

## Macrocytic Anemia during Low-dose Cisplatin and 5-Fluorouracil through Implanted Infusion Port for Unresectable Hepatobiliary Malignancies

NORIIHIKO YAMAMOTO, KAZUMOTO MURATA, HIROYUKI FUKU, TOMOKO INOUE, YUTAKA YAMANAKA, YUKIKO SAITOU, KEIICHI ITO, KAZUSHI SUGIMOTO, MUTSUMI KOYAMA, KATSUYA SHIRAKI and TAKESHI NAKANO

*First Department of Internal Medicine, Mie University School of Medicine, Japan*

**Abstract.** *The efficacy of continuous arterial infusion chemotherapy through a subcutaneously implanted port has been reported with less adverse effects than systemic chemotherapy in hepatobiliary malignancies. However, macrocytic anemia is sometimes seen during this therapy. In 25 patients (22 with hepatocellular carcinoma, 3 with cholangiocellular carcinoma) treated with cisplatin (10mg/day) and 5-Fluorouracil (5-FU) (250 mg/day), the frequency of anemia and its etiologies were evaluated. Moreover, the two groups ("anemia" and "no anemia" group) were compared with their backgrounds. Nine cases (36%) showed macrocytic anemia without any evident etiologies during therapy. The cumulative appearance rate of anemia was 19% at 12 weeks and 51% at 18 weeks. The Child-Pugh score or Japanese integrated staging (JIS) score were significantly higher in the "anemia" group than that in the "no anemia" group. Conclusion: Attention should be paid to slow progressive macrocytic anemia during low-dose cisplatin and 5-FU, especially in patients with advanced liver cirrhosis.*

The prognosis of advanced hepatobiliary malignancies is extremely poor. Recently, the efficacy of continuous arterial infusion chemotherapy using a low-dose cisplatin (CDDP) and 5-Fluorouracil (5-FU) via a subcutaneously implanted port has been reported in unresectable hepatocellular carcinoma (HCC) (1-4) or cholangiocellular carcinoma (CCC) (5) with improvement of the prognosis (2).

*Correspondence to:* Kazumoto Murata, M.D., Ph.D., First Department of Internal Medicine, Mie University School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. Tel: +81-592-31-5015, Fax: +81-592-31-5201, e-mail: atarum@clin.medic.mie-u.ac.jp

**Key Words:** Macrocytic anemia, arterial infusion, hepatobiliary malignancy, 5-FU.

Few major complications are reported with this regimen, except for nausea, leukocytopenia and thrombocytopenia, which were controllable by medical treatment without cessation of this therapy (3). However, slow progressive severe macrocytic anemia was sometimes experienced during therapy, even in patients without any other side-effects. There are no reports about the etiologies or frequency of anemia during this therapy. On the other hand, in patients with systemic full-dose 5-FU therapy, the blockade of DNA biosynthesis by 5-FU itself contributes to macrocytic anemia (6). Macrocytic anemia could occur even in our regimen through the same mechanism. Therefore, we evaluated the frequency and background of anemia in patients receiving continuous arterial infusion chemotherapies for HCC or CCC, using a low-dose CDDP and 5-FU through a subcutaneously implanted port.

### Patients and Methods

Twenty-five patients with unresectable hepatocellular carcinoma (HCC) (n=22) or cholangiocellular carcinoma (CCC) (n=3) were treated by arterial infusion of CDDP (10mg/1 hour on days 1 to 5) and subsequent 5-FU (250 mg/5 hours on days 1 to 5) every 4 to 6 weeks through a subcutaneously implanted infusion port. This treatment was continued until disappearance of tumors or regression of tumors against treatment. The efficacy of the treatment was evaluated by the tumor size based on computed tomography (CT) and tumor markers. The tumor size was evaluated by the following criteria: complete response (CR), disappearance of tumors; partial response (PR), decrease of over 30% in the size of tumors; no change (NC), decrease within 30% or increase within 25%; progressive disease (PD), increase over 25% even after therapy. Tumor markers (either  $\alpha$ -fetoprotein or des-gamma-carboxy prothrombin) were evaluated by the following criteria: decrease, decrease over 30% or normalized; no change, within 30% change; increase, increase over 30% even after therapy. The appearance of anemia was defined as 20% reduction of hemoglobin (Hb) in comparison with that before therapy. We evaluated the time of appearance, the frequency or etiologies of anemia and their background factors. We divided the 25 patients

Table I. Patients' characteristics.

	Anemia	No Anemia	p-value
no.	9	16	NS
age	69	67	NS
Pre Hb (g/dl)	12.6	12.8	NS
Pre MCV (fl)	97.2	96.3	NS
Child-Pugh score	6.44	5.46	0.035
CLIP score	2.44	1.73	NS
JIS score	2.78	2	0.022

into two groups ("anemia" group, "no anemia" group) and compared the background factors of patients between the two groups. Statistical analysis of the change of Hb and mean capsular volume (MCV) level before and after therapy in the "anemia" group was calculated by *t*-test, the efficacy of therapies in the two groups was evaluated by the Mann-Whitney's *U*-test, while the cumulative appearance rate of anemia was calculated by the Kaplan-Meier method.

## Results

All HCC patients (n=22) (M:F=15:7) had liver cirrhosis (LC), while the other 3 (M:F=2:1) patients with CCC showed normal liver function. In LC patients, 20 patients were HCV-positive, one was alcoholic and the other 2 were cryptogenic. No patients had any extrahepatic metastasis. Nine cases (36%) showed 20% reduction of Hb level during therapy. The cumulative appearance rate of anemia was 19% at 12 weeks and 51% at 18 weeks (Figure 1). The anemia, in our study, was not very severe, but 2 cases out of 9 needed to stop or reduce the chemotherapy. Longer periods of therapy showed more frequent appearance of anemia. However, no new anemia appeared after 20 weeks. In the "anemia" group, all showed macrocytic hyperchromic anemia with normal reticulocytes. However, none of them had any gastrointestinal bleeding, vitamin B12 deficiency, foliate acid deficiency or hemolysis. After the first or second course of therapy, the Hb level started to decrease. Inversely, the MCV level increased in comparison with that before therapy. These changes were statistically significant (Figure 2). On the other hand, the white blood cell count (WBC) or platelet (plt) count tended to decrease, but not significantly (WBC:  $5,280 \pm 2,680 /\text{mm}^3 \rightarrow 4,090 \pm 1,500 /\text{mm}^3$ , plt:  $16.4 \pm 9.7 \times 10^4 /\text{mm}^3 \rightarrow 11.9 \pm 7.0 \times 10^4 /\text{mm}^3$ ). In patients with LC (n=22), the Child-Pugh score and Japanese integrated staging (JIS) score were significantly higher in the "anemia" group than in the "no anemia" group ( $p=0.035$ ,  $p=0.022$ , respectively). However, age, pre Hb, pre MCV and the Cancer of the Liver Italian Program (CLIP) score were not significantly different between the two

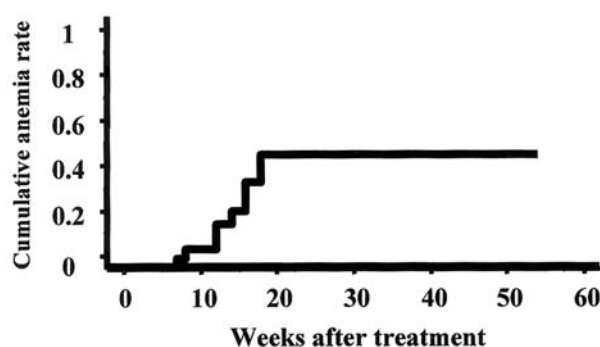


Figure 1. The cumulative appearance of anemia during low dose chemotherapy. The appearance of anemia was defined as 20% reduction of hemoglobin after treatment.

groups (Table I). In the 25 patients, with regard to changes in the tumor size, CR was seen in one (4%), PR in 8 (32%), NC in 11 (44%) and PD in 5 (20%). Regarding changes of tumor markers, decrease was seen in 11 (44%), no change in 6 (24%) and increase in 8 (32%). However, there were no significant differences in the tumoricidal effects between the "anemia" group and the "no anemia" group (data not shown). In Figure 3 is shown the clinical course of a patient in the "anemia" group. A 74-year-old man, who had HCV-positive LC, showed multiple HCC 6 months after radiofrequency ablation (RFA) for solitary HCC. Arterial infusion chemotherapy was chosen because of no indication for conventional local therapies or operation. CDDP (10mg/1 hour on days 1 to 5) and subsequent 5-FU (250mg/5 hours on days 1 to 5) were used through an implanted port every 4 weeks. One month after the initial therapy, the Hb level started to decrease and the MCV level inversely increased at the same time. Eighteen weeks after initial therapy, the Hb level showed 20% reduction in comparison with that before therapy. There was no evidence of gastrointestinal bleeding, iron deficiency anemia, vitamin B12 deficiency or foliate acid deficiency. The therapy was continued with careful observation for anemia progression since the chemotherapy was effective without other side-effects and the anemia was tolerable.

## Discussion

We found that macrocytic anemia with normal reticulocytes count appeared in 9 cases (36%) during our regimen. The frequency of anemia increased after therapy and the Hb level decreased in accordance with the increasing MCV level. These findings suggest that low-dose CDDP and 5-FU therapy, especially 5-FU, contributes to this anemia. Furthermore, macrocytic anemia tended to appear in patients with advanced LC.

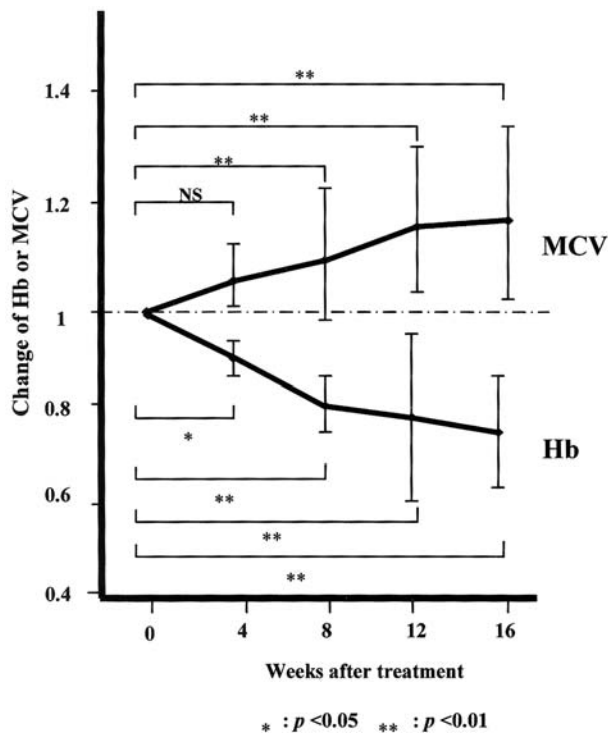


Figure 2. Change of hemoglobin (Hb) and mean corpuscular volume (MCV) after initial treatment in the "anemia" group (n=9). The changing rate was shown in comparison with Hb or MCV level before therapy. Hb level gradually decreased accompanied by increase of MCV after treatment, suggesting the appearance of macrocytic anemia.

Macrocytosis of red blood cells (RBC) is commonly associated with vitamin B12 or folate acid deficiency, caused by alcoholism or drugs (7, 8). Alcoholism contributes to the development of macrocytosis of RBC because of folate deficiency and bone marrow toxicity (6). On the other hand, drugs alone can result in megaloblastic change of RBC by direct or indirect cellular DNA biosynthesis. Blockade of DNA biosynthesis by drugs can be divided into the following categories according to their mechanism: i) DNA assembly, ii) ribonucleotide reduction, iii) thymidylate biosynthesis, iv) pyrimidine precursor biosynthesis, v) purine precursor biosynthesis, vi) unknown mechanism (6). The mechanism of 5-FU is categorized as direct inhibition of thymidylate synthetase, which leads to reduction of DNA biosynthesis (6, 9). Since megaloblastic change of RBC results from an inadequate rate of DNA replication with a consequent rate of cell division of the erythrocyte series, 5-FU could contribute to macrocytic anemia since there are no reports about anemia in relation to CDDP.

In our study, macrocytic anemia appeared in 9 cases (36%). None of them had GI bleeding, vitamin B12 deficiency or folic acid deficiency without reticulocytosis,

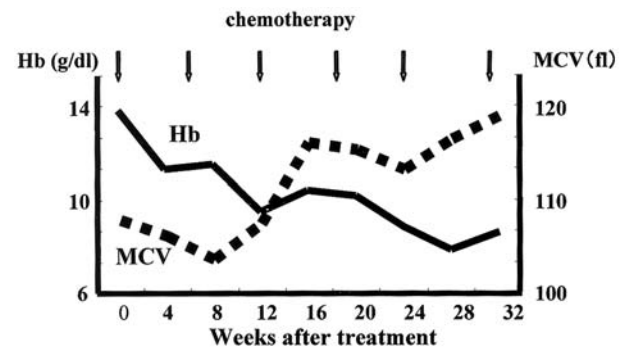


Figure 3. The clinical course of a 74-year-old man with liver cirrhosis (HCV+).

suggesting that bone marrow suppression occurred in these patients, although leukocytopenia or thrombocytopenia was less frequent. Macrocytic anemia is a common feature in patients with LC. The degree of macrocytic anemia in LC is closely related to the Child-Pugh score (10). In our study, however, macrocytic anemia appeared after initial therapy and the Hb levels decreased in accordance with the increase of MCV levels. These findings suggest that macrocytic change of RBC should be attributed to continuous low-dose 5-FU as well as systemic full-dose 5-FU therapy, although low-dose 5-FU therapy generally shows less side-effects than systemic therapy. Furthermore, the cumulative appearance of anemia increased in accordance with the duration of therapy, but no new anemia appeared after 20 weeks. This suggests that this anemia depends on individual sensitivity to 5-FU. On the other hand, the Child-Pugh score and JIS score were significantly higher ( $p=0.035$ ,  $p=0.022$ , respectively) in the "anemia" group, although age, pre Hb level, pre MCV level and CLIP score were not significantly different between the two groups. This suggests that macrocytic anemia tends to appear in patients with advanced liver cirrhosis.

In conclusion, attention should be paid to macrocytic anemia even during low-dose CDDP and 5-FU therapy, as well as systemic full-dose administration of 5-FU, especially in patients with advanced liver cirrhosis.

## References

- 1 Toyoda H, Nakano S, Takeda I, Sugimachi K, Osada T, Kiriyaama S and Suga Tandy Takahashi M: The efficacy of continuous local arterial infusion of 5-fluorouracil and cisplatin through an implanted reservoir for severe advanced hepatocellular carcinoma. *Oncology* 52: 295-29,1995.
- 2 Murata K, Shiraki K, Kawakita T, Yamamoto N, Okano H, Nakamura M, Sakai T, Deguchi M, Ohmori S and Nakano T: Low-dose chemotherapy of cisplatin and 5-fluorouracil or doxorubicin *via* implanted fusion port for unresectable hepatocellular carcinoma. *Anticancer Res* 23: 1719-1722, 2003.

- 3 Ando E, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori, K, Sumie S, Yano Y, Okuda K and Sato M: Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis. *Cancer* 95: 588-595, 2002.
- 4 Okuda K, Tanaka M, Shibata J, Ando E, Ogata T, Kinoshita H, Eriguchi N, Aoyagi S and Tanikawa K: Hepatic arterial infusion chemotherapy with continuous low dose administration of cisplatin and 5-fluorouracil for multiple recurrence of hepatocellular carcinoma after surgical treatment. *Oncol Rep* 6: 587-591, 1999.
- 5 Tanaka N, Yamakado K, Nakatsuka A, Fujii A, Matsumura K and Takeda K: Arterial chemoinfusion therapy through an implanted port system for patients with unresectable intrahepatic cholangiocarcinoma—initial experience: *Eur J Radiol* 41: 42-8, 2002.
- 6 Scott JM and Weir DG: Drug- induced megaloblastic change. *Clin Haematol* 9: 587-606.
- 7 Konrad H: Hepatogenic anemia. *Z Gesamte Inn Med* 78-81, 1983.
- 8 Savage DG, Ogundipe A, Allen RH, Stabler SP and Lindenbaum J: Etiology and diagnostic evaluation of macrocytosis: *Am J Med Sci* 319: 343-352, 2000.
- 9 Arai K, Awane Y, Kitamura M and Miyashita K: Macrocytic anemia as a possible adverse effect of fluoropyrimidines. *Gan To Kagaku Ryoho* 17: 1489-1494, 1990.
- 10 Maruyama S, Hirayama C, Yamamoto S, Koda M, Udagawa A, Kadowaki Y, Inoue M, Sagayama A and Ueki K: Red blood cell status in alcoholic and non- alcoholic liver disease. *J Lab Clin Med* 138: 332-337, 2001.

*Received September 24, 2004*

*Revised February 7, 2005*

*Accepted February 18, 2005*