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Effective Management of Acute Promyelocytic Leukemia with High Risk of Fatal Intracranial Hemorrhage

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Abstract

Although the prognosis of acute promyelocytic leukemia (APL) are favorable because of disease-specific drugs, such as all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), early death due to fatal intracranial hemorrhage has been observed in many cases. The aim of this study is to examine the relationship between the treatment and intracranial hemorrhage complication in APL patients.46 patients diagnosed of APL during a period from 2000 to 2014 in our hospital were examined. The distribution of fatal intracranial hemorrhage (FICH) risk score in the 46 APL patients showed 23.9%, 58.6% and 17.3% for low, intermediate, and high categories, respectively. Among the 46 patients, 5 patients developed intracranial hemorrhage before remission, including 4 patients who developed such hemorrhage after chemotherapy and ATRA administration, and 1 patient who developed intracranial hemorrhage before treatment. All of the 5 patients were included in the high risk group of FICH score, including 1 patient who died and 3 patients who had serious paralysis. These hemorrhage tended to expand for several days because of progression of disseminated intravascular coagulation (DIC) accompanied by tumor lysis syndrome after chemotherapy. Based on this experience, we firstly provided single administration of ATRA for 5 days to a patient with intracranial hemorrhage and then added chemotherapy after improvement of DIC. As a result, we could lead remission with no expansion of intracranial hemorrhage. In most of induction therapy protocols for APL, patients with high white blood cell counts are recommended to receive combination of chemotherapy and ATRA with a focus on ATRA syndrome, but the risk of fatal intracranial hemorrhage is not reflected in the treatment regimen. Such a complication may be prevented using initial single administration of ATRA followed by concomitant chemotherapy after treatment for DIC in patients with a high-risk FICH score.

Keywords: APL; Fatal; Intracranial hemorrhage; ATRA; Acute promyelocytic leukemia

Introduction

The treatment of acute promyelocytic leukemia (APL) has improved remarkably during the last two decades mainly due to disease-specific drugs, such as all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) [1,2]. However, early death due to fatal complications such as intracranial hemorrhage, before remission occurs in many cases [1,3]. Despite the improvements in APL treatment, early death remainsa problem with reported early death rates ranging between 7 and 14% [1]. Previous study reported an early death rate of 32% in a study of APL patients at 12 Brazilian institutions receiving treatment with ATRA and anthracyclines. Intracranial hemorrhages, caused by disseminated intravascular coagulation (DIC), hypercoagulability, fibrinolysis, proteolysis and thrombocytopenia, constitute the major cause of early death of APL patients [4,5]. Thus, prevention of intracranial hemorrhage before remission is important for improvement of prognosis of patients with APL.

The fatal intracranial hemorrhage risk score (FICH) score was introduced to categorize acute myeloid leukemia (AML) patients based on their risk of hemorrhage [6]. The score is derived from 5 items related to the risk of intracranial hemorrhage, with one point each given for white blood cell (WBC) count >50,000 /μL, blood platelet count <35,000 /μL, APL, PT/INR >1.5, and female gender. The sum of these scores is used to define low (0-1), intermediate (2-3), and high (4-5) risk categories. A significant difference in intracranial hemorrhage events was found based on risk factors for hemorrhage upon remission induction in patients with AML [6]. The aim of this study is to examine the relationship between the treatment and intracranial hemorrhage complication in APL patients based on FICH score.

Methods

The subjects were 46 patients who were diagnosed with APL from 2000 to 2014 at Nippon Medical School Hospital. Molecularly confirmed diagnosis was defined as a finding of t (15;17) in cytogenetic analysis, andor positivity for PML-RAR in fluorescence in situ hybridization or reverse transcription-PCR analysis. Remission-induction therapy was performed in accordance with Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed Oncologia Pediatrica Cooperative Groups (GIMEMA-AIEOP) protocol [7,8]. In short, patients received oral ATRA 45 mg/m^2 daily, starting on day 1 and continuing until CR or for a maximum of 90 days; 12 mg/m^2 of intravenous idarubicin (IDA) was added to ATRA on days 2, 4, 6, and 8. In patients younger than 20 years, the dosage of ATRA was reduced to 25 mg/m^2 daily, whereas the dosage of IDA remained the same. Supportive platelet transfusions were administered only in the presence of overt hemorrhage or if the

platelet count was less than 30,000/μL with or without laboratory signs of severe coagulopathy (fibrinogen <150 mg/dL and fibrin degradation products >40 μg/mL). The relationship between remission-induction therapy (ATRA with or without chemotherapy) and changes in CT images of intracranial hemorrhage was examined in 5 patients who developed hemorrhage before remission (including one patient with intracranial hemorrhage before treatment). The relationship between FICH scores and intracranial hemorrhage before remission was examined in all 46 APL patients.

Results

Categorization of the 46 subjects with APL based on FICH scores indicated that 23.9%, 58.6%, and 17.3% were at low, intermediate, and high risk for intracranial hemorrhage, respectively (Table 1).

Characteristics	n=46 (all)
Sex, n (%)	
Male	27 (58.6)
Female	19 (41.3)
Age, median (range)	54 (26-87)
Plt (x10^4/μl), median (range)	2.2 (0.5-12.7)
WBC (x10^3/μl), median (range)	1.8 (0.3-103.4)
PT/INR, median (range)	1.39 (0.9-3.3)
ATRA syndrome, n (%)	16 (34.7)
Intracranial Hemorrhage, n (%)	5 (10.8)
FICH score, n (%)	
Low	11 (23.9)
Intermediate	27 (58.6)
High	8 (17.3)

Table 1: Clinical characteristics of patients (n=46) with acute promyelocytic leukemia.

The actual in cidences of intracrani al hemorrhage were 0%, 0%, and 62.5% in these respective groups, with the incidence being extremely high in the high risk group (Table 2).

Data for a case under follow-up observation is shown in Figure 1. The patient had a WBC count of 35,000 /μL at a visit to our hospital, and thus we commenced concomitant treatment with 45 mg/m^2/day of ATRA and 12 mg/m^2/day idarubicin (IDA), in accordance with GIMEMA-AIEOP protocol. Aggravation of DIC accompanied by tumor lysis occurred after the start of treatment and intracranial hemorrhage developed in the right occipital lobe on day 1. Since coagulation control was difficult with multidisciplinary therapy, the hemorrhage expanded for 1 week until PT/INR was decreased to <1.5. All four patients who developed intracranial hemorrhage after treatment based on GIMEMA-AIEOP protocol showed similar courses.

Based on this experience, we obtained remission without aggravation of intracranial hemorrhage in a patient who developed intracranial hemorrhage before treatment using initial single administration of ATRA for 5 days followed by concomitant chemotherapy with ATRA after improvement of DIC (Figure 2). This is in contrast to most of protocols including GIMEMA-AIEOP protocol, which suggest that chemotherapy should be given concomitantly with ATRA for patients with a WBC count >18,000/μL. The patient developed ATRA syndrome during follow-up observation, but the syndrome was controlled by administration of glucocorticoids.

Clinical characteristics	FICH score		
	High (4-5) n=8	Intermediate (2-3) n=27	Low (0-1) n=11
Intracranial Hemorrhage, n (%)	5 (62.5)	0 (0.0)	0 (0.0)
Sex, n (%)			
Male	2 (25.0)	15 (55.5)	10 (90.9)
Female	6 (75.0)	12 (44.4)	1 (9.0)
Age, median (range)	49 (26-74)	55 (21-87)	58 (53-62)
Plt (x10^4/μl), median (range)	1.5 (0.6-6.4)	2.2 (0.5-20.6)	4.2 (1.4-12.7)
WBC (x10^3/μl), median (range)	39.3 (0.3-103.4)	1.9 (0.4-51.0)	1.7 (1.0-4.0)
PT/INR, median (range)	1.75 (1.52-3.3)	1.39 (0.9-2.88)	1.19 (0.99-1.58)
ATRA syndrome, n (%)	4 (50.0)	8 (34.7)	3 (37.5)

Table 2: Clinical characteristics of patients with acute promyelocytic leukemia based on FICH score.

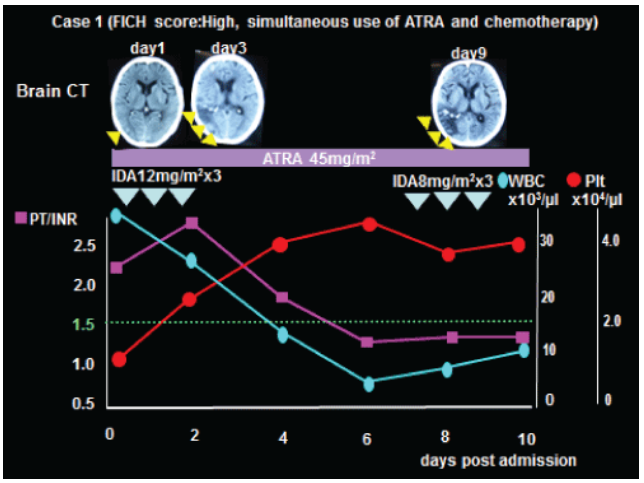

Figure 1: Course of a patient with intracranial hemorrhage who was treated with concomitant ATRA and chemotherapy.

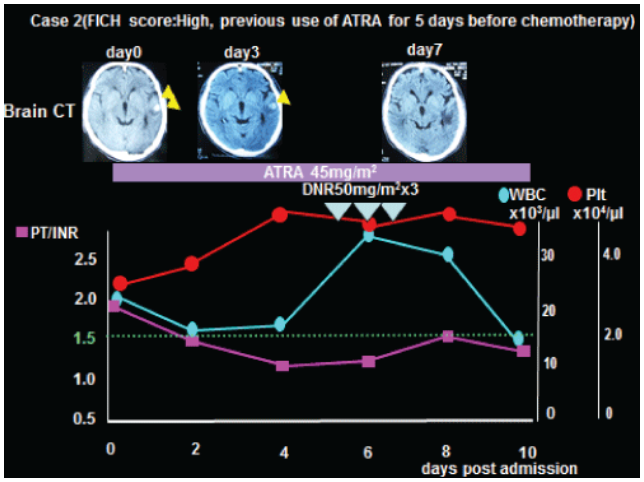

Figure 2: Course of a patient with intracranial hemorrhage who was treated with ATRA for 5 days before the start of chemotherapy.

Discussion

This paper is, to our knowledge the first paper that suggests the induction therapy focused on FICH. While the cure rates for APL are remarkable, early death continues to be a major cause of treatment failure [9]. The major cause of early death is intracranial hemorrhage.

In most of induction therapy protocols for APL, patients with high white blood cell counts are recommended to receive combination of chemotherapy and ATRA with a focus on ATRA syndrome, but the risk of FICH is not reflected in the treatment regimen. Such a complication may be prevented using initial single administration of ATRA followed by concomitant chemotherapy after treatment for DIC in patients with a high-risk FICH score.

We have succeeded in rescue of a patient who developed intracranial hemorrhage before treatment using initial single administration of ATRA for 5 days followed by concomitant chemotherapy with ATRA after improvement of DIC. We consider that it is important to decrease PT/INR to <1.5 for improvement of intracranial hemorrhage that develops during treatment for APL. However, once chemotherapy is administered, it is extremely difficult to decrease PT/INR to <1.5. In this case, PT/INR <1.5 was achieved by initial single administration of ATRA for 5 days before chemotherapy, and expansion of intracranial hemorrhage was prevented. This approach may increase the risk of ATRA syndrome, but many tactics including glucocorticoids, cytotoxic chemotherapy, mechanical ventilation remains. Thus, further research of large population of APL patients with high-risk FICH should be needed to assess this approach.

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