Hypocalcemia Associated with 5-Fluorouracil and Low Dose Leucovorin in Patients with Advanced Colorectal or Gastric Carcinomas

Yuichiro Kido, M.D.[1]
Takeshi Okamura, M.D.[2]
Morimasa Tomikawa, M.D.[2]
Manabu Yamamoto, M.D.[2]
Morio Shiraishi, M.D.[2]
Yasuyo Okada, M.D.[2]
Toshinari Kimura, M.D.[2]
Keizo Sugimachi, F.A.C.S.[1]

[1] Department of Surgery II, Kyushu University, Fukuoka, Japan.

[2] Fukuoka Shakai-hoken Nakabaru Hospital, Fukuoka, Japan.

Address for reprints: Yuichiro Kido, M.D., Department of Surgery II, Kyushu University, 3-1-1 Maidashi higashi-ku Fukuoka, 812 Japan.

Received December 14, 1995; revisions received April 19, 1996, and July 2, 1996; accepted July 2, 1996.

BACKGROUND. The biochemical modulation of 5-fluorouracil (5-FU) by leucovorin (LV) has demonstrated significantly increased response rates in comparison with the use of 5-FU alone in patients with advanced colorectal carcinoma. However, the higher response rate of LV/5-FU may occur at the expense of increased toxicity and side effects such as diarrhea, myelosuppression, and mucositis. During chemotherapy, a high incidence of hypocalcemia associated with this chemotherapy regimen was noted. This study was therefore aimed at assessing the side effects of chemotherapy using low dose LV/5-FU on calcium metabolism.

METHODS. Twenty-five patients with advanced gastric or colorectal carcinoma were treated with chemotherapy comprised of low dose LV administered at 20 mg/m^2/day by intravenous bolus, followed by 1-hour intravenous infusion of 5-FU at 425–600 mg/m^2/day for 5 consecutive days every 28 days.

RESULTS. The toxic effects were generally mild, and included diarrhea, mucositis, leukopenia, and nausea/vomiting. Fifteen patients (65%) experienced hypocalcemia. The plasma 1,25-$(OH)_2D_3$ levels were significantly reduced on Day 5 due to the chemotherapy.

CONCLUSIONS. The toxic effects of the regimen were generally mild. However, a high percentage of hypocalcemia occurred with the combination of LV/5-FU. It is therefore necessary to examine carefully the serum calcium levels of patients when using this chemotherapeutic modality. ***Cancer* 1996; 78:1794–7.**

KEYWORDS: leucovorin, 5-fluorouracil, hypocalcemia, gastric carcinoma, colorectal carcinoma.

The biochemical modulation of 5-fluorouracil (5-FU) by leucovorin (LV) has demonstrated significantly increased response rates (33–48%) in comparison with the use of 5-FU alone (7–15%) in patients with advanced colorectal carcinoma.[1–3] A recent review reported the results of Phase III trials with a combination of LV/5-FU in patients with advanced colorectal carcinoma,[4] and both low dose (20–25 mg/m^2) and high dose (200–500 mg/m^2) LV combination regimens revealed a significantly better response rate than 5-FU alone. However, controversy still exists concerning the optimal dosage and schedule.

The higher response rate of LV/5-FU may occur, however, at the expense of increased toxicity, because a high incidence of dose-limiting diarrhea, myelosuppression, and mucositis has been observed.[2,5,6] We have administered a 5-day, low dose LV (20 mg/m^2) and 5-FU (425–600 mg/m^2) regimen for patients with advanced gastric or colorectal carcinoma since April 1994. During the administra-

tion, we noticed a high incidence of hypocalcemia associated with this chemotherapy.

This study was designed to assess the side effects of chemotherapy with low dose LV/5-FU, especially with regard to calcium metabolism.

PATIENTS AND METHODS

Patients

From April 1 1994, to August 31 1995, 25 consecutive patients were entered into the study. All patients were required to have either a histologic or cytologic confirmation of locally unresectable, residual, metastatic, or recurrent colorectal or gastric carcinoma. A patient performance status of 4 according to the Eastern Cooperative Oncology Group (ECOG) made the patient ineligible. All patients were required to be free of any infection, to have a leukocyte count of greater than 3000/mm^3, a platelet count of greater than 100,000/mm^3, a serum creatinine level of less than 2 mg/dL, and a total bilirubin level of less than 3 mg/dL. In addition, no patient was permitted to have any previous history of chemotherapy or radiotherapy for recurrent or metastatic disease. Six patients showed mild hypoalbuminemia (3.1–3.3 mg/dL) before chemotherapy. Baseline data of ionized calcium and magnesium were within normal range. The patients with prior adjuvant or neoadjuvant chemotherapy were eligible for the study if they had a drug free period of 2 months or longer. Informed consent was obtained from all patients before treatment. The patient characteristics are listed in Table 1.

TABLE 1
Patient Characteristics

Characteristic	No.
No. of patients	25
M/F	17/8
Median age (range) (yrs)	61 (46–79)
ECOG performance status	
0-1	19
2	5
3	1
Primary site	
Stomach	7
Colon	11
Rectum	7
Site of disease[a]	
Liver	11
Lung	8
Local	6
Lymph nodes	4
Peritoneum	3
No. of treatment courses	
1-3	10
4-6	7
7-10	5
11+	3

M: male; F: female; ECOG: Eastern Cooperative Oncology Group.
[a] Some patients had more than one disease site.

Treatment

The chemotherapy regimen was comprised of low dose LV administered at 20 mg/m^2/day by intravenous bolus, followed by a 1-hour intravenous infusion of 5-FU at 425–600 mg/m^2/day for 5 consecutive days every 28 days, modified by O'Connell's study.[4] Treatment was given either until the disease progressed or side effects appeared. Standard antiemetic regimens, such as ondansetron plus metoclopramide, were administered. All chemotherapeutic drug doses were calculated based on the body surface area. The treatments were delayed for 1 week if the patients had not recovered from the toxicity.

Toxicity

Toxicity was graded using the Common Toxicity Criteria (1988) from the National Cancer Institute (NCI) (Bethesda, MD). All patients who received at least one course of chemotherapy were considered evaluable for toxicity.

1,25-$(OH)_2D_3$ and Parathyroid Hormone Analysis

To determine the effect of chemotherapy on calcium metabolism, 12 patients were randomly assigned to the study. Preliminary study revealed a Day 5 calcium and 1,25-$(OH)_2D_3$ levels nadir that resolved on Day 10. Blood specimens were obtained before chemotherapy and at the endpoint of chemotherapy (Day 5). The 1,25-$(OH)_2D_3$ was quantified by a radio recepter assay and parathyroid hormone (PTH) was measured by a radioimmunoassay.

Statistical Analysis

The comparison of the pre- and posttreatment 1,25-$(OH)_2D_3$ values after treatment was analyzed by the Wilcoxon signed rank test. Differences were considered significant if $P < 0.05$.

RESULTS

Patients

The characteristics of all 25 registered patients are summarized in Table 1. The median age was 61 years (range, 46–79 years) and those were 17 male and 8 female patients. The performance status (PS) was generally good: PS 0–1 ($n = 19$); PS 2 ($n = 5$); PS 3 ($n =$

TABLE 2
Toxicity (NCI Grades) (n = 25)

Toxicity	No. of patients (%)	NCI toxicity grade 1	2	3	4
Nausea or vomiting	6 (26%)	4	1	1	0
Mucositis	8 (35%)	5	3	0	0
Diarrhea	13 (57%)	11	2	0	0
Leukopenia	8 (35%)	1	4	3	0
Hypocalcemia	15 (65%)	10[b]	5[b]	0	0
Tetany	2 (9%)[a]	—	—	—	—
Hiccup	2 (9%)[a]	—	—	—	—

NCI: National Cancer Institute.
[a] Mild and easily controlled by the administration of calcium.
[b] Grade 1: 8.4–7.8 mg/dL; Grade 2: 7.7–7 mg/dL.

1); and PS was not recorded in 4 patients. In 7 patients, the primary disease site was in the stomach, the colon in 11, and the rectum in 7. Ten patients received 1–3 courses; 7 patients, 4–6 courses; 5 patients, 7–10 courses; and 3 patients, more than 11 courses. Fifteen patients had previously received adjuvant chemotherapy with 5-FU, 200 mg/body/day orally, and the drug free period was at least 2 months, which was enough time for drug elimination and recovery from the influence of 5-FU. There were no patients with liver dysfunction.

Toxicity

All 25 patients were evaluated for toxicity (Table 2). Diarrhea, mucositis, leukopenia, and nausea/vomiting were the most frequent symptoms. The toxic effects were generally mild, with no cases of Grade 4 toxicity. However, 5-FU dosage was reduced (425 mg/m^2/day) in patients with Grade 3 toxicity. Two patients required additional antiemetics. In the majority of patients, the symptoms were well controlled with standard antiemetics and antidiarrheal drugs. Fifteen patients (65%) experienced hypocalcemia. Of these, two patients experienced tetany and two had hiccups. These four patients required the administration of calcium drugs, after which the symptoms were well controlled. The serum albumin levels were decreased in 4 patients and unchanged in 21 patients after treatment.

1,25-$(OH)_2D_3$ and PTH Analysis

To determine the effect of chemotherapy on calcium metabolism, 12 patients were subjected to the study. Blood specimens were obtained before chemotherapy and at the endpoint of chemotherapy (Day 5) and 1,25-$(OH)_2D_3$ and PTH were measured. Four of the 12 patients (33%) hypocalcemia developed by Day 5. The

TABLE 3
Changes in the Plasma Concentration of Calcium, PTH, and 1,25-$(OH)_2D_3$ before and after Treatment[a]

Patient	Calcium (8.2–9.7 mg/dL[b]) Pre	Post	1,25-$(OH)_2D_3$ (20–76 pg/mL) Pre	Post	PTH (180–560 pg/mL) Pre	Post
1	8.3	8	30	17	788	853
2	8.7	8.1	20	18	177	201
3	8.7	8.3	25	22	453	772
4	9.4	8.4	35	25	330	246
5	8	8.6[c]	32	15	294	163
6	8.2	8.7	27	25	455	292
7	8.3	8.6	28	30	607	565
8	7.8	7.7	34	23	121	220
9	8.6	9.4	44	36	232	284
10	8.8	8.8	18	23	188	298
11	8.5	7.6	30	21	354	493
12	7.6	9.1[c]	39	25	348	181

PTH: parathyroid hormone.
[a] Blood samples were collected on Day 1 before treatment and Day 5 after treatment.
[b] The numbers in parenthesis indicate the normal range value.
[c] This patient was given calcium before chemotherapy.

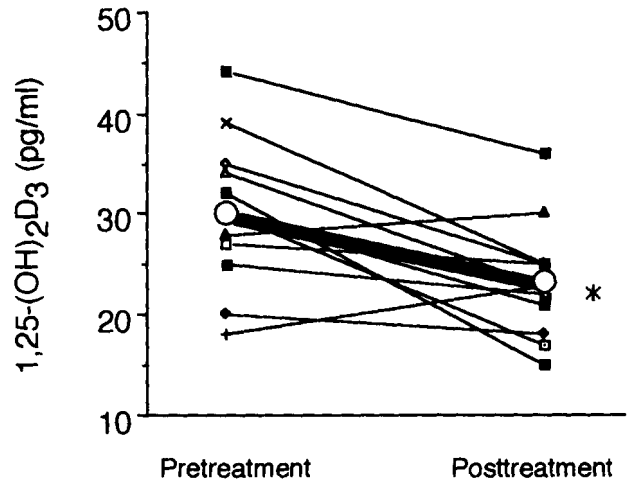

FIGURE 1. Changes in the plasma 1,25-$(OH)_2D_3$ levels before and 5 days after treatment. The mean level is indicated by the thick line (*P = 0.0119; n = 12).

1,25-$(OH)_2D_3$ levels were significantly affected by chemotherapy (Table 3; Fig. 1). In all, the plasma concentration was observed to decrease in 10 patients (83%) on Day 5 (P = 0.0119). Conversely, the PTH levels did not show any specific pattern of change.

DISCUSSION

Although the efficacy of chemotherapy is a major goal, its toxic effects must also be as low as possible, espe-

cially for patients receiving palliative treatment. The biochemical modulation of 5-FU by LV is a significant therapeutic response in patients with colorectal carcinoma; however, diarrhea, mucositis, and leukopenia are often dose-limiting factors.[8] In this study, a 5-day low dose LV (20 mg/m^2) and 5-FU (425–600 mg/m^2) regimen was utilized for patients with advanced gastric and colorectal carcinoma since April 1994. The toxic effects encountered were diarrhea (57%), mucositis (35%), leukopenia (35%), and nausea/vomiting (26%) and were similar to those observed in other studies.[4,8]

Combination chemotherapy, such as biochemical modulation, might cause unexpected adverse effects. In this study, a high incidence of hypocalcemia was observed that was associated with the chemotherapy regimen (Table 2). Data showed hypocalcemia occurred in 65% of the patients receiving this regimen. The serum level of calcium was regulated for both PTH and vitamin D_3. PTH affects both the kidneys and bone and results in an increased serum calcium level while decreasing calcium clearance in the kidneys and promoting a release of calcium in the bones. Vitamin D increases the intestinal absorption of calcium. Vitamin D is metabolized first in the liver into 25-hydroxyvitamin D_3 (25-OHD_3) and subsequently in the kidney into 1,25-$(OH)_2D_3$ (active form of vitamin D_3) or 24R,25-dihydroxyvitamin D_3 (24,25-$(OH)_2D_3$) before it can show activity.

Gao et al. have previously reported effective chemotherapy including cisplatin on patients with gynecologic malignancies.[9] According to their findings, 1,25-$(OH)_2D_3$ decreased significantly (50%) after only 1 or 2 courses of treatment. They thus suggested that these findings may be due to an impairment by cisplatin of the mitochondrial function in proximal tubles and the inhibition of the 1α-OHase activity. Vokes et al. reported the results of Phase I–II studies of cisplatin, 5-FU, LV, and interferon-alpha-2b.[10] They also indicated that patients with diabetes mellitus were found to have to have a significantly increased risk of severe leukopenia, thrombocytopenia, increased serum creatinine, and hypocalcemia.

In an attempt to examine the mechanism of hypocalcemia associated with LV/5-FU, the serum level of 1,25-$(OH)_2D_3$ and PTH were analyzed before and after chemotherapy. The 1,25-$(OH)_2D_3$ levels were significantly affected by this chemotherapy regimen (Table 3; Fig. 1). The plasma concentration of 1,25-$(OH)_2D_3$ decreased in 10 of the patients (83%) on Day 5 (P = 0.0119). Conversely, the PTH levels did not show any specific pattern of change. The percentage of hypocalcemia was 65% (Table 2), and the serum calcium level fell in 5 patients (42%), (Table 3). Hypocalcemia was not a specific side effect, although the 1,25-$(OH)_2D_3$ levels were significantly affected by the chemotherapy (Table 3; Fig. 1). To our knowledge, only a few reports were published regarding hypocalcemia associated with chemotherapy, especially in the LV/5-FU regimen.[9,10] Currently, the mechanism for the decrease in 1,25-$(OH)_2D_3$ remains to be clarified. The absorption of vitamin D_3 from the intestine may also be impaired by mucositis of the intestine. Another possibility is the inhibition of the enzyme (1α-OHase, 25-OHase) activity by this chemotherapy. Further studies are necessary to clarify the mechanism for the decrease in 1,25-$(OH)_2D_3$.

In conclusion, although the toxic effects of this regimen were generally mild, a high percentage of hypocalcemia occured with the combination of LV/5-FU, and therefore it is necessary to examine patient serum calcium levels carefully during administration. As a result, a calcium agent may be required when using this chemotherapeutic regimen to prevent any unfavorable effects in patients with hypocalcemia.

REFERENCES

1. Petrelli N, Herrera L, Rustum Y, Burke P, Creaven P, Stulc J, et al. A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. *J Clin Oncol* 1987; 5:1559–65.
2. Erlichman C, Fine S, Wong A, Elhakim TA. A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1988;6:469–75.
3. Poon MA, O'Connel MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989;7:1407–18.
4. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *Cancer* 1989;63:1026–30.
5. Arbuck SG. Overview of clinical trials using 5-fluorouracil and leucovorin for the treatment of colorectal cancer. *Cancer* 1989;63:1036–44.
6. Grem JL, Shoemaker DD, Petrelli NJ, Douglass HO Jr. Severe life-threatening toxicities observed in study using leucovorin with 5-fluorouracil. *J Clin Oncol* 1987;5:1704.
7. Miller AB, Hoogstraten B, Staquest N, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
8. Petrelli N, Douglass HO, Herrera L Jr. Russell D, Stablein DM, Bruckner HW, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. *J Clin Oncol* 1989;7:1419–26.
9. Gao Y, Shimizu M, Yamada S, Ozaki Y, Aso T. The effect of chemotherapy including cisplatin on vitamin D metabolism. *Endocr J* 1993;40:737–42.
10. Vokes EE, Ratain MJ, Mick R, McEvilly JM, Haraf D, Kozloff M, et al. Cisplatin, fluorouracil, and leucovorin augmented by interferon alfa-2b in head and neck cancer: a clinical and pharmacologic analysis. *J Clin Oncol* 1993;11:360–8.