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5-Fluorouracil-Induced Leukoencephalopathy in Patients with Breast Cancer

The purpose of this study is to determine the characteristic clinical features, radiologic findings, and precipitating and prognostic factors in the patients with breast cancer and with 5-Fluorouracil (5-FU)-induced leukoencephalopathy. We reviewed the medical records of six breast cancer patients who developed leukoencephalopathy after chemotherapy which included 5-FU and also evaluated thorough neurological examinations including mini-mental status examination, cerebrospinal fluid studies, brain images and brain biopsies. Six patients exhibited slowly progressing neurologic symptoms characterized by the impairment of cognitive function, abulia, ataxic gait, and/or akinetic mutism. None of the patients had any specific causes or etiologic factors for leukoencephalopathy. Brain MRI in all patients showed diffuse periventricular white matter changes in the T2-weighted MR image. Brain biopsy in Patient 1 showed fragmented axonal fiber and minimally deprived myelination with many scattered macrophages. Five patients who treated with steroids at the onset of neurological symptoms showed clinical improvement, regardless of their age, sex, the pathology and stage of breast cancer, or the total dosage of chemotherapeutic agents. We conclude that leukoencephalopathy in these cases could be attributable to 5-FU neurotoxicity and suggest that the administration of steroids might be the treatment of choice.

Key Words : *Leukoencephalopathy; Breast Neoplasms; Fluorouracil*

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INTRODUCTION

It has been known that the central nervous system is less susceptible to toxicity resulting from chemotherapy because of the low proliferation rate of cells and low permeability across the blood-brain barrier of most chemotherapeutics. However, as a result of new chemotherapeutic agents, various delivering methods, and combinations with radiotherapy, there have been numerous reports concerning the neurologic complications of chemotherapy.

5-fluorouracil (5-FU) has been used as a standard regimen in breast cancer chemotherapy. There have been limited number of reports on cases of 5-FU-induced neurologic complications, including organic mental disorder (1), dementia (2), and akinetic mutism associated with white matter hypodensity on brain computed tomography (CT) (3). However, there has been no systematic analysis of 5-FU-induced neurologic complications in Korea.

We report the characteristic clinical and radiologic features, and the precipitating and prognostic factors in six breast cancer patients who exhibited leukoencephalopathy characterized by cognitive impairment, abulia, ataxia and akinetic mutism while they were taking Carmofur® (1-hexylcarbamoyl-5-fluorouracil; 5-FU derivative) or CEF (cyclophosphamide, epirubicin, 5-FU) and Carmofur®.

MATERIALS AND METHODS

There were six breast cancer patients in whom leukoencephalopathy developed during chemotherapy with Carmofur® alone or with CEF and Carmofur® from January 1996 to December 1998 at Chonnam National University Hospital.

Each case was assessed through a standardized protocol devised for this study. We used information abstracted from the patient's medical records, including age at the onset of neurologic symptoms, interval between the beginning of chemotherapy and the onset of neurologic

symptoms, past history, pathology and stage of breast cancer, and the total dosage of chemotherapeutic agents. We also performed thorough neurological examinations including mini-mental status examination (MMSE), routine laboratory tests, tumor marker studies for breast cancer, cerebrospinal fluid (CSF) studies, electroencephalography (EEG), brain images, and brain biopsies.

Outcome was measured by the score of MMSE checked at admission, discharge and 1 month later.

RESULTS

From January 1996 to December 1998, we had encountered six patients who developed leukoencephalopathy during chemotherapy with 5-FU derivative for breast cancer. The clinical characteristics including the pathology and stage of breast cancer and the dosage of chemotherapeutic agents in these six patients are presented in Table 1. The mean age at the onset of symptoms was 46 yr (range, 33 to 57 yr), and the mean interval between the beginning of chemotherapy and the onset of neurologic symptoms was 26 weeks (range, 8 to 36 weeks). None of the patients had evidences for metastatic disease or a prior history suggestive of demyelinating disease.

Four patients (Patients 1, 2, 3, 6) exhibited abnormal behavior including touching kitchen utensils, turning on the tap for no reason, and keeping her hands in and out their pockets. Some patients exhibited disorientation, gait disturbance, memory disturbance, dizziness, and nausea. On neurologic examination after being diagnosed as leukoencephalopathy, abulia and cognitive dysfunction were revealed in three patients, cognitive dysfunction only in

Table 1. Clinical characteristics of the six patients with leukoencephalopathy

Patient No.	Age (yr)	Pathology	Stage	Total dose (mg)			
				5-FU (IV)	Cyclophosphamide (IV)	Epirubicin (IV)	Carmofur (PO)
1	33	Infiltrating ductal cancer	II (T2N0M0)	9,600	4,800	480	31,800
2	56	Infiltrating ductal cancer	II (T2N0M0)	8,000	4,000	400	52,800
3	48	Infiltrating ductal cancer	II (T2N1M0)	8,400	4,200	336	36,000
4	37	Infiltrating ductal cancer	II (T2N1M0)	9,300	4,650	462	28,200
5	46	Invasive cancer (undetermined type)	II (T2N0M0)	-	3,768	376	67,200
6	57	Mucinous cancer	I (T1N0M0)	-	-	-	34,200

IV, intravenous; PO, per-oral

Table 2. Neurologic characteristics of the six patients

Patient No.	Interval* (days)	Initial symptoms	Signs at diagnosis	Cerebrospinal fluid examination	Outcome
1	No treatment	Disorientation, abnormal behavior	Akinetic mutism	Not performed	Poor
2	10	Abnormal behavior, cognitive dysfunction	Abulia, cognitive dysfunction	Leukocyte 4/μL; glucose 50 mg/dL (blood 88 mg/dL); protein 53 mg/dL; IgG index† 0.329; MBP‡ 20.2 ng/mL; oligoclonal band (-)	Good§
3	6	Abnormal behavior	Cognitive dysfunction	Leukocyte (-); glucose 78 mg/dL (blood 125 mg/dL); protein 29 mg/dL; IgG index‖; MBP 3.1 ng/mL; oligoclonal band (-)	Good
4	58	Memory disturbance, dizziness	Abulia, cognitive dysfunction	Not performed	Good
5	18	Gait disturbance	Gait disturbance, memory disturbance	Not performed	Good
6	4	Abnormal behavior, dizziness, nausea	Abulia, cognitive dysfunction	Leukocyte 5/μL; glucose 55 mg/dL (blood 88 mg/dL); protein 59 mg/dL; IgG index 0.645; MBP 7.2 ng/mL; oligoclonal band (-)	Good

*Interval; Interval between the onset of neurologic symptoms and steroid treatment
†Cerebrospinal fluid (CSF) immunoglobulin G (IgG) index: (CSF IgG/CSF albumin)/(serum IgG/serum albumin); normal range is 0-0.77.
‡CSF myelin basic protein (MBP); normal range is <1.0 ng/mL
§Good prognosis; mini-mental status examination (MMSE) at 1 month >25
‖We cannot calculate IgG index due to missing laboratory results

Patient 3, and akinetic mutism followed by a vegetative state in Patient 1 (Table 2).

Routine laboratory tests, carcinoembryonic antigen (CEA), and CA 15-3 showed normal results in all patients. CSF examination results in three patients were normal, except for an elevated myelin basic protein (MBP) (Table 2).

EEG in four patients (Patients 3-6) showed diffuse irregular low amplitude slow waves with frontal predominancy in Patients 3 and 6, frontal intermittent rhythmic delta activity (FIRDA) in Patient 5, and normal rhythms in Patient 4.

Magnetic Resonance Imaging (MRI) at admission demonstrated diffuse signal intensity changes on periventricular white matter which was high signal in the T2-weighted images, and low signal in the T1-weighted images without gadolinium enhancement. There were no abnormal findings in the cerebral cortex, basal ganglia, brain stem or cerebellum. In Patient 4, follow-up MRI revealed a decreased signal intensity of white matter in the T2-weighted image, which ran parallel with symptomatic improvement (Fig. 1). On the other hand, in Patient 6, follow-up MRI on the 7th day of hospitalization showed an increased signal intensity of white matter in the T2-weighted image compared with the previous MRI findings, which was correlated with the aggravation of neurologic symptoms (Fig. 2).

Brain biopsy in Patient 1 showed that axonal fibers were fragmented on immunohistochemical stain for glial fibrillary acidic protein (GFAP) and neurofilament (NF), myelination was minimally deprived on Luxol fast blue stain, and there were many scattered plump macrophages with granular cytoplasm.

Treatment of the neurological illnesses in all patients, except Patient 1, was empirical and consisted of corticosteroids and cessation of all chemotherapeutics. Steroid treatment began with intravenous methylprednisolone 3,000 mg for 3 days (1,000 mg/day), followed by oral prednisolone 1 mg/kg for 2 weeks. In Patient 6, neurologic symptoms were aggravated at 1 week and methylprednisolone 3,000 mg was administered again. Cognitive dysfunction assessed by MMSE improved in all patients treated with steroids in the early stages of the symptoms. However, Patient 1, in whom steroids were not administered, showed aggravation of the neurologic symptoms (Table 3). There were no significant differences between Patient 1 and the other five patients in pathology and stage of breast cancer, total dosage of chemotherapeutic agents, or age (Table 1). There was no significant correlation between the interval from the onset of neurologic symptoms to the steroid treatment and the changes of MMSE in patients with good prognosis (Patients 2-6).

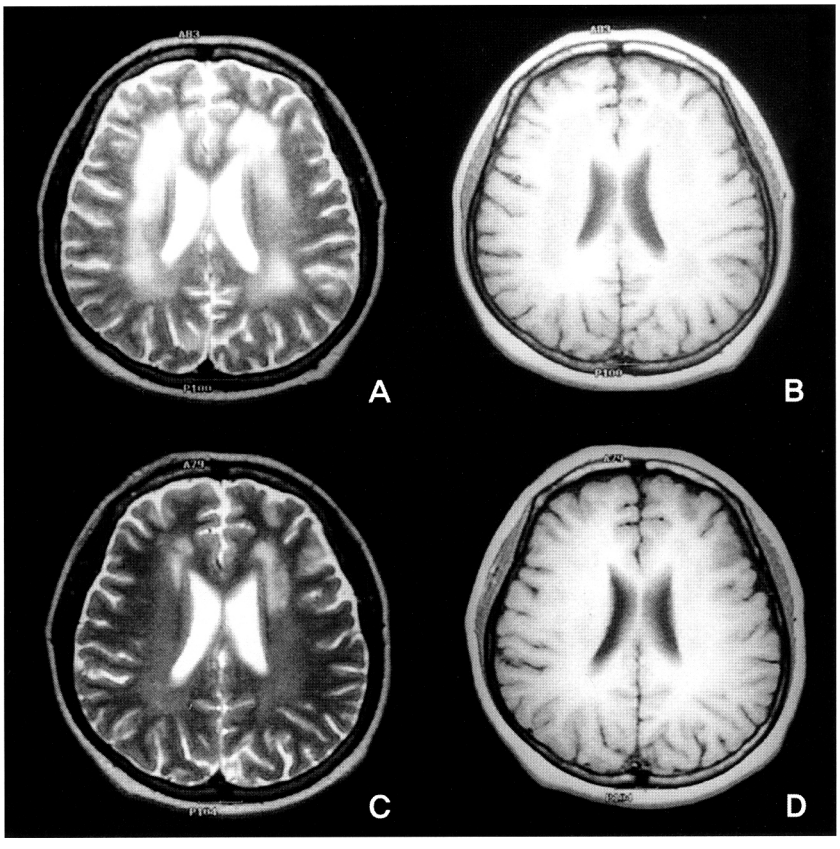

Fig. 1. In Patient 4, MRI at the beginning of neurologic symptoms **(A, B)** show diffuse signal intensity change (high in T2 weighted image and low in T1 weighted image) in the periventricular white matter. Follow-up MRI at the time of improvement of neurologic symptoms **(C, D)** show a decrease of abnormal signal intensities.

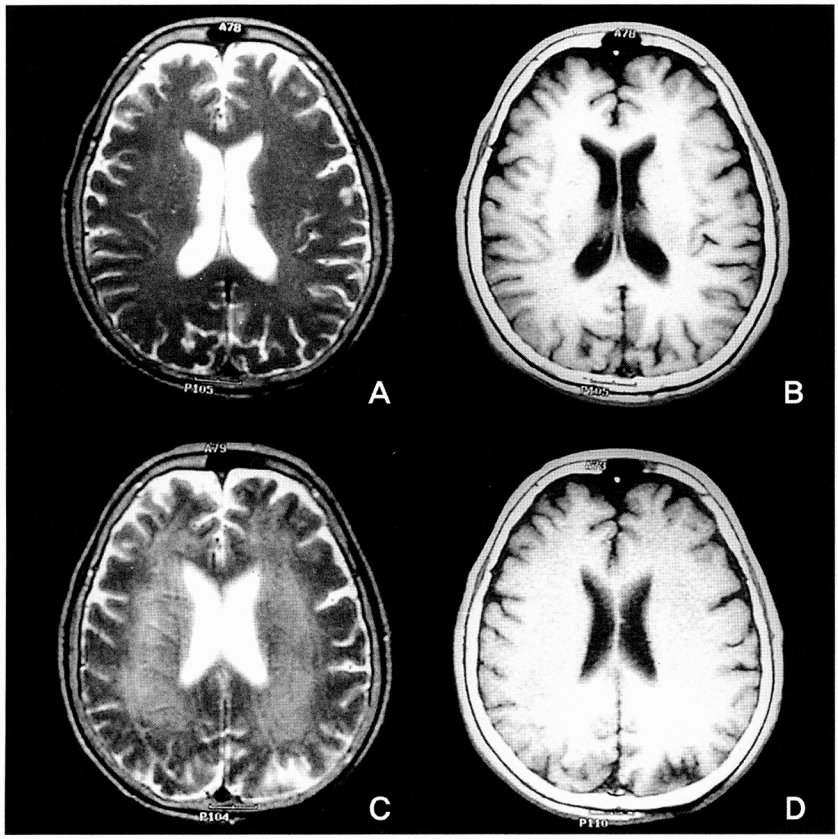

Fig. 2. In Patient 6, MRI at the beginning of neurologic symptoms (A, B) show diffuse signal intensity change (high in T2 weighted image and low in T1 weighted image) in the periventricular white matter. Follow-up MRI at the time of aggravation of neurologic symptoms (C, D) show an increase of abnormal signal intensities.

Table 3. Changes of mini-mental status examination

Patient No.	Admission	Discharge	>1 month
1	-	-	0
2	0	5	30
3	9	17	29
4	23	25	30
5	26	30	30
6	8 (0*)	6	26

*MMSE score at 7th hospital day when neurologic symptoms were aggravated

DISCUSSION

Chemotherapeutic agents which have been reported to cause leukoencephalopathy include 5-FU and levamisole (4, 5), Camofur® (3, 4, 6), methotrexate (7, 8), cisplatin plus ectoposide or bleomycin (9-11), BCNU [1,3-bis-(2-chloroethyl)-1-nitrosourea] (12, 13), and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) (14). The leukoencephalopathy usually develops after intrathecal injection or combination of injection and cranial irradiation, but can develop after intravenous injection or oral medication as our cases (3, 4, 6).

5-FU is a fluorine-substituted analogue of pyrimidine uracil. The main action of this agent is block DNA synthesis by reducing thymidine monophosphate formation via inhibition of the enzyme thymidylate synthetase. It also incorporate into RNA. More importantly, 5-FU readily penetrates blood-brain barrier. Various neurological complications including cerebellar dysfunction, encephalopathy, peripheral neuropathy (15, 16), parkinsonian syndrome (17), oculomotor disturbance (18), and multifocal inflammatory leukoencephalopathy (19, 20) have been reported in cancer patients treated with derivatives of 5-FU. These neurotoxic effects are dose- and schedule-dependent and are reversible with drug withdrawal or dose reduction (15).

The pathogenesis of the neurological disorders in these six patients is unclear. Their neurologic symptoms might have been attributable to brain metastasis and unrelated to the chemotherapy. However, these patients exhibited no evidences for metastatic lesions in brain either by MRI or CSF cytology. Another possibility is paraneoplastic syndrome. Paraneoplastic disorders in breast cancer patients include hypercalcemia, fever, polyarthritis, erythematous rash (21, 22), cerebellar degeneration, encephalomyelitis, limbic encephalitis, and sensorimotor neuropathy (23, 24). Paraneoplastic syndrome, however, could not be the cause in that the neurologic symptoms of the patients occurred after the removal of the tumor mass

and there was neither recurring or metastatic lesion, nor increment of CEA or CA 15-3. Still, paraneoplastic syndrome cannot be excluded because anti-Hu and anti-Yo auto-antibodies which are present when there are neurologic symptoms associated with neoplasm (23, 25) were not checked. The third possible cause might be multiple sclerosis. It is possible that these patients had coincidental onsets of multiple sclerosis or had had subclinical multiple sclerosis that was exacerbated by chemotherapy. Good response to steroid was consistent with multiple sclerosis. However, none of these patients had a prior history to suggest multiple sclerosis, nor exhibited subsequent neurological events to suggest this disorder in the follow-up period. In addition, brain MRI of our cases showed diffuse white matter lesions rather than multifocal enhancing white matter lesions in multiple sclerosis. Further evidences were the normal IgG index, and the negative oligoclonal band in CSF. The last possible cause might be direct neurotoxicity of 5-FU derivatives. Cerebellar dysfunction and encephalopathy are more frequently induced by 5-FU than other chemotherapeutics (4, 5, 15, 16, 19, 20). 5-FU neurotoxicity might be a cause of those neurologic symptoms and MRI lesions emerged after chemotherapy and there was clear improvement after discontinuation of the agents. Although we cannot exclude the effects of cyclophosphamide and epirubicin, 5-FU, especially the oral agent Carmofur®, may be the main cause of leukoencephalopathy because it also appeared in the patient treated with Carmofur® alone.

The pathogenesis of the neurotoxicity associated with 5-FU administration is not clear. 5-FU given to experimental animals causes lesions in myelin and axon, and these lesions disappear in 6 months after the discontinuation of chemotherapeutics (26, 27). This is comparable with our case (Patient 1) who exhibited destruction of the axon and myelin. Koenig and Patel (28) have insisted that 5-FU neurotoxicity be caused by fluorocitrate, a terminal metabolite of 5-FU, and induced by tissue accumulation of citrate which cannot be converted to isocitrate by fluorocitrate. Hook et al. (19) reported multifocal inflammatory leukoencephalpathy in colon cancer patients who received 5-FU and levamisole. Pathologic studies showed that the myelin loss was associated with numerous dispersed, as well as vasocentric, macrophages, sparing of axons, and perivascular lymphocytic inflammation. CSF examinations showed mild pleocytosis. Hook et al. believed that the pathologic and the CSF findings were indicative of an immune-mediated process. Despite the continuation of 5-FU, however, the resolution of contrast-enhancing lesions on MRI, without further neurologic sequelae, occurred when levamisole was discontinued (29), and similar lesions could be induced by levamisole alone (30). Therefore, leukoencephalopathy may be induced by levamisole rather than by 5-FU when these two agents are administered together. According to our recent experience, most oligodendrocytes were damaged by 5-FU dose-dependently, but there was little damage on astrocytes. And these 5-FU-induced oligodendrocyte deaths were attenuated by not only cycloheximide (protein synthesis inhibitor) and Z-VAD-FMK (caspase inhibitor), which are known to block apoptosis, but also trolox, a vitamin E analog antioxidant (31). These findings suggest that 5-FU induces oligodendrocyte death via apoptotic process, and that anti-oxidants may prevent 5-FU-induced white matter injury in cancer patients.

Several cases of neurologic complications after administration of 5-FU have been reported in Korea (1-3). Also, leukoencephalopathies induced by Carmofur have been reported sporadically, but increasingly, especially in Japan (4, 32). Neurologic signs and symptoms in our cases were higher cortical dysfunctions such as memory disturbance, abnormal behavior, and akinetic mutism and were similar to previous reports (3, 19). CSF examinations in three patients showed an increase in MBP, which would be caused by the destruction of myelin. Generally the basic protein level in spinal fluid is known to be useful in diagnosing diseases in which acute breakdown of myelin occurs, especially in leukoencephalopathy resulting from irradiation and chemotherapy, as well as in multiple sclerosis (33). EEG findings in two patients showed diffuse irregular low amplitude slow waves with frontal predominancy and were similar to previous reports (3, 10). But EEG in other patients showed FIRDA or normal. Thus it seems that there are no specific EEG patterns in 5-FU-induced leukoencephalopathy. Diffuse white matter lesions on brain MRI changed according to each patient's clinical status. As the severity of CT abnormalities parallels the clinical signs of leukoencephalopathy (34, 35), and as MRI is more sensitive than CT in detecting white matter abnormalities (36, 37), MRI should be checked as soon as possible when the above-mentioned symptoms develop in patients treated with chemotherapy. Prognosis was good in five patients in whom the chemotherapeutics had been replaced by conservative treatment with steroids at the onset of the neurologic symptoms. Prognosis, however, was not good in one patient who had not received steroid treatment. These suggest that early steroid treatment is an important prognostic factor. The interval from the onset of neurologic symptoms to the beginning of steroid treatment exhibited no correlation with the change of MMSE. This might be due to the early treatment with steroids in most patients and thus should not reduce the importance of early steroid treatment.

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