Influence of initiation time and white blood cell count on the efficacy of cytotoxic agents in acute promyelocytic leukemia during induction treatment

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Abstract. The present study retrospectively analyzed 96 newly diagnosed acute promyelocytic leukemia (APL) patients with low-intermediate mortality risk to identify the optimum timing to initiate cytotoxic chemotherapy following all-trans retinoic acid (ATRA) administration. Based on white blood cell (WBC) at chemotherapy initiation, the patients were divided into three groups: low WBC (WBC count ≤4x10^9/l), intermediate WBC (WBC count >4x10^9/l and <15x10^9/l) and high WBC group (WBC count ≥15x10^9/l). According to the period from ATRA commencement to chemotherapy, 96 patients were further divided into two groups: ≤3 days group (chemotherapy within 3 days of ATRA) and >3 days group (chemotherapy >3 days after ATRA). Clinical effects were compared by univariate analysis and multivariate analyses. The incidence rate of differentiation syndrome (DS; also termed retinoic acid syndrome) was 0.0, 11.1 and 40.0% in the low, intermediate and high WBC groups, respectively (P<0.001); complete remission (CR) rate was 90.5, 100.0 and 73.3%, respectively (P<0.001); and the rate of early mortality (defined as fatality during induction treatment) was 4.8, 0.0 and 26.7%, respectively (P<0.001). No differences were identified in clinicolaboratory parameters between the ≤3 days and >3 days groups, except in time to achieve CR (P=0.004) and rate of bleeding related to chemotherapy (P=0.009), both being higher in the >3 days group. Multivariate analyses indicated WBC count at chemotherapy was the only independent risk factor for the occurrence of DS [P=0.002; odds ratio (OR) =1.058, 95% confidence interval (CI) =1.021-1.095] and early mortality (P=0.036; OR =1.036, 95% CI =1.002-1.070). For newly diagnosed APL patients with low-intermediate risk, chemotherapy initiation should be recommended until WBC count rises to between 4x10^9/l and 15x10^9/l during induction treatment.

Introduction

Coagulopathy resulting in critical hemorrhage is a leading cause of early fatality in acute promyelocytic leukemia (APL). The introduction of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO)-based chemotherapy has notably improved clinical outcome for patients with APL, with the disease now considered as a curable malignant pathology (1,2). The National Comprehensive Cancer Network (NCCN) recommends ATRA and anthracycline-based chemotherapy with or without combination with ATO as the standard induction treatment (3). It has been reported that complete remission (CR) rate may reach higher than 80% and that an early mortality rate (occurring during induction treatment) lower than 10% can be achieved following this treatment (4-9). However, epidemiological studies based on American and European populations indicated that early mortality of newly diagnosed APL may be underestimated, since a marked number of patients with poor physical status were excluded by the clinical trials or did not survive prior to recruitment (10-12). These findings suggest that initial treatment of APL may not be sufficient to reduce early mortality, and therefore, that induction treatment requires further improvement.

Following use of ATRA, patients may have increased risk of developing leukocytosis and differentiation syndrome (DS) (1). This complication usually occurs during induction therapy, in which leukemic blasts become present in abundance. The syndrome is characterized by unexplained fever, acute respiratory distress and/or capillary

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Abbreviations: APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; NCCN, National Comprehensive Cancer Network; WBC, white blood cell; DS, differentiation syndrome; CR, complete remission; ATO, arsenic trioxide; PLT, platelet

Key words: acute promyelocytic leukemia, low-intermediate risk, induction treatment, initiation time, prognosis, chemotherapy

leak syndrome leading to acute renal failure (13). Therefore, cytotoxic therapeutic agents are required to regulate white blood cells (WBCs). However, considering the possible effects of chemotherapy on coagulation functions, clinicians tend to initiate cytotoxic treatment including anthracycline agents at least 3 days after use of ATRA or until coagulation functions are recovered (2). However, it remains difficult to determine the appropriate time to initiate chemotherapy, and NCCN have not yet provided definitive recommendations. The present study attempted to evaluate the effect of different initiation timings of chemotherapy during induction treatment for APL.

Patients and methods

Patients. A total of 212 patients with *de novo* APL were hospitalized at Nanfang Hospital of Southern Medical University (Guangzhou, China) between January 2003 and December 2014. Of these patients, 169 accepted ATRA and cytotoxic agents during induction treatment, among which 96 were categorized into a low-intermediate risk group, and the remaining patients categorized into a high risk group, based on Sanz's risk stratification model for survival prediction (14). All 96 patients [47 males and 49 females with a median age of 32 years (range 15-66)] with low-intermediate risk were retrospectively enrolled in the present study. Disease diagnosis was confirmed by bone marrow aspiration, chromosome karyotyping analysis, fluorescence *in situ* hybridization analysis and polymerase chain reaction tests. Informed consent prior to and regarding the treatment protocol was obtained from all patients analyzed in the present study.

Treatments. When a diagnosis of APL was suspected, ATRA (30 mg/m^2/day) was administered as early as possible, until CR was achieved. Chemotherapy comprised treatment with idarubicin (8 mg/m^2/day on days 1, 3 and 5), daunorubicin (45 mg/m^2/day on days 1, 3 and 5) or homoharringtonine (2 mg/m^2/day on days 1-5); induction treatment was combined with cytarabine (100 mg/m^2/day on days 1-7) and/or hydroxyurea (2.0-3.0 g/day, adjusted according to regular blood tests). In addition, 36 patients simultaneously received ATO (0.15 mg/kg/day for 14 days). Chemotherapy was applied 0-21 days after initiation of ATRA (median time, 7 days; range, 0-20 days). Blood product support was applied to maintain a platelet (PLT) level ≥30x10^9/l, hemoglobin level ≥70 g/l and plasma fibrinogen level ≥1.5 g/l. All adverse events related to treatments, including bone marrow depression, infection and bleeding were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (15).

Definitions. Retinoic acid syndrome, also known as DS, was diagnosed based on the incidence of at least two of the following clinical features: unexplained fever, acute respiratory distress with interstitial pulmonary infiltrates, acute renal failure, weight gain >5 kg, unexplained hypotension and pleuropericardial effusion (13). Prevention strategies included dexamethasone (10 mg q12h) and discontinuation of ATRA and ATO. All 96 patients were categorized according to Sanz's risk stratification score (14) as low risk (WBC count <10.0x10^9/l and PLT ≥40.0x10^9/l at diagnosis) and intermediate risk (WBC count <10x10^9/l and PLT <40.0x10^9/l). CR was defined as the presence of <5% blast cells in bone marrow aspirates, PLT >100x10^9/l and no juvenile cells in peripheral blood according to the criteria set by the US National Cancer Institute (16). Early mortality was defined as fatality during induction treatment from the first day of hospitalizations. Eastern Cooperative Oncology Group performance status score (0-4 score) was applied to investigate patient's physical status prior to chemotherapy (17).

Groups. In most cases, WBC count increased as ATRA was used. Thresholds were initially set according to the WBC count at chemotherapy initiation as ≤4x10^9/l, >4x10^9 and <10x10^9/l, and ≥10x10^9/l, since normal WBC count is between 4x10^9 and 10x10^9/l. However, no significant difference was determined using these classes. The thresholds were therefore altered until it was apparent when use of cytotoxic agents was appropriate. Thus, based on the WBC count at chemotherapy initiation, the 96 patients were divided into three groups: low WBC group (WBC count ≤4x10^9/l), intermediate WBC group (WBC count >4x10^9 and <15x10^9/l), high WBC group (WBC count ≥15x10^9/l). Table I presents a comparison of the baseline clinical and laboratory parameters of the low, intermediate and high WBC groups. According to the period from ATRA commencement to chemotherapy, the 96 patients were also divided into two groups: ≤3 days group (treated with chemotherapy within 3 days of ATRA) and >3 days group (treated with chemotherapy at least 3 days after ATRA). Table II presents a comparison of the baseline clinical and laboratory parameters of these two groups.

Statistical analysis. Statistical analysis was performed with SPSS v.17.0 software (SPSS, Inc., Chicago, IL, USA). All data were collected in January, 2015. Clinical features are presented as percentages (%) for categorical variables and as mean values ± standard deviation for normally distributed continuous variables. The χ^2 test was used to analyze the significance of differences in the distribution of categorical variables between the patient subsets, and Bonferroni's correction was used post-hoc to compare every two groups. The unpaired Student's test or Mann-Whitney test was used to analyze the significance of differences in the distribution of continuous parametric variables and the distribution of ranked variables. Multivariate analysis was performed by using a binary logistic regression model. WBC count at diagnosis, PLT count at diagnosis, WBC count at chemotherapy initiation and the period from ATRA to chemotherapy were considered in the multivariate analysis to evaluate their effects on DS, early mortality and remission. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparisons of clinical effects among low, intermediate and high WBC groups. Comparison of the baseline clinical and laboratory parameters showed no notable differences between these groups (Table I). As depicted in Table III, the incidence of DS was 0.0, 11.1 and 40.0% respectively

Table I. Baseline demographic, clinical and laboratory characteristics of the low, intermediate and high WBC groups.

	WBC group			
Parameter	Low	Intermediate	High	P-value
Cases	21	45	30	
Age, years	31.6±10.2	33.8±10.9	31.8±12.1	0.542
15-54	21 (100.0)	44 (97.8)	28 (93.3)	
55-70	0 (0.0)	1 (2.2)	2 (6.7)	
Sex, male/female	11/10	23/22	13/17	0.755
WBC count at diagnosis	1.76±0.93	1.94±0.79	6.32±7.03	0.056
PLT count at diagnosis	49.9±37.7	41.2±33.7	32.6±25.9	0.196
Sanz's risk stratification				
Low risk	11 (52.4)	16 (35.6)	10 (33.3)	0.331
Intermediate risk	10 (47.6)	29 (64.4)	20 (66.7)	
ECOG score				
1-2	14 (66.7)	23 (51.1)	14 (46.7)	0.346
3-4	7 (33.3)	22 (48.9)	16 (53.3)	
Induction treatment				
Combined with arsenic trioxide	9 (42.9)	18 (40.0)	9 (30.0)	0.578
Combined with cytarabine	6 (28.6)	19 (42.2)	15 (50.0)	0.310
Combined with hydroxyurea	6 (28.6)	15 (33.3)	20 (66.7)	0.006
Cytotoxic agent distribution				
Daunorubicin	6 (28.6)	14 (31.1)	16 (53.3)	0.178
Idarubicin	11 (52.4)	19 (42.2)	7 (23.3)	
Homoharringtonine	4 (19.0)	12 (26.7)	7 (23.3)	

Values are provided as number of cases (%) or as the mean ± standard deviation. WBC, white blood cell; PLT, platelet; ECOG, Eastern Cooperative Oncology Group.

Table II. Baseline demographic, clinical and laboratory characteristics of the ≤3 and >3 days interval groups.

	Interval group		
Groups	≤3 days	>3 days	P-value
Cases	27	69	
Age, years	30.5±10.4	33.2±11.6	0.292
15-54	27 (100.0)	66 (95.7)	
55-70	0 (0.0)	3 (4.3)	
Sex, male/female	15/12	32/37	0.419
WBC count at diagnosis	3.72±2.62	2.87±2.44	0.139
PLT count at diagnosis	26.3±18.9	45.8±35.3	0.001
Sanz's risk stratification			
Low risk	5 (18.5)	32 (46.4)	0.012
Intermediate risk	22 (81.5)	37(53.6)	
ECOG score			
1-2	14 (51.9)	37 (53.6)	0.876
3-4	13 (48.1)	32 (46.4)	
Induction treatment			
Combined with arsenic trioxide	13 (48.10)	23 (33.30)	0.178
Combined with cytarabine	8 (29.6)	32 (46.40)	0.135
Combined with hydroxyurea	6 (22.20)	35 (50.70)	0.011
Cytotoxic agent distribution			
Daunorubicin	8 (29.6)	28 (40.6)	0.584
Idarubicin	10 (37.0)	20 (29.0)	
Homoharringtonine	9 (33.3)	21 (30.4)	

Values are provided as number of cases (%) or as the mean ± standard deviation. WBC, white blood cell; PLT, platelet; ECOG, Eastern Cooperative Oncology Group.

in the low, intermediate and high WBC groups, respectively (P<0.001). DS incidence was significantly lower in the low and intermediate WBC groups compared with in the high WBC group (P=0.001 and 0.003). There was no difference in the extent of bone marrow suppression between the three groups. Grade 3-4 infection rates were 71.4, 33.3 and 43.3% (P=0.015). Multiple comparisons indicated grade 3-4 infection in the low WBC group was significantly more prevalent than that in the intermediate WBC group (P=0.004). Grade 3-4 bleeding rates were 9.5, 26.7 and 40.0%, respectively (P=0.055), which in the low WBC group was significantly lower than in the high WBC group (P=0.016). CR rates were 90.5, 100 and 73.3%, respectively (P<0.001), which of the intermediate WBC group was significantly higher than of the high WBC group (P=0.001). Early mortality rate in each group was 4.8, 0.0 and 26.7%, respectively (P<0.001), and determined as significantly higher in the high WBC group than in the intermediate WBC group (P=0.003). The time to achieve CR was similar between the three groups (P=0.498; Table III).

Comparisons of clinical effects between the ≤3 days and >3 days groups. Comparison of the baseline clinical and laboratory parameters revealed that PLT count was higher in the >3 days group (P=0.001). Time between ATRA and chemotherapy was also associated with the distribution of Sanz's risk stratification (P=0.012; Table II). Regarding the initiation time of chemotherapy, there were no significant differences in DS incidence, grade 3-4 bone marrow suppression rate, grade 3-4 infection rate, CR rate and early mortality rate between the ≤3 days and >3 days groups (Table IV). Time to achieve CR was longer in the >3 days group (37.6±10.0 vs. 30.8±11.7 days; P=0.004). Although PLT count was higher in the >3 days group, bleeding related to chemotherapy was also more prevalent in the >3 days group

Table III. Comparisons of clinical effects in the low, intermediate and high WBC groups.

Parameter	WBC group			P-value
	Low	Intermediate	High	
Cases	21	45	30	
DS incidence	0 (0.0)[a]	5 (11.1)[b]	12 (40.0)	<0.001
Grade 3-4 bone marrow depression	20 (95.2)	42 (93.3)	23 (82.1)	0.047[g]
Grade 3-4 infection	15 (71.4)[c]	15 (33.3)	13 (43.3)	0.015
Bleeding related to chemotherapy	2 (9.5)[d]	12 (26.7)	12 (40.0)	0.055
Lowest WBC count x10^9/l	0.78±9.18	1.21±0.70	1.07±0.57	0.033
Highest WBC count x10^9/l	9.02±9.18	14.91±9.98	39.24±24.45	<0.001
CR rate	19 (90.5)	45 (100.0)[e]	22 (73.3)	<0.001
Time to achieve CR, days	34.8±15.6	35.1±10.3	31.6±8.8	0.498
Early mortality rate	1 (4.8)	0 (0.0)[f]	8 (26.7)	<0.001
Mortality cause				0.704
Hemorrhage	1	0	3	
DS	0	0	2	
Infection	0	0	1	
Other	0	0	2	

Values are provided as number of cases (%) or as the mean ± standard deviation. [a]P=0.001 vs. high WBC group; [b]P=0.003 vs. high WBC group; [c]P=0.004 vs. intermediate WBC group; [d]P=0.016 vs. high WBC group; [e]P=0.001 vs. high WBC group; [f]P=0.003 vs. high WBC group. WBC, white blood cell; DS, differentiation syndrome; CR, complete remission; [g]The expected count of 2 cells was <5, thus the dataset did not satisfy requirements of χ^2 test and the P-value is not significant.

Table IV. Comparison of clinical effects in the ≤3 and >3 days interval groups.

Parameter	Interval group		P-value
	≤3 days	>3 days	
Cases	27	69	
DS incidence	4 (14.8)	13 (18.8)	0.867
Grade 3-4 bone marrow depression	23 (88.5)	62 (91.2)	0.993
Grade 3-4 infection	12 (44.4)	31 (44.9)	0.966
Bleeding related to chemotherapy	2 (7.4)	23 (33.3)	0.009
Lowest WBC count x10^9/l	1.16±0.69	1.05±0.61	0.435
Highest WBC count x10^9/l	18.4±12.0	22.8±22.5	0.347
CR rate	24 (88.9)	62 (89.9)	1.000
Time to achieve CR, days	30.8±11.6	37.6±10.0	0.004
Early mortality rate	3 (11.1)	6 (8.7)	1.000
Mortality cause			
Hemorrhage	1	3	0.771
DS	1	1	
Infection	0	1	
Other	1	1	

Values are provided as number of cases (%) or as the mean ± standard deviation. WBC, white blood cell; DS, differentiation syndrome; CR, complete remission.

(33.3 vs. 7.4%, P=0.009; Table IV). To eliminate the effect of PLT count, multivariate analysis was performed to correct for bias.

Multivariate associations. The results of multivariate analysis revealed that WBC count at chemotherapy initiation was an independent risk factor for the occurrence of DS [P=0.002, odds ratio (OR) =1.058, 95% confidence interval (CI) =1.021-1.095]. WBC count at chemotherapy initiation was also indicated to influence the occurrence of early mortality (P=0.036, OR =1.036, 95% CI =1.002-1.070). However, the period from ATRA to chemotherapy, WBC count at diagnosis and PLT count at diagnosis were not independent risk factors for DS, early mortality or remission failure (Table V).

Discussion

NCCN guidelines recommend anthracycline-based chemotherapy as one part of induction treatment for newly diagnosed APL in order to reduce WBC count (3). However, the guidelines do not specify when to initiate chemotherapy. Tallman and Altman (2) suggested that chemotherapy should be used at least 1-3 days after ATRA and in newly diagnosed, low-intermediate-risk APL with WBC >5x10^9/l. To the best of our knowledge, there is a lack of studies on the optimal timing of chemotherapy during induction treatment. Therefore, this was a focus of the present study, investigated through univariate and multivariate analyses.

de Botton *et al* (18) reported that early addition of chemotherapy to ATRA therapy in newly diagnosed cases of APL with low WBC counts significantly reduced the incidence of ATRA syndrome (9.2%), compared with in those who received chemotherapy until CR was achieved (18.0%). Furthermore, the incidence of early mortality related to DS was lower (0.5 vs. 2.5%). In the present study, DS incidence was 17.7%, similar to that reported by de Botton *et al*, but >24.8% reported for clinical trials LPA96 and LPA99 (18,19). Inconsistent diagnostic criteria for DS may account for the differences. In the study by de Botton *et al*, DS diagnosis was established on the basis of satisfying at least three clinical signs. In the present study, and LPA96 and LPA99, DS diagnosis was made on the basis of satisfying at least two clinical signs. However, de Botton *et al* investigated newly diagnosed APL with low or intermediate risk, as in the present study; whereas LPA96 and LPA99 did not stratify the patients included in the clinical trials. Furthermore, de Botton *et al* focused on the effect of chemotherapy used in different periods on DS incidence.

Table V. Multivariate analysis of WBC count at chemotherapy, the period from ATRA to chemotherapy, and WBC and PLT counts at diagnosis.

Dependent variable	Independent variables	B	Standard error	Wald coefficient	P-value	Odds ratio	95% confidence interval
Differentiation syndrome	WBC count on chemotherapy	0.056	0.018	9.918	0.002	1.058	1.021-1.095
	Period from ATRA to chemotherapy	0.003	0.044	0.006	0.964	1.003	0.921-1.093
	WBC count at diagnosis	0.164	0.107	2.342	0.111	1.179	0.955-1.455
	PLT count at diagnosis	-0.001	0.011	0.011	0.796	0.999	0.978-1.020
Early mortality	WBC count on chemotherapy	0.035	0.017	4.391	0.036	1.036	1.002-1.070
	Period from ATRA to chemotherapy	-0.010	0.063	0.024	0.519	0.990	0.876-1.120
	WBC count at diagnosis	0.140	0.133	1.109	0.217	1.150	0.887-1.491
	PLT count at diagnosis	-0.021	0.019	1.202	0.200	0.979	0.943-1.017
Remission failure	WBC count on chemotherapy	0.031	0.019	2.616	0.106	1.032	0.993-1.071
	Period from ATRA to chemotherapy	0.039	0.053	0.559	0.455	1.040	0.938-1.153
	WBC count at diagnosis	0.130	0.128	1.036	0.309	1.139	0.887-1.463
	PLT count at diagnosis	-0.024	0.018	1.799	0.180	0.976	0.942-1.011

WBC, white blood cell; ATRA, all-trans retinoic acid; PLT, platelet.

The present study also assessed other factors related to early mortality, including infection, bleeding and CR rate, among others, which may be influenced by the initiation time of chemotherapy.

Following the use of ATRA, WBC count typically rises gradually, and risk associated with DS increases (13). Initiation of chemotherapy at different intervals during induction treatment for APL may lead to different outcomes. The present study demonstrated that when chemotherapy was initiated at a WBC count $<4x10^9$/l and $>15x10^9$/l, the patients exhibited higher CR rate (100.0%), lower early mortality rate (0.0%) and reduced possibility of infection (33.3%). For those who received chemotherapy at a WBC count $<4x10^9$/l, infection rate was the most notable issue (71.4%) despite the lower incidence of DS (5.9%). As for the patients treated with chemotherapy at a WBC count $\geq5x10^9$/l, DS incidence, bleeding rate, early mortality, CR rate and time to CR all appeared worse compared with the other two groups. These results may have been due to the following reasons: firstly, once the patients were treated with chemotherapy when WBC counts rose $\geq15x10^9$/l, both the risk of DS and early mortality associated with DS may have increased markedly. Secondly, if WBC counts were too low, particularly if resulting in neutropenia, when chemotherapy was applied, infection may have been a main cause of increased early mortality rate. Therefore, the present study suggests treatment of newly diagnosed APL with chemotherapy when WBC count is between $4x10^9$ and $15x10^9$/l. However, for those whose WBC counts are consistently low, whether chemotherapy is needed is worthy of further investigation. It is generally viewed that coagulant function may be improved at least 3 days after the initiation of ATRA (2,20). However, in terms of the period from ATRA commencement to chemotherapy, the patients treated with chemotherapy within 3 days of ATRA did not exhibit differences from those treated at least 3 days after with regards to early mortality rate, DS incidence and CR rate.

Due to the retrospective nature of the present study, to decrease selection bias, the study aimed to confirm risk factors by multivariate analyses. The effects of WBC count at diagnosis, PLT count at diagnosis, WBC count at chemotherapy initiation and the period from ATRA commencement to chemotherapy were considered. The results indicated WBC count at chemotherapy was the only index capable of influencing the incidence of DS and early mortality. With regard to ethics, it is difficult to design a prospective randomized controlled trial to evaluate the appropriate time to use cytotoxic agents. However, a single-arm prospective trial may be considered for comparison with historical data.

Overall, for newly diagnosed APL with low-intermediate risk, patients may benefit more when chemotherapy is initiated at a WBC count between $4x10^9$/l and $15x10^9$/l during induction treatment.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

FX and FYM conceived the study and analyzed and interpreted the data. FX wrote the draft manuscript and performed the statistical analyses. CXY, CLW, BJD, QXZ, XJJ, LJ and ZXW collected patient data, reviewed the manuscript, and revised it critically for intellectual content. All authors read and approved the final study to be published.

Ethics approval and consent to participate

Ethical approval was not obtained for the present study due to its retrospective nature. Informed consent prior to and regarding the treatment protocol was obtained from all patients analyzed in the present study.

Patient consent for publication

Informed consent for publication was obtained from all patients analyzed in the present study.

Competing interests

The authors declare that they have no competing interests.

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