



Acute Promyelocytic Leukemia Patients Receiving ATRA with and without Voriconazole Prophylaxis: Effect on Incidence and Outcomes of Differentiation Syndrome

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Authors' contributions

This work was carried out in collaboration between all authors. Authors JNB, JCK, CSP, RAD, NG and MMP participated in concept and design, data collection, data analysis/interpretation and manuscript creation involving critical writing and revising of the intellectual content. All authors read and approved the final version of this manuscript.

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ABSTRACT

Background: The combination of all *trans*-retinoic acid (ATRA) and voriconazole may lead to increased ATRA exposure resulting in a higher incidence of differentiation syndrome (DS).
Patients and Methods: This single center analysis evaluated the incidence and outcomes of ATRA-induced DS in 46 adult patients with acute promyelocytic leukemia (APL) undergoing induction chemotherapy.
Results: Thirty-one patients (69% by day 60) received a chemotherapy regimen including ATRA coinciding with voriconazole administration and 15 patients underwent treatment without

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voriconazole. The overall incidence of DS was 36% (n=16) by day 60, with patients receiving voriconazole showing a trend towards a higher incidence (HR 2.31, CI 0.78-6.847, p=0.1308). This trend persisted after adjusting for BMI (HR 1.96, CI 0.65-5.94, p=0.23); however, a small number of DS events precluded statistical significance.

Conclusion: A trend towards an increased incidence and severity of ATRA-mediated DS was seen in adult APL patients receiving voriconazole prophylaxis during induction chemotherapy. This important finding warrants validation in larger studies.

Keywords: Acute promyelocytic leukemia; all-trans retinoic acid (ATRA); voriconazole; differentiation syndrome.

1. INTRODUCTION

The differentiation syndrome (DS) is a potentially fatal complication related to all *trans*-retinoic acid (ATRA) use in induction chemotherapy for patients with acute promyelocytic leukemia (APL). While the exact pathogenesis of DS remains incompletely understood, reported incidence and mortality rates range between 2-31% and 1-33% respectively [1-4]. Recent studies have shown that administration of corticosteroids at early onset can reduce the mortality; however, increased morbidity and increased use of hospital resources remains a major concern [5-9].

The metabolism of ATRA is mediated through human cytochrome P450 (CYP) enzyme pathways, most notably CYP2C9 and CYP3A4 [10,11]. Triazole derivatives, such as voriconazole, are potent antifungal agents that act by inhibiting the Cytochrome P-450 mediated conversion of lanosterol to ergosterol [12]. Voriconazole is known to be a strong inhibitor of CYP2C9 and CYP2C19 with moderate inhibition of CYP3A4, in contrast to fluconazole which has less potent CYP interactions [13]. Other adverse effects of ATRA when combined with azole antifungals have been previously reported in case reports [14-18]. The potentially clinically significant drug-drug interaction with ATRA and voriconazole may lead to increased ATRA exposure resulting in a greater incidence and severity of DS.

There has been a trend amongst leukemia physicians to support the use of voriconazole as antifungal prophylaxis. We conducted this study to report the incidence and outcomes of suspected DS during induction-phase treatment with ATRA, comparing patients with and without concomitant voriconazole administration.

2. MATERIALS AND METHODS

This single-center, retrospective chart review was conducted in accordance with the principles laid out in the Declaration of Helsinki approved by the Mayo Clinic Institutional Review Board. All patients provided consent for review of their medical records for research purposes. Consecutive adult patients with a diagnosis of APL between January 2000 and October 2011 were evaluated. Patients were included if they were newly diagnosed or in their first relapse and undergoing intensive-phase treatment with a combination chemotherapy regimen that included ATRA. Patients were excluded if they received concomitant arsenic trioxide as part of their chemotherapy regimen.

Diagnosis of APL was determined by bone marrow morphologic examination and confirmed through cytogenetic and molecular techniques [19]. ATRA-induced DS was defined as a clinical entity having 3 or more of the following criteria: elevated white blood cell (WBC) count, fever, chills, weight gain, dyspnea, hypoxia, respiratory distress, pulmonary infiltrates, pleural or pericardial effusion, hypotension, and renal failure. Patients meeting 4 or more of the above criteria were classified as having severe DS. The Sanz stratification model was used to stratify patients into three risk categories: low, intermediate and high [20]. Patients were also stratified into four different categories based on their body mass index (BMI): underweight, normal weight, overweight and obese as this has been shown to be a risk factor associated with the DS [21-24].

2.1 Data Collection

Clinical and demographic data were retrospectively abstracted. Bone marrow biopsy slides, cytogenetic and molecular results were centrally reviewed. Data collected for analysis

included voriconazole dose, route of administration, frequency, therapeutic drug monitoring, duration of therapy and days of overlap between voriconazole and ATRA use. Data for determination of DS included: elevated WBC, fever, chills, weight gain, dyspnea, hypoxia, respiratory distress, pulmonary infiltrates, pleural or pericardial effusion, hypotension, and elevated serum creatinine. Morbidity assessment included the necessity for: dexamethasone administration, duration of dexamethasone, rapid response activation, intensive care unit (ICU) admission, mechanical ventilation, vasopressor support, subspecialty consults and ICU length of stay.

The primary endpoint was the incidence of proven or suspected DS up to 60 days after receiving induction-phase chemotherapy utilizing ATRA. Secondary endpoints included characterization of symptoms associated with DS diagnosis, severity of the ATRA-mediated DS, and need for ICU admission with intensive care support.

2.2 Statistical Analysis

A Cox proportional hazards model measured the association of voriconazole use and body mass index (BMI) with DS occurrence, where voriconazole use was considered a time-dependent covariate. Cox proportional hazards models were then adjusted for one covariate at a time to determine an association of voriconazole and DS occurrence. Kaplan-Meier curve was used to summarize days to diagnosis of DS. Interobserver agreement was calculated by using the κ statistic and was interpreted utilizing the scale of Landis and Koch [25].

3. RESULTS AND DISCUSSION

Forty-six (82%) of 56 consecutive patients with a diagnosis of APL between January 2000 and October 2011 met inclusion criteria. Patients were excluded due to an incomplete medical record (n=6), alternate diagnosis (n=2), and age less than 18 years (n=2). The clinical and demographic characteristics are shown in Table 1. Thirty-one patients (69% by day 60) received a chemotherapy regimen including ATRA coinciding with voriconazole administration and 15 patients received the same without voriconazole prophylaxis. Patients received ATRA chemotherapy for a median of 46 days (IQR 22-56 days) and voriconazole for a median of 18 days (IQR 11 – 27 days). The median days

of overlap between ATRA and voriconazole was 18 days (IQR 7–27 days) and the median time between the start of ATRA administration and the addition of voriconazole was 4 days (IQR 0 - 8 days). With the exception of BMI, which was positively related to receiving voriconazole therapy (HR 1.04, CI 1.001-1.078, p=0.0427), there was no difference between the two groups.

Sixteen patients (36% by day 60) experienced the DS with a trend towards higher incidence in patients that also received voriconazole (HR 2.31, CI 0.78-6.874, p=0.1308). This trend persisted even after adjusting for BMI (HR 1.96, CI 0.65-5.94, p=0.23). Table 2 shows the relationship between voriconazole and DS when adjusting for WBC, peripheral blast count, serum albumin, lactate dehydrogenase, dexamethasone prophylaxis and interacting medications of the cytochrome P450 3A4, 2C8, 2C9 and 2C19 pathways concurrently being administered. The hazard ratios and corresponding p-values for voriconazole are similar across all 12 multivariate Cox models. This demonstrates that the association between voriconazole and DS is unaffected by these well known, confounding variables and further establishes the trend of increased risk of DS when voriconazole is added to ATRA during induction chemotherapy. It must be acknowledged that adjusting for more than one variable at a time is not warranted because there are only 16 patients with DS and doing so could result in an over fitted model.

The median number of DS-related symptoms was 4 (range 3-8) and the frequency of individual signs/symptoms were: dyspnea (87.5%), pulmonary infiltrates (81.25%), hypoxia (62.5%), fever (56.25%), pleural effusion (43.75%), hypotension (31.25%), pericardial effusion (12.5%), renal impairment (12.5%), and chills (6.25%). Twelve of 16 patients (75%) experiencing DS were classified as severe DS, including 8 that received voriconazole and 4 patients who did not. Seven patients (44%) required ICU admission attributable to DS, five (71%) from the ATRA and voriconazole group and 2 from the ATRA only group. The particular constellation of signs and symptoms for each patient that met criteria for DS is provided in Table 3. The mean length of stay in the ICU was 4 days (range, 1-7 days) and 29% required vasopressor support. No patients required mechanical intubation. The days from initiation of ATRA or voriconazole to diagnosis of DS are represented in the Kaplan-Meier curves in Fig. 1. One patient's death was attributed to DS.

The definition of DS was based on previous studies [1-9]; however, the diagnosis remains subjective with a wide range of variability and lacks a general consensus. The κ value for interobserver agreement for the diagnosis of DS was 0.9042 (95% CI 0.7743-1.0000) demonstrating an almost perfect agreement among reviewers independently evaluating patient records according to the proposed definitions (J.N.B., J.C.K., C.S.P. and N.G.) according to Landis-Koch criteria [25]. This result validates the incidence of DS and strengthens the likelihood of the effect of adding voriconazole to ATRA.

Table 1. Baseline characteristics of patients at time of inclusion

Characteristic	All patients n=46	Hazard ratio	95% HR confidence limits	P value
Age (years), median (range)	56 (18-80)	1.002	0.983–1.022	0.8179
Male, No. (%)	27 (59)	1.784	0.838–3.796	0.1330
Caucasian, No (%)	42 (91)	0.858	0.26–2.828	0.8009
Body Mass Index, median (range)	31 (20-76)	1.039	1.001–1.078	0.0427
WHO class II	4 (9)	REF	REF	
WHO class III	17 (37)	1.902	0.424–8.520	0.4009
WHO class IV	25 (54)	1.9	0.438–8.247	0.3912
Serum Creatinine, mg/dL, median (range)	0.9 (0.6-1.7)	1.082*	0.907–1.291*	0.3784
Albumin, mg/dL, median (range)	3.9 (2.9-4.9)	1.833	0.819–4.104	0.4331
LDH (per 100 Units), median (range)	233 (124-2412)	0.957†	0.874–1.047†	0.338
WBC count, $\times 10^9/L$, median (range)	1.4 (0.2-79.9)	1.003	0.973–1.033	0.8659
≤ 10	38 (83)			
> 10	8 (17)			
Platelet count, $\times 10^9/L$, median (range)	45.5 (10-330)	1.005‡	0.96–1.051‡	0.8424
≤ 40	20 (43)			
> 40	26 (57)			
Sanz risk assessment, no. (%)				0.8142
Low	24 (52)	REF	REF	
Intermediate	14 (30)	0.824	0.364–1.868	0.6436
High	8 (17)	1.143	0.446–2.929	0.7813
FAB subtype, no. (%)				0.6977
Hypogranular	8 (17)	REF	REF	
Hypergranular	37 (80)	1.166	0.486–3.448	
Microgranular	1 (2)	0	0–8.834	
PML-RAR α isoform (%), median (range)	88 (0-99.2)	0.994	0.984–1.005	0.2979
Peripheral Blasts (%), median (range)	3 (0-95)	0.997	0.985–1.008	0.5534
Chemotherapy regimen,				0.0975
ATRA+ Anthracycline	39 (85)	∞	1.171– ∞	
ATRA + Anthracycline + Cytarabine	5 (11)	∞	1.051– ∞	
ATRA monotherapy	2 (4)	REF	REF	
Dexamethasone prophylaxis	5 (11)	0.516	0.123–2.162	0.3652
CYP3A4 pathway				
Inducer, n (%)	11 (24)	1.087	0.486–2.433	0.8386
Inhibitor, n (%)	22 (48)	0.666	0.326–1.362	0.2659
CYP2C8 pathway				
Inducer, n (%)	0 (0)	N/A	N/A	N/A
Inhibitor, n (%)	3 (7)	0.95	0.227–3.987	0.9446
CYP2C9 pathway				
Inducer, n (%)	1 (2)	0	0–1.748	0.1355
Inhibitor, n (%)	15 (33)	0.573	0.256–1.284	0.176
CYP2C19 pathway				
Inducer, n (%)	3 (7)	0.935	0.223–3.925	0.9273
Inhibitor, n (%)	34 (74)	1.026	0.458–2.297	0.9509

WHO = World Health Organization; LDH = Lactose Dehydrogenase; WBC = White Blood Count;
REF = Reference Value; * per 0.1 units; † per 100 units; ‡ per 10 units

The DS occurred in 36% of APL patients receiving ATRA based induction therapy by day 60, consistent with previous studies [1-3]. Although numbers were limited for statistical significance, patients receiving concomitant antifungal prophylaxis with voriconazole were more likely to experience DS compared to those without. This trend persisted after adjusting for BMI. Admission to an ICU was necessary in almost half of patients experiencing DS. Severe DS occurred in a majority of patients with a median of 4 symptoms establishing the diagnosis and resulted in the death of one patient.

Limitations of this study include its retrospective design, small sample size, dependence on the accuracy and completeness of the medical record, and the many confounding variables interfering with an accurate diagnosis of the DS [1-9]. Distinguishing between DS and alternative clinical diagnoses remains subjective with a wide range of variability; however, our interobserver agreement of 0.9042 indicated minimal variation when utilizing pre-specified criteria and almost perfect agreement for the diagnosis of DS.

Table 2. The relationship between voriconazole and DS adjusted by individual covariates

Model	Covariate	Adjusted voriconazole hazard ratio	Adjusted voriconazole HR 95% CI	P value
1	WBC count	2.314	0.782–6.847	0.1297
2	Peripheral blast count	2.138	0.721–6.345	0.1708
3	Serum albumin	3.845	0.687–21.524	0.1254
4	LDH (per 100 units)	2.752	0.8558–8.853	0.0895
5	Dexamethasone prophylaxis	2.149	0.726–6.357	1.1668
6	CYP3A4 inducers	2.340	0.791–6.923	0.1243
7	CYP3A4 inhibitors	2.456	0.822–7.332	0.1075
8	CYP2C8 inhibitors	2.375	0.795–6.982	0.1219
9	CYP2C9 inducers	2.738	0.85–8.819	0.0914
10	CYP2C9 inhibitors	2.662	0.874–8.107	0.0850
11	CYP2C19 inducers	2.201	0.735–6.595	0.1588
12	CYP2C19 inhibitors	2.286	0.768–6.803	0.1372

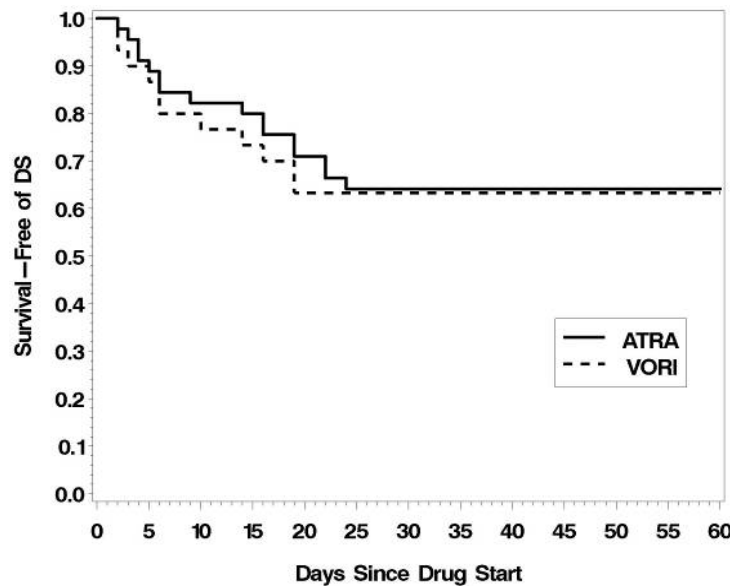


Fig. 1. Estimated days from initiation of voriconazole to diagnosis of DS
 Sixteen patients (36% by day 60) in total experienced the DS with a trend towards higher incidence in patients that received voriconazole (HR 2.31, CI 0.78-6.874, p=0.1308)

Table 3. The signs and symptoms contributing to the diagnosis of DS in patients receiving ATRA during induction chemotherapy

No	Age (yrs)	Sex	Weight change (kg)	WBC count	Fever	Chills	Dyspnea	Hypoxia	Respiratory distress	Pulmonary infiltrate on X-ray or CT	Pericardial effusion	Pleural effusion	Hypotension	Renal impairment	Total factors
1	63.2	F	-1.6	2.7	Yes	No	Yes	Yes	Yes	Yes	No	No	No	No	5
2	30.8	F	-0.8	0.1	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	6
3	18.8	M	-1.8	18.9	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	8
4	66.4	F	1.9	2.9	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	5
5	62.2	F	-1.3	0.9	No	No	Yes	Yes	Yes	Yes	No	No	No	No	4
6	76.1	M	3.1	0.4	No	No	Yes	No	Yes	Yes	Yes	No	No	No	5
7	77.8	M	3.2	0.9	No	No	Yes	Yes	No	Yes	No	Yes	Yes	No	6
8	42.6	M	1.2	1.6	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No	5
9	39.1	M	0.3	12.9	No	No	Yes	Yes	Yes	No	No	No	Yes	Yes	6
10	60.6	M	-4.8	0.1	Yes	No	Yes	No	No	Yes	No	No	No	No	3
11	24.7	M	1.8	51.2	No	No	Yes	Yes	No	Yes	No	Yes	No	No	5
12	21	M	5.7	23.1	Yes	No	No	No	No	No	No	No	Yes	Yes	5
13	56	F	12.4	1.6	Yes	No	Yes	Yes	No	Yes	No	No	No	No	5
14	68	F	5.8	1.2	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	6
15	65	F	6.2	0.9	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	6
16	46	M	-1.7	0.4	Yes	No	Yes	No	No	Yes	No	No	No	No	3

4. CONCLUSION

Our study demonstrates a trend towards increased incidence of ATRA-mediated DS in APL patients receiving voriconazole as fungal prophylaxis during induction therapy. Despite this being a non-statistically significant increase in DS, providers should exercise caution and vigilant monitoring for DS when using voriconazole concurrently with ATRA until additional, prospective investigation is conducted.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Avvisati G, Lo Coco F, Diverio D, Falda M, Ferrara F, Lazzarino M, Russo D, Petti MC, Mandelli F. AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: A gruppo italiano malattie ematologiche maligne dell'adulto (GIMEMA) pilot study. *Blood*. 1996;88(4):1390-8.
2. Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E, Fey M, Rayon C, Huguet F, Sotto JJ, Gardin C, Makhoul PC, Travade P, Solary E, Fegueux N, Bordessoule D, Miguel JS, Link H, Desablens B, Stamatoullas A, Deconinck E, Maloisel F, Castaigne S, Preudhomme C, Degos L. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *The European APL Group. Blood*. 1999;94(4):1192-200.
3. Frankel SR, Eardley A, Lauwers G, Weiss M, Warrell RP, Jr. The "retinoic acid syndrome" in acute promyelocytic leukemia. *Annals of Internal Medicine*. 1992;117(4):292-6.
4. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH, Ogden A, Shepherd L, Rowe JM, Francois C, Larson RS, Wiernik PH. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. *Blood*. 2000;95(1):90-5.
5. Ades L, Chevret S, Raffoux E, de Botton S, Guerci A, Pigneux A, Stoppa AM, Lamy T, Rigal-Huguet F, Vekhoff A, Meyer-Monard S, Maloisel F, Deconinck E, Ferrant A, Thomas X, Fegueux N, Chomienne C, Dombret H, Degos L, Fenaux P. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. *J Clin Oncol*. 2006;24(36):5703-10.
6. De Botton S, Chevret S, Coiteux V, Dombret H, Sanz M, San Miguel J, Caillot D, Vekhoff A, Gardembas M, Stamatoulas A, Conde E, Guerci A, Gardin C, Fey M, Cony Makhoul D, Reman O, De la Serna J, Lefrere F, Chomienne C, Degos L, Fenaux P. Early onset of chemotherapy can reduce the incidence of ATRA syndrome in newly diagnosed acute promyelocytic leukemia (APL) with low white blood cell counts: Results from APL 93 trial. *Leukemia*. 2003;17(2):339-42.
7. De Botton S, Dombret H, Sanz M, Miguel JS, Caillot D, Zittoun R, Gardembas M, Stamatoulas A, Conde E, Guerci A, Gardin C, Geiser K, Makhoul DC, Reman O, de la Serna J, Lefrere F, Chomienne C, Chastang C, Degos L, Fenaux P. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. *The European APL Group. Blood*. 1998;92(8):2712-8.
8. Kelaidi C, Chevret S, De Botton S, Raffoux E, Guerci A, Thomas X, Pigneux A, Lamy T, Rigal-Huguet F, Meyer-Monard S, Chevallier P, Maloisel F, Deconinck E, Ferrant A, Fegueux N, Ifrah N, Sanz M, Dombret H, Fenaux P, Ades L. Improved outcome of acute promyelocytic leukemia with high WBC counts over the last 15 years: The European APL Group experience. *J Clin Oncol*. 2009;27(16):2668-76.
9. Wiley JS, Firkin FC. Reduction of pulmonary toxicity by prednisolone prophylaxis during all-trans retinoic acid treatment of acute promyelocytic leukemia. *Australian Leukaemia Study Group. Leukemia*. 1995;9(5):774-8.
10. Vesanoid [package insert]. Nutley, NJ: Roche Laboratories Inc; 1998.
11. Marill J, Cresteil T, Lanotte M, Chabot GG. Identification of human cytochrome P450s involved in the formation of all-trans-retinoic acid principal metabolites. *Mol Pharmacol*. 2000;58(6):1341-8.

12. Terrell CL. Antifungal agents. Part II. The azoles. *Mayo Clin Proc.* 1999;74(1): 78-100.
13. Johnson LB, Kauffman CA. Voriconazole: A new triazole antifungal agent. *Clin Infect Dis.* 2003;36(5):630-7.
14. Bennett MT, Sirrs S, Yeung JK, Smith CA. Hypercalcemia due to all trans retinoic acid in the treatment of acute promyelocytic leukemia potentiated by voriconazole. *Leukemia & lymphoma.* 2005;46(12): 1829-31.
15. Cordoba R, Ramirez E, Lei SH, Lopez de la Guia A, Sanjurjo MJ, Carcas AJ, Hernandez-Navarro F. Hypercalcemia due to an interaction of all-trans retinoic acid (ATRA) and itraconazole therapy for acute promyelocytic leukemia successfully treated with zoledronic acid. *Eur J Clin Pharmacol.* 2008;64(10):1031-2.
16. Dixon KS, Hassoun A. Pseudotumor cerebri due to the potentiation of all-trans retinoic acid by voriconazole. *Journal of the American Pharmacists Association: JAPhA.* 2010;50(6):742-4.
17. Vanier KL, Mattiussi AJ, Johnston DL. Interaction of all-trans-retinoic acid with fluconazole in acute promyelocytic leukemia. *Journal of Pediatric Hematology/Oncology.* 2003;25(5):403-4.
18. Yarali N, Tavit B, Kara A, Ozkasap S, Tunc B. Acute renal failure during ATRA treatment. *Pediatric Hematology & Oncology.* 2008;25(2):115-8.
19. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellstrom-Lindberg E, Tefferi A, Bloomfield CD. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: Rationale and important changes. *Blood.* 2009;114(5):937-51.
20. Sanz MA, Lo Coco F, Martin G, Avvisati G, Rayon C, Barbui T, Diaz-Mediavilla J, Fioritoni G, Gonzalez JD, Liso V, Esteve J, Ferrara F, Bolufer P, Bernasconi C, Gonzalez M, Rodeghiero F, Colomer D, Petti MC, Ribera JM, Mandelli F. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: A joint study of the PETHEMA and GIMEMA cooperative groups. *Blood.* 2000;96(4): 1247-53.
21. World Health Organization Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. World Health Organization Technical Report, Series 894. 2000;1-253.
22. Breccia M, Mazzarella L, Bagnardi V, Disalvatore D, Loglisci G, Cimino G, Testi AM, Avvisati G, Petti MC, Minotti C, Latagliata R, Foa R, Pelicci PG, Lo-Coco F. Increased BMI correlates with higher risk of disease relapse and differentiation syndrome in patients with acute promyelocytic leukemia treated with the AIDA protocols. *Blood.* 2012;119(1):49-54.
23. Jeddi R, Ghedira H, Mnif S, Gouider E, Fenaux P, Meddeb B. High body mass index is an independent predictor of differentiation syndrome in patients with acute promyelocytic leukemia. *Leuk Res.* 2010;34(4):545-7.
24. Jeddi R, Kacem K, Ben Neji H, Mnif S, Gouider E, Aissaoui L, Ben Amor R, Ben Lakhal R, Ben Abid H, Belhadjali Z, Meddeb B. Predictive factors of all-trans-retinoic acid related complications during induction therapy for acute promyelocytic leukemia. *Hematology.* 2008;13(3):142-6.
25. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* 1977;33(1):159-74.

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