Kitakanto Med J
2007；57：317～320

Sub-acute Toxicosis Caused by a Multiple Doses Tegafur/Uracil (UFT) for Suicide: A Case Report

Shuichi Hagiwara,[1] Takashi Ogino,[1] Yuga Takahashi,[1]
Akira Isaka,[1] Taro Nameki,[1] Kaie Kagoshima,[1]
Takuro Yamada,[1] Kouichi Ishihara,[1] Hikaru Hiraishi,[1]
Kazutaka Kurabayashi,[2] Hiroshi Handa [2] and Yuichi Iino [1]

Tegafur/uracil (UFT) is an oral anticancer drug composed of tegafur which is a derivative of fluorouracil (5-FU) and uracil in a molar ratio of 1 : 4. UFT is effective as adjuvant chemotherapy for breast cancer[2], colorectal cancer[3], non-small cell lung carcinoma[4], head and neck cancer[5] and other tumors. We report a 41-year-old man who orally ingested a large dose of UFT (tegafur : 40000 mg/uracil 9960mg) in an effort to commit suicide, and suffered from sub-acute toxicosis (main symptoms were bone-marrow suppression, and hair loss) of UFT. His life was saved by empiric antibiotic chemical treatment (meropenem, isapamicin, and micafungin), and granulocyte colony-stimulating factor (G-CSF). In the case of toxicosis of UFT, strong antibacterial empiric chemotherapy and G-CSF are necessary for rescue. If G-CSF is not work, biopsy of bone marrow woud be necessary, and the case of no stem cells, bone marrow transfusion should be thought. (Kitakanto Med J 2007；57：317～320)

Key Words：tegafur/uracil (UFT), toxicosis, suicide attempt, pancytopenia

Introduction

Tegafur/uracil (UFT) is an oral anticancer drug composed of tegafur which is a derivative of fluorouracil (5-FU) and uracil in a molar ratio of 1 : 4. Tegafur is rapidly absorbed following oral administration and is gradually converted to 5-FU because of its prolonged retention level in vivo.[1] Co-administering uracil with tegafur competitively inhibits the degradation of 5-FU converted from tegafur by dehydropyrimidine dehydrogenase (DPD), and the concentration of 5-FU in tumour tissue and blood remains at a high level for a long time. UFT is effective as adjuvant chemotherapy for breast cancer,[2] colorectal cancer,[3] non-small cell lung carcinoma,[4] head and neck cancer[5] and other tumors.

We report a 41-year-old man who orally ingested a large dose of UFT (tegafur : 40000mg/uracil 9960mg) in an effort to commit suicide, and suffered from sub-acute toxicosis (main symptoms were bone-marrow suppression, and hair loss) of UFT. His life was saved by empiric antibiotic chemical treatment (meropenem, isapamicin, and micafungin), and granulocyte colony-stimulating factor (G-CSF).

Case report

Our patient was a 41-year-old man, intoxicated by alcohol and drugs. His wife was a terminal cancer patient. He impulsively took his wife's tegafur/uracil (UFT)(tegafur : 40000mg/uracil 9960mg) in an attempt to kill himself 18 days before arriving at our hospital. He experienced intense nausea, vomiting, and diarrhea on that day. At 14 days after taking UFT (4 days before admission), his hair fell out. At 17 days after taking UFT, he was not able to walk alone due to severe unsteadiness, general fatigue and a high fever. In addition, a strong pain developed in throat. The next day (at 18 days after taking the UFT), his condition deteriorated. He was thus transported to our hospital by ambulance.

His main symptom was pharyngalgia. His body weight (BW) was 60kg, and temperature 38.4℃. His

1 Department of Emergency Medicine 2 Department of Medicine and Clinical Science, Gunma University, Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma, 371-8511, Japan
Received : September 18, 2007
Address : SHUICHI HAGIWARA Department of Emergency Medicine, Graduate School of Medicine, 3-39-15 Showa-machi, Maebashi, Gunma, 371-8511, Japan

blood pressure (BP) was 118/88mmHg, and pulse 128 beat per minute. His consciousness was E3V4M6 on the GCS (Glasgow coma scale). He showed hair loss (fig. 1).

The blood test results showed of white blood cell (WBC) count of 400/mm³ , platelet (PLT) count of 2.6million/mm³, red blood cell (RBC) count of 3.96million/mm³ of, hematocrit (Hct) of 40.9%, haemoglobin (Hb) of 14.5g/dl, prothrombin time international ratio (PT-INR) of 1.64, activated partial thromboplastin time (APTT) of 58.7sec., fibrinogen (Fib) of 928mg/dl (normal range 150 to 330mg/dl), fibrin degradation products (FDP) of 3.7ug/ml (normal range 0.0 to 4.0ug/ml), a total bilirubin (T-Bil) of 2.3 mg/dl (normal range 8 to 20mg/dl), alanine aminotransminase (ALT) of 60 IU/ml (normal range 8 to 42 IU/ml), aspartate aminotransferase (AST) of 44 IU/ml (normal range 13 to 33 IU/ml), creatine phosphokinase (CPK) 235 IU/ml (normal range 62 to 287 IU/ml), blood urea nitrogen (BUN) 15mg/dl (normal range 8 to 20mg/dl), creatinine of 1.0mg/dl (normal range 0.8 to 1.3mg/dl), C-reactive protein of 39.8mg/dl (normal range 8 to 20mg/dl), sodium (Na) of 135mEq/l, potassium (K) 3.8mEq/l, and chlorine (Cl). 97mEq/l. Blood culture was negative for bacteria.

His fever was thought to have arisen caused by bicytopenia. We thus performed antibacterial empiric chemotherapy (meropenem 2g/day, isapamicin 400mg/day, micafungin 150mg/day) after hospitalization. In addition to antibacterial chemotherapy, we administered granulocyte colony-stimulating factor (G-CSF) (100μg/day) daily until discharge. On day 4, the fever subsided. However his pharyngalgia persisted, such that on day 10, computed tomography (CT) was

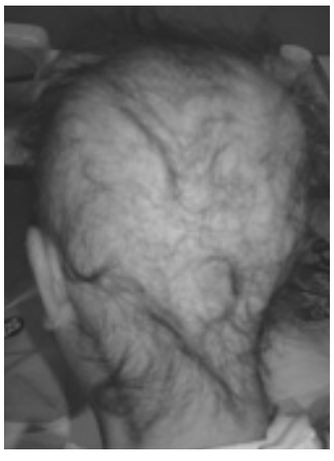

Fig. 1 Hair loss at the time of his addmisson

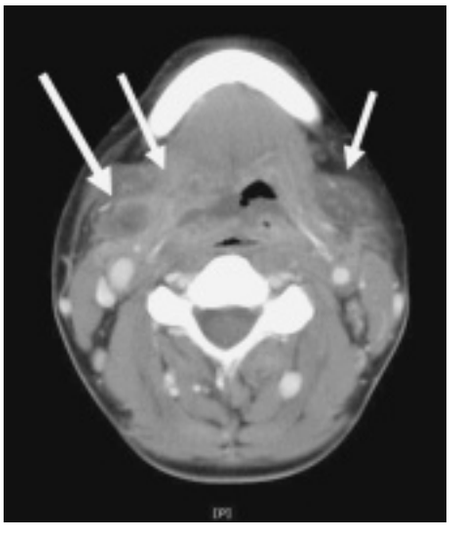

Fig. 2 CT scan of neck on day 10. Abscess was shown.

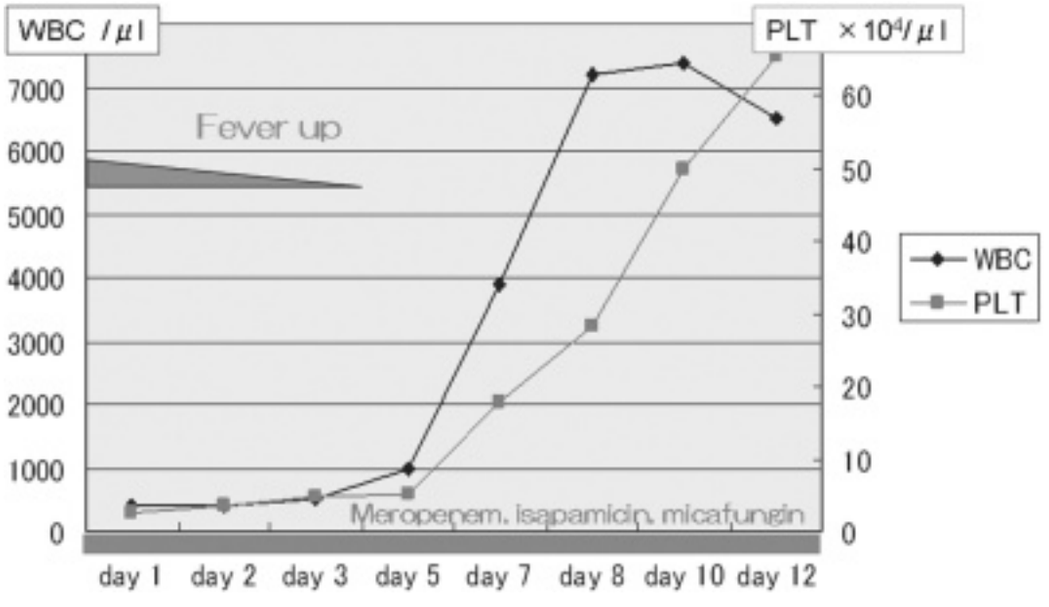

Fig. 3 Changes in blood tests values.

done, and neck abscesses were seen (Fig. 2). Changes in WBC and Plt values are shown in Fig. 3. As the vitamin K, due to PT-INR, did not appear to be improving, we administered vitamin K (10mg/day) from day 8 to day 10. On day 13, an otorhinolaryngologist was consulted for his treatment of the neck abscesses.

Discussion

5-FU[6] is a chemotherapeutic drug widely used as basic therapy for various kinds of solid carcinomas. Although 5-FU is one of the most appropriate oral chemotherapeutic drugs in terms of its pharimacological characteristics, derivatives of 5-FU are usually applied rather than 5-FU itself because the blood level of orally administered 5-FU can vary to some extent with administration of intact oral 5-FU[7,8] Tegafur, synthesized by Hiller et al.,[9] is a prodrug that is metabolized to 5-FU in the liver, and the blood level of tegafur is maintained for a long period due to its intestinal malabsorption. Although tegafur has been applied clinically in Japan,[1] adequate blood levels have not been achieved, due to the degradation of 5-FU by DPD. After uracil, which inhibits the degradation of 5-FU by DPD, was discovered, UFT, a combination of tegafur and uracil, was developed[11].

Tegafur/uracil (UFT) is an oral anticancer drug composed of tegafur, which is a derivative of 5-FU, and uracil in a molar ratio of 1 : 4. Tegafur is rapidly absorbed following oral administration and is gradually converted to 5-FU because of its prolonged retention in vivo1. Co-administering uracil with tegafur competitively inhibits the degradation of 5-FU converted from tegafur by DPD, and the concentration of 5 -FU in tumor tissue and blood remains high for a long time. UFT is effective as adjuvant chemotherapy for breast cancer,[2] colorectal cancer,[3] non-small cell lung carcinoma,[4] head and neck cancer[5] and other tumors. thus, in Japan, UFT is a common anticancer drug, and the number of patients receiving fluorouracil agents is estimated to be 79,000-81,000 a year in Japan.[11] However, there are no previous reports of human poisoning with UFT due to attempted to suicide. This is the first report of toxicosis caused by UFT.

Generally, UFT has numerous side-effects,[2] for example, leukopenia, thrombocytopenia, liver dysfunction,[12,13] anorexia, nausea/vomiting, diarrhea, fatigue, pigmentation, hair loss, skin lesions,[11,14] and so on. However, most of these are tolerable. Nearly the same types of side effects were apparent in this patient. In addition, the blood level of tegafur was kept high because of uracil which inhibited the degradation of 5 -FU by DPD, such that his symptoms were prolonged.

One of our treatment strategies for UFT toxicosis was a device designed to treat leucopenia. If there had been no G-CSF effect, we would have had to perform a bone marrow biopsy, and look for a bone marrow donor for this case lacking stem cells in the bone marrow. Fortunately, there were stem cells in his bone marrow, and he recovered. However, when a patient attempts suicide because of depression, it is very difficult to save the person's life. In our case, the patient took his wife's UFT. It is difficult to take care of the mental health needs of patients' family members. All oncologists must direct their attention to their patients' mental conditions, and for those with severe mental disorders, oral anti-cancer drugs should not be prescribed without a psychiatrisc consultation.

The 50% lethal dose (LD50) of UFT in mice measured for 21 days after drug treatment is 401mg/kg.[15] However, there no data on the LD 50 of UFT in human are available. If LD50 is equal between a mouse and a human, the dose of UFT with this oral use is equivalent to the LD50 of a person weighing 124kg. The reason that our treatment turned out well was the strong empiric therapy administered. In the UFT poisoning case, strong antibacterial empiric chemotherapy should be performed.

Conclusion

In the case of toxicosis of UFT, strong antibacterial empiric chemotherapy and GCSF are necessary for rescue. If G-CSF is not work, biopsy of bone marrow woud be necessary, and the case of no stem cells, bone marrow transfusion should be thought.

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