to the rare complications of 5-FU, including seizures and cardiotoxicity.[14-16] Unfortunately, treatment of fluoroacetate intoxication is supported.

Blocking the Krebs cycle, through impairment of urea synthesis, can result in hyperammonemia.[17] Hyperammonemia can induce cerebral metabolic disturbances by blocking the TCA cycle enzyme alpha-ketoglutarate dehydrogenase and maybe also by blocking

pyruvate dehydrogenase.[18] Fluoroacetate can also promote the entry of ammonia into the brain.[19] Reported risk factors for hyperammonemic encephalopathy include azotemia, body fluid insufficiency, infections, and hypotriglyceridemia.[5,20] Our data suggest that hyperammonemia can occur also through the administration of 5-FU in insufficient volume. Thus, we recommend that 5-FU be given in a volume of at least 2000 ml saline. Also, we advise measuring patients' BUN/creatinine ratio before the administration of 5-FU because of our finding that a ratio > 20 may predispose to complications. We also advocate adequate hydration in order to avoid the consequences of depleted body fluid volume.

Our retrospective study have limitation because large difference in case number between encephalopathy or not. Considering patient safe, we cannot change back regimen with limited fluid to make our research more powerful. We hope our data can initiate an idea about how to prescribe an appropriate regimen for chemotherapy.

Conclusion

Despite insufficient cases, we still conclude that the administration of 5-FU in a low volume (500 ml) of fluid compared with higher volume (2000 ml) increases the risk of hyperammonemic encephalopathy and probably the need to reduce the doses of chemotherapeutic agents because of other complications. Chemotherapeutic regimens with 5-FU in 500 ml saline should be avoided, especially if the pre-chemotherapy BUN/creatinine ratio is greater than 20.

References

1. Nadler SH, Moore GE. Fluorouracil colon-rectum adjuvant chemotherapy. *Archives of Surgery* 1964;89:592-5.
2. Mori A, Bertoglio S, Guglielmi A, Aschele C, Bolli E, Tixi L, et al. Activity of continuous-infusion 5-fluorouracil in patients with advanced colorectal cancer clinically resistant to bolus 5-fluorouracil. *Cancer Chemotherapy and Pharmacology* 1993;33:179-80.
3. de Gramont A, Vignoud J, Tournigand C, Louvet C, Andre T, Varette C, et al. Oxaliplatin with high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer. *European Journal of Cancer* 1997; 33:214-9.
4. NCCN. NCCN guideline. 2015.
5. Liaw CC, Wang HM, Wang CH, Yang TS, Chen JS, Chang HK, et al. Risk of transient hyperammonemic encephalopathy in cancer patients who received continuous infusion of 5-fluorouracil with the complication of dehydration and infection. *Anti-cancer Drugs*. 1999;10:275-81.
6. Bernadou J, Armand JP, Lopez A, Malet-Martino MC, Martino R. Complete urinary excretion profile of 5-fluorouracil during a six-day chemotherapeutic schedule, as resolved by 19F nuclear magnetic resonance. *Clinical Chemistry* 1985;31:846-8.
7. Koenig H, Patel A. Biochemical basis for fluorouracil neurotoxicity. The role of Krebs cycle inhibition by fluoroacetate. *Archives of Neurology* 1970;23:155-60.
8. Naguib FN, el Kouni MH, Cha S. Enzymes of uracil catabolism in normal and neoplastic human tissues. *Cancer Research* 1985;45:5405-12.
9. Mercier C, Ciccolini J. Profiling dihydropyrimidine dehydrogenase deficiency in patients with cancer undergoing 5-fluorouracil/capecitabine therapy. *Clinical Colorectal Cancer* 2006;6:288-96.
10. Ciccolini J, Gross E, Dahan L, Lacarelle B, Mercier C. Routine dihydropyrimidine dehydrogenase testing for anticipating 5-fluorouracil-related severe toxicities: hype or hope? *Clinical Colorectal Cancer* 2010;9:224-8.
11. Van Kuilenburg AB, Vreken P, Abeling NG, Bakker HD, Meinsma R, Van Lenthe H, et al. Genotype and phenotype in patients with dihydropyrimidine dehydrogenase deficiency. *Human Genetics* 1999;104:1-9.
12. Papanastasopoulos P, Stebbing J. Molecular basis of 5-fluorouracil-related toxicity: lessons from clinical practice. *Anticancer Research* 2014;34:1531-5.
13. Yamashita K, Yada H, Ariyoshi T. Neurotoxic effects of alpha-fluoro-beta-alanine (FBAL) and fluoroacetic acid (FA) on dogs. *The Journal of Toxicological Sciences* 2004;29: 155-66.
14. Cheung WY, Fralick RA, Cheng S. The confused cancer patient: a case of 5-fluorouracil-induced encephalopathy. *Current Oncology* 2008;15:234-6.
15. Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. *Cardiology Journal* 2012;19:453-8.
16. Proudfoot AT, Bradberry SM, Vale JA. Sodium fluoroacetate poisoning. *Toxicological Reviews* 2006;25:213-9.
17. Anand UAaV. Connecting links between the urea cycle and the TCA cycle: A tutorial exercise. *Biochemical Education* 1999;27:153-4.
18. Ott P, Clemmesen O, Larsen FS. Cerebral metabolic disturbances in the brain during acute liver failure: from hyperammonemia to energy failure and proteolysis. *Neurochemistry International* 2005;47:13-8.

19. Szerb JC, Redondo IM. Astrocytes and the entry of circulating ammonia into the brain: effect of fluoroacetate. *Metabolic Brain Disease* 1993;8:217-34.
20. Yeh KH, Cheng AL. High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. *British Journal of Cancer* 1997;75: 464-5.

原　著

大腸直腸癌患者接受濃縮的含氟尿嘧啶的化學治療會增加高血胺性腦病變

呂宗儒　陳莊偉　楊雪儷　蕭光宏

佛教慈濟醫療財團法人　台北慈濟醫院

目的　越來越多的大腸直腸癌患者在大腸直腸外科接受術前或術後之化學治療，本回顧性研究的目的在於探討同劑量不同配法的化療處方對於高血胺性腦病變發生之影響。

材料與方法　本篇研究藉由分析於 2010 年至 2014 年於本院大腸直腸外科接受以氟尿嘧啶為主的化學治療患者之病歷，化療處方及配法，併發症發生及治療方式。

結果　經統計整理後共 93 名患者於這段期間接受住院的以氟尿嘧啶為主的化學治療，其中 80 個接受 FOLFOX6，13 個接受 FOLFIRI (為施打 bevacizumab)。其中共 4 位患者發生高血胺性腦病變並接受藥物治療復原。經分析發現氟尿嘧啶若僅配賦於 500 毫升的溶液中有較高的發生率。而 BUN/creatinine 比值 > 20 也是觸發因子。

結論　以氟尿嘧啶為主的化學治療應避免減少靜脈注射的水分，以降低氟尿嘧啶的代謝產物氟乙酸及氟代檸檬酸所造成之併發症。

關鍵詞　高血胺性腦病變、氟尿嘧啶、化學治療。