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Efficacy and safety of early switching to an outpatient therapy model using oral arsenic plus retinoic acid based-regimen in newly diagnosed acute promyelocytic leukemia

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ABSTRACT

Realgar-Indigo naturalis formula(RIF)is an oral form of arsenic developed for treatment of acute promyelocytic leukemia (APL). We retrospectively evaluated the efficacy and safety of a novel RIF combined with all-trans retinoic acid (ATRA) based chemotherapy-free approach in newly diagnosed APL patients. Patients received oral ATRA (25 mg/m^2/day in 2 divided doses) plus intravenous arsenic trioxide (0.15 mg/kg/day) or oral RIF (60 mg/kg/day in 3 divided doses) as induction chemotherapy, followed by 2 consolidations with ATRA plus RIF and maintenance therapy with intermittent ATRA and RIF. From January 2015 to December 2017, 40 subjects were enrolled. Eighteen subjects were male. Median age was 42 years (range, 14–77 years) and 10 subjects were ≥ 60 years. All subjects achieved a complete morphologic remission after initial induction. Molecular complete remission achieved 100% after second RIF plus ATRA consolidation. Median follow-up of survivors was 27 months (range, 7–43 months). The 2-year event-free survival (EFS) and overall survival (OS) were both 100%. Adverse events were modest and all patients needed only outpatient care during postremission therapy. Compared to our historical RIF plus ATRA with chemotherapy regimen (the Chinese APL07 trial), the inpatient treatment duration was greatly reduced by the RIF plus ATRA regimen. Our data indicates that early switching to RIF plus ATRA based chemotherapy-free approach has yielded encouraging outcomes and might be considered a practicable option to treat patients with newly diagnosed APL.

1. Introduction

All-trans retinoic acid (ATRA) and intravenous arsenic trioxide (ATO) is a commonly used therapy of acute promyelocytic leukemia [1,2]. Realgar-Indigo naturalis formula (RIF) is an oral form of arsenic containing major components of tetra-arsenic tetra-sulfide (As4S4) [3]. Wang et al. reported efficacy of RIF in a mouse model of APL [3]. In 2002, Lu et al. reported efficacy of oral tetra-arsenic tetra-sulfide, which was prepared from natural Realgar in persons with newly diagnosed and advanced APL [4]. Subsequently, a randomized controlled trial (Chinese APL07) reported oral RIF was equally effective as intravenous ATO in subjects ≤ 60 years old with APL [5]. A randomized study confirmed ATRA and oral RIF was not inferior to ATRA and intravenous ATO in subjects with low-intermediate risk APL (white blood cell [WBC] ≤10 × 10^9/L) [6].

However, more data is needed to determine if oral RIF plus ATRA is effective, especially in elderly or high-risk persons with APL. The optimal regimens for RIF remain to be defined. An oral RIF plus ATRA chemotherapy-free regimen was started in our center from 2015. Results are retrospectively described herein.

2. Materials and methods

2.1. Subjects

From January 2015 to December 2017, 40 subjects with APL were assigned to receive ATRA and RIF. Eligibility criteria were: newly diagnosed APL with confirmation by the PML-RARA fusion transcript, age over 14 years without upper age limit, Eastern Cooperative Oncology Group performance status between 0 and 3, and written informed consent. Exclusion criteria were concurrent active neoplasms, heart failure NYHA III and IV; severe liver disease with serum total

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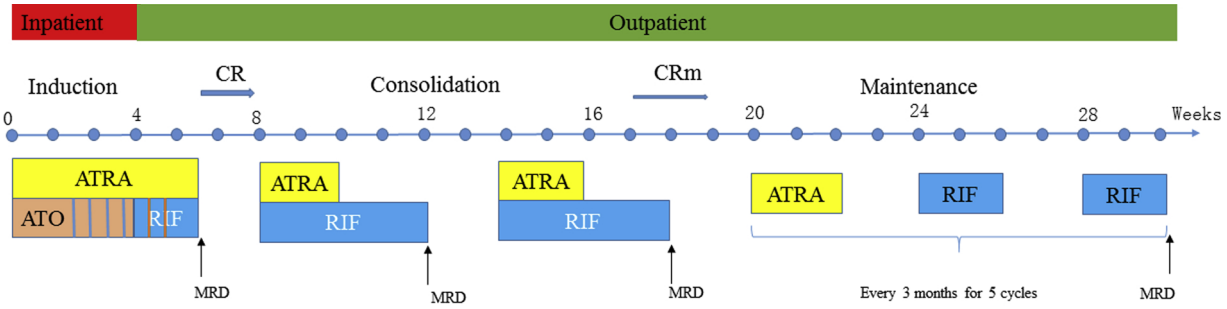

ATRA: 25mg/m²/day oral in 2 divided doses; ATO: 0.15 mg/kg/day intravenous; RIF: 60 mg/kg/day oral in 3 divided doses.
CR: Complete remission; CRm: Complete molecular remission; MRD: Minimal residual disease monitoring.
ATO= Arsenic trioxide; ATRA = All-trans retinoic acid. RIF= Realgar-Indigo naturalis formula.

Fig. 1. Treatment schema of induction and postremission therapy.

bilirubin > 2.5 times the upper limit of normal; chronic renal failure with serum creatinine ≥3 mg/dL, life-threatening bleeding and pregnant or lactating women. The study was approved by the institutional review board in accordance with the Declaration of Helsinki (IRB No. 2018-914).

2.2. Therapy

The therapy scheme is displayed in Fig. 1. In brief, the induction treatment consisted of two stages: stage I (inpatient setting: ATRA + ATO), the study subjects received induction therapy with ATRA (25 mg/m^2/day in 2 divided doses) and ATO (0.15 mg/kg/day intravenously). Hydroxyurea (1.5–4.0 g daily in 3–4 divided doses) was added if the WBC was > 4 × 10^9/L at any time from 14 days during induction. For high-risk patients (WBC > 10 × 10^9/L) or those whose WBC increased to > 20 × 10^9/L prior to day 5 during induction, 1–5 doses idarubicin (6 mg/m^2/day) was allowed for leukocytosis. Subjects received standard supportive measures including blood product transfusions and prophylactic and therapeutic antibiotics. Patients were discharged to outpatient treatment once in clinically stable condition, including the recovery of coagulopathy, platelet count > 50 × 10^9/L independent transfusion and no life-threatening complications. Then switching to the stage II induction (outpatient setting: RIF + ATRA), ATRA (25 mg/m^2/day by mouth in 2 divided doses) and RIF (60 mg/kg/day by mouth in 3 divided doses) were given to subjects until complete remission (CR). Response was assessed 4–5 weeks after start of induction. RIF was purchased through commercial suppliers (Yifan Pharmaceutical Co, Tianchang, China).

After achieving hematologic CR, subjects received two consolidation courses of ATRA (25 mg/m^2/day) for 14 days and RIF (60 mg/kg/day) during 28 days. Subjects then received maintenance therapy for 5 cycles with intermittent ATRA (25 mg/m^2/days for 15 days for the first month) and oral RIF (60 mg/kg/day for 15 days for the second and third months) every 3 months. Prophylaxis for central nervous system (CNS) leukemia was given to each patient (at least 2 times of intrathecal chemotherapy with methotrexate 10 mg, cytarabine 50 mg and dexamethasone 5 mg) according to Chinese APL guidelines. In addition, the historical Chinese APL07 protocol as previously reported [5].

2.3. Toxicity evaluation

Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria (version 4.03, 2010).

2.4. PML-RARA monitoring

Access bone marrow PML-RARA molecular status was routinely recommended for all patients by using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) at diagnosis, post induction, each consolidation, and each cycle (3 months) during the maintenance phase, thereafter every 3–6 months for at least 2 more years after the end of maintenance. qRT-PCR was performed according to international standards in central laboratories [7]. Patients with molecular relapse should be confirmed in two consecutive (2 weeks apart) bone marrow samples.

2.5. Statistical analysis

Complete molecular remission (CRm) required the absence of PML-RARA transcripts, with a sensitivity level of at least 10^{-4}. Overall survival (OS) was measured from the time of initial diagnosis to the time of death or last follow-up. Event-free survival (EFS) was calculated from time of diagnosis to failure to achieve CR, relapse (hematologic, molecular or extramedullary), or death from any causes. The follow-up of the patients was updated on May 2018. Survival curves (OS and EFS) were evaluated using the Kaplan-Meier method and tested for significant differences between groups using the log-rank test. Categorical data was compared using Chi-square or Fisher's exact test. Mann Whitney *U* test was used for continuous variables. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed with GraphPad Prism 5 software (GraphPad Software Inc., La Jolla, CA).

3. Results

3.1. Patients' characteristics

A total of 40 patients (22 women and 18 men) were enrolled during the study period. The median age of the patients at diagnosis was 42 years (range, 14–77) with 10 patients being older than 60. According to Sanz score criteria, 87.5% (35/40) patients were in low-intermediate group (WBC count ≤10 × 10^9/ L), while the other 5 patients had high-risk disease (WBC count > 10 × 10^9/ L). Patient characteristics were summarized in Table 1.

3.2. Remission induction

All 40 patients achieved morphological CR after completion of induction. The median hospital stay was 23 days (range, 7–40). All 12 low-risk patients were discharged in two weeks (7–13 days). Five of twelve (41.7%) low-risk and six of twenty-three (26.1%) intermediate-risk and patients received hydroxyurea therapy during induction. In addition, All five high-risk, three of twenty-three (13.0%) intermediate-risk and one of twelve (8.3%) low-risk patients received idarubicin

Table 1
Characteristics of patients with RIF plus ATRA with or without chemotherapy.

Characteristics	ATRA + RIF (n = 40)	ATRA + RIF + Chemotherapy (n = 19)	P
Age (years), median (range)	42(14-77)	33 (18-52)	0.03
Age ≥ 60 years, n (%)	10(25)	0(0)	
Gender, n %			1.00
Male	18(45)	8(42.1)	
Female	22(55)	11(57.9)	
ECOG PS, n (%)			0.65
0-1	35(87.5)	18(94.7)	
2	5(12.5)	1(5.3)	
WBC (10^9/L), n (%)			0.30
< 5	28(70)	11(57.9)	
5–10	7(17.5)	4(21.1)	
> 10	5(12.5)	4(21.1)	
Platelets (10^9/L), n (%)			1.00
< 40	26(65)	12(63.2)	
40 or more	14(35)	7(36.8)	
Risk group (Sanz Score)			0.23
Low	12(30)	7(36.8)	
Intermediate	23(57.5)	8(42.1)	
High	5(12.5)	4(21.1)	
Follow up(months), median (range)	26.6(6.8-42.9)	98.3(87.3-127.6)	< 0.001
Hospitalization during consolidation (days), median (range)	0	43(31-67)	< 0.001
2-year event-free survival	100%	88.9%	0.09
2-year overall survival	100%	94.7%	0.06

therapy during induction (See supplementary Table 1). No primary resistance was observed.

3.3. Consolidation and maintenance therapy

All 40 patients who achieved CR after induction were able to complete the two courses of ATRA plus RIF consolidation as scheduled in an outpatient manner. As scheduled, all 40 patients proceeded to the planned maintenance therapy. Moreover, 29 patients have completed the maintenance therapy and 11 patients are still on treatment at last follow-up.

3.4. Safety and toxicity

A summary of treatment-emergent adverse events was shown in Table 2. The adverse events occurred frequently during induction. During post remission therapy, the side effects of RIF were almost mild and reversible. No patient experienced grade 3–4 hematologic or non-hematologic toxicity. No toxicity forced discontinuation of ATRA or RIF was observed during the postremissing therapy. No clinical cardio-myotoxicity, treatment-induced myelodysplastic syndromes or secondary malignancy were reported until the last follow-up.

Table 2
Toxicity profile during RIF plus ATRA based outpatient postremission therapy.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematological, no. (%)				
Anemia	4(10)	0(0)	0(0)	0(0)
White blood cell decreased	9(22.5)	0(0)	0(0)	0(0)
Neutrophil count decreased	7(17.5)	0(0)	0(0)	0(0)
Platelet count decreased	2(5)	0(0)	0(0)	0(0)
Nonhematologic, no. (%)		0(0)	0(0)	0(0)
Dry mouth	3(7.5)	0(0)	0(0)	0(0)
Dyspepsia	8(20)	1(2.5)	0(0)	0(0)
Nausea	4(10)	0(0)	0(0)	0(0)
Vomiting	3(7.5)	0(0)	0(0)	0(0)
Edema face	8(20)	0(0)	0(0)	0(0)
Edema limbs	5(12.5)	0(0)	0(0)	0(0)
Fatigue	8(20)	0(0)	0(0)	0(0)
Headache	3(7.5)	1(2.5)	0(0)	0(0)
Bone pain	1(2.5)	0(0)	0(0)	0(0)
Alanine aminotransferase increased	4(10)	1(2.5)	0(0)	0(0)
Cholesterol high	3(7.5)	1(2.5)	0(0)	0(0)

3.5. Longitudinal molecular monitoring

Fifteen patients (37.5%) achieved molecular negative after induction. Thirty-eight patients (95%) achieved molecular negativity at the end of the first consolidation. All of the patients achieved CRm at the end of the second course of consolidation therapy. All patients were in CRm at last follow-up.

3.6. OS and EFS

With a median follow-up of 26.6 months (range, 6.8–42.9 months), the 2-year estimated EFS was 100%. The 2-year estimated OS was 100% (Fig. 2).

3.7. Comparison with historical ATRA plus RIF with chemotherapy data

We compared these results to our historical ATRA plus RIF with chemotherapy data (RIF arm, n = 19) [5]. Eighteen patients achieved CR except one patient, who died of intracranial hemorrhage during induction. Molecular relapse had occurred in one patient at 41 months. One patient treated with ATRA plus RIF with chemotherapy developed a therapy-related AML 21 months after achieving CR and died from disease progress. There was no statistical difference in EFS and OS between the two groups (Table 1 and Fig. 2). However, Patients who treated with the chemotherapy-free regimen had fewer admissions and days in hospital comparing with RIF plus ATRA with chemotherapy regimen (Table 1).

4. Discussion

We report here that early switching to RIF plus ATRA based chemotherapy-free protocol had high efficacy with a 2-year EFS and OS rate of 100% and 100%, respectively. All patients were feasible shift to an outpatient model during postremission therapy. Thus, our results supported the oral model of the RIF plus ATRA based chemotherapy-free protocol for newly diagnosed APL patients.

Generally, our results were in line with the results of previous RIF-based trials [6]. In the study conducted by Zhu et al, RIF plus ATRA (n = 72) induced CR in 100% with 2-year EFS and OS rates of 97% and

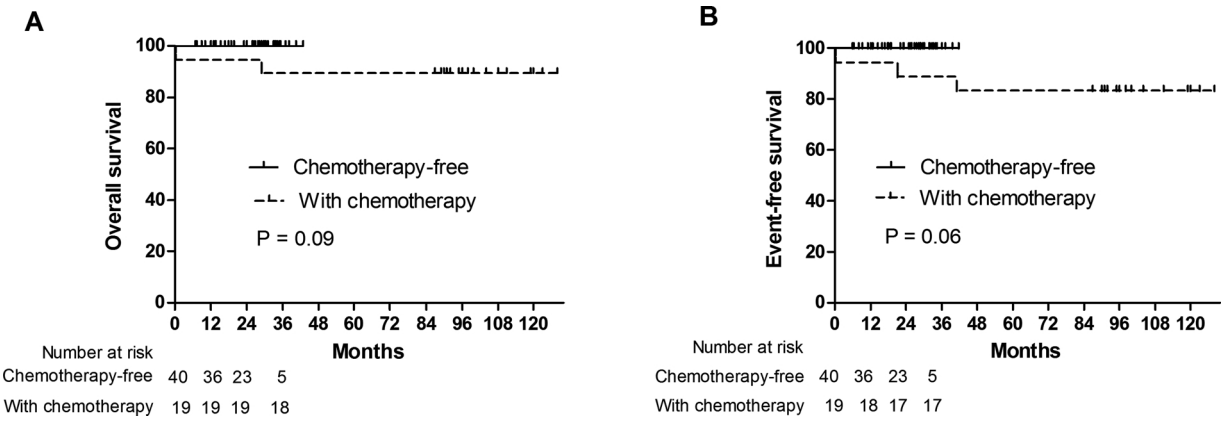

Fig. 2. Comparing Kaplan–Meier estimates for overall survival (A) and event-free survival (B) curves of patients with ATRA plus RIF with or without chemotherapy.

100%, respectively. However, our study differs from the previous study in several ways.

First, our protocol was designed according to our own experience. The ATRA plus ATO therapeutic regimen has been relatively successful during induction, the early complications were manageable, especially in patients with low-intermediate risk [8,9]. In addition, oral RIF was absorbed in the gastrointestinal tract and may cause gastrointestinal discomfort. We agree with Lo-Coco et al [10], early discharge of APL patients should be made with caution, particularly in intermediate or high-risk patients. Thus, in this protocol, we preferred ATRA plus intravenous ATO protocol for inpatient schedule and changed to the oral RIF for an outpatient setting.

In addition, we replaced the three courses of intensive chemotherapy of the previous APL07 trial with two courses of RIF plus ATRA. We found that the RIF plus ATRA with or without chemotherapy protocol yielded nearly identical efficacy. Thus, despite obvious confounders comparing different populations, our data suggested that the chemotherapy-free protocol does not compromise the outcome of patients with APL.

Along with high efficacy, the safety and health-related quality of life is another concern of RIF. In line with the previous trials [6], the regimen was generally well tolerated. In fact, all patients in the present study were able to complete two consolidation courses and no deaths in remission were recorded. All of these patients treated the postremission therapy on a home-based treatment without hospitalization. Most patients were able to resume normal activities after CR. Very recently, Zhu et al reviewed the clinical efficacy and safety profile of oral RIF, over 5000 patients have been given with RIF in China [11].

Older patients with APL are more likely to be unfit for intensive chemotherapy [12]. Treatment-associated mortality rate was higher in elderly patients comparing with younger age groups during intensive consolidation chemotherapy [13]. The favorable safety profile of combining RIF and ATRA regimen supported its use in frail and elderly patients. To our knowledge, data with RIF in elderly APL patients were limited. Of note, within our cohort of patients with 10 elderly APL, we demonstrated a 2-year EFS rate of 100%. Therefore, the RIF with ATRA regimen might be a therapeutic option for elderly APL.

Achieving CRm could be considered a surrogate endpoint in modern clinical trials [14]. Our approach to consolidation resulted in a 100% rate of CRm at the end of consolidation, and is similar to that reported by Zhu et al [6,15]. Thus, the efficacy of RIF plus ATRA chemotherapy-free protocol is strengthened by the high CRm rates.

Finally, high WBC ($> 10 \times 10^9$/L) was recognized as a high-risk feature in the ATRA plus chemotherapy era. Our previous study suggested that the gap in survival between high-risk group and low-intermediate risk group might be closed in the ATO era [16]. Interestingly, we observed a good outcome in this high-risk subgroup who received the RIF plus ATRA without intensive consolidation chemotherapy. Our finding is agreed with the more recent findings reported by Zhu et al, who also omitted chemotherapy from post-remission therapy in 20 high risk patients [17]. These studies suggested the view that intensive chemotherapy consolidation might be spared in postremission courses for high-risk patients.

One major limitation of our study was its single-institution design. Although the CR rate may appear relatively high (100%), it should be noted that early switching from ATO to RIF was often decided after 1–2 weeks of induction and only patients in stable condition were enrolled. In addition, the control group was historical in nature.

Despite the limitations described, our results demonstrated the feasibility and high efficacy of early switching to oral RIF plus ATRA based frontline therapy in newly diagnosed APL patients. This novel strategy appears to have a substantial reduction in the duration of hospitalization and had has a better quality of life, especially in elderly patients. Further studies are warranted to confirm such a strategy to be effective.

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