Ten-year Experience on Acute Promyelocytic Leukemia at Inha University Hospital

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Background: Acute promyelocytic leukemia (APL) is a distinct subtype of acute myeloid leukemia in its morphology as well as molecular or genetic profiles, conferring a good prognosis owing to the active roles of all-*trans*-retinoic acid (ATRA) and anthracyclines.
Methods: Patients diagnosed as APL from March 1997 to April 2006 were analyzed on their clinical features, laboratory profiles, methods of treatment including remission induction, consolidation and maintenance, treatment outcomes, and treatment-related morbidity.
Results: Chemotherapy naïve were all the 12 patients in our study consisting of 3 males and 9 females. All patients showed typical morphologic feature of APL with cytogenetic abnormality, t(15;17), and PML/RARα fusion gene was confirmed in 10 patients by FISH or PCR. The combination of cytarabine with daunorubicin (n=2) or idarubicin (n=9) was used as an induction regimen with concurrent ATRA administration. For consolidation therapy, cytarabine with anthracycline (n=4) or idarubicin monotherapy (n=8) was used with ATRA. Cytogenetic and molecular remissions were documented after induction chemotherapy (n=11) or first consolidation therapy (n=1). Maintenance therapy with ATRA was done in 11 patients. CR was obtained in 12 patients, with median remission duration of 30.5+ months (range 2 to 86+) at a median follow up duration of 33.5+ months (range 4 to 89+). One patient relapsed after completion of maintenance therapy and died of infection during reinduction chemotherapy.
Conclusion: Herein is the report of ten years' experience of our hospital in the treatment of APL with favorable results as seen by high CR rate and fewer complications. ***(Korean J Hematol 2006;41:289-296.)***

Key Words: Acute promyelocytic leukemia, All-*trans*-retinoic acid, Anthracycline, Treatment, Complication

INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of acute myelocytic leukemia (AML) comprising 10~15% of AML, with distinct morphologic, cytogenetic and molecular characteristics such as abnormal promyelocytes, specific chromosomal translocation t(15;17)(q22;q21), and PML/RARα fusion gene transcript. Clinical course is

접수 : 2006년 8월 29일, 수정 : 2006년 10월 16일
승인 : 2006년 10월 27일
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Table 1. The schedule of chemotherapeutic regimen

Induction			Consolidation		
1) AI			1) I		
Ara-C	100mg/m^2/d	D1~7	Idarubicin	12mg/m^2/d	D1~3
Idarubicin	12mg/m^2/d	D1~3	2) AD		
2) AD			Ara-C	1g/m^2/d	D1~7
Ara-C	100mg/m^2/d	D1~7	Daunorubicin	45mg/m^2/d	D1~3
Daunorubicin	45mg/m^2/d	D1~3	3) MA		
3) ATRA*	45mg/m^2/d	Max. 100 days	Ara-C	1g/m^2/d	D1~7
			Mitoxantrone	12mg/m^2/d	D1~3
			4) M		
			Mitoxantrone	12mg/m^2/d	D1~3

*ATRA was concurrently given with remission induction chemotherapy except for one case where ATRA monotherapy was used for remission induction. The maintenance protocol consisted of ATRA at 40mg/m^2 for 2 weeks every 8 weeks for 2 years used in all patients except one.

also unique with frequent manifestation of leukopenia, fibrinogenopenia, and disseminated intravascular coagulation (DIC) often worsened by chemotherapy.[1] The advent of all trans-retinoic acid (ATRA) in the remission induction altered the dismal prognosis of APL to the best one, owing to the dramatic control of DIC and subsequently decreased peri-treatment mortality.[1] As far as remission induction is concerned, ATRA monotherapy or ATRA combined with conventional chemotherapy was proven to be better than conventional chemotherapy containing cytosine arabinoside (Ara-C) and anthracycline.[2-4] In consolidation therapy, the comparable efficacy of anthracycline monotherapy with andthracycline and Ara-C combination was reported.[5-7] Some studies asserted better disease free survival (DFS) and overall survival (OS) with maintenance therapy[4,9,10] using ATRA, 6-mercaptopurine or oral methotrexate.

We report here a ten-year experience of our hospital in treatment of APL, with emphasis on the clinical manifestation, updated therapeutic option, and complication.

MATERIALS AND METHODS

1. Patients

Twelve patients who were newly diagnosed as APL at the Inha University Hospital between March 1997 and April 2006 were enrolled in this study. All patients were diagnosed as AML M3 on French-American-British (FAB) classification by conventional morpholocytochemical criteria.[11] Chromosomal analysis was done in all patients, and molecular analysis for APL (fluorescence in situ hybridization [FISH] or polymerase chain reaction [PCR] for PML/RARα transcript) was done in 11 patients.

2. Chemotherapy regimen

For remission induction, 11 of 12 patients were treated with standard dose of Ara-C and anthracycline (idarubicin : n=9, daunorubicin : n=2) combination chemotherapy with the exception of one who was treated with ATRA alone. Consolidation chemotherapy consisted of idarubicin monotherapy (n=8), Ara-C/daunorubicin combination (n=2), mitoxantrone/Ara-c combination (n=1), or mitoxantrone alone (n=1) for two or three cycles. ATRA was given in induction remission as well as in consolidation (n=11) or in remission in-

duction alone (n=1). Maintenance therapy consisted of ATRA at 45mg/m^2 for 2 weeks every 8 weeks for 2 years (n=11) (Table 1).

3. Response criteria

Complete remission and relapse were defined according to NCI criteria.[12] In addition to hematologic and cytogenetic remission by microscopic examination and chromosomal analysis including FISH, molecular remission was defined by qualitative PCR.

4. Statistical method

Descriptive statistic values of this study were analyzed by SPSS version 10.0 programs. The variables of patients' characteristics and results of this study were listed at Tables 2 and 3.

RESULTS

1. Patients' characteristics

The clinical and biological characteristics of the 12 patients are shown in Table 2. The median age of the 12 patients (3 men and 9 women) was 40 years (range, 26 to 59). All patients showed laboratory evidence of DIC and 10 of 12 showed clinically overt DIC manifestations such as gum bleeding, gastrointestinal bleeding, petechia, or intracranial hemorrhage. Variable degrees of leukopenia (n=7, median 1,800/uL, range 1,400~4,300) or leukocytosis (n=5, median 15,800/uL, range 13,900~30,100), profound anemia, and thrombocytopenia were shown at the presentation. Reciprocal translocation of chromosomes 15 and

Table 2. The characteristics of patients

	No. of patients (total n=12)
Sex	
Male : Female	3 : 9
Age (median/range)	39/26~59
DIC (clinical/laboratory)	10/12
Fever at diagnosis	10
Hematologic profile (median/range)	
Leukocyte (/μL)	2,100 (1,200~30,100)
Hemoglobin (g/dL)	8.5 (5.2~14)
Platelet (/μL)	37,000 (4,000~97,000)
t(15 : 17)	12
PML-RARα (PCR or FISH) at diagnosis	10/11

Table 3. The cytogenetic and molecular changes during chemotherapy

Patient	Time (month) 0	1	2	4	8	12	18	24	36	Last f/u
1*	● ATRA	☆ AD	☆ M	☆ M	☆ M	☆				☆
2	● AD	★ AI	☆ MA	☆ MA	☆ ——	——	——	——	——	☆
3	● AI	☆	AD	☆ AD	☆ AD	☆ ——	——	——	——	☆
4	● AD	☆	AD	☆ AD	☆ AD	——	——	——	—— ● AI ● //	Death
5	● AI	☆ I	☆	I	☆ ——	——	——	——	——	☆
6	● AI	☆ I	☆	I	☆ ——	——	——	——	——	☆
7	● AI	☆ I	☆	I	☆ I	☆ ——	——	——	——	☆
8	● AI	★☆ I	☆	I	☆ I	☆ ——	——	——	——	☆
9	● AI	★☆ I	☆	I	☆ I	☆ ——	——	——	——	☆
10	● AI	☆ I	☆	I	☆ I	☆ ——	——			☆
11	● AI	☆ I	☆	I	☆ —					☆
12	● AI	☆ I	☆	I						☆

● Hematologic disease, ★ Hematologic remission, ☆ Cytogenetic remission, ——: maintenance using ATRA.
Abbreviations: AI, Ara-C+Idarubicin; AD, Ara-C+Daunorubicin; I, Idarubicin; MA, Mitoxantrone+Ara-C; M, Mitoxantrone.
*ATRA was concurrently administrated with chemotherapy during remission induction and used as maintenance therapy in all patients except for the case.

17 was found in all patients on marrow culture. FISH and/or PCR for PML/RARα were tested in 11 patients, and positive result was reported in 10 patients on diagnosis.

2. Clinical outcome

All patients attained cytogenetic or molecular remission after induction chemotherapy with the exception of one who reached remission after repeated induction therapy. Once remission was achieved using ATRA monotherapy (n=1) or Ara-C and anthracycline combination (n=11), all patients were treated by 2 or 3 cycles of consolidation chemotherapy consisting of idarubicin alone (n=8) or anthracycline and/or intermediate high dose of Ara-C (n=4). Maintenance therapy consisted of ATRA at 45mg/m^2 for 2 weeks every 2 months for 2 years. Eleven of 12 patients actually entered the maintenance therapy program. One of them relapsed after completion of maintenance therapy and died of infection during the salvage chemotherapy. Eleven of 12 patients were in continuous CR including one with no maintenance therapy. The median duration of follow-up was 33.5 months (range, 4~89), and the median duration of CR or disease free survival (DFS) was 30.5 month (range, 2~86+). The median duration of overall survival (OS) has not been reached with a range from 5+ to 89+ month (Table 4).

The clinical outcome and the results of cytogenetic and molecular monitoring are illustrated in Fig. 1 and Table 3. The amount of transfusion required during the treatment is shown at Table 5.

3. Complications of chemotherapy

ATRA-related adverse events occurred in 7 patients including overt ATRA syndrome (n=2), fever (n=3), rash (n=3), leukocytosis (n=1), arthritis (n=1), or vomiting/diarrhea (n=1) as shown in Table 6. Patients in ATRA syndrome were fully recovered after parenteral administration of corticosteroid without mortality or sequela. Thirty eig-

Table 4. The result of chemotherapy

	No. of patients (total n=12)
CR after induction or re-induction	12
	Median month/range
Follow-up duration	33.5/(4~89)
CR duration	30.5/(2~86)
Overall survival duration	5~89
Median survival	Not reached

Table 5. Transfusion requirement during chemotherapy

	RBC (pack)	Platelet (unit)
Induction (median/range)	8/(4~30)	80/(44~345)
Total (median/range)	16.5/(9~34)	196.5/(140~461)

Table 6. The complications during chemotherapy

	No. of events
ATRA-related (total 7 patients)	13
ATRA syndrome	2
Fever	3
Rash	3
Leukocytosis	1
Arthritis	1
Vomiting/diarrhea	1
Fever (event/total chemotherapy)	38/45
Infection, microbiolocally proven	13

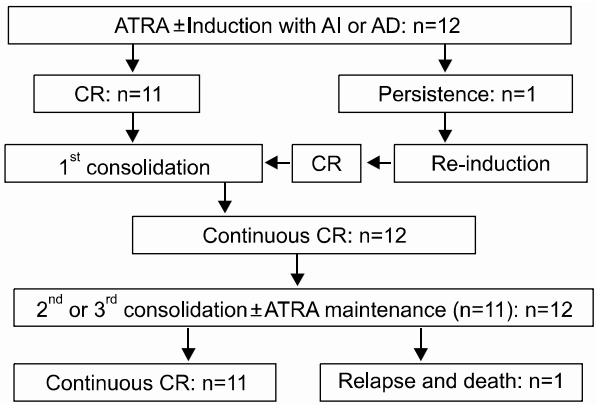

Fig. 1. The clinical outcome of chemotherapy.

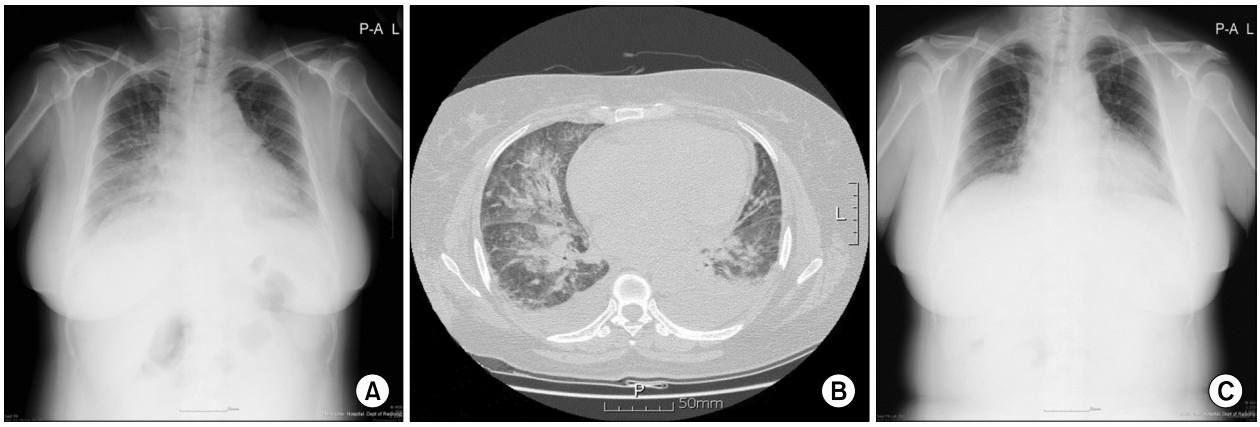

Fig. 2. ATRA syndrome. Diffuse bilateral pulmonary infiltration 20 days after ATRA administration (A, B), and disappearance after 20 days' parenteral steroid treatment (C).

ht febrile episodes were noted among a total of 45 course of chemotherapy including induction and consolidation, and microbiologically proven bacteremia or fungemia was documented in 13 (*Staphylococcus*=3, *Aspergillus*=3, *Enterococcus*=2, *E.coli*=2, *Streptococcus*=1, *Citrobacter*=1, *Candida*=1).

DISCUSSION

The treatment outcome of APL has been improved dramatically in recent decade. Before advent of ATRA, anthracycline and Ara-C containing chemotherapies were used in patients with APL similar to the other subtypes of AML. The treatment accompanied high treatment-related mortality caused by DIC or fatal hemorrhage.[13,14,16] Since ATRA proved to be a useful chemotherapeutic agent for APL, the mainstay of chemotherapy of APL shifted to ATRA-based regimen. Induction chemotherapy with ATRA showed excellent outcome with 5-year OS of about 70%, and ATRA maintenance chemotherapy added significant benefit in 5-year DFS, yielding 60% versus 30% for patients with no maintenance therapy.[10] The studies using consolidation composed of ATRA and anthracycline monotherapy appeared in the middle of 1990's in an attempt to reduce toxicity of chemotherapy.[5,6] The studies of ATRA and anthracycline monotherapy consolidation actually showed reduced treatment-related morbidity and mortality while preserving comparable antileukemic effects regardless of age.[7,8] Nowadays, the combination of ATRA and anthracycline (especially idarubicin) or anthracycline alone is accepted as a standard post-induction chemotherapy in APL.[5,6,9,10] In our study, there was no treatment-related mortality during induction chemotherapy, and symptom and sign of DIC resolved as soon as ATRA was started. Severe ATRA syndrome was noticed in one patient with hypoxia, dyspnea, diffuse pulmonary infiltrates, and pleural effusion, which fully recovered after parenteral corticosteroid treatment, (Fig. 2) but it did not require any specific treatment in other patients with mild ATRA syndrome.

During consolidation chemotherapy neutropenic fever was frequent in our study (38 episodes out of a total of 45 chemotherapy courses). There was no mortality except one patient who died of infection after high dose chemotherapy for recurrent disease. The use of idarubicin monotherapy with ATRA in our study might have reduced toxicity as well as mortality during consolidation. Our study showed good clinical outcome with early cytogenetic response right after induction or re-induction in all patients as well as durable continuous CR in 11 of 12 patients. It was unfortunate that one patient who relapsed opted a risky treatment and died of therapy related complication in view of many other treatment op-

tions[15,16] available. The reason for the better treatment outcome in our study compared with previous two studies in Korea[17,18] is uncertain. Better supportive care or attenuated chemotherapy using anthracycline alone might explain the difference.

The importance of PML/RARα in the diagnosis and the treatment is now well established[3,4,19] mandating the measurement of PML/RARα transcript using FISH or reverse-transcription polymerase chain reaction (RT-PCR) to be an essential evaluation step during the clinical course of APL.[5,20,21] The use of RT-PCR for the detection of the PML/RARα and RARα/PML fusion genes has emerged as the only technique that defines the PML breakpoint type and that allows the definition of a correct strategy for subsequent minimal residual disease (MRD) monitoring.[22] Standardized conditions for RT-PCR analysis of fusion transcripts from chromosome aberrations in acute leukemia, including APL, have recently been reported in the context of the Biomed-1 Concerted Action.[22]

In our study, 11 of 12 patients were tested for PML/RARα transcript with FISH or qualitative PCR, and 10 patients were positive. The technical error might explain the discrepancy in one case between the results of conventional cell culture and molecular method. There have been several reports of rare cryptic translocations in APL,[23,24] and all of them showed superior results of molecular technique to conventional cell culture.

There is a controversy regarding the optimal time of response evaluation after induction chemotherapy. When ATRA is used in the induction chemotherapy, it is recommended that bone marrow examination should be performed on days 40~50 post-induction therapy rather than days 7~14 post-induction, a conventional time for a rapid response assessment in other subtypes of AML, because delayed blast maturation or persistence of detectable atypical promyelocyte during the induction with ATRA may lead to false interpretation.[25] In our study, we occasionally performed bone marrow study earlier than they recommended, and 2 patients showed persistent disease in marrow at 3 weeks after induction, which was converted to cytogenetic or molecular remission at 7 weeks under continuous ATRA administration (Table 3, patients No. 8 and 9).

In conclusion, we experienced the 12 cases of newly diagnosed APL between March 1997 and April 2006 with no mortality secondary to DIC or treatment. Early cytogenetic response was achieved in nearly all patients, and idarubicin monotherapy was effective in combination with ATRA as induction as well as consolidation. The treatment outcome was excellent showing DFS of 92% at a median follow up duration of 33.5+ months.

요 약

배경: 급성 전골수성 백혈병(APL)은 급성 골수성 백혈병의 아형 중 하나로, 특징적인 형태학적, 분자유전학 특성을 나타내며, anthracycline과 all-trans-retinoic acid (ATRA)의 사용으로 좋은 예후를 보이고 있다.

방법: 1997년 3월부터 2006년 4월까지 인하대병원에서 APL로 진단된 환자들의 임상양상, 검사소견, 유도 및 경화, 유지 요법, 치료결과, 합병증 등을 분석하였다.

결과: 남자 3명, 여자 9명의 총 12명의 환자를 대상으로 항암요법이 시행되었다. 모든 환자들은 전형적인 APL의 형태학적 및 세포유전학적 특성을 보였으며, t(15;17) 염색체 이상을 나타내었다. 10명의 환자에서 FISH나 PCR의 방법으로 PML/ RARα 결합 유전자가 발견되었다. 유도요법으로는 Cytarabine과 함께 daunorubicin (n=2)이나 idarubicin (n=9)이 병합요법으로 사용되었고 ATRA가 동시에 투여되었다. 공고요법으로는 cytarabine-anthracycline 병합요법(n=4)이나, idarubicin 단독요법(n=8)이 사용되었다. 분자유전학적 관해는 유도요법 후나(n=11), 1차 공고요법 후에(n=1) 모두 도달하였다. 유지요법으로 ATRA가 11명의 환자에게서 사용되었다. 관해유지기간의 중앙값은 30.5+개월이었고(2~86+개월), 추적기간은 33.5+개월(4~89+개월)이었다. 한 명의 환자가 유지요법 후 재발하였으며, 재유도요법 시행 시 감염으로 사망하였다.

결론: 지난 10년간 본원에서 경험한 APL 환자들

의 치료를 분석하여, 높은 관해율과(12명 중 11명) 적은 합병증을 보고하는 바이다.

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