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Difference in clinical features between Japanese and German patients with refractory anemia

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Differences between Japanese and German patients in RA

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Abstract

Several reports indicate that there might be differences in clinical features between Asian and Western myelodysplastic syndromes (MDS) cases. We analyzed refractory anemia (RA) in the French-American-British (FAB) classification cases diagnosed in Japan and Germany in order to perform a more exact comparison between Asian and Western MDS types. In the first step, we analyzed the concordance rate of morphological diagnosis between Japanese and German hematologists. The blood and bone marrow slides of 129 patients with MDS or aplastic anemia (AA) diagnosed by Japanese or German groups were selected randomly, and evaluated separately by Japanese and German groups. The concordance rate of morphological diagnosis was 98.4%. Secondly, we compared clinical features between 131 Japanese and 597 German FAB-RA patients. The median age of Japanese patients was younger than that of German patients (Japan:57 years, Germany:71 years, $p<0.0001$). Japanese patients had severer cytopenias. However, the prognosis of Japanese patients was more favorable than that of German patients (median overall survival Japan: 175 months, Germany: 40 months, $p<0.0001$). German patients had a higher cumulative risk of acute leukemia evolution than Japanese patients ($p=0.0027$). In conclusion, our results indicate that the clinical features of Japanese FAB-RA patients differ from those of German patients.

Introduction

Myelodysplastic syndromes (MDS) are acquired clonal stem cell disorders characterized by ineffective hematopoiesis with myelodysplasia[1] and are associated with a high risk of progression to acute leukemias.[2] MDS are very heterogeneous in terms of their morphology, clinical features and survival.[3] Refractory anemia (RA) according to the French-American-British (FAB) classification is generally classified as a low-risk group in MDS[4], comprising 30-50% of all MDS cases. It was reported that the International Prognostic Scoring System (IPSS) was useful for assessing the prognosis in the whole group of MDS patients according to the FAB classification.[5]

There are several reports that indicate possible differences in clinical features between Western MDS types and Eastern MDS types. It has been reported that the median age of Japanese MDS patients is 60 years.[6] The median age of MDS patients in Korea and Thailand and the mean age of those in Central Africa were reported to be 57[7], 56[8] and 57 years[9], respectively. On the other hand, large MDS studies from Western countries showed a median or mean age of 68 to 73 years.[5,10-12] Previous reports also indicated that Japanese MDS patients had a lower frequency of FAB-RARS and a higher frequency of FAB-RA than the Western IPSS study[13,14] and that there were different prognostic factors between Japanese and Western MDS patients.[6,13] In cytogenetic analysis, it was indicated that the frequency of Japanese MDS with isolated del(5q) was lower than that in the IPSS study.[14] We additionally reported that FAB-RA patients demonstrated favorable outcomes compared to those of the IPSS study.[13] We consider that there are different clinical features between Asian and Western MDS patients. In the present study, we compared the clinical features of Japanese and German patients in FAB-RA in detail, after first confirming that the interpretation of myelodysplasia was consistent between the Japanese and German groups.

Patients and methods

Patients

A total of 728 consecutive patients (Japan:131 cases, Germany:597 cases) with a diagnosis of primary RA were included in this retrospective analysis. Japanese patients were diagnosed at the Saitama Medical School Hospital, Nagasaki University Hospital or affiliated hospitals in Japan between January 1976 and October 1996. German patients were diagnosed at the Department of Hematology, Oncology and Clinical Immunology of the Heinrich-Heine University in Germany between 1975 and 1999. Patients who had previously been treated with antineoplastic drugs or ionizing radiation were excluded from the study.

Interobserver variation study

Hematological examinations were performed using standard methods (peripheral blood (PB) and bone marrow (BM) Wright-Giemsa or May-Giemsa stained films). PB and BM differential counts were performed on 100 and 500 cells, respectively. The concordance rate of morphological diagnosis between Japanese and German hematologists was analyzed. In this analysis, the slides of 129 patients (110 FAB-RA, 7 FAB-RARS, 12 aplastic anemia (AA) diagnosed by Japanese or German groups were selected randomly, and were evaluated separately by the Japanese and German groups. The observers were blinded to the clinical and laboratory data including cytogenetics, until the morphologic review was complete.

Cytogenetic analysis

Cytogenetic analyses were performed with a trypsin-Giemsa banding technique on BM cells from aspirates. Ordinarily 20 to 30 metaphases were examined. Cytogenetic aberrations were grouped according to the IPSS publication.[5]

Clinical studies

Comparisons of the clinical features and the prognostic factors between 131 Japanese and 597 German

FAB-RA patients were analyzed. Patients were followed for overall survival (OS) and leukemic progression through June 2004 in Japanese cases and July 2003 in German cases.

Statistical methods

The Kaplan-Meier method was used to estimate the probability of OS and the cumulative risk of acute myelogenous leukemia (AML) evolution. Statistical comparisons were performed by use of the nonparametric Mann-Whitney test for continuous data. Patient characteristics were compared using the χ^2 test. Univariate analysis of each clinical variable was analyzed using the Kaplan-Meier method and log rank test.

Results

Morphological consensus

Of the 129 cases reviewed, the concordance rate of morphological diagnosis according to FAB classification between Japanese and German hematologists was 98.4%. There were 2 cases whose diagnoses did not agree between Japanese and German hematologists. One case was diagnosed as AA by Japanese group, but the diagnosis by German group was FAB-RA. The final diagnosis of this case as AA was reached by consensus among the Japanese and German groups by joint review. Another case was diagnosed as RA with excess of blasts by the Japanese group, but the diagnosis by the German group was FAB-RA. The final diagnosis of this case as FAB-RA was reached by consensus among the Japanese and German groups by joint review.

Comparison of clinical features and prognostic factors between Japanese and German FAB-RA patients

The median age of Japanese FAB-RA patients was younger than that of German FAB-RA patients (Japan:57 years, Germany:71 years, $p<0.0001$). The gender ratios (female : male) were 1.14 in Japan and 1:1.07 in Germany. Japanese FAB-RA patients had lower absolute neutrophil counts (ANC) (Japan:1.8±1.3 $x10^9$/L, Germany:2.9±2.9, $p<0.0001$), lower hemoglobin (Hb) concentration (Japan:8.6±2.9 g/dL, Germany:9.4±2.4,

p=0.0016), lower platelet (PLT) counts (Japan:66±71 x10^9/L, Germany:180±175, p<0.0001) and higher frequency of 2 or 3 lineage cytopenias according to the IPSS definition than German FAB-RA patients (Japan:68%, Germany:37%, p<0.0001)(**Table 1**). Cytogenetic analysis was performed in 102 Japanese and 199 German patients. In the Japanese FAB-RA group, the frequency of cytogenetic abnormalities was 29 patients (28%). In contrast, cytogenetic abnormalities were found in 101 (51%) of the German FAB-RA patients. Japanese FAB-RA patients had a lower frequency of cytogenetic abnormalities than German FAB-RA patients (p=0.0002). The subgroups of cytogenetic abnormalities according to IPSS are summarized in **Table 2**. The distribution of the cytogenetic subgroups according to IPSS showed no significant difference between Japanese and German FAB-RA patients. Japanese FAB-RA patients had a lower frequency of FAB-RA associated with an isolated del(5q) cytogenetic abnormality (5q- syndrome) than German FAB-RA patients (Japan:5.9%, Germany:19.6%, p=0.0032).

Follow-up periods ranged from 1 to 292 months (median 69 months) in Japanese FAB-RA patients. Follow-up periods in German FAB-RA patients ranged from 0 to 313 months (median 13 months). Japanese FAB-RA patients had a more favorable prognosis than German FAB-RA patients (median survival Japan:175 months, Germany:40 months, p<0.0001) (**Figure 1A**). For those aged less than 60 or 40 years, Japanese FAB-RA patients had a more favorable prognosis than German FAB-RA patients (p<0.0001) (**Figure 1B-C**). German patients had a higher cumulative risk of AML evolution than Japanese patients (P=0.0027) (**Figure 2**).

In Japanese FAB-RA patients, the clinical variables of age >60 years old (p<0.0001) and Hb <7g/dL (p=0.0145) were significantly correlated with OS. Gender, Hb <10g/dL, PLT<100 x10^9/L, ANC<1.5 x10^9/L, cytopenias (2 or 3 lineages) and IPSS cytogenetic subgroups were not significantly correlated with OS (**Table 3A**). In German FAB-RA patients, age >60 years old (p<0.0001), Hb < 10g/dL (p=0.0003), PLT < 100 x10^9/L (p<0.0001), cytopenias (2 or 3 lineages) (p<0.0001) and IPSS cytogenetic subgroups (p<0.0001) were

significantly correlated with OS. Gender, and ANC <1.5 x10^9/L were not significantly correlated with OS (**Table 3B**). The IPSS cytogenetic subgroups (p=0.0007) and IPSS subgroup (p=0.0007) were significantly correlated with cumulative risk of AML evolution in Japanese FAB-RA patients (**Table 3A**). The other clinical variables in Table 3A were not significantly correlated with cumulative risk of AML evolution. ANC <1.5 x10^9/L (p=0.0142), PLT < 100 x10^9/L(p=0.0008), cytopenias (2 or 3 lineages) (p<0.0001), IPSS cytogenetic subgroups (p=0.0002) and IPSS subgroup (p<0.0001) were significantly correlated with cumulative risk of AML evolution in German FAB-RA patients. Age, Gender, Hb concentrations were not significantly correlated with cumulative risk of AML evolution (**Table 3B**).

Discussion

Different clinical features between Asian and Western MDS patients have been reported by several studies.[6,13] These data are based on local series of patients without central morphological reviewing. Speculation about certain differences is problematic because there might be differences in the interpretation of dysplasia in blood and bone marrow by different observers. The present study aimed to characterize the racial features of Western and Asian MDS cases. We thought that an assessment of interpretation of morphologic findings and definition of diagnostic criteria was warranted to check that the diagnoses by the Japanese group were in line with those of the German group, before comparing the clinical features between Japanese and German FAB-RA patients. In the present study, the concordance rate of morphological diagnosis between Japanese and German hematologists was 98.4%. It was confirmed that the diagnoses according to FAB classification or AA were not different between the Japanese and German groups.

Comparing Japanese and German FAB-RA cases we found that the median age of Japanese FAB-RA patients was lower than that of German FAB-RA patients. The population pyramids and life expectancies in

Japan and Germany are almost the same (http://www.census.gov/ipc/www/idbpyr.html). Therefore, we think that this difference of median age is real. Furthermore, Japanese FAB-RA patients had more pronounced cytopenia, especially more severe thrombocytopenia and a higher frequency of pan- or bicytopenia, as compared to German RA patients. Also the cytogenetic characteristics differed between Japanese and German RA cases. Although there was no difference in the distribution of cytogenetic subgroups according to IPSS, the frequency of chromosomal abnormalities was lower in Japanese RA patients; notably that of isolated del(5q) was lower in Japan. Regardless of age, Japanese FAB-RA patients had a more favorable prognosis than their German counterparts. Japanese patients had a lower cumulative risk of AML evolution than German patients. Our results indicate that the clinical features of Japanese FAB-RA cases differ from those of German cases.

In the present study, IPSS was useful for assessing OS in German FAB-RA cases but not in Japanese FAB-RA cases. This was mainly due to the lack of a significant correlation between the number and degree of cytopenias and OS in Japanese FAB-RA patients. Management of thrombocytopenia seems to be similar between Japan and Germany. Concerning the prognostic impact of Hb concentration, the threshold was different between Japanese and German FAB-RA patients. Most of the Japanese patients with Hb level greater than 7 g/dL had no symptoms related to anemia and did not require red cell transfusion. In fact, most Japanese patients with Hb level lower than 7 g/dL had received red cell transfusion. In contrast, most German patients with Hb level lower than 9 g/dL had received red cell transfusion. We presumed that the cause of the different prognostic Hb level thresholds by Japanese and German patients may be related to these red cell transfusion procedures. We also presume that the difference in Hb concentration used as a threshold for red cell transfusion may be related to the different general characteristics among races rather than the different characteristics of FAB-RA between Asian and Western FAB-RA patients. The Italian guideline recommends that all patients with Hb concentration lower than 8 g/dL should receive red cell transfusion.[15] Japanese FAB-RA patients with Hb

concentration greater than 7 g/dL do not usually require regular red cell transfusion. We compared Japanese RA patients with Hb concentrations greater than 10 g/dL and those with Hb concentrations of 7-10 g/dL. In fact, the latter group (7-10 g/dL) did not differ in clinical course from patients with Hb concentrations greater than 10 g/dL (p=0.8575). Moreover, Japanese patients with Hb concentrations of 7-10 g/dL had a more favorable prognosis than those with Hb concentrations lower than 7 g/dL (p=0.0389) (**Figure 2**). This result indicates that the Hb threshold below which transfusion is recommended may be different between Asian and Western FAB-RA patients.

We think that our results concerning the prognostic OS impact of chromosomal findings may be insufficient and may include some problematic issues. In particular, the observation periods of Japanese patients with 'poor risk karyotype' according to IPSS may be problematic. Four out of 8 Japanese patients with 'poor risk karyotype' are surviving. However, the observation periods of the 2 surviving patients were insufficient (1 and 6 months, respectively). Concerning AML evolution, the impact of chromosomal findings was not different between Japanese and German patients. We think that the prognostic impact on OS of chromosomal findings may be not different between Japanese and German patients, if sufficient observation periods for Japanese patients with 'poor risk karyotype' are available.

A few studies have shown that, according to the World Health Organization (WHO) classification[16], most FAB-RA patients are classified as refractory cytopenia with multilineage dysplasia (RCMD) or, less frequently, as WHO-RA. It was reported that WHO-RA patients had more favorable prognoses than RCMD patients.[17-19] The original diagnoses according to the WHO classification by each group in the present series show that the frequency of WHO-RA in Japanese patients (approximately 65%) was higher than in German patients (approximately 25%) (detailed data not shown). Although there is still no confirmation of consensus between the two groups concerning WHO classification among Japanese and German hematologists, this finding

indicates that one reason for the better prognosis of Japanese patients may be the different distribution of subgroups by WHO classification between Asian and Western FAB-RA patients, namely a higher frequency of WHO-RA patients in Japan.

This is the first report to compare clinical features between Asian and Western FAB-RA patients after confirming a morphological consensus. Our results indicate that the clinical features of Japanese FAB-RA cases differ from those of German cases. These differences are not due to the different interpretation of morphologic features by different observers. Several guidelines[15,20] have been published in Western countries. In order to adapt these Western guidelines to Asian patients, some modifications may be required by taking into account ethnic characteristics.

Figure legends

Figure 1.

Cumulative overall survival of FAB-RA patients. (A) Japanese patients had more favorable prognoses than German patients ($p<0.0001$). (B) Among patients less than 60 years old, Japanese patients had more favorable prognoses than German patients ($p<0.0001$). (C) Among patients less than 40 years old, Japanese patients had more favorable prognoses than German patients ($p<0.0001$).

Figure 2.

Cumulative risk of acute leukemia evolution of FAB-RA patients. Japanese patients had a lower cumulative risk of acute leukemia evolution than German patients ($P=0.0027$).

Figure 3.

Cumulative overall survival of Japanese FAB-RA patients. The group with hemoglobin of 7-10 g/dL showed no significant prognostic difference from the group with hemoglobin greater than 10 g/dL in Japanese FAB-RA patients ($p=0.8475$). The group with hemoglobin of 7-10 g/dL had a more favorable prognosis than the group with hemoglobin lower than 7 g/dL in Japanese FAB-RA patients ($p=0.0389$).

Table 1. Clinical and laboratory features at the time of diagnosis in patients with RA classified according to the FAB criteria

	Japan	Germany	p value
Patients = n	131	597	
Gender(Male/Female)	70/61	309/288	NS
Median age, y (range)	57 (12-88)	71 (7-93)	p<0.0001
Neutrophils ($x10^9$/L)	1.8±1.3	2.9±2.9	p<0.0001
Hemoglobin (g/dL)	8.6±2.9	9.4±2.4	p=0.0016
Platelets ($x10^9$/L)	66±71	180±175	p<0.0001
2 or 3 lineage cytopenias* (%)	68	39	p<0.0001
Abnormal Karyotype (%)	28	51	p=0.0002
Median survival (Months)	175	40	p<0.0001

*cytopenia according to IPSS: hemoglobin concentration<10g/dL, absolute neutrophil count<$1.5x10^9$/L, platelet count<$100x10^9$/L.
NS indicates not significant.

Table 2. Cytogenetic findings at the time of diagnosis in patients with RA classified according to the FAB criteria

	Japan	Germany	p value
Patients = n	102	199	
Good	78(76.4%)	143(71.8%)	p=0.5192
Intermediate	16(15.7%)	31(15.6%)	
Poor	8(7.9%)	25(12.6%)	

Good, normal, -Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

Table 3-A. Univariate analysis of overall survival and cumulative risk of acute leukemia in Japanese patients with RA classified according to the FAB criteria

variable	No. of patients	Percentile of OS (months)		p value	Percentile of Cumulative risk of AML (months)			p value
		75%	50%		10%	25%	50%	
Age (y)								
≤60	72	114	217	p<0.0001	NR	NR	NR	p=0.1195
>60	59	18	59		51	NR	NR	
Gender								
Male	70	42	176	p=0.8524	74	NR	NR	p=0.5288
Female	61	53	129		104	NR	NR	
Neutrophils								
<1.5 x10^9/L	63	52	157	p=0.8432	51	NR	NR	p=0.1629
≥1.5 x10^9/L	68	53	176		NR	NR	NR	
Hemoglobin								
<10 g/dL	81	52	114	p=0.2372	92	NR	NR	p=0.9453
≥10 g/dL	50	53	202		38	NR	NR	
Hemoglobin								
<7 g/dL	45	23	100	p=0.0145	104	NR	NR	p=0.8139
≥7 g/dL	86	62	202		92	NR	NR	
Platelets								
<100 x10^9/L	109	52	175	p=0.3705	92	NR	NR	p=0.3536
≥100 x10^9/L	22	54	109		14	NR	NR	
Cytopenias (IPSS)								
0/1	42	53	202	p=0.8396	NR	NR	NR	p=0.8329
2/3	89	52	157		92	NR	NR	
Chomosome (IPSS)								
Good	78	76	176	p=0.1421	104	NR	NR	p=0.0007
Int	16	19	129		NR	NR	NR	
Poor	8	27	102		4	37	NR	
IPSS*								
Low	21	76	202	p=0.2913	NR	NR	NR	p=0.0007
INT-1	73	52	175		104	NR	NR	
INT-2	8	27	102		4	22	NR	

Variable are defined in Table 1,2.

Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0 according to IPSS score.

OS, overall survival; LFS, leukemia free survival; NR, not reached.

Table 3-B. Univariate analysis of overall survival and cumulative risk of acute leukemia in German patients with RA classified according to the FAB criteria

variable	No. of patients	Percentile of OS (months)		p value	Percentile of Cumulative risk of AML (months)			p value
		75%	50%		10%	25%	50%	
Age (y)								
≤60	133	26	66	p<0.0001	13	91	NR	p=0.8538
>60	461	14	35		21	136	173	
Gender								
Male	309	16	41	p=0.9180	21	78	173	p=0.4097
Female	288	16	43		19	NR	NR	
Neutrophils								
<1.5 x10^9/L	162	14	43	p=0.5371	17	52	173	p=0.0142
≥1.5 x10^9/L	301	16	37		25	NR	NR	
Hemoglobin								
<10 g/dL	337	9	30	p=0.0003	14	136	NR	p=0.1782
≥10 g/dL	217	23	57		42	173	NR	
Hemoglobin								
<9 g/dL	235	8	29	p=0.0002	17	136	NR	p=0.1510
≥9 g/dL	319	20	51		40	173	NR	
Platelets								
<100 x10^9/L	207	9	23	p<0.0001	11	50	136	p=0.0008
≥100 x10^9/L	339	23	53		35	NR	NR	
Cytopenias (IPSS)								
0/1	288	23	55	p<0.0001	63	NR	NR	p<0.0001
2/3	188	7	22		10	28	136	
Chomosome (IPSS)								
Good	143	27	66	p=0.0009	25	NR	NR	p=0.0002
Int	31	26	44		10	91	91	
Poor	25	7	16		4	14	52	
IPSS*								
Low	82	43	82	p<0.0001	NR	NR	NR	p<0.0001
INT-1	78	12	31		10	27	91	
INT-2	11	4	7		2	5	52	

Variable are defined in Table 1,2.

Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0 according to IPSS score.

OS, overall survival; LFS, leukemia free survival; NR, not reached.

Figure 1A

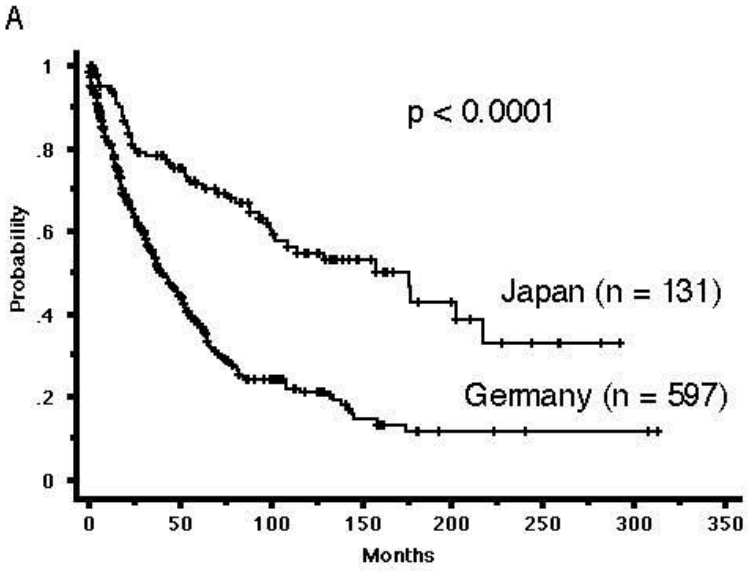

A
p < 0.0001
Japan (n = 131)
Germany (n = 597)
Probability
1
.8
.6
.4
.2
0
0
50
100
150
200
250
300
350
Months

Figure 1B

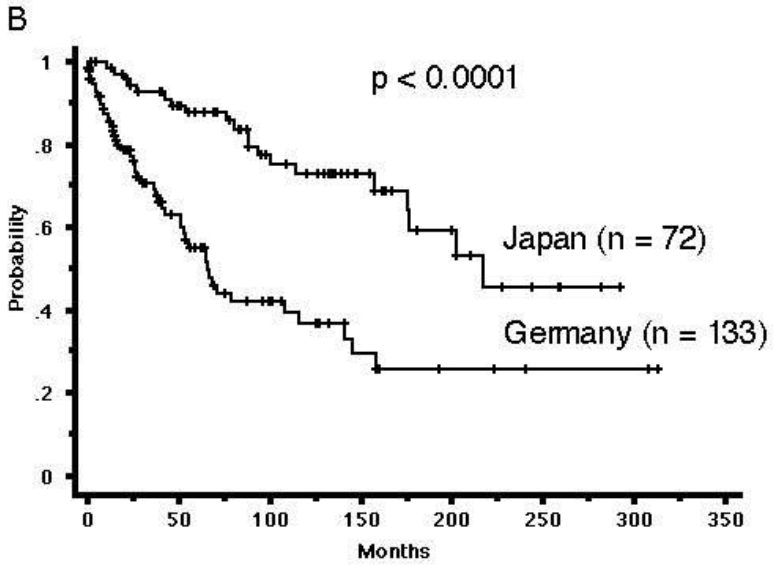

B
p < 0.0001
Japan (n = 72)
Germany (n = 133)
Probability
1
.8
.6
.4
.2
0
0
50
100
150
200
250
300
350
Months

Figure 1C

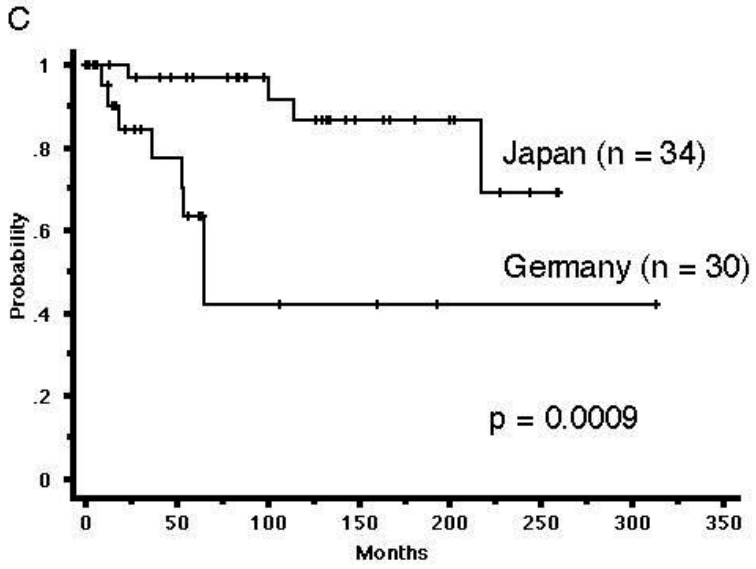

C
1
.8
.6
.4
.2
0
Probability
0
50
100
150
200
250
300
350
Months
Japan (n = 34)
Germany (n = 30)
p = 0.0009

Figure 2

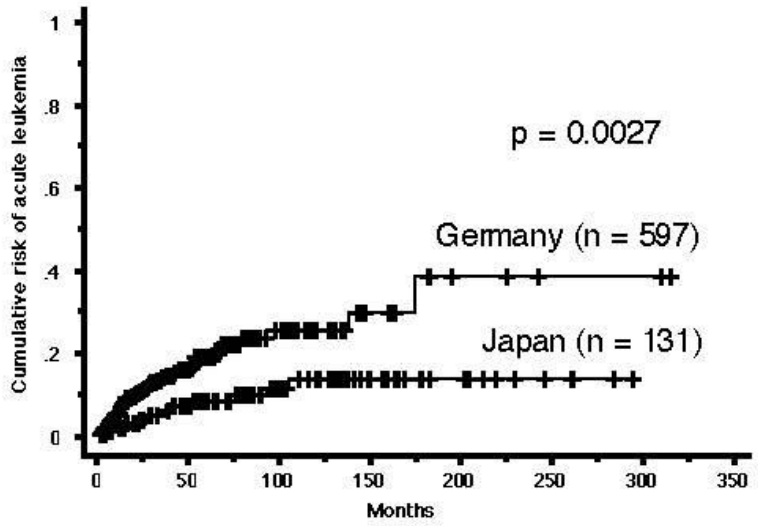
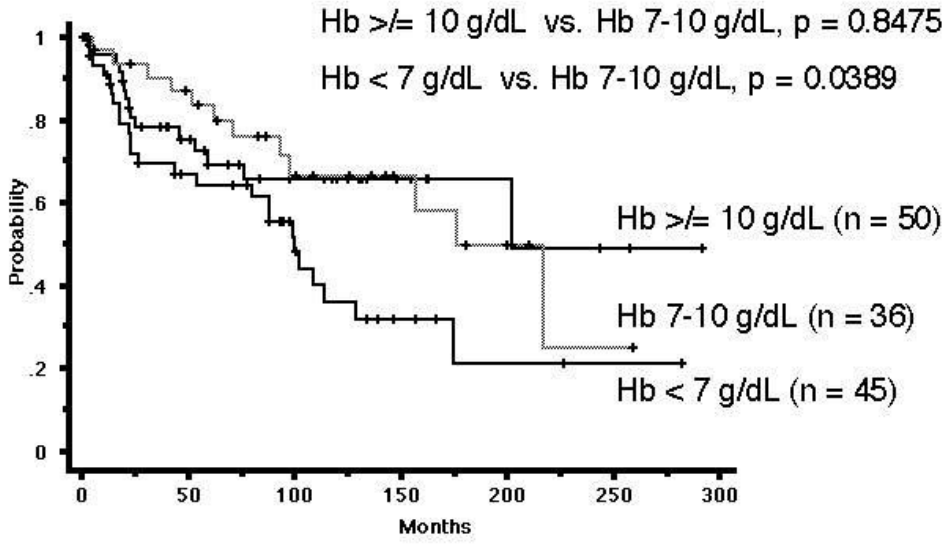

Cumulative risk of acute leukemia
1
.8
.6
.4
.2
0
p = 0.0027
Germany (n = 597)
Japan (n = 131)
0
50
100
150
200
250
300
350
Months

Figure 3


Hb >/= 10 g/dL vs. Hb 7-10 g/dL, p = 0.8475
Hb < 7 g/dL vs. Hb 7-10 g/dL, p = 0.0389
Hb >/= 10 g/dL (n = 50)
Hb 7-10 g/dL (n = 36)
Hb < 7 g/dL (n = 45)
Probability
1
.8
.6
.4
.2
0
0
50
100
150
200
250
300
Months

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