doi.org/10.36721/PJPS.2022.35.1.REG.023-028.1

Alternate application of all-trans-retinoic acid and arsenic trioxide combined with idarubicin/daunorubicin in treatment of acute promyelocytic leukemia

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Abstract: The present study aimed to investigate the efficacy and safety for alternate application of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO) combined with idarubicin (IDA)/daunorubicin (DNR) in treatment of acute promyelocytic leukemia (APL). a total of 72 ALP patients were divided into the low/medium risk and high risk groups according to the WBC and PLT levels. All APL patients received induction therapy, consolidation therapy and maintenance therapy in treatment under careful nursing monitoring. The complete response (CR) rate was 87.5% (63/72), with 95.12% (39/41) in the low/medium risk group, which was markedly higher than the 77.42% (24/31) high risk group. The PML/RAR α fusion negative rate was also markedly higher in the low/medium risk group (95.12%, 39/41) than the high risk group (77.42%, 24/31). The duration for PML/RAR α fusion negative was also significantly shorter in the low/medium risk group. Recurrence was found in cases in the low/medium risk group, markedly lower than cases in the high risk group. The overall survival (OS) time was markedly longer in low/medium risk patients high. Alternate application of the combination strategy could achieve well CR rate with less complications. And patients with low/medium risk had better clinical outcomes and prognosis than high risk patients.

Keywords: ATRA, idarubicin/daunorubicin, APL, nursing.

INTRODUCTION

Acute promyelocytic leukemia (APL) is a common hematological tumor accounting for about 10~15% acute myelogenous leukemia (AML) and mainly developing in adults (Cicconi *et al.,* 2019; Noguera *et al.,* 2019; Sanz *et al.,* 2019 and Zhao *et al.,* 2019). Since disseminated intravascular coagulation (DIC) is usual in APL treatment and is a main cause for patient's early death, the treatment strategy for APL still needs to improve (Ader *et al.*, 2019; Kwaan *et al.*, 2019 and Sanz *et al.*, 2020).

Currently, application of all-trans-retinoic acid (ATRA) is considered as an effective therapeutic method to improve the efficacy and safety of chemotherapy (Cicconi *et al.*, 2019 and Orfali et al, 2020). Studies found ATRA could decrease the DIC and infection rates during chemotherapy (Abaza *et al.*, 2017 and Lo-Coco *et al.*, 2013). However, complications during ATRA treatment and the drug resistance, as well as the recurrence are still problems (Barragán *et al.*, 2011 and Park *et al.*, 2011). Thus, the therapeutic strategy in APL treatment becomes important.

Besides for ATRA, anthracyclines including idarubicin (IDA) or daunorubicin (DNR), as well as arsenic trioxide (ATO) are reported to apply to APL treatment and might enhance the treatment efficacy (Creutzig *et al.*, 2013 and Ohtake et al, 2011). The usage of ATO could prolong the patients' disease-free time (DFS) and might complete response (CR) rate (Ghavamzadeh *et al.*, 2011 and Tomita *et al.*, 2013). However, up to now, clinical evidences for combination use of ATRA, ATO and IDA or DNR are still inadequate, and there is still room for improvement of the therapeutic strategy.

In the present work, we performed a prospective cohort study to show an alternate application of ATRA and ATO combined with IDA or DNR in treatment of primary APL patients. We found that alternate application of the combination strategy could achieve well CR rate with less complications and patients with low/medium risk had better clinical outcomes and prognosis than high risk patients. This study might provide more clinical evidence for rational treatment strategy of APL.

MATERIALS AND METHODS

Patients' enrollment

The present prospective cohort study included a total 72 cases with APL who came to our department during March 2017 to October 2019. All patients were consecutively enrolled and were diagnosed as acute promyelocytic leukemia according to the following criteria: 1) patients showed clinical symptoms including infection, anemia, bleeding, fever, pale skin mucosa, skin ecchymosis and bleeding points, as well as lymph nodes and liver and spleen swelling, sternum and other parts of bone and joint pain when leukemic cell infiltration; 2) leukemic blasts in blood smear and extremely active proliferation of bone marrow cells, as well as abnormal promyelocytes with increased granules, often more than 30% (non-erythroid) by morphological examination; 3)

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strong positive peroxidase staining, and positive non-specific esterase staining which could not be inhibited by NaF; 4) positive CD33 and CD13, as well as negative CD34 and HLA-DR, which were sometimes positive; 5) chromosomal heterotopia: T (15; 17) (q22; q21) by cytogenetic examination; 6) positive PML/RAR α fusion gene. Other inclusion criteria were: 1) patients ≥18 years; 2) patients with primary APL; 3) patients signed the written informed consent and agree the study. The following patients were excluded: 1) pregnant patients; 2) patients not with mutant of (q22; q21) or patients with negative PML/RAR α fusion gene. Patients who lost follow-up or quit the study were already excluded. The present study was approved by the ethic committee of First Affiliated Hospital of Soochow University.

Grouping and treatment

All patients were divided into low/medium risk and high risk groups according to the WBC and PLT levels. Low-risk group was defined as WBC $\leq 10*10^9$/L and platelet (PLT) $>40*10^9$/L, and medium-risk group was defined as WBC $\leq 10*10^9$/L and PLT $<40*10^9$/L, while high risk group was defined as WBC $>10*10^9$/L.

All APL patients received induction therapy first. The induction therapy including oral ATRA (20 mg/m^2/d), intravenous injection of ATO (0.16 mg/kg/d) dissolved in 500 ml normal saline once/d. The whole treatment lasted for 14~28 d. When the WBC $\geq 4*10^9$/L, intravenous injection of DNR (25~45 mg/m^2/d) or IDA (8~12 mg/m^2/d) was performed for 3 d at the same time.

After complete response (CR), consolidation therapy was performed. For low/medium risk patients, the consolidation therapy included: 1) ATRA (20mg/m^2/d, for 14~28d) + ATO (0.16mg/kg/d, for 14~28d) + DNR (25~45mg/m^2/d, for 3d) or IDA (8~12mg/m^2/d, for 3 d); 2) ATRA (20mg/m^2/d, for 14~28d) + mitoxantrone (MTN, 6~8mg/m^2/d, for 3d); 3) ATRA (20mg/m^2/d, for 14~28 d) + DNR (25~45mg/m^2/d, for 3 d) or IDA (8~12 mg/m^2/d, for 3 d). For high risk group, the consolidation therapy included: 1) ATRA (20mg/m^2/d, for 14~28d) + ATO (0.16 mg/kg/d, for 14~28d) + DNR (25~45 mg/m^2/d, for 3 d) or IDA (8~12mg/m^2/d, for 3d); 2) ATRA (20mg/m^2/d, for 14~28 d) + mitoxantrone (MTN, 6~8 mg/m^2/d, for 3 d); 3) ATRA (20mg/m^2/d, for 14~28 d) + ATO (0.16mg/kg/d, for 14~28d) + DNR (25~45mg/m^2/d, for 3 d) or IDA (8~12mg/m^2/d, for 3 d); 4) ATRA (20 mg/m^2/d, for 14~28 d) + ATO (0.16 mg/kg/d, for 14~28 d) + DNR (25~45mg/m^2/d, for 3 d) or IDA (8~12mg/m^2/d, for 3 d); 5) ATRA (20mg/m^2/d, for 14~28d) + mitoxantrone (MTN, 6~8mg/m^2/d, for 3 d).

For maintenance therapy, the low/medium risk patients received treatment of 1) ATRA (20 mg/m^2/d, for 14 d) and then the treatment stopped for 14 d in the first month; 2) ATO (0.16 mg/kg/d, for 14 d) and then the treatment stopped for 14 d in the second month; 3) ATO (0.16 mg/kg/d, for 14 d) and then the treatment stopped for 14 d in the third month. The whole treatment strategy lasted for 5 cycles. For high risk group, the maintenance therapy included: 1) ATRA (20 mg/m^2/d, for 14 d) and then the treatment stopped for 14 d in the first month; 2) ATO (0.16 mg/kg/d, for 14 d) and then the treatment stopped for 14 d in the second month; 3) DNR (25~45 mg/m^2/d, for 3 d) or IDA (8~12 mg/m^2/d, for 3 d) and cytarabine (100 mg/m^2/d, for 7 d) and then homoharringtonine (2 mg/m^2/d, for 7 d) and cytarabine (100 mg/m^2/d, for 7 d) in the third month. The whole treatment strategy lasted for 5 cycles.

The CR was defined as no leukemic cell infiltration and no leukemic blasts in blood smear, as well as promyelocyte and promyelocyte ≤5%. The recurrence was defined as 1) promyelocyte and promyelocyte >5% and <20% who didn't achieve CR after one course anti-ALP treatment (oral ATRA (20 mg/m^2/d), intravenous injection of ATO (0.16mg/kg/d) for 28 d); 2) promyelocyte and promyelocyte >20%; 3) extramedullary leukemia cell infiltration.

Monitoring and nursing

For patients' monitoring and nursing, all patients and the families received psychological counseling and health education before treatment. Antiemetic (such as azasetron, tropisetron), anti-acid, hydration and alkalization drugs were used to prevent uric acid nephropathy. During treatment, patients' condition was strictly monitored and when patients showed acute renal failure, severe dyspnea, weight gain (generally >5kg), unexplained fever, unexplained hypotension and multiple serous effusion in the body, the retinoic syndrome (RAS) should be considered and the usage of ATRA should be reduced or stopped when necessary, following with using of dexamethasone. The usage of ATRA could be gradually recovered after disappear of RAS. Similarly, when patients showed liver dysfunction, the usage of ATO should be stopped until the recovery of liver function. When neutrophil level $<0.01*10^9$/L, rhG-CSF (300 μg/d) was used and when hemoglobin (Hb)<60 g/L, transfusion of red blood cells was conducted. Antibiotics were used when patients showed combined infection.

Data measurement and follow-up

Routine test including blood routine, urine routine, gas and blood analysis and liver and kidney functions were monitored during the treatment. The CR rate and PML/RAR α fusion positive/negative rate were the main outcomes of the study. Treatment duration, overall survival (OS) time, recurrence rate, disease-free survival (DFS) time were all recorded and analyzed. Complications during the study period were also recorded. All patients were followed up for 1 year.

STATISTICAL ANALYSIS

Data was expressed by mean ± SD or median (range). Comparison between data before or after treatment was performed using the paired Student *t*-test and comparison between two different groups was performed by the unpaired Student *t*-test. Kaplan-Meier (K-M) curve was used for survival analysis. P<0.05 was considered as significant difference. All calculations were made using SPSS 22.0.

RESULTS

Characteristics of all patients

The present prospective cohort research included 72 adult APL patients. The mean age of all patients was 47.56±10.72, with 46.34±10.80 in low/medium risk group and 49.19±10.56 in high risk group (table 1). Among all patients, the WBC was 37.36±44.32*10^9/L, with 4.96±2.83*10^9/L in low/medium risk group and 80.22±36.13*10^9/L in high risk group, while the PLT was 55.26±42.17*10^9/L, with 78.69±42.11*10^9/L in low/medium risk groups and 24.27±10.07*10^9/L in high risk group. The WBC value was remarkably lower and PLT value was significantly higher in low/medium risk group compared with the high risk group (P<0.05). No significant difference was found in other characteristics.

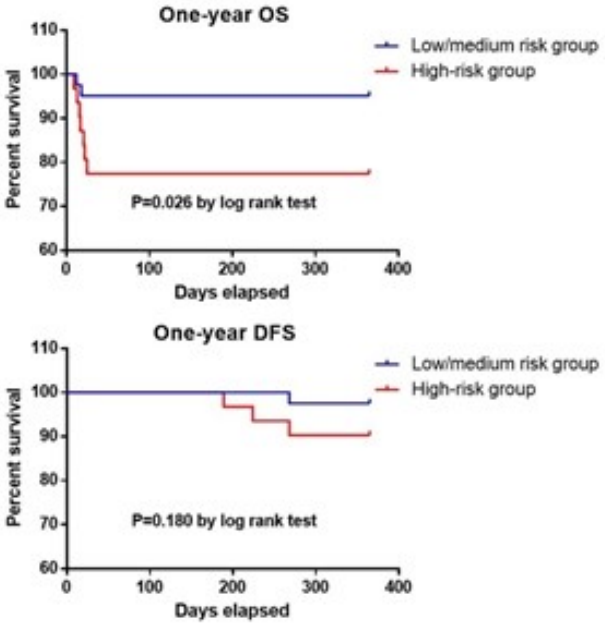

Fig. 1: K-M curves for OS and DFS in low/medium risk and high risk groups.

CR and PML/RAR α fusion negative rate in low/medium risk and high risk groups

To show the treatment efficacy of ATRA and ATO combined with IDA/DNR, the CR and PML/RAR α fusion negative rates, as well as the treatment duration were analyzed and compared in different groups of patients. It was found both the CR and PML/RAR α fusion negative rates were markedly higher in the low/medium risk group (P<0.05, table 2). All CR patients showed PML/RAR α fusion negative. Besides, the duration for PML/RAR α fusion negative was also significantly shorter in the low/medium risk group (P<0.05). These results suggested that the treatment strategy was efficacy for both low/medium risk and high risk patients, however, was better in low/medium risk cases.

Complications and recurrence in low/medium risk and high risk groups

The complications and recurrence in low/medium risk and high risk groups were then analyzed. As shown in table 3, 1 (2.44%) case with recurrence was found in the low/medium risk group, significantly lower than 3 (9.68%) cases in the high risk group (P<0.05). Besides, RAS was found in 7 (9.72%) cases of all patients and disseminated intravascular coagulation was found in 6 (8.33%) cases during induction therapy. No significant difference was found in complications during the treatment period.

Patients' 1-year OS and DFS conditions in low/medium risk and high risk groups

Finally, the patients' 1-year OS and DFS conditions were analyzed by K-M curve. Among all patients, mortality was found in 2 (4.88%) cases in the low/medium risk group, remarkably lower for 7 (22.58%) cases in the high risk group (P<0.001). All patients died during induction therapy and were early death. K-M curves showed the OS time was markedly longer in low/medium risk patients compared with the high risk group, while no significant difference was found for the DFS time (P> 0.05, fig. 1), indicating that patients with low/medium risk group had better prognosis.

DISCUSSION

Despite development of chemotherapy, the treatment for APL still faces to complications, drug resistance and recurrence. In 1990s, it was found ATRA had the potential in treatment of APL, however, how to maximize its efficacy with lowest side effects is still a problem. In the present study, we demonstrated that alternate application of the combination use of ATRA and ATO combined with IDA or DNR showed well efficacy with low complication rates. And patients with low/medium risk had better clinical outcomes and prognosis than high risk patients.

Several studies have already reported some treatment strategies for ATRA in APL treatment. In 2015, Sanz *et al.* compared two cohort studies using ATRA combined with IDA or DNR in APL treatment and found that the CR rates were similar of 85% and 94% for the two researches (MA Sanz, 2015). In another research, Lou *et al.* found

Table 1: Basic characteristics of all patients

Variables	All APL patients, n=72	Low/medium risk, n=41	High risk, n=31	P value
Age, y	47.56±10.72	46.34±10.80	49.19±10.56	0.267
Sex, female (%)	30 (41.67)	17 (41.46)	13 (41.94)	0.945
WBC, 10^9/L	37.36±44.32	4.96±2.83	80.22±36.13	<0.001
PLT, 10^9/L	55.26±42.17	78.69±42.11	24.27±10.07	<0.001
Hb, g/L	95.63±36.64	93.63±34.80	98.28±39.37	0.598
Symptoms, n (%)				0.874
Hemorrhage	59 (81.94)	33 (80.49)	26 (83.87)	
Anemia	46 (63.89)	24 (58.54)	22 (70.97)	
Fever	40 (55.56)	21 (51.22)	19 (61.29)	
Infection	32 (44.44)	18 (43.90)	14 (45.16)	

Table 2: CR and PML/RAR α fusion negative rate in low/medium risk and high risk groups

Variables	All APL patients, n=72	Low/medium risk, n=41	High risk, n=31	P value
CR, n (%)	63 (87.5)	39 (95.12)	24 (77.42)	<0.001
PML/RAR α fusion negative, n (%)	63 (87.5)	39 (95.12)	24 (77.42)	<0.001
Duration for PML/RAR α fusion negative, treatment course	2.37±1.16	1.80±1.03	3.12±0.88	<0.001

Table 3: Complications and recurrence in low/medium risk and high risk groups

Variables	All APL patients, n=72	Low/medium risk, n=41	High risk, n=31	P value
Recurrence, n (%)	4 (5.56)	1 (2.44)	3 (9.68)	0.032
Complications, n (%)				0.903
RAS	7 (9.72)	3 (7.32)	4 (12.90)	
Gastrointestinal side effects	11 (15.28)	5 (12.20)	6 (19.35)	
Disseminated intravascular coagulation	6 (8.33)	2 (4.88)	4 (12.90)	
Liver dysfunction	12 (16.67)	6 (14.63)	8 (25.81)	
Headache	7 (9.72)	3 (7.32)	4 (12.90)	
Dropsy	6 (8.33)	2 (4.88)	4 (12.90)	
Erythra	6 (8.33)	3 (7.32)	3 (9.68)	
Central nervous system leukemia (CNSL)	0 (0)	0 (0)	0 (0)	

that combination of ATRA and ATO could reach 93.4% CR rates (Lou *et al.*, 2013). However, in this study the patients didn't receive chemotherapy in maintenance therapy. In a meta-analysis, the authors compared ATRA combined with ATO and ATRA combined with chemotherapy in APL treatment and concluded that ATRA combined with ATO might be better than ATRA combined with chemotherapy, especially for low/medium risk patients (Ma *et al.*, 2016). In our research, we used an alternate application of ATRA and ATO and chemotherapy. In maintenance therapy, ATRA, ATO and chemotherapy were alternately used in a treatment cycle to achieve better efficacy and we found this treatment strategy showed well CR rate and low complication rate.

The application of ATO and IDA or DNR was also found to be efficacy in APL therapy. Iland *et al.* demonstrated that combination of ATO, ATRA and oral methotrexate, and 6-mercaptopurine in maintenance therapy resulted in 95% CR and 3.2% early death (Iland *et al.*, 2012). In an early research, Ravandi *et al.* reported application of ATRA, ATO and gemtuzumab ozogamicin was effective in APL treatment with 92% CR and 85% 3-year survival rate (Ravandi *et al.*, 2009). In a randomized-control study, Lee *et al.* demonstrated that high dose daunorubicin (90 mg/m^2/d) was more effective than darubicin in APL patients with FLT3-ITD mutation (Lee *et al.*, 2017). In our research, the combination of ATO and IDA or DNR along with ATRA was also found to be effective and safe in APL patients.

The present study also has some limitations. First the enrolled cases are limited and are from a single center. Secondly, this is a cohort study. To further confirm the treatment efficacy and safety, randomized-control researches are still needed.

CONCLUSION

In conclusion, this prospective cohort study demonstrated that the alternate application of ATRA and ATO combined with IDA or DNR showed well CR rate with less

complications, especially for low/medium risk patients. This study might provide more clinical evidence for rational treatment strategy of APL.

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