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PROGNOSTIC IMPLICATIONS OF ADDITIONAL CHROMOSOME ABNORMALITIES AMONG PATIENTS WITH DE NOVO ACUTE PROMYELOCYTIC LEUKAEMIA WITH t(15;17)

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Summary

This retrospective study performed by the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group (SWOG) enrolled 140 acute promyelocytic leukaemia (APL) patients with t(15;17) to determine the influence of additional karyotypic abnormalities on treatment outcome. Karyotypes were centrally reviewed by both study groups. The complete response (CR) rate after induction for patients with t(15;17) treated with chemotherapy, or all-trans retinoic acid (ATRA) as induction therapy was not affected by additional cytogenetic aberrations. Disease-free (DFS) and overall survival (OS) were unaffected by additional cytogenetic abnormalities if treatment was chemotherapy without ATRA. Patients with t(15;17) only, treated with ATRA with or without chemotherapy, had an improved DFS (P=0.06) and a better OS (P=0.01) compared with ATRA-treated patients with additional cytogenetic abnormalities. Patients with APL and t(15;17) alone are significantly more sensitive to treatment with ATRA than are patients with t(15;17) and additional cytogenetic abnormalities.

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Authorship

PHW Suggested the study, coordinated it, and wrote the ms. Z S and HTK performed the statistical analyses. HG collected the SWOG cytogenetic data. GD reviewed the ECOG karyotypes and accepted or rejected cases. MLS reviewed the SWOG karyotypes and accepted or rejected cases. EP contacted individual investigators for karyotype prints for central review (ECOG) and coordinated data collection. FRA, PAC, MST and PHW were instrumental in the design of the clinical trials that provided data for this study.

Keywords

acute promyelocytic leukemia; karyotype; all-trans retinoic acid; t(15;17)

Karyotype evolution is usually considered a marker of disease progression in hematologic malignancies. Abnormal clones with complex karyotypes (3 or more numerical and/or structural chromosome aberrations) occur in 10% of adults with acute myeloid leukaemia (AML) and confer a poor prognosis (1). This retrospective Eastern Cooperative Oncology Group (ECOG) and Southwest Oncology Group (SWOG) study was performed to determine whether the outcome of treatment of acute promyelocytic leukaemia (APL) patients with t(15;17)(q22;q21) is influenced by additional chromosome alterations. There are conflicting data in the literature on this point. Identification of an unfavorable subgroup among these patients would encourage the testing of different therapy for that subgroup.

Methods

A total of 140 patients (56 contributed by ECOG and 84 by SWOG) aged 16 to 77 years (median, 40 years) with de novo APL, diagnosed by morphology, histochemistry, cytogenetics and immunophenotyping, with t(15;17)(q22;q21) enrolled in E3489 and E2491 clinical trials activated in 1990 and 1992, respectively were included in this study (Table 1). These studies were approved by all relevant institutional review boards and all participants gave written informed consent to participate in them. In E2491, patients with APL were randomized to receive either daunorubicin-based chemotherapy or all-trans retinoic acid (ATRA) for induction. Patients who achieved complete remission (CR) received consolidation therapy with daunorubicin and cytarabine and, if still in CR, were randomized to maintenance ATRA or observation (2). In E3489, which was not restricted to APL, all patients received idarubicin-based induction chemotherapy and patients who achieved CR were randomized to autologous stem cell transplantation or high-dose cytarabine. Patients with an HLA-compatible sibling donor were offered allogeneic transplantation without randomization (3). Patients with secondary leukemia were not eligible for these studies. Standard supportive care measures were employed in both studies. Karyotyping was performed by standard G-banding techniques at the treating institutions, and both ECOG and SWOG reviewed all karyotypes centrally. The distribution of karyotypes between the two cooperative groups is shown in Table 1. Standard hematologic data and physical findings at diagnosis were evaluated for all patients. Complete response was determined by NCI Working Group criteria (4).

Ninety-five patients with t(15;17) alone were compared with 45 patients with t(15;17) plus additional chromosome abnormalities by the treatment they received. The interest was in whether additional chromosome abnormalities predicted clinical outcomes to ATRA. Major comparisons within groups were complete response rate, disease-free, and overall survival. There was a trend towards more SWOG patients having additional cytogenetic abnormalities compared with ECOG patients (38% vs. 23.2% respectively, $p=0.07$). This difference cannot be explained and it is most likely due to chance. It is highly unlikely due to cases of t(15;17) + other being under-diagnosed in ECOG or over-diagnosed in SWOG since all karyotypes were centrally reviewed by highly competent cytogeneticists (GD, MLS). Others have reported an identical frequency of patients with cytogenetic abnormalities in addition to t(15;17) as observed by ECOG (5).

Statistical Analyses

Overall survival (OS) was measured from induction registration/randomization to death from any cause. Disease-free survival (DFS) was defined as the time from documented

complete response to relapse or death from any cause. The protocol effect was compared between cytogenetic groups using two-sided Fisher's exact tests (6). The cooperative group (ECOG vs. SWOG) effect and the baseline patient demographic factors and disease characteristics were compared between cytogenetic groups using the Cochran-Mantel-Haenszel test stratified on protocols (7). For all patients and by induction treatment (ATRA or chemotherapy), the induction complete remission rates were also compared between cytogenetic groups using the Cochran-Mantel-Haenszel test stratified on protocols.

A time-varying stratum analysis was performed on all 140 patients where patients enter the ATRA stratum when the patient started ATRA therapy either as induction or maintenance therapy. Univariate and multivariate Cox models (8) stratified on protocol were performed on OS and DFS. The stratified univariate models included the cytogenetic subgroup, indicators of whether a patient had ever received ATRA (time-varying), and the interaction between the ATRA indicator and cytogenetic group (time-varying). In addition to those terms, the stratified multivariate models were further adjusted for cooperative group (ECOG vs. SWOG) and potential risk factors such as age (<30, 30–54, vs. >55), sex (male vs. female), WBC (<10,000 cells/ μ L, 10,000–50,000 cells/ μ L, vs >50,000/ μ L), platelet count (<10,000/ μ L, 10,000–50,000/ μ L, and >50,000/ μ L), and hemoglobin concentration (<10g/dL vs. >10g/dL) at baseline. The comparisons of the t(15; 17) only vs. t(15; 17)+ others groups were made within the ATRA stratum and the non-ATRA stratum (both time-varying). All P values were based on 2-sided tests.

Results

112 patients from E2491 and 28 patients from E3489 were included in this analysis. The median follow-up on patients still alive was 12.3 years. Table 2 gives demographic factors and disease characteristics of the patients at the time of enrollment. Patients with t(15;17) only were younger ($p=0.02$), and had higher WBC ($p=0.05$), and significantly more of them were females ($p=0.05$).

CR Rates Comparison by Induction Treatment

Table 3 gives the CR rates by study, induction treatment and cytogenetic groups. There was no difference in CR rate between patients with t(15;17) only and patients with t(15;17) + other ($p=0.54$). Thirty-four (75.6%) patients with t(15;17)+ other achieved CR while 67 (70.5%) patients with t(15;17) only achieved CR. For the 55 patients who received ATRA induction therapy, patients with t(15;17) + other had a 78.9% CR rate while patients with t(15;17) only had a 77.8% CR rate ($p=0.92$). For the 85 patients who received induction chemotherapy, patients with t(15;17) + other achieved a 73.1% CR rate and patients with t(15;17) only had a 66.1% CR rate ($p=0.52$).

OS and DFS Comparisons by Never Received ATRA and Ever Received ATRA

A time-varying stratum analysis was performed, whereby a patient enters the ATRA stratum when starting ATRA therapy either during induction or maintenance. For those patients from E2491, 55 patients started ATRA during induction (18 of them received ATRA both during induction and maintenance), and 11 patients started ATRA during maintenance. All E3489 patients remained in the non-ATRA stratum because none of them received ATRA. All 140 patients were included in the analysis of OS, and 101 patients who achieved CR were included in the analysis of DFS. Table 4 reports the hazard ratios (HR), 95% confidence intervals (CI) and p-values comparing t(15;17) only vs. t(15;17) + other within the time-varying ATRA stratum and non-ATRA stratum in univariate and multivariate Cox models. The multivariate Cox model was adjusted for cooperative groups (ECOG vs. SWOG) and potential risk factors such as age (<30, 30–54, vs. 55), sex (male vs. female),

WBC (<10,000 cells/ μ L, 10,000–50,000, vs. 50,000), platelet count (<10,000 cells/ μ L, 10,000–50,000, and 50,000), and hemoglobin concentration (<10g/dL vs. 10 g/dL) at baseline. For patients who received ATRA, those with t(15;17) only did significantly better than patients with t(15;17) + other in terms of OS (HR=0.43, p=0.04 in the univariate model and HR=0.34, p=0.01 in the multivariate model) and also tended to do better with respect to DFS if they achieved CR (HR=0.44, p=0.09 in the univariate model and HR=0.37, p=0.06 in the multivariate model). By contrast, for patients who did not receive ATRA, no differences were observed in OS and DFS. With adjustment for age, WBC, platelet count and hemoglobin concentration as continuous variables, the results were similar. There was strong interaction between treatment group and cytogenetic group for OS (p=0.03), and also for DFS (p=0.09) when all potential risk factors were included as categorical variables. Without including the potential risk factors, the p-values for the interaction term with OS and DFS were both 0.13.

Figure 1 gives Kaplan -Meier curves of OS and DFS for each cytogenetic subgroup by whether the patient never received ATRA or received ATRA at one time point (either as induction or maintenance therapy). To avoid potential bias from early events, those figures were restricted to the patients randomized to maintenance therapy on E2491. The OS and DFS were measured from maintenance randomization. For the 47 patients who received ATRA either during induction or maintenance, the 10-year OS rates were 84% and 56%, respectively, for patients with t(15;17) only and patients with t(15;17) + other. The 10-year DFS rates were 74% and 50%, respectively, for patients with t(15;17) only and patients with t(15;17) + other. For the 19 patients who never received ATRA, the 10-year OS rates were 10% and 29%, respectively, for patients with t(15;17) only and patients with t(15;17) + other. The 10-year DFS rates were 13% and 14%, respectively, for patients with t(15;17) only and patients with t(15;17) + other.

Discussion

Secondary chromosomal abnormalities occur in approximately one-third of patients with newly diagnosed APL (9,10). The CR rate was equivalent for APL patients treated with ATRA or only chemotherapy in the North American Intergroup study (E2491) (2,11), and in the present study the presence or absence of chromosome abnormalities in addition to t(15;17) did not affect CR rates of either ATRA or chemotherapy induction treatment group. Furthermore, additional chromosome abnormalities did not influence the DFS or OS of t(15;17) patients never treated with ATRA. However, additional chromosome abnormalities were associated with worse OS (P=0.01) and DFS (P=0.06) in APL Patients with t(15;17) treated with ATRA. Patients with t(15;17) alone are more sensitive to ATRA and have significantly greater OS and DFS with ATRA compared with patients with t(15;17) + additional chromosome aberrations. Other reports of the influence of additional cytogenetic abnormalities on the outcome of treatment of patients with APL are summarized in Table 5.

Our observation that karyotype evolution in APL reduced clinical efficacy when therapy is employed that specifically targets the molecular defect in this disease is novel. It is particularly intriguing in view of current results with imatinib therapy in chronic myelocytic leukemia (CML) and Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ ALL) (12,13). The reduced sensitivity to imatinib in accelerated and blast phases of CML and Ph+ ALL when compared with chronic phase CML may in part be due to additional chromosome abnormalities present in those advanced disease stages (14,15).

Trisomy 8 is the most common secondary chromosomal abnormality in APL (16). Previously, SWOG found trisomy 8 to worsen outcome in AML only when associated with unfavorable cytogenetics, while in patients with t(15;17) no differences on survival were

observed (16). In the present study, we confirmed trisomy 8 as the most common additional aberration, occurring in 43% of our APL patients with secondary cytogenetic abnormalities (Table 1). Although this study includes APL patients from two large national studies, subgroups of patients were too small to allow us to analyze whether the observed decrease in the sensitivity of APL cells to ATRA in vivo varied with specific additional cytogenetic aberrations. However, our data suggest the presence of trisomy 8 and other secondary aberrations may have an adverse effect on the efficacy of ATRA by decreasing sensitivity to the drug. The inability by SWOG to previously observe such an effect most likely resulted from the combined analysis of ATRA and non-ATRA-containing regimens in their patients (16).

The question of the nature of secondary chromosomal aberrations may be a very relevant one given that specific chromosome losses or gains appear to be driven by distinct mutations cooperating with PML/RAR α (17). This leads to the question whether our observation of decreased responsiveness to ATRA by PML/RAR α leukemic promyelocytes with additional cytogenetic abnormalities results from that newly acquired mutation, e.g., *FLT3*-internal tandem duplication.

This study of the effect of cytogenetics on outcome of therapy for APL demonstrates the lesser sensitivity to ATRA of patients with karyotypic evolution, compared with patients whose leukemia is characterized by t(15;17) alone.

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Figure 1.
OS and DFS by Never Received ATRA and Ever Received ATRA Restricted to Patients
Randomized on Maintenance on E2491

Table 1**Distribution of Patients Between Study Groups and Studies**

Eastern Cooperative Oncology Group (ECOG)	
No. patients enrolled in E2491	44
E3489	12
Total	56
No. patients with t(15;17) alone	43
t(15;17) + other	13 (23.2%)
Other = trisomy 8 only	5
3 aberrations	3
Various	4
Southwest Oncology Group (SWOG)	
No. patients enrolled in E2491	68
E3489	16
Total	84
No. patients with t(15;17) alone	52
t(15;17) + other	32 (38.1%)
Other = trisomy 8 only	14
3 aberrations	3
Various	15

Table 2

Baseline Characteristics

	t(15;17)+Other		t(15;17)Only		p-value
	N	%	N	%	
Protocol					
E2491	36	80.0	76	80.0	1.00
E3489	9	20.0	19	20.0	
Age (year)					
<30	7	15.6	27	28.4	0.02
30–54	22	48.9	53	55.8	
55+	16	35.6	15	15.8	
Sex					
Male	31	68.9	49	51.6	0.05
Female	14	31.1	46	48.4	
WBC (cells/mm³)					
<10,000	37	82.2	72	75.8	0.05
10,000–50,000	8	17.8	12	12.6	
>=50,000	0	0	11	11.6	
Platelets (cells/mm³)					
<10,000	3	6.7	6	6.3	0.88
10,000–50,000	25	55.6	57	60.0	
>=50,000	17	37.8	32	33.7	
Hemoglobin (g/dL)					
<10	27	60.0	62	65.3	0.54
>=10	18	40.0	33	34.7	

Table 3

Induction Complete Response Rates

	Induction Treatment										Total			
	ATRA				Chemo									
	t(15;17)+Other		t(15;17)Only		t(15;17)+Other		t(15;17)Only		t(15;17)+Other		t(15;17)Only			
	N	%	N	%	N	%	N	%	N	%	N	%		
E2491	15	78.9	28	77.8	13	76.5	27	67.5	28	77.8	55	72.4		
E3489	.	.	.	.	6	66.7	12	63.2	6	66.7	12	63.2		
Total	15	78.9	28	77.8	19	73.1	39	66.1	34	75.6	67	70.5		
P-value	0.92				0.52				0.54					

Table 4

Results from Time-varying Stratum Analysis

	Univariate Model			Multivariate Model		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
OS						
ATRA, t(15;17)only vs t(15;17)+other	0.43	[0.19,0.96]	0.04	0.34	[0.15, 0.78]	0.01
Non-ATRA, t(15;17)only vs t(15;17) + other	0.96	[0.49,1.89]	0.91	110	[0.54, 2.27]	0.79
DFS						
ATRA, t(15;17)only vs t(15;17)+other	0.44	[0.18, 1.12]	0.09	0.37	[0.13, 1.03]	0.06
Non-ATRA, t(15;17)only vs t(15;17)+other	1.15	[0.52, 2.54]	0.73	1.14	[0.48, 2.66]	0.77

Table 5

Previously Reported Investigations of Cytogenetic in APL and Outcome

Ref	No. APL	No. (%) with t(15;17)+ other	Rx	Outcome
9	80	26 (32)	CT only	Longer CR and EFS with t(15;17)+other. No diff in OS
10	161	52 (32)	80 pts-CT	Secondary cytogenetic changes: longer CR and EFS duration. No OS diff compared with t(15;17) alone
18	47	17 (36)	N/A	No diff
19	292	76 (26)	ATRA+CT	No diff
20	113	34 (30)	Anthracycline+ ATRA	No diff
21	43	14 (33)	ATRA	Poorer CR rate, early death rate, and overall survival with t(15;17) + other
22	42	12 (29)	N/A	No diff, but if induction deaths are excluded, OS significantly better for t(15;17) alone. Late relapses may be more common with t(15;17) + other
23	54	21 (39)	N/A	t(15;17)+ other had an adverse effect on prognosis independent of other Prognostic indicators.
24	41 (secondary)	17 (41)	CT	N/A
17	284	26 (9) at dx or relapse	ATRA	Impaired prognosis associated with t(15;17) + other
12	17	10 (59)	ATRA+CT	No diff
25	513	81 (15.8)	N/A	N/A
26	158	29 (18.4)	ATRA + Arsenic + CT	Relapse rate higher with t(15;17)+other (13.8% v. 6.2%). No diff in OS
Present Study	140	45 (32)	CT +/- ATRA	t(15;17) alone had significantly better OS. CT alone, No diff
Total	1986	469 (23.6)		