Spontaneous intracranial hemorrhage has been associated with coagulopathy, vascular lesions, drug and hematologic disorder. Although the advances in platelet transfusion procedures and the management of disseminated intravascular coagulopathy have reduced the incidence of severe hemorrhagic complications in patients treated with intensive chemotherapy for acute leukemia[11], spontaneous intracranial hemorrhage is still the frequent cause of death in the hematologic disorder including leukemia[4,15,18].

The authors conducted retrospective clinical analysis of intracranial hemorrhage in patients with hematologic disorder including laboratory and radiologic findings.
intraventricular hemorrhage and subdural hemorrhage in 3 patients and 4 patients, respectively were combined. In 3 cases, only subarachnoid hemorrhage was observed. In case of intracerebral hemorrhage, 28 cases showed subcortical lobar hemorrhage, and 5 cases in basal ganglia, 3 cases in thalamus and 3 cases in cerebellum. Subcortical lobar hemorrhages were classified morphologically on brain computerized tomography into three types: type I (Fig. 1), a single hematoma with smooth contour (8 cases), type II (Fig. 2, 3), clustered multifocal hematomas (9 cases), and type III (Fig. 4), isolated multifocal hematomas (11 cases). Twenty (48%) of the 42 patients had multifocal hematomas. Intracranial hemorrhage occurred in 24 patients before treatment and 18 patients during chemotherapy or after bone marrow transplantation.

Underlying hematologic disorders included aplastic anemia (4), acute myeloblastic leukemia (20), acute lymphoblastic leukemia (6), chronic myeloblastic leukemia (8), myelodysplastic syndrome (2), multiple myeloma (1), and polycythemia vera (1). Among the acute myeloblastic leukemia patients, M3 (acute promyelocytic leukemia) by French-American-British system classification who the most common cause of intracranial hemorrhage, as 13 of 20 patients. Thirty-six patients (86%) had moderate and severe thrombocytopenia (less than 100 × 10^9/L) (Table 1). Twenty four patients (57%) had moderate and severe leukocytosis (greater than 20 × 10^9/L) (Table 2).

**Discussion**

Spontaneous intracranial hemorrhage is a well-known event associated with leukemia, occurring either at presentation or during the treatment courses. Graus, et al. reported that the incidence of intracerebral hemorrhage and subdural hemorrhage of leukemic patients as about 15% and 6%, respectively. Pomeranz, et al. reported that the intracranial hemorrhage resulted from thrombocytopenia primarily and abnormal leukemic infiltration in central nervous system about 30%. Our analysis showed that thrombocytopenia was the important cause of cerebral hemorrhage with hematologic disorders. In many cases, it is the result of platelet consumption due to disseminated intravascular coagulopathy, and reduced pla-

| Table 1 | Incidence of thrombocytopenia in patients with intracranial hemorrhage |
|---------|-----------------------------|----------------|----------------|---------------|---------------|---------------|---------------|---------------|
| PLT (x 10^9/L) | AA | ALL | AML | CML | MDS | MM | PV |
| 0 ~ 100 | 3 | 4 | 18 | 7 | 2 | 1 | 1 |
| > 100 | 1 | 2 | 2 | 1 | 0 | 0 | 0 |
| Total | 4 | 6 | 20 | 8 | 2 | 1 | 1 |

| Table 2 | Incidence of leukocytosis in patients with intracranial hemorrhage |
|---------|-----------------------------|----------------|---------------|---------------|---------------|---------------|---------------|
| WBC (x 10^9/L) | AA | ALL | AML | CML | MDS | MM | PV |
| 0 ~ 20 | 4 | 3 | 8 | 1 | 1 | 1 | 0 |
| > 20 | 0 | 3 | 12 | 7 | 1 | 0 | 1 |
| Total | 4 | 6 | 20 | 8 | 2 | 1 | 1 |
Ich with Hematologic Disorders

telet production secondary to leukemic cell infiltration in the bone marrow and/or the myelotoxic effect of intensive chemotherapy. Gmür, et al.7) suggested that in the absence of any other abnormality such as coagulation or an accompanying platelet dysfunction, intracranial hemorrhage is unusual if the platelet count is greater than $20 \times 10^9/L$. However it has been supposed that most of hematologic disorders are also associated with various types of platelet function disorders and coagulation disorders. In our study, intracranial hemorrhage developed in 21 patients who had the platelet count from more than $20 \times 10^9/L$ to less than $100 \times 10^9/L$.

It is reported that leukocytosis has an increased risk for intracranial hemorrhage4,5). Creutzig, et al.5) reported that leukemic cell infiltration was found in patients with chronic leukemia in blastic crisis or acute monocytic leukemia. Aggregated leukemic cells would injure the vascular endothelial cells as well as the local circulation, resulting in hemorrhage. It has been known that acute myeloblastic leukemia causes intracranial hemorrhage more than acute lymphoblastic leukemia does. The larger size of myeloblasts as compared with lymphoblasts makes circulation through small vessels more difficult and leads to a greater blood viscosity, leukostasis, vascular dilatation, tissue hypoxia and vascular damage, and eventually induced hemorrhage2,13). In our study, twenty patients of intracranial hemorrhage were acute myeloblastic leukemia and six patients were acute lymphoblastic leukemia. Among the acute myeloblastic leukemia patients, M3(acute promyelocytic leukemia) by French-American-British system classification3) who the most common cause of intracranial hemorrhage, as 13 of 20 patients. Disseminated intravascular coagulopathy is a feature of M3 and is particularly marked in patients with leukocytosis. It appears soon after the beginning of chemotherapy, presumably occurring because a tissue factor with procoagulant activity is released from the granules of destroyed leukocytes, particularly promyelocytes2,10). As like that, in the case of chronic myeloblastic leukemia, hemorrhage is caused by not only thrombocytopenia but also leukocyte infiltration in blastic crisis stage, 7 of 8 cases also showed leukocytosis of more than $20 \times 10^9/L$ in this study.

Analysis of some small autopsy series has revealed that multifocal subcortical hemorrhages are characteristic of intracranial hemorrhage in acute leukemia9). In our study, 28 cases showed subcortical hemorrhage. Anatomically the vasculature of subcortical white matter is characterized by multiple small, tortuous vessels with a thin media, no external elastic lamina, and little adventitia15). Congestion or hemorrhage can occur easily in the white matter because of the coarse capillary network and poor collateral circulation. Among 42 patients with intracerebral hemorrhage, subarachnoid hemorrhage and subdural hemorrhage in 3 patients and 4 patients, respectively were combined. Price17) reported that subarachnoid hemorrhage resulted from the destruction of the pia mater by leukemic infiltrate or interference with local perfusion through constriction of the blood vessels by perivascular arachnoid infiltration. Subdural hemorrhage associated with intracranial hemorrhage may occur because the arachnoid covering the cortex is disrupted by rapid enlargement of the intracranial hemorrhage.

Ochiai, et al.14), reported that the good results could got by operation if the patients who had intracranial hemorrhage with hematologic disorders were in remission state of underlying disorders. However, in these patients, we usually treated conservatively because of a high risk of massive bleeding by a coagulation difficulty during or after operation. We performed the operation in only one of 42 cases. Del Zoppo, et al.6), has recommended platelet transfusions and the use of induction chemotherapy to maintain the platelet count at least more than $20 \times 10^9/L$ prophylactically and to maintain a platelet count at least more than $50 \times 10^9/L$.

**Conclusion**

Based on our experiences and a review of the literature, this study showed that (1) the risk factors of intracranial hemorrhage in hematologic disorders are thrombocytopenia, leukocytosis and disseminated intravascular coagulopathy; (2) intracerebral hemorrhage in hematologic disorders occur preferentially in the subcortical portion; (3) intracranial hemorrhage in hematologic disorders consist of various combinations of subcortical lobar hemorrhage, subarachnoid hemorrhage, subdural hemorrhage and intraventricular hemorrhage; (4) intracerebral hemorrhage in hematologic disorders tend to be multiple.

In addition to cytoreductive treatment of underlying disease,
platelet transfusions should be used on the emergency basis if a severe hemorrhagic event occurs.

References