Retinoic Acid Syndrome in Patients following the Treatment of Acute Promyelocytic Leukemia with All-trans Retinoic Acid

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Background: Retinoic acid syndrome (RAS) is a potentially lethal complication during all-trans retinoic acid (ATRA) treatment of acute promyelocytic leukemia (APL). The incidence and risk factors have been shown to vary in different series. In this study we want to establish the incidence of RAS in our hospital and try to elucidate factors that increase its risk.

Methods: We retrospectively analyzed 102 patients diagnosed with APL between August 1993 and December 2007 at Chang Gung Memorial Hospital, Taiwan. All patients received ATRA as an induction regimen with or without conventional chemotherapy.

Results: Eight of the 102 patients (7.8%) experienced RAS which developed after a median of 9 days (range: 2 to 23 days) of ATRA treatment. Respiratory distress and fever were the most common presentations, occurring in 7 of 8 patients (87.5%). Age, gender, morphological or molecular subtypes, an initial white blood cell (WBC) count of more than 10×10^9/L and concurrent chemotherapy did not statistically attribute to the occurrence of RAS. One patient developed RAS manifesting with pulmonary hemorrhage but experienced a complete recovery after administration of high-dose dexamethasone. The RAS-related mortality was 12.5% (1 out of 8 patients).

Conclusion: The incidence of RAS in this study was similar to those of other series with ATRA and concurrent chemotherapy. Age, gender, morphological or molecular subtypes, an initial leukocyte count of more than 10×10^9/L or the presence of concurrent chemotherapy is not significantly associated with the occurrence of the RAS.

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Key words: acute promyelocytic leukemia, all-trans retinoic acid, retinoic acid syndrome, high-dose steroid

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Acute promyelocytic leukemia (APL) is a distinctive subtype of acute myeloid leukemia (AML), characterized by its unique morphology and reciprocal translocation involving chromosome 15 and 17, resulting in the fusion transcript of promyelocytic leukemia/retinoic acid receptor α chain *(PML/RARα)*. APL is frequently associated with disseminated intravascular coagulopathy (DIC) and therefore, initial treatment with conventional chemotherapy had been highly risky in the past.[1-2] The introduction of all-trans retinoic acid (ATRA), a differentiating agent, into the treatment of APL has substantially reduced such risks and also improved the complete remission rate.[3-16]

ATRA is often well tolerated. However, the retinoic acid syndrome (RAS), a potentially fatal complication,[17-19] has been reported in patients receiving ATRA therapy. This syndrome, first described by Frankel et al., usually manifests with fever, respiratory distress, hypotension, pleural or pericardial effusion, weight gain, leg edema and renal failure.[17] Morbidity and mortality can often be avoided with early recognition and steroid treatment.

In the present report, we retrospectively analyzed the RAS incidence and tried to correlate its incidence with clinical features, including age, gender, morphological or molecular subtypes, an initial leukocyte count of more than 10×10^9/L and the presence of concurrent chemotherapy. In addition, we report the outcome of one severe RAS case who presented with massive hemoptysis and respiratory failure and responded to high-dose steroid.

METHODS

Patients

We investigated medical records for 102 newly-diagnosed APL patients who had been admitted to Chang Gung Memorial Hospital between August 1993 and December 2007 and had received ATRA-containing regimens as their induction therapy. The diagnosis was based on the presence of either reciprocal translocation of chromosome 15 and 17 or *PML/RARα* fusion transcript. The morphological classification of classical form (M3) and microgranular variant (M3v) was based on the French-American-British (FAB) criteria. We divided the patients into 2 groups by the presence or absence of RAS and analyzed the patients according to age, gender, initial leukocyte counts, morphologic subtypes, molecular forms of *PML/RARα* fusion transcripts and the presence of concurrent chemotherapy.

Cytogenetic studies

Cells of bone marrow or peripheral blood samples were sent for direct preparation and overnight (24-hour) cultures and then arrested at meta-phase by addition of colchicine solution (0.1 ug/ml). They were subsequently treated with a hypotonic solution of 0.07 M potassium chloride and fixed in methanol-glacial acetic acid (3:1), followed by staining with Wright Giemsa-banding technique. Karyotypes were analyzed on the basis of the International System for Human Cytogenetic Nomenclature (ISCN).[20]

Detection of PML/RARα fusion transcripts

A reverse transcription-polymerase chain reaction (RT-PCR) assay was performed to detect *PML/RARα* transcripts. Three different subtypes of fusion transcripts, long (L), short (S) and variant (V) forms, were recognized. We extracted RNA from leukemic cells taken from bone marrow or peripheral blood samples and then reverse transcription was performed. Complementary DNA (cDNA) products were amplified by PCR reaction with *Taq* polymerase, using 2 forward primers and 1 reverse primer. The products of the PCR reaction were then separated by gel electrophoresis and the gels transferred to nylon membranes by the Southern blot assay. After hybridization with a *RARα* probe, chemiluminescent detection of hybridization was performed. Direct sequencing was performed for each PCR product generated by V-form *PML/RARα*. All patients except 1 received RT-PCR for detection of *PML/RARα* fusion transcripts.

ATRA-based treatment

All patients received ATRA (45 mg/m^2-day) for induction. For patients without RAS, ATRA was administered throughout the induction course until complete remission (CR) had been achieved. This study defined CR as promyelocytes comprising less than 5% of all nucleated cells in the bone marrow. ATRA treatment was immediately withdrawn when patients developed RAS and was not resumed throughout the rest of the induction course. In 19 patients (18.6%), ATRA was the only treatment administered. The remaining 83 patients (81.4%)

received concurrent chemotherapy, comprising an anthracycline (either daunorubicin 60 mg/m^2 or idarubicin 12 mg/m^2) for 3 days and Ara-C (100 mg/m^2) for 7 days. After CR had been achieved, an anthracycline (either daunorubicin 60 mg/m^2 or idarubicin 12 mg/m^2) with or without Ara-C (100 mg/m^2) was administered as the post-remission treatment in 3 monthly courses, followed by maintenance therapy for 2 years. Maintenance therapy included 6-mercaptopurine (50 mg/m^2-day) and methotrexate (50 mg/m^2-week) with or without ATRA (45 mg/m^2-day for 15 days every 3 months).

RAS diagnosis

The RAS diagnosis in this study was based primarily on the clinical manifestations defined by Frankel in 1994.[8] These manifestations included unexplained fever, respiratory distress, weight gain, hypotension, pleural or pericardial effusion, pulmonary infiltrates in chest radiographs, leg edema, renal failure after exclusion of infection, DIC, and other clinical cardiopulmonary disorders. To establish a reliable RAS diagnosis, we conducted a number of exclusion tests, including urinalysis, blood, sputum and urine cultures, DIC profiles, chest radiographs, electrocardiography, and cardiac ultrasonography with or without pericardiocentesis. Finally, Nicolls et al. reported that pulmonary hemorrhage can be a manifestation of RAS,[21] and therefore it was also included as one of the clinical criteria of RAS in this study.

RAS treatment

Once RAS was identified, ATRA was immediately discontinued and intravenous dexamethasone was initiated at a dosage of 10 mg every 12 hours. Dexamethasone was tapered off after the symptoms had completely resolved. The resolution of RAS was based on both clinical and imaging analyses, which indicated that the symptoms present in individuals subsided or disappeared. Simultaneously, individuals exhibited improvement in pulmonary infiltrates and pleural and pericardial effusion in chest radiographs.

Statistical method

Except for age, univariate analyses to evaluate the impact of different variables on the occurrence of the RAS were conducted with Fisher's exact test because of the small sample size of the RAS patients. Wilcoxon-rank-sum test was used to analyze the age of the two groups. It was considered to be significant if p value was less than 0.05.

RESULTS

The median age of the patients in this study was 41 years, and ranged from 17 to 77 years. Eight of the 102 patients (7.8%) developed RAS during ATRA treatment. Of these 8 RAS patients, 4 were male and 4 were female. Table 1 shows the clinical features, morphological subtypes, and molecular subtypes between patients with and without RAS. There was no statistically significant difference in age or gender between the two groups. Microgranular variants accounted for 12.5% (1 out of 8) in the RAS group and 4.2% (4 out of 94) in the non-RAS group, without statistical significance ($p = 0.341$). This study did not conduct RT-PCR to determine the *PML/RARα* subtype for one patient in the non-RAS group. Although the RAS group patients had a higher percentage of L-form (87.5%) than the non-RAS group (54.8%), the distribution of L, S, and V forms in both groups did not reach a clinically significant level ($p = 0.081$). None of the RAS patients had initial leukocyte counts of more than 10 x 10^9/L and there was no statistical significance between RAS

Table 1. Characteristics of Patients with and without RAS

Characteristics	RAS (n = 8)	Non-RAS (n = 94)	p value
Median age (range)	54 (27-77)	40 (17-74)	0.107
Gender (%)			
M	4 (50%)	47 (50%)	1.000
F	4 (50%)	47 (50%)	
Initial leukocyte count (%)			
>10 x 10^9/L	0	22 (23.4%)	0.196
M3v (%)	1 (12.5%)	4 (4.26%)	0.341
Subtypes of PML/RARα (%)			
L form	7 (87.5%)	51 (54.8%)	0.081
S form	1 (12.5%)	33 (35.5%)	
V form	0	9 (9.7%)	
Concurrent chemotherapy (%)	7 (87.5%)	76 (81.4%)	1.000

Abbreviations: RAS: retinoic acid syndrome; M: male; F: female; M3v: microgranular variant.

and non-RAS patients ($p = 0.196$). In the RAS group, 7 out of 8 patients (87.5%) received concurrent chemotherapy while 76 out of 84 patients (81.4%) received concurrent chemotherapy in the non-RAS group. There was no significant difference in the ratio of patients receiving chemotherapy in either group ($p = 1.000$).

Of all 102 patients, 69 received cytogenetic studies and typical reciprocal translocation of chromosome 15 and 17 was detected in 62 of 69 patients (89.9%). No atypical translocation involving chromosome 11 and 17 or 5 and 17 was found. In the remaining 7 patients who failed to exhibit typical reciprocal translocation in chromosome studies, the diagnosis of APL was mainly based on the detection of *PML*/*RARα* fusion transcripts. As mentioned above, 101 patients received RT-PCR for detection of *PML*/*RARα* fusion transcripts and positive results were obtained in all of them. The only patient who did not receive RT-PCR was confirmed to have typical reciprocal translocation of chromosome 15 and 17 in the chromosome study.

Table 2 shows the clinical features of the eight RAS patients. RAS symptoms developed in a median period of 9 days after initiating ATRA therapy (range: 2-23 days). The most common manifestations of RAS were fever (87.5%) and respiratory distress (87.5%). Pulmonary infiltrates in the chest radiographs were found in 6 out of 8 patients (75.0%). Three patients (37.5%, No. 1, 5 and 8) developed severe respiratory distress and respiratory failure and required mechanical ventilatory support. One patient (No. 8) received prednisolone (15 mg three times daily) prophylaxis when her leukocyte count exceeded 10 x 10^9/L on the second day of ATRA therapy. She developed severe pulmonary hemorrhage and respiratory failure on day 18 and required ventilatory support. She achieved complete resolution after receiving high-dose dexamethasone (10 mg twice daily) for 2 weeks.

Three patients in the RAS group died during induction. One of them (No. 6) died of acute respiratory distress syndrome resulting from RAS, and the other two (No. 1 and No. 5) died of severe sepsis after they achieved partial or complete resolution of RAS. Therefore the RAS-related mortality was 12.5% (1 out of 8 patients). Patient No. 1 developed RAS and respiratory failure on the second day of ATRA therapy, and was subsequently transferred to an intensive care unit after endotracheal intubation. High-dose dexamethasone (10 mg twice daily) was administered after ATRA was discontinued, and the

Table 2. Clinical and Laboratory Features of 8 RAS Patients

No.	Sex	Age	Morphology (M3 or M3v)	Molecular subtype (L, S, V)	Initial WBC	Manifestations	Timing* (days)	Duration of CR (months)
1	M	54	M3	L	2700	fever, pulmonary infiltrates, respiratory distress	2	–
2	F	36	M3	L	2200	fever, pulmonary infiltrates, respiratory distress	23	12.5
3	M	43	M3	S	1700	fever, leg edema, respiratory distress	6	114+
4	F	60	M3	L	1000	respiratory distress ,pulmonary infiltrates, pleural effusion	8	86+
5	F	55	M3	L	3400	fever, respiratory distress, pulmonary infiltrates, pulmonary hemorrhage	5	–
6	M	77	M3	L	1900	fever, pleural effusion	10	–
7	M	54	M3	L	8600	fever, respiratory distress, skin lesions(Sweet-like neutrophilic dermatitis), pulmonary infiltrates	7	22+
8	F	27	M3v	L	4100	fever, respiratory distress, pulmonary infiltrates, pulmonary hemorrhage	18	8+

Abbreviations: RAS: retinoic acid syndrome; M: male; F: female; M3: classical form; M3v: microgranular variant; WBC: white blood cell; CR: complete remission; *: The term "Timing" means the time point of RAS occurrence after ATRA therapy was initiated.

level of pulmonary infiltrates improved significantly within 1 week. He failed to undergo extubation due to secondary infection (*streptococcal sepsis*) on day 13, and died of multi-organ failure one month later. Patient No. 5 developed RAS symptoms on the fifth day of ATRA therapy. Complete resolution of pulmonary lesions after steroid administration was achieved 6 days later, and extubation was conducted smoothly. Due to a progressive increase in leukocyte counts, conventional chemotherapy with daunorubicin and Ara-C was administered on day 18. Shock developed on day 21, and blood cultures yielded oxacillin-resistant *Staphylococcus aureus* on the next day. The patient died of profound and irreversible shock 4 days later.

DISCUSSION

ATRA is a successful model of differentiation therapies in the treatment of APL.[22,23] The application of ATRA has decreased the bleeding complications resulting from DIC and improved the complete remission and survival rates.[2] Now ATRA has been widely accepted as a part of standard treatment for APL.

Frankel and colleagues first described RAS in 9 out of 35 APL patients (26%) treated with ATRA. More than 80% of the patients exhibited fever and respiratory distress.[17] In other series, the RAS incidence rate ranges from 6% to 36%.[1,8-10,13,14] This syndrome usually develops after 2 to 47 days of ATRA therapy.[17,18,24] Other literature states that the incidence of RAS treated with ATRA alone is approximately 25%.[8,10] However, its incidence rate decreases to approximately 10% if the patients receive chemotherapy and ATRA simultaneously.[1,9,13,14] Because most of our patients (81.4%) received concurrent chemotherapy, the RAS incidence of 7.8% is similar to those in previously published reports. Of the 83 patients receiving concurrent chemotherapy, 7 (8.4%) developed RAS while one out of 19 patients (5.3%) treated with ATRA alone experienced RAS. Although researchers believe that the addition of concurrent chemotherapy is able to reduce the occurrence of RAS, it seems that the presence of concurrent chemotherapy does not decrease the risk of RAS in this series ($p = 1.000$). The reason why our findings are quite different from other studies remains unresolved, but the small sample size of RAS group in this study may play a role. The timing of RAS onset in this study ranges from day 2 to day 23, which agrees with the results in previous studies.

Regarding the risk factors of RAS, an initially high leukocyte count may contribute to the occurrence of RAS.[10,12] However, Tallman et al. analyzed 44 RAS patients and demonstrated that there was no correlation between the initial leukocyte counts and the RAS incidence.[24] In addition, no difference was observed between RAS and non-RAS groups in age, gender, performance status, or molecular subtypes of PML/RARα transcript. The only independent variable significantly associated with the incidence of RAS in that study was the morphological subtypes of APL. In that study, M3v comprised 4% (2 out of 44 patients) in the RAS group and 17% (12 out of 123 patients) in the non-RAS group ($p < 0.05$). Therefore, M3v exhibited a protective effect, preventing the occurrence of RAS. In the current study, the difference of M3v prevalence between patients with and without the RAS did not reach a statistical significance level ($p = 0.341$).

Most reports show no correlation between the subtypes of *PML/RARα* transcripts and the development of RAS. In the present study, patients with L-form *PML/RARα* transcript comprise the majority (87.5%) of the RAS group and they were more apt to develop RAS (12.07%) than the non-L-form patients (2.4%) (odds ratio: 5.76, $p = 0.13$). However, in spite of this trend, there is no statistical significance. The sample sizes of both RAS and M3v patients are too small to achieve a final conclusion.

Although dexamethasone has proven effective in preventing mortality in most cases, the RAS mechanism remains unclear. The pulmonary manifestations of RAS resemble those of acute respiratory distress syndrome, and researchers therefore postulate that the interaction between pulmonary epithelial cells and ATRA-treated leukemic cells accounts for these clinical findings. Tsai et al. found that the migration of ATRA-treated APL cells to pulmonary microcirculation was mediated by interleukin-8 and growth-regulated oncogene-α secreted by pulmonary endothelial cells. In addition, untreated APL cells have no migration ability. Therefore, ATRA activation is essential for APL cells to migrate and produce pulmonary infiltration.[25] Details of the ATRA activation process remain unresolved, and further studies are needed.

Nicolls et al. reported a rare form of RAS in an 18-year-old female who developed pulmonary hemorrhage 15 days after ATRA therapy.[21] Lung biopsy results demonstrated diffuse interstitial infiltration of neutrophils with fibrinoid necrosis and alveolar hemorrhaging. The patient received high-dose steroid therapy (methylprednisolone 1 g/day) for 3 days, and complete recovery was achieved. In our study, one patient (No. 8) also developed severe pulmonary hemorrhaging on day 18 of ATRA therapy. However, we did not perform diagnostic bronchoscopy or a lung biopsy due to the patient's critical condition. High-dose dexamethasone (10 mg twice daily) was given and a complete response was achieved 8 days later. Although this experience is limited, it is important to keep in mind that pulmonary hemorrhaging can be a clinical manifestation of RAS and it often occurs 2 weeks after ATRA therapy. Early administration of a high-dose steroid can help prevent mortality, and complete recovery may be expected.

It has been suggested that the occurrence of RAS may increase the risk of extramedullary relapse of APL and 60% (3 out of 5 patients) developed extramedullary relapse with CR durations of 3, 10 and 29 months, respectively.[26] In our study, only one patient experienced disease relapse with a CR duration of 12.5 months and no extramedullary relapse was found. The remaining 4 patients who completed the induction therapy have not experienced relapse up to the present time with follow-up duration of 8 to 114 months.

In summary, the incidence of RAS in the current series is similar to those of other series with ATRA and concurrent chemotherapy. Based on the limited RAS cases, we did not find a significant association of age, gender, morphological subtypes or molecular isoforms of *PML/RARα* transcript, an initial WBC count of more than 10×10^9/L or the presence of concurrent chemotherapy with the occurrence of RAS. A severe form of RAS manifesting with pulmonary hemorrhage and respiratory failure may occur. Clinicians should be alert to this rare, life-threatening but potentially curable complication. Complete recovery is possible with timely diagnosis and administration of high-dose steroid treatment. Further studies are needed to find out the factors that increase the risk of RAS and therefore provide a better insight for steroid prophylaxis.

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急性前髓性白血病經使用全反式維甲酸所引起之維甲酸症候群

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背 景： 分析急性前髓性白血病的患者經維甲酸治療後，發生維甲酸症候群的比例與危險因子。

方 法： 本回顧性研究共分析 102 例於 1993 年 8 月至 2007 年 12 月在林口長庚醫院診斷爲急性前髓性白血病的患者，經維甲酸治療後，發生維甲酸症候群的比例與危險因子。

結 果： 在 102 例經維甲酸治療的急性前髓性白血病患者中，共有 8 例 (7.8%) 發生維甲酸症候群，發生的時間爲治療後 2 至 23 日。發燒與呼吸窘迫爲最常見的臨床表現，佔了 87.5%，其次爲肺部浸潤 (75%)。年齡、性別、型態學及分子診斷學上的分類皆與維甲酸症候群的發生與否無關。其中一位患者發生維甲酸症候群的臨床表現爲肺部出血，並在給予高劑量類固醇之後完全康復。發生維甲酸症候群的 8 位患者中，有 1 例死於維甲酸症候群引發之呼吸衰竭 (12.5%)。5 例在完成誘導性治療之後皆可達到完全緩解，並於維持性治療時再度使用維甲酸，無人再次發生維甲酸症候群。

結 論： 在本研究中，維甲酸症候群的發生率不高，且因大多數患者 (81.4%) 皆有合併化學治療，故與國外併用化學治療患者之發生率相近。年齡、性別、型態學及分子診斷學上的分類和治療前白血球總數增加與否皆與維甲酸症候群的發生率無統計學上的相關性。另外，值得一提的是，患者是否併用化學治療在本研究中並沒有明顯影響維甲酸症候群的發生率。維甲酸症候群也可以肺部出血作爲臨床表現，早期診斷與儘速給予高劑量類固醇可以有極佳的療效。

(長庚醫誌 2009;32:535-42)

關鍵詞： 急性前髓性白血病，全反式維甲酸，維甲酸症候群，高劑量類固醇

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