Impact of additional chromosomal abnormalities in patients with acute promyelocytic leukemia: 10-year results of the Japan Adult Leukemia Study Group APL97 study

The t(15;17) chromosome translocation in acute promyelocytic leukemia is classified as a favorable cytogenetic feature among acute myeloid leukemia patients.[1-4] However, the prognostic impact of additional chromosomal abnormalities (ACAs) in acute promyelocytic leukemia has been debated.[5-9] We analyzed the clinical features, biological markers and clinical outcome of Japanese acute promyelocytic leukemia patients with or without ACAs who were treated by all-*trans* retinoic acid (ATRA) and chemotherapy, and tried to determine the role of ACAs on a 10-year follow up.

Adult patients with previously untreated *de novo* acute promyelocytic leukemia were registered consecutively into the JALSG APL97 study.[4] This study was approved by the institutional review boards of each participating institution and registered at *http://www.umin.ac.jp/ctrj/* under C000000206. Informed consent was obtained from patients before registration in the study in accordance with the Declaration of Helsinki.

Chromosomes analyzed by G-banding on bone marrow samples from patients before treatment were classified according to the 1995 International System for Human Cytogenetic Nomenclature (ISCN). Patients were categorized into two groups: those with t(15;17) and ACAs, and those with t(15;17) but without ACAs. Patients with der(17)t(15;17), der(15)t(15;17) or three-way translocation were placed in the group with ACAs.

Details of treatment protocol have been described previously.[4] In brief, remission induction consisted of ATRA and chemotherapy including idarubicin and cytarabine. Dose and duration of chemotherapy were based on initial leukocyte count. After completion of consolidation chemotherapy, patients negative for the *PML-RARA* tran-

Table 1. Clinical features of patients.

	Total		t(15;17)		t(15;17) with ACAs		
Parameters	N.(%)	Median (range)	N.(%)	Median (range)	N.(%)	Median (range)	*P*
N. of patients	225		158		67		
Age, years		48 (15-70)		49 (15-70)		45 (19-70)	0.08
15-29	39 (17%)		21 (13%)		18 (27%)		
30-49	84 (37%)		62 (39%)		22 (33%)		0.06
50-70	102 (46%)		75 (48%)		27 (40%)		
Gender							0.24
Male	122 (54%)		90 (57%)		32 (48%)		
Female	103 (46%)		68 (43%)		35 (52%)		
Leukocyte count, $\times 10^9$/L		1.7 (0.03-256)		1.65 (0.03-256)		1.7 (0.4-70.9)	0.77
Less than 3.0	135 (60%)		93 (59%)		42 (63%)		
3.0-10.0	48 (21%)		31 (20%)		17 (26%)		0.21
10.0 or higher	42 (19%)		34 (21%)		8 (12%)		
Platelet count, $\times 10^9$/L		29 (2-238)		30 (2-238)		29 (3-180)	0.69
Less than 10	31 (14%)		26 (16%)		5 (7.4%)		
10-40	10 (48%)		71 (45%)		38 (57%)		0.12
40 or higher	85 (38%)		61 (39%)		24 (36%)		
DIC score*	n = 213	6 (0-12)	n = 151	6 (0-12)	n = 62	6 (0-11)	0.46
3 or higher	198		139 (92%)		59 (95%)		
10 or higher	12		16 (11%)		5 (8%)		
FAB subtype							0.04
Typical	210 (93%)		144 (91%)		66 (99%)		
Variant	15 (7%)		14 (9%)		1 (1%)		
CD56 expression	n = 192		n = 128		n = 64		0.45
positive	19 (10%)		11 (9%)		8 (13%)		
negative	173 (90%)		117 (91%)		56 (87%)		
Peripheral blood count, $\times 10^9$/L							
leukocyte < 10, platelet > 40	72 (32%)		51 (32%)		21 (31%)		
leukocyte < 10, platelet < 40	112 (50%)		74 (47%)		38 (57%)		0.22
leukocyte > 10	41 (18%)		33 (21%)		8 (12%)		
Incidence of secondary							
MDS/AML	5 (2%)		4 (3%)		1 (1%)		0.63

*FAB: French-American-British; EFS: event free survival; RFS: relapse free survival. NA: not applicable; *DIC score, Score 3 indicates suspected DIC; scores from 4 to 10, definitive DIC; score 10 or more, severe DIC.*

script were randomly allocated either to receive 6 courses of intensified maintenance chemotherapy or to observation. Patients who were positive for the *PML-RARA* fusion transcript received late ATRA therapy followed by maintenance therapy, and received allogeneic hematopoietic stem cell transplantation if they had a human leukocyte antigen-identical donor.

Hematologic response was evaluated by standard criteria according to a previous report.[2] Hematologic and molecular relapse detected by RT-PCR analysis of *PML-RARA* was considered a relapse event.

The primary end point of the JALSG APL97 study was overall survival and disease free survival of patients who achieved complete remission. Overall survival for all patients was calculated from the first day of therapy to death or last visit. Disease free survival was measured from the date of complete remission to relapse, death from any cause or last visit. We also evaluated overall and disease free survival from the time of randomization to maintenance chemotherapy or observation.

Clinical and biological characteristics were compared between patients with or without ACAs by the χ^2 test or Fisher's exact test for categorical data, and Wilcoxon's rank-sum test for continuous data. Overall and disease free survival were estimated by the Kaplan-Meier method and then compared by the log rank test. Clinical outcomes were updated on January 2009 and the median follow-up period is 7.3 years. Statistical analyses were performed using SPSS 11.0 software (SPSS Inc, Chicago, IL, USA).

Among 302 patients enrolled between May 1997 and June 2002, 283 patients were evaluable.[4] Of these, 58 patients were excluded because of insufficient data for ACAs status. Thus, the present analysis was carried out on 225 patients.

Sixty-seven (30%) of 225 patients had ACAs. Trisomy 8 was the most frequently observed ACA and detected in 21 cases (31%). Seven cases (11%) had ACAs in chromosome 15 in addition to t(15;17), 6 (9%) in chromosome 9, 6 (9%) in chromosome 7, 4 (6%) in chromosome 15, and 4 (6%) in chromosome 6. There was no significant difference in clinical or biological characteristics between the two groups, except the frequency of M3v (1% *vs.* 9%, *P*=0.04) (Table 1).

Complete remission rates in patients with or without ACAs were 97% and 95%, respectively (*P*=0.72). There was no difference in cumulative incidence of early death at 50 days, severe hemorrhagic complication or retinoic acid syndrome between the two groups (*P*=0.16, *P*=0.46 and *P*=0.16, respectively). There was also no difference in overall survival, disease free survival or cumulative incidence of relapse between the two groups (91% *vs*. 84%, *P*=0.18; 68% *vs.* 71%, *P*=0.59; 26% *vs*. 22%, *P*=0.51, respectively). Overall and disease free survival are shown in Figure 1A and B. In addition, clinical outcome was analyzed among subgroups of patients with ACAs. However, ACAs including chromosome 8, 7, 9, 15 and 17 did not influence outcomes.

Clinical and biological characteristics have been compared between patients with or without ACAs. ACAs have been detected in 26% to 33% of newly diagnosed acute promyelocytic leukemia patients in whom trisomy 8 was consistently the most frequent ACA.[5-9] In this study, 67 patients (30%) had ACAs, and trisomy 8 was the most frequent (31%). There was no significant difference in overall survival, disease free survival or relapse rate between patients with or without trisomy 8.

The frequency of M3v was significantly lower among our patients with ACAs. This agrees with the report by Schoch *et al.*,[10] although several previous studies showed that the morphology of M3v was not related to the presence of ACAs.[5,6,8] The inconsistency of these results may be caused by a considerably smaller number of M3v cases (16% to 27% of APL). Some authors have reported that the morphology of M3v is related to fms-like tyrosine kinase 3 mutations.[8,11,12] Future analysis of this with ACAs is needed.

Several authors have discussed the clinical importance of ACAs in acute promyelocytic leukemia patients treated with ATRA and chemotherapy. Cervera *et al.*[9] found in the LPA99 trial that ACAs were associated with lower relapse free survival in univariate analysis but not in mul-

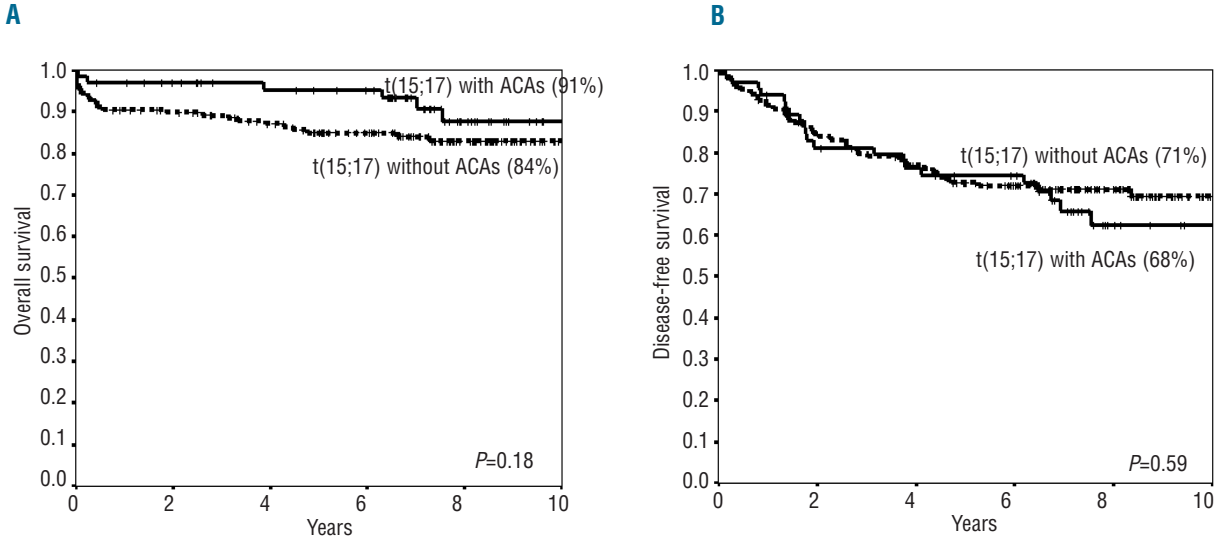

Figure 1. Overall survival and disease free survival of APL patients between with or without additional chromosomal abnormalities in addition to t(15;17). (A) Overall survival (91% *vs.* 84% at 10 years, *P*=0.18), (B) Disease-free survival (68% *versus* 71% at 10 years, *P*=0.59) were similar between two groups.

tivariate analysis. Schlenk *et al.*[8] analyzed 82 patients and reported that ACAs were an unfavorable prognostic marker for overall survival due to early death during the induction therapy. On the contrary, Botton *et al.*[6] and Hernandez *et al.*[7] reported that ACAs had no impact on clinical outcome. In our study, ACAs also did not show any prognostic significance. One of the reasons for this discrepancy would be that the clinical outcome of acute promyelocytic leukemia has recently improved dramatically. The outcome of each subgroup has also been greatly improved, although with some limitations, because patients have been stratified according to risk factors and consequently recent studies have used risk-adapted therapies. Thus, it may become more difficult to identify prognostic factors in acute promyelocytic leukemia.

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