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Delay in the administration of all-*trans* retinoic acid and its effects on early mortality in acute promyelocytic leukemia: Final results of a multicentric study in the United States

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ABSTRACT

Early death (ED) occurs in 10–30% of patients with acute promyelocytic leukemia (APL). Is all-*trans* retinoic acid (ATRA) promptly given and does it decrease overall early mortality? ATRA was administered within 24 h of morphological suspicion in only 44% of the 120 consecutive patients treated in the four collaborating centers. Absence of disseminated intravascular coagulation ($p = 0.012$) and admission to a non-university-affiliated hospital ($p = 0.032$) were independent predictors of ATRA delay. ED occurred in 17% of patients, and was independently correlated only with ICU admission ($p = 0.002$). Our results do not demonstrate that prompt (versus delayed) ATRA administration decreases overall early death.

1. Introduction

Approximately 600–800 new cases of acute promyelocytic leukemia (APL) are diagnosed each year in the United States [1]. When untreated, APL is the most rapidly fatal acute myeloid leukemia (AML). However, with the introduction of all-*trans* retinoic acid, and recently arsenic trioxide (minimizing requirements for use of cytotoxic chemotherapy), APL has become the most curable acute myeloid leukemia, with complete remission and cure rates exceeding 90% and 70%, respectively, in those who do not succumb to early death [2–6]. Several major practice guidelines recommend starting all-*trans* retinoic acid (ATRA) as soon as APL is morphologically and clinically suspected without waiting for cytogenetic confirmation [7–11].

This recommendation is supported by the following facts: ATRA is known to correct biologic signs of APL coagulopathy, is only rarely associated with clinically significant side effects, and, as shown recently, may decrease the relative risk of early hemorrhagic death [11,12].

During the last few years, we have noticed that prompt initiation of ATRA upon suspicion of APL is suboptimal at least in some hospitals in the United States, and early mortality rates are frequently higher than expected. These observations prompted us to conduct a retrospective multicentric study in an attempt to answer the following two questions: (i) Are oncologists optimally adherent to the strategy of prompt ATRA administration, and if not, what factors are associated with suboptimal adherence? (ii) Does prompt ATRA administration independently decrease overall early mortality? In other words, in reducing the high mortality of the "sick" APL patient, what is the independent role of prompt ATRA administration relative to factors such as aggressive transfusion support and intensive care unit (ICU) level of care? We have recently reported a preliminary report of our findings as related to early outcome effects of ATRA [13]. The results of the now completed study enable us to

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Table 1
Characteristics of the entire study population and comparison between groups A and B.

	All	A (early death)	B (no early death)	*p*-value
n	120	20	100	–
Age (years)	49 ± 16	53 ± 16 (*n* = 20)	48 ± 15 (*n* = 100)	0.19
Male	54/120 (45%)	11/20 (55%)	43/100 (43%)	0.34
University-affiliated hospital	105/120 (88%)	17/20 (85%)	88/100 (88%)	0.71
Additional cytogenetic abnormalities	26/85 (31)	3/11 (27)	23/74 (31)	1.00
Delayed ATRA	71/120 (59%)	8/20 (40%)	63/100 (63%)	0.08
Differentiation syndrome	28/115 (24%)	3/19 (16%)	25/96 (26%)	0.57
DIC	63/115 (55%)	17/20 (85%)	46/95 (48%)	0.003**
ICU admission/transfer	39/112 (35%)	17/20 (85%)	22/92 (24%)	<0.001**
Sanz's risk score (L:H)	74:41	6:14	68:27	0.001**

ATRA: all-*trans* retinoic acid; DIC: disseminated intravascular dissemination; ICU: intensive care unit.
** $p < 0.01$.

assess clinical practice attitudes with regards to timing of ATRA administration.

2. Materials and methods

The study protocol was approved by the institutional review boards of all collaborating centers (Sentara Hospitals, Norfolk, VA; University of Virginia, Charlottesville, VA; West Virginia University, Morgantown, WV, and Penn State Milton S. Hershey Medical Center, Hershey, PA). Data for all patients who were diagnosed with APL and treated with ATRA (with or without cytotoxic chemotherapy) in one of the collaborating centers between January 1996 and March 2013 were retrospectively collected. All data were pooled, anonymized, and analyzed by one of the authors (AR). The diagnosis of APL required cytogenetic confirmation of *t*(15;17) and/or presence of PML-RARα on reverse-transcriptase polymerase chain reaction. Disseminated intravascular coagulation (DIC) was defined as described elsewhere [14]. The Sanz's risk scoring system was used for risk stratification [15], with high-risk disease defined as white blood cell count (WBC) > 10,000/μL and low-risk disease as WBC≤10,000/μL. Delayed ATRA was defined as administration more than 24 h following the first suspicion of APL. The time of first suspicion of APL was determined by reviewing the oncologists' notes as well as the results of peripheral blood smears (and when they were relayed to the oncologists). Early death was defined as death occurring within the first 30 days from the date of admission to the hospital. The criteria for ICU admission or transfer was according to the physician's discretion but general medical criteria such as hemodynamic instability, presence of DIC, intensive monitoring of vital signs, and aggressive transfusion support were applied to determine the need for critical care.

2.1. Statistical analysis

Data are presented as mean ± standard deviation or frequency (%). Intergroup analysis was performed using Chi-squared test and Fisher's exact test for frequencies, Student's *t*-test for means of variables with a normal distribution, and Mann–Whitney *U*-test for medians of variables with a skewed distribution. Univariate analysis was first performed to identify variables with significant difference between the two groups. These variables were then entered as potential predictors in a multivariate binary logistic regression model with a categorical (binary) variable of interest being the dependent variable. The effects of significant predictors in multivariate models were assessed by odds ratio (OR). All analyses were done using the Statistical Software for Social Sciences (SPSS 21.0) and a *p*-value of smaller than 0.05 was considered statistically significant throughout analyses.

3. Results

A total of 120 patients were included. The mean ± standard deviation age of patients was 49 ± 16 years, and 55% were female. Bleeding (48%), symptoms of anemia (25%), and infections (20%) were the most common presenting symptoms ($n = 93$). According to Sanz's risk stratification, 74 (64%), and 41 (36%) patients were low- and high-risk, respectively ($n = 115$). A total of 63/115 (55%) patients presented with or later developed DIC, and 26/85 (31%) patients had additional cytogenetic abnormalities, consistent with previous reports [16]. A total of 105/120 (88%) patients presented directly and were admitted to a university-affiliated hospital. A total of 39/112 (35%) patients required intensive care unit (ICU) admission or transfer during the course of their hospitalization, and 28/111 (25%) patients developed the differentiation syndrome. The exact time of ATRA administration was available in 102 patients. Among these patients, ATRA was administered within 24 h of the time APL was morphologically suspected in 45 (44%) patients, 24–48 h later in 30 (29%) patients, and with a longer delay in the remainder (27%). The median (5–95th percentile) delay between the first suspicion of APL and ATRA administration was 1 (0–3.9) days. ATRA was readily available in the pharmacy in all cases, with no limitations. Early death occurred in 20/120 (17%) patients, 11 (55%) of which was due to catastrophic intracranial or intrapulmonary hemorrhage.

Table 2
Comparison between groups A and B restricted to low-risk patients according to Sanz's risk score.

	A (early death)	B (no early death)	*p*-value
n	6	68	–
Age (years)	51 ± 21	49 ± 15	0.77
Male	2/6 (33%)	31/68 (46%)	0.69
University-affiliated hospital	4/6 (67%)	57/68 (84%)	0.28
Additional cytogenetic abnormalities	1/4 (25)	15/52 (29)	1.00
Delayed ATRA	3/6 (50%)	46/68 (68%)	0.40
Differentiation syndrome	0/6 (0%)	15/68 (22%)	0.34
DIC	4/6 (67%)	28/68 (41%)	0.39
ICU admission/transfer	4/6 (67%)	11/65 (17%)	0.016*

ATRA: all-*trans* retinoic acid; DIC: disseminated intravascular dissemination; ICU: intensive care unit.
* $p < 0.05$.

We first divided our patients into two groups (Table 1): A (early death; $n = 20$) and B (no early death, $n = 100$). There was no significant difference between the groups with regards to hospital type (university-affiliated vs. community; $p = 1.0$), age ($p = 0.19$), sex ($p = 0.34$), presence of additional cytogenetic abnormalities ($p = 1.0$), development of the differentiation syndrome ($p = 0.57$), and whether or not ATRA was delayed ($p = 0.08$). However, DIC on admission and ICU admission/transfer were significantly more common among patients in group A than B ($p = 0.003$ and <0.001, respectively). Also, there were more high-risk patients in group A than in group B ($p = 0.001$). In a multivariate binary logistic regression model with group (A vs. B) as the dependent variable and DIC (0 vs. 1), ICU admission/transfer (0 vs. 1), and Sanz's risk score (L vs. H) as potential categorical predictors, only ICU admission/transfer emerged as a significant independent predictor of early mortality (OR = 10, $p = 0.002$; R^2 for model: 0.39).

Next, we restricted the analysis to patients who were low-risk according to Sanz's risk score. As shown in Table 2, ICU admission/transfer was the only variable with significant difference between the groups, being more frequent in group A