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The Time to Treatment: A Retrospective Analysis of the Time to All-trans Retinoic Acid (ATRA) in Patients with Suspected Acute Promyelocytic Leukemia (APL)

Grant Jirka, MD
University of Southern California

Tara Rakiewicz, MD
Thomas Jefferson University Hospital

Navya George, MD
Boston University Medical Center

Misung Yi, PhD
Dankook University

Lindsay Wilde, MD
Thomas Jefferson University Hospital

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Authors: Grant Jirka, MD[a], Tara Rakiewicz, MD[b]; Navya George, MD[c]; Misung Yi, PhD[d]; and Lindsay Wilde, MD[b]

[a] University of Southern California
Department of Hematology
1441 Eastlake Avenue, NTT 3440
Los Angeles, CA 90033

[b] Thomas Jefferson University Hospital
Department of Medical Oncology
Division of Hematologic Malignancies
834 Chestnut St., Suite 315
Philadelphia, PA 19107

[c] Boston University Medical Center
Department of Internal Medicine
72 East Concord Street, Evans 124
Boston, MA 02118

[d] Dankook University
Department of Statistics and Data Sciences
152 Jukjeon-ro, Suji-gu, Yongin-si, Gyeonggi-do, 16890, South Korea

Corresponding Author:
Grant Jirka, MD
Department of Hematology
1441 Eastlake Avenue, NTT 3440
Los Angeles, CA 90033
Grant.jirka@med.usc.edu

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Micro Abstract:

Acute promyelocytic leukemia (APL) can cause fatal bleeding. Prompt administration of all-trans retinoic acid (ATRA) is crucial to decreasing early morbidity and mortality. We performed a retrospective review of 91 patients with suspected APL at a tertiary care hospital and found that the average time from admission to administration of ATRA was 6 hours and 28 minutes.

Abstract:

PURPOSE: Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) defined by the chromosomal translocation t(15;17), which creates fusion of the promyelocyte gene and the retinoic acid receptor alpha gene. Dysplastic promyelocytes induce aberrations in coagulation leading to hemorrhage and disseminated intravascular coagulation (DIC), which often devolves into a rapidly fatal course. Prompt administration of all-trans retinoic acid (ATRA) reverses the coagulopathy in patients with suspected APL, which ultimately decreases morbidity and mortality. **PATIENTS AND METHODS:** This retrospective study examines 91 patients over a 5-year period who received ATRA for a suspected or confirmed diagnosis of APL at a tertiary care hospital. We quantified the time for ATRA to be ordered and administered in addition and analyzed variables that potentially influenced time to treatment. **RESULTS:** The mean time from hospital admission to administration of ATRA was 6 hours and 28 minutes. The clinical variable that improved the time to administration was signs or symptoms of bleeding upon admission. Notably, 89% of the patients in this study were accepted as a transfer from an outside hospital. **CONCLUSIONS:** Even in tertiary care centers with substantial resources, the time to ATRA remains too long. The need to rapidly recognize, triage, and treat patients with suspected APL is further heightened by the fact that the majority of

patients initially present to community hospitals where there is a dearth of ATRA available and transfer times to tertiary hospitals can sometimes be days.

Keywords:

Disseminated Intravascular Coagulation, Bleeding, Time to Administration, Coagulopathy

Introduction:

Acute promyelocytic leukemia (APL) is a rare subtype of acute myeloid leukemia that accounts for 5-10% of nearly 22,000 new cases of acute myeloid leukemia diagnosed each year[1,2]. The hallmark of APL is the chromosomal translocation t(15;17), which results in fusion of the promyelocyte gene and the retinoic acid receptor alpha gene (PML-RARα). Other defining features of APL are dysplastic promyelocytes and aberrations in coagulation including hemorrhage and disseminated intravascular coagulation (DIC)[3,4].

When APL was first described in 1957, it was reported to have a "very rapid fatal course of only a few weeks' duration" due to its tendency to produce a severe hemorrhagic diathesis[5]. However, if initiated early, treatment with all-trans retinoic acid (ATRA) induces the differentiation of promyelocytes and can rapidly prevent or reverse the coagulopathy, improving early mortality[6,7]. Unfortunately, APL still has a high early death rate (EDR) of up to 10-30% due to delayed recognition of coagulopathy and failure to initiate ATRA in a timely manner[4,8-11]. It is estimated that the median onset of bleeding is five days and approximately two-thirds of early death in cases of APL occurs within 1 week after diagnosis[12,13].

A retrospective review that evaluated the timing of ATRA administration in more than 200 patients between 1992-2009 showed that delayed ATRA administration in the high-risk APL group (white blood cell count > $10x10^9$/L and/or patients older than 60 years of age) had much higher EDR than those receiving ATRA immediately after suspicion arose. The same study also reported that EDR was even higher for those never receiving ATRA[14]. Thus, the timing of ATRA administration is critical to the acute management of suspected or confirmed APL, and

the treatment guidelines reflect that urgency as the recommendation is that ATRA should be initiated immediately based on the clinical suspicion for APL and/or review of the peripheral blood smear[15-17].

Given the importance of early treatment with ATRA, in this retrospective review, we quantify the time from hospital admission to ATRA being ordered and administered for patients with suspected or confirmed APL at a tertiary care university hospital. We also analyze both clinical and demographic variables that may affect the time to treatment.

Methods:

Patient Data

Following approval by the local Institutional Review Board, we retrospectively reviewed 107 unique medical records from patients who received at least one dose of ATRA between April 2017-December 2021 at Thomas Jefferson University Hospital (TJUH) in Philadelphia, Pennsylvania. TJUH is the main tertiary care hospital in the 18-hospital network that comprises the Jefferson Health enterprise, which spans the Philadelphia and Delaware Valley region, and is affiliated with the Sidney Kimmel Cancer Center (a National Cancer Institute designated Cancer Center). TJUH has over 900 inpatient beds and over 39,000 inpatient visits each year[18]. Since TJUH has physicians from more than 30 specialties, our hospital sees a high transfer volume of medically complex patients (both from hospitals inside and outside the Jefferson Health network).

Of the 107 patients, 16 were excluded as they were either under the age of 18 upon admission, were previously diagnosed with APL and already receiving treatment with ATRA or received ATRA prior to transfer. Thus, we performed our final analysis on 91 patients. The following demographic data for each patient was obtained: age, gender identity, and ethnicity. Laboratory data collected at the time of admission included: white blood cell count (WBC), hemoglobin (Hgb), platelet count, absolute peripheral blast or "other cells" count, prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen. Clinical data for the index admission including whether a patient was admitted through the emergency department, fever upon admission (temperature ≥ 100.4ºF), number of packed red blood cell (pRBC) transfusions, number of platelet transfusions, number of cryoprecipitate transfusions, number of fresh frozen plasma (FFP) transfusions, signs or symptoms of bleeding upon admission (as documented in the initial history and physical by the admitting physician), admitted overnight (1700-0700), ATRA ordered overnight (1700-0700), ATRA administered overnight (1700-0700), confirmed diagnosis of APL prior to receiving ATRA, and whether a patient was eventually diagnosed with APL. Time of admission was defined as the time when the admission order was placed in the electronic medical record (EMR). Time of administration was defined as the time the bedside nurse marked the medication as administered in the EMR.

Statistical Analysis

A simple general linear model was used to evaluate univariate association between each single covariate and each log transformed outcome (time interval A: time from admission to ordering ATRA, time interval B: time from ordering ATRA to administration, time interval C: time from

admission to administration of ATRA). All outcomes A, B, and C were right-skewed and needed to be log transformed.

Model selection by Akaike information criterion (AIC) was conducted to identify the best model according to the goodness of fit criteria (AIC). The smaller the AIC value, the better the model fit. The parsimonious models were obtained using backward elimination of non-significant predictors (p-values > 0.05) from the best models according to goodness of fit criteria (AIC).

All statistical analyses were performed using R 4.1.2 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results:

The mean time for interval A (time from hospital admission to ordering ATRA) was 284 minutes, the mean time for interval B (time from ATRA order being placed to ATRA administration) was 104 minutes, and the mean time for interval C (time from admission to ATRA administration) was 388 minutes. Table I shows further analysis of the time intervals.

The results of our demographic and clinical variables are presented in Table II. The majority of patients were transferred from an outside hospital (89%) and admitted overnight (87%). Thus, ATRA was most commonly ordered (76%) and administered (70%) overnight. Of the 91 patients examined, only 26 (29%) were diagnosed with APL after completion of their workup. The mean complete blood cell counts upon admission were: WBC 55 B/L with an absolute blast count of

33 B/L, Hgb 8.4 g/dL, platelet count 53 B/L; the mean coagulation studies upon admission were: PT 16 seconds, PTT 29 seconds, and fibrinogen 309 mg/dL. During the index admission, patients required a mean of 6 units of pRBC's and 9 units of platelets. Of note, only a quarter of patients were noted to have signs or symptoms of bleeding upon admission.

When the multiple linear regression analysis is performed, as shown in Table III, documented signs or symptoms of bleeding is the only variable that shows a statistically significant improvement in time to ATRA for time intervals A and C. It took on average 39% less time from admission to ATRA being ordered (95% CI: 0.396-0.946, p=0.030) and 31% shorter time from admission to ATRA administration for patients who had signs or symptoms of bleeding as compared to those with no signs or symptoms of bleeding (95% CI: 0.489-0.967, p=0.034). None of the covariates were significantly associated with time from the ATRA order being placed to ATRA administration at 5% significance level.

Discussion:

The primary objective of this study was to assess the time to ATRA at our institution, and we were surprised to find that the time from admission to treatment at a tertiary care center with substantial resources was greater than 6 hours. To our knowledge, this study is the first to report the time to ATRA for patients with suspected APL, and it should not be viewed as a benchmark to beat but rather as a cautionary tale that even resource rich hospitals still have significant delays in delivering potentially lifesaving care. To further identify where the delays may arise, we turned to our analysis of the clinical and demographic variables.

The only statistically significant variable that decreased the time to treatment was documented signs or symptoms of bleeding upon admission. This variable decreased the time to ordering ATRA by 39% and overall time to receiving ATRA by 31%. While this is reassuring, as hemorrhagic complications are one of the more recognizable signs of APL, nearly 75% of patients in this study did not have signs or symptoms of bleeding upon presentation. Thus, it may be prudent to provide additional education to front-line healthcare workers regarding the need for additional laboratory testing in patients that have findings concerning for acute leukemia such as coagulation studies to assess for DIC. Additionally, both Geer et al. and Bolds et al. noted that pharmacist unfamiliarity with ATRA was another barrier to care and could influence whether the medication was kept on formulary[19,20]. Thus, education of non-oncology trained pharmacists may also be beneficial to hasten the time to ATRA.

It is worth noting that there were multiple variables in our study that did not show a statistically significant difference in time to ATRA across all time intervals. Even though hospitals provide 24/7 care for patients, it is well known that staffing is decreased during the overnight hours. In this study, we found that the majority of patients were admitted overnight, but there were no statistically significant delays in time to ATRA for these patients or when ATRA was ordered overnight. Thus, it is reassuring to note that despite decreased staffing, there were no additional delays in care. Time interval B (time from ATRA order to administration) also had no statistically significant difference across all variables examined. Since this time variable is heavily affected by nursing and pharmacy response times, it seems that most of the variability in time to ATRA comes from the physician team recognizing the concern for APL and making the decision to initiate treatment with ATRA.

Our data revealed that the mean time from admission to ATRA administration was 6 hours and 28 minutes. Given that the majority of our patients were outside hospital transfers, this is not a completely accurate reflection of time from patient presentation to ATRA administration. There is likely a significantly greater delay in providing a potentially lifesaving medication to patients as many hospitals do not stock ATRA and a patient's first dose of the medication is often not until they arrive at a tertiary care center. This is contrary to recommendations from the National Cancer Center Network for APL guidelines which state that ATRA should be available in all community hospitals so that treatment can be initiated early[21].

Various studies have aimed to assess the question of ATRA availability. In 2015, Wheeler et al. published their telephone survey results of 134 hospitals in the state of Georgia, which revealed that of the 114 hospitals that did not treat leukemia patients, only one of these hospitals had ATRA available[22]. In Michigan and Louisiana, Bolds et al. conducted a similar telephone survey where only six of the 23 hospitals that indicated they treat APL had ATRA available on formulary or in stock[20]. To address the question of ATRA availability from a national perspective, a paper published in 2021 queried 118 hospitals (both tertiary care and community based) that were randomly selected from six regions of the United States (about 20 hospitals per region) and asked various questions regarding their experience with ATRA and APL. Results showed that less than one third of these hospitals had ATRA in stock. Of the hospitals that referred patients to other centers for APL treatment, only 14% (7/49) had the medication readily available to administer prior to transfer, most relying on tertiary care hospitals or cancer centers to provide the medication. Additionally, neither hospital size nor academic status were found to

have influenced ATRA availability. Of the 69 hospitals that indicated they treat leukemia in that same study, 42% did not have ATRA immediately in stock and available for patients[19].

The nationwide lack of ATRA availability presents a significant problem and can lead to alarming delays of care, especially since it is also reflected in health centers that treat leukemia. We have deduced several reasons as to why the medication is not on standard hospital formulary, one of the most obvious being rarity of APL. Of the 22,000 new cases of acute myeloid leukemia, 5-10% are the subclass of APL, resulting in a total of 1,100-2,200 new cases every year[1]. Along with the diagnosis being rare, the medication itself can be expensive. Upon review of drug information sources, the cost of ATRA is $37.35 per 10 mg capsule; for a standard order of 100 capsules, this would approximate $4,000 an order[23]. Given the cost and low incidence of disease, hospitals have little incentive to carry the medication. However, this price is dependent upon each hospital's contract. Upon query of our institution's inpatient pharmacy, it is under contract for about $800 (at time of check) for 100 capsules.

Not only are price and education barriers to care, but the availability to purchase ATRA from pharmaceutical companies has also become an issue. It is manufactured by various pharmaceutical companies including Glenmark, Teva, and Par Pharmaceuticals and since January 2023 it has been listed as under shortage with no explanation, nor a time in the future when it will become more available. These supply chain issues make an already complicated issue even more challenging[24].

Many large U.S. healthcare systems are adopting the spoke and hub model of community hospitals referring to their affiliated large academic medical centers. As mentioned, our institution is a tertiary care center and 89% of our patients in this study were transferred from outside hospitals, most of those being regional care centers. Since transfer times can stretch between hours to days, patients can quickly decompensate before arrival to a tertiary care center. In an effort to decrease time to ATRA, hospital enterprises should prioritize supply of the medication in the regional hospitals that patients often present to or establish a courier system that can be utilized for distributing time sensitive medications such as ATRA. This is especially needed in the era of a global pandemic when hospital bed shortages run rampant leading to significant delays in care and access to life saving medication.

While the aforementioned interventions may help reduce the time to ATRA in patients who present to a community hospital or a hospital that is not equipped to evaluate and treat a patient with new leukemia, a simple yet very important intervention that can be taken at tertiary care centers is enhanced transfer center acceptance note documentation. When patients are transferred for evaluation of a new acute leukemia from another hospital to our institution, the accepting oncologist writes a brief note. We propose that this note should be filed in the EMR at the time of acceptance and provide robust documentation regarding the concern for APL and proposed next steps for evaluation and treatment, including whether prompt initiation of ATRA should be started upon arrival. Since most tertiary care centers are staffed by residents and fellows as the primary team, this may help convey the heightened sense of urgency for rapid triage and treatment.

Additionally, in our study, 95% of patients received ATRA prior to confirming the diagnosis of APL and only 29% of patients given ATRA were ultimately diagnosed with APL. Thus, over 70% of patients did not need treatment with ATRA. However, we are in favor of providers having a low threshold to initiate ATRA while awaiting a diagnosis of APL as side effects from a few doses of ATRA are relatively benign. The most common adverse reactions reported on the package insert are headache, fever, mucosal dryness, and bone pain[25]. The results of peripheral RT-PCR testing for the PML-RARα gene generally results within 24-48 hours[26,27]. Thus, if a patient does not have APL, they may be exposed to only 2-4 doses prior to treatment discontinuation.

While this study analyzed patient data at a single tertiary care center, the patients' demographics are similar in comparison to those reported in larger studies that assess the epidemiology of AML and APL patients[28-30]. Thus, our study holds external validity despite the relatively small size.

We recognize that our study omits some important variables such as provider variability in recognizing and treating APL in addition to variability in nursing and pharmacy familiarity with administration and dosing based on the patient's unit (oncology unit vs. non-oncology unit vs. emergency department). Further studies may aim to include these variables in their analysis to further clarify if these affect the time to ATRA.

Conclusions:

The urgency for ATRA administration in patients with suspected APL has been well established. Our study highlights that there is still a significant delay in ATRA administration at a large academic medical center. While this study found that the majority of patients were transferred from an outside hospital or directly admitted from the community, we were not able to quantify how long they were waiting for transfer. This remains an important variable in addressing the delays in initial treatment as we suspect the cost-benefit ratio of stocking ATRA in community hospitals, general lack of ATRA availability due to supply chain issues, and unfamiliarity with the medication to be major reasons delaying the overall time to ATRA. Thus, this study underscores a fundamental need to recognize, triage, and treat patients with suspected acute leukemia in a more rapid manner, even at centers of excellence. We proposed multiple next steps that can be taken to further help decrease the time to ATRA including increasing ATRA availability at community hospitals, increasing education of front-line providers regarding the prompt recognition of coagulopathy in the setting of acute leukemia, and enhancing transfer center acceptance documentation emphasizing the concern for APL and the appropriate next steps in evaluation and treatment.

Clinical Practice Points:

- Acute promyelocytic leukemia (APL) is associated with major bleeding complications and prompt administration of all-trans retinoic acid (ATRA) from the moment the diagnosis is suspected is important for reducing morbidity and mortality.
- The time to ATRA at a tertiary medical center was approximately 6.5 hours for patients with suspected APL, and the majority of patients in this study were transferred from an

outside hospital. Thus, the overall time to treatment for most patients was substantially longer.

- Signs or symptoms of bleeding improve the time to treatment but surprisingly laboratory features of coagulopathy did not.
- Further studies of the barriers to treatment are necessary both at tertiary medical centers and community hospitals to more expeditiously recognize, triage, and treat patients with suspected acute leukemia.

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Tables:

Table I: Time to ATRA

Time Intervals	**N=91**
Time Interval A (Time from Admission to ATRA Order), *in minutes* Mean ± Standard Deviation Skewness; Shapiro-Wilk Range	 284.0 ± 274.6 1.7 22.0 - 1,227.0
Time Interval B (Time from ATRA Order to Administration), *in minutes* Mean ± Standard Deviation Skewness; Shapiro-Wilk Range	 103.7 ± 81.1 1.5 2.0 - 476.0
Time Interval C (Time from Admission to Administration), *in minutes* Mean ± Standard Deviation Skewness; Shapiro-Wilk Range	 387.7 ± 298.9 1.5 49.0 - 1,305.0

Table II: Demographic and Clinical Variables

Demographic and Clinical Variables	**N=91**
Age, *in years*	
Mean ± Standard Deviation	56.9 ± 18.0
Range	18.0 - 90.0
Gender, *n (%)*	
Female	41 (45.1)
Male	50 (54.9)
Ethnicity, *n (%)*	
White or Caucasian	55 (60.4)
Black or African American	21 (23.1)
Other or Unknown	15 (16.5)
Admitted Through the Emergency Department, *n (%)*	
No	81 (89.0)
Yes	10 (11.0)
Admitted Overnight (1700 - 0700), *n (%)*	
No	12 (13.2)
Yes	79 (86.8)
ATRA Ordered Overnight (1700 - 0700), *n (%)*	
No	22 (24.2)
Yes	69 (75.8)
ATRA Administered Overnight (1700 - 0700), *n (%)*	
No	27 (29.7)
Yes	64 (70.3)
Fever (Temperature ≥ 100.4°F) Present Upon Admission, *n (%)*	
No	78 (85.7)
Yes	13 (14.3)
Signs or Symptoms of Bleeding Upon Admission, *n (%)*	
No	68 (74.7)
Yes	23 (25.3)
APL Diagnosis Prior to ATRA Administration, *n (%)*	
No	86 (94.5)
Yes	5 (5.5)
Diagnosed with APL, *n (%)*	
No	65 (71.4)
Yes	26 (28.6)
Fresh Frozen Plasma Transfused During Admission, *units*	
Mean ± Standard Deviation	0.3 ± 0.9
Range	0.0 - 6.0
Platelets Transfused During Admission, *units*	
Mean ± Standard Deviation	9.4 ± 11.6
Range	0.0 - 59.0
Cryoprecipitate Transfused During Admission, *units*	
Mean ± Standard Deviation	1.0 ± 2.2
Range	0.0 - 13.0
Packed Red Blood Cells Transfused During Admission, *units*	
Mean ± Standard Deviation	6.4 ± 5.8
Range	0.0 - 33.0
White Blood Cell Count Upon Admission, *B/L*	

Mean ± Standard Deviation Range	55.3 ± 70.0 0.7 - 355.6
Absolute Blast Count or Other Cell Count Upon Admission, *B/L* Mean ± Standard Deviation Range	 33.0 ± 54.8 0.0 - 352.0
Hemoglobin Upon Admission, *g/dL* Mean ± Standard Deviation Range	 8.4 ± 1.9 3.2 - 12.8
Platelet Count Upon Admission, *B/L* Mean ± Standard Deviation Range	 53.3 ± 51.0 4.0 - 244.0
Prothrombin Time Upon Admission, *seconds* Mean ± Standard Deviation Range	 15.7 ± 2.6 11.7 - 25.2
Partial Thromboplastin Time Upon Admission, *seconds* Mean ± Standard Deviation Range	 28.7 ± 6.7 18.0 - 67.0
Fibrinogen Upon Admission, *mg/dL* Mean ± Standard Deviation Range	 308.6 ± 184.8 47.0 - 792.0

Table III: Univariate Linear Regression Analyses

	Time Interval A	**Time Interval B**
Variables	Geometric Mean Ratio (95% Confidence Interval)	Geometric Mean Ratio (95% Confidence Interval)
Gender (Male vs. Female)	1.207 (0.818-1.780)	1.273 (0.857-1.889)
Age	1.006 (0.995-1.017)	0.999 (0.988-1.010)
Ethnicity (Black vs. White)	0.843 (0.524-1.357)	0.704 (0.436-1.139)
Ethnicity (Others vs. White)	1.112 (0.648-1.909)	0.764 (0.443-1.319)
Admitted Through the Emergency Department (Yes vs. No)	1.319 (0.710-2.448)	1.721 (0.923-3.209)
Admitted Overnight (Yes vs. No)	1.429 (0.808-2.525)	1.048 (0.584-1.881)
ATRA Ordered Overnight (Yes vs. No)	-	0.977 (0.615-1.552)
Fever (Yes vs. No)	1.229 (0.707-2.138)	1.157 (0.657-2.035)
Signs or Symptoms of Bleeding (Yes vs. No)	**0.612* (0.396-0.946)**	0.803 (0.510-1.263)
Log_2(White Blood Cell Count)	1.016 (0.937-1.101)	1.007 (0.927-1.094)
Log_2(Absolute Blast Count or Other Cell Count)	1.012 (0.933-1.098)	1.014 (0.933-1.101)
Hemoglobin Upon Admission	0.956 (0.861-1.062)	1.020 (0.917-1.135)
Platelet Count Upon Admission	1.001 (0.997-1.005)	0.997 (0.993-1.001)
Prothrombin Time Upon Admission (PT)	1.040 (0.966-1.120)	1.043 (0.968-1.125)
Partial Thromboplastin Time Upon Admission (PTT)	0.993 (0.964-1.022)	1.004 (0.975-1.034)
Fibrinogen Upon Admission	1.001 (1.000-1.002)	1.000 (0.999-1.002)

***P-value <0.05**