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Clinical commentary

Risk factors and clinical characteristics of non-promyelocytic acute myeloid leukemia of intracerebral hemorrhage: A single center study in China

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ABSTRACT

Background: Although high mortality in patients with acute leukemia (AL) is associated with intracranial hemorrhage (ICH), the clinical features and pathogenesis of AL patients with cerebral hemorrhage are not well known.
Methods: We diagnosed 90 patients with ICH from a total of 1467 patients with non-promyelocytic AL who had been hospitalized in the First Affiliated Hospital of Medical School of Zhejiang University from January 2010 to October 2015. Moreover, the risk factors of ICH death were evaluated.
Result: Median age at ICH was 51 years old, in which men accounted for 52.2%. They also accounted for 85.6% of acute myeloid leukemia. The relative incidence of ICH was the highest in M2 and M5 (60.1%). ICH presented with higher peripheral blood white blood cell count (WBC) ($P < 0.001$), lower peripheral platelet counts ($P < 0.001$), lower albumin ($P < 0.001$), lower fibrous protein ($P < 0.001$) and prolongation of prothrombin time ($P < 0.001$) compared to those observed in the patients of NICH group; multivariate analysis, independent risk factors for death in patients with ICH include: WBC $\geq 30.00 \times 109/l$ and prothrombin time ≥ 12.91 s.
Conclusions: Leukocytosis and coagulation dysfunctions might be the main pathogenesis of acute leukemia complicated with cerebral hemorrhage.

1. Introduction

As a devastating disease, intracerebral hemorrhage (ICH) has high rates rate of mortality and morbidity [1]. Approximately 10–23% of strokes are caused by the rupture of cerebral blood vessels [2], and the overall ICH incidence worldwide is 24.6 per 100,000 person-years [3]. ICH is a common complication of cancer [4,5]. As shown by recent studies, the risk of ICH is quite high in cancer patients [6], indicating that cancer itself can directly or indirectly cause the development of cerebral hemorrhage.

In general, ICH is resulted from cancer-related coagulation disorders [7–10]. Notably, ICH in various hematological malignancies in the clinical manifestations of the relative research is relatively limited [11]. This study was designed to explore the risk factors and clinical characteristics of ICH of non-promyelocytic acute myeloid leukemia (AML). We retrospectively reviewed the medical records of patients admitted to the First Hospital of Zhejiang University from 2010 to 2015, and then examined the relationships among likely causes, age, gender, laboratory examination, past medical history, and habits.

2. Patients and methods

2.1. Patient

The ethics committee of the First Hospital of Zhejiang University approved this retrospective analysis. To be specific, we reviewed 90 newly diagnosed patients with non-promyelocytic AML who had consecutive cerebral ICH within 30 days after diagnosis. Furthermore, we retrospectively analyzed the demographic characteristics, underlying medical conditions, hematological disease status, and laboratories, as well as the results of all adult

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patients with non-promyelocytic AML from January 2010 to October 2015 at the First Affiliated Hospital of Medical School of Zhejiang University.

2.2. Treatment

For patients with AML, they were initially treated with a standard "3 + 7" regimen (darubicin/idarubicin + cytarabine). For older patients, CAG regimen (cytarabine + aclarubicin + granulocyte-colony stimulating factor) was administered. The first induced complete remission (CR), the consolidation of the original program once. For some patients aged above 60, four courses of cytarabine 2 g/m^2 (cytarabine at 1 g/m^2) were needed for consolidation therapy. Consolidation chemotherapy consisted of high-dose cytarabine-based regimens. Patients, who were diagnosed with acute lymphoblastic leukemia, received a Cancer and Leukemia Group B 8811 (CALGB8811) [12] or Group for Research on Adult Acute Lymphoblastic Leukemia 2003 (GRAALL 2003) chemotherapy protocol [13].

2.3. Methods

Each patient's ICH diagnosis was determined from both clinical (examination, manifestation, symptoms, and signs) as well as neuroimaging findings. ICH was diagnosed by computed tomography or magnetic resonance imaging. Patients, who were suspected of ICH but not confirmed by imaging, were excluded. The starting point was the diagnosis date of AL, and the primary end point was ICH within 30 days.

2.4. Statistical analysis

The SPSS 19.0 software was used for conducting statistical analysis. The survival rate was estimated by Kaplan-Meier method, and log-rank test was utilized to compare the survival curves between different groups of patients. Moreover, Univariate and multivariate Cox proportional hazards regression models were used to identify risk factors. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Clinical characteristics

Among 1467 patients with non-promyelocytic AL who were treated at our institution between 2010 and 2015, a total of 90 patients (6.1%) developed ICH (47 men and 43 women). This could be seen from the brain CT or MRI diagnosis (AML, n = 77/962, 8.0%; ALL, n = 13/304, 2.6%). The age of the ICH group was 50.74 ± 15.64 years old. Apart from M1, the incidence of cerebral hemorrhage is no different. AL patients with clinical features of cerebral hemorrhage were shown in Tables 1 and 2.

Among the 90 patients with ICH, the proportion of ICH participants in M2 and M5 were 36.7% and 24.4%, respectively. Higher white blood cell count ($P < 0.001$), lower peripheral platelet counts ($P < 0.001$), lower serum albumin ($P < 0.001$), lower fibrinogen ($P < 0.001$) and prolongation of prothrombin time ($P < 0.001$) may be the potential major cause of ICH potential.

The clinical characteristics, including sex, age, hemoglobin, diabetes, hyperlipemia, smoke, drink wine, family history, marrow blasts, creatinine and lactate dehydrogenase, had no statistical difference in patients with different groups (Tables 1 and 2).

Table 1
Clinical characteristics of patients.

Patient characteristics	Result
Totel	228
Age, median (year) (range)	50 (17–89)
Sex	
Male, n (%)	135 (59.2%)
Female, n (%)	93 (40.8%)
FAB classification	
M0, n (%)	19 (8.3%)
M1, n (%)	19 (8.3%)
M2, n (%)	87 (38.2%)
M4, n (%)	9 (3.9%)
M5, n (%)	60 (26.4%)
M6, n (%)	2 (0.9%)
ALL, n (%)	32 (14.0%)
Peripheral blood cells	
Leukocyte ($\times 10^9$/l)	54.19 ± 77.94
Hemoglobin (g/l)	82.21 ± 22.94
Platelet ($\times 10^9$/l)	49.65 ± 47.39
Marrow blasts, n (%)	62.59 ± 23.49
Albumin (g/L)	38.64 ± 5.13
Creatinine (umol/L)	65.32 ± 25.10
Lactate dehydrogenase (u/L)	777.50 ± 1642.69
Coagulation function	
Fibrinogen (g/L)	2.92 ± 1.35
Activated partial thromboplastin time (s)	30.69 ± 9.28
Prothrombin time (s)	12.91 ± 2.12
Anamnesis	
Hypertension, n (%)	30 (13.2%)
Diabetes, n (%)	12 (5.3%)
Hyperlipemia, n (%)	61 (26.8%)
Habits and customs	
Smoke, n (%)	56 (24.6%)
Drink wine, n (%)	31 (13.6%)
Family history, n (%)	0

Table 2
Clinical characteristics of Patients with Intracranial Hemorrhage (ICH).

	ICH group (n = 90)	No ICH Group (n = 138)	*P* value
Age (mean ± SD), year	50.74 ± 15.64	49.04 ± 15.87	0.427
Sex			
Male, n (%)	47 (52.2)	88 (63.3)	0.096
Female, n (%)	43 (47.8)	50 (36.7)	
FAB classification			
M0, n (%)	6 (6.7)	13 (9.4)	0.472
M1, n (%)	13 (14.4)	6 (4.3)	0.007
M2, n (%)	33 (36.7)	54 (38.8)	0.740
M4, n (%)	2 (2.2)	7 (5.0)	0.284
M5, n (%)	22 (24.4)	38 (27.3)	0.627
M6, n (%)	1 (1.1)	1 (0.7)	0.756
ALL, n (%)	13 (14.4)	19 (13.7)	0.869
Peripheral blood cells			
Leukocyte ($\times 10^9$/l)	86.63 ± 98.26	33.04 ± 51.48	0.0001
Hemoglobin (g/l)	79.22 ± 21.91	84.16 ± 23.46	0.112
Platelet ($\times 10^9$/l)	36.14 ± 30.68	58.46 ± 53.96	0.0004
Marrow blasts, n (%)	65.58 ± 27.03	61.59 ± 21.80	0.220
Albumin (g/L)	35.77 ± 4.71	39.14 ± 5.26	0.0001
Creatinine (umol/L)	71.06 ± 21.94	66.67 ± 22.11	0.142
Lactate dehydrogenase (u/L)	690.45 ± 572.18	621.52 ± 653.55	0.414
Coagulation function			
Fibrinogen (g/L)	2.15 ± 1.43	3.22 ± 1.21	0.0001
Activated partial thromboplastin time (s)	32.04 ± 10.65	29.81 ± 8.19	0.076
Prothrombin time (s)	14.01 ± 2.32	12.19 ± 1.62	0.0001
Anamnesis			
Hypertension, n (%)	10 (11.1)	20 (14.4)	0.473
Diabetes, n (%)	3 (3.3)	9 (6.5)	0.297
Hyperlipemia, n (%)	21 (23.3)	40 (28.8)	0.363
Habits and customs			
Smoke, n (%)	17 (18.9)	39 (28.1)	0.115
Drink wine, n (%)	9 (10.0)	22 (15.8)	0.208
Family history, n (%)	0 (0)	0 (0)	