Haematologica 1998; 83:714-717 original paper

Management of acute promyelocytic leukemia relapse in the ATRA era

CARLO CASTAGNOLA, MONIA LUNGHI, ALESSANDRO CORSO, MONICA TAJANA, PATRIZIA ZAPPASODI, MELISSA DABUSTI, MARIO LAZZARINO, CARLO BERNASCONI
Divisione di Ematologia, IRCCS Policlinico S.Matteo di Pavia, Istituto di Ematologia, Università degli Studi di Pavia, Italy

Abstract

Background and Objective. **The use of all-trans retinoic acid (ATRA) has changed the natural course of acute promyelocytic leukemia (APL), increasing the percentage of lasting complete remissions. However, management of the few relapses remains undefined. The purpose of the present study was to evaluate the different behavior of APL patients relapsed after induction chemotherapy which had or had not included ATRA.**

Design and Methods. **We retrospectively studied 8 patients (3 male and 5 female) who had relapsed after a clinical and molecular complete remission (CR). Five patients relapsed after conventional chemotherapy including antracyclines, without ATRA which was not available at the onset (group A), 3 relapsed after induction treatment according to AIDA protocol (idarubicin + ATRA) (group B). Seven patients had both molecular and clinical relapses, 1 (group B) had only a molecular relapse. The median first CR duration was 33 months (range 8-63). To induce a second CR all patients were treated with ATRA 45 mg/m²/day given orally until CR, combined with mitoxantrone 6 mg /m²/day for 6 days and cytarabine 1 g/m²/day for 6 days.**

Results. **Seven out of 8 patients (87.5%) achieved second CR, 1 (group A) did not respond and died within two months. Second CR duration was 21, 43+, 56+, 62+ months in group A and 5, 10,12+ (with molecular relapse) months in group B. Therefore, only one patient relapsed in group A, while all the group B patients relapsed.**

Interpretation and Conclusions. **ATRA combined with chemotherapy is an effective approach to treating APL relapse. It produces a high incidence of second CR with an acceptable toxicity. The duration of the second CR seems, however, to be longer in patients never treated with ATRA before than in patients who relapsed after the AIDA protocol. Therefore, it might be appropriate to adopt more aggressive protocols in this latter subset of patients.**

Key words: acute promyelocytic leukemia, acute myeloid leukemia, relapse, ATRA, second remission

Correspondence: Carlo Castagnola, M.D., Divisione di Ematologia, IRCCS Policlinico S. Matteo, piazzale Golgi, 27100 Pavia, Italy. Phone: international +39-0382-503073-503070 • Fax: international +39-0382-502250 • E-mail: castagnola@smatteo.pv.it

Acute promyelocytic leukemia (APL) is a rare type of acute myeloid leukemia (AML), characterized by distinct molecular and clinical features including the presence of a specific t(15;17) translocation in blast cells, frequent association at diagnosis with severe hemorrhagic diathesis, and sensitivity to the all-trans retinoic acid (ATRA) drug. The t(15;17) fuses the promyelocytic leukemia gene (PML) on chromosome 15 to the retinoic acid receptor α gene (RARα) on chromosome 17. This chimeric gene encodes the PML-RARα fusion protein which plays a central role in the pathogenesis of APL inducing a differentiation block.[1] The use of ATRA has changed the natural course of the disease by inducing the differentiation of APL blasts and consequently reducing the incidence of life-threatening hemorrhagic diathesis.[2,3] The therapeutic approach with ATRA and antracycline-based chemotherapy has, thus, increased the percentage of APL patients potentially cured to 70%.

The management of APL relapsed patients, however, remains a challenge for the clinician since the best therapeutic strategy has not yet been defined. We retrospectively analyzed 8 APL patients, 5 of whom had relapsed after conventional chemotherapy and 3 after treatment with ATRA and idarubicin.

Materials and Methods

Eight patients with relapsed APL were admitted to our hospital up to March 1997 following initial treatment between October 1987 and May 1992. The diagnosis of recurrent APL was made according to the French-American-British (FAB) criteria and confirmed by the presence of t(15;17) obtained through fluorescent *in situ* hybridization (FISH) or cytogenetic analysis or by reverse transcriptase-polymerase chain reaction (RT-PCR) for PML/RARα gene rearrangement. The clinical and laboratory data at the onset of disease are shown in Table 1. There were 3 males and 5 females. Median age was 35 years (range 17-62). The median white blood cell (WBC) count was 1.6×10^9/L (range 0.4-34.6), hemoglobin concentration 9.8 g/dL (range 6.2-14) and platelet count 29×10^9/L (range 5-100). All patients had clinical and/or laboratory evidence of disseminated intravascular coagulation.

Previous chemotherapeutic treatment included

Table 1. Clinical and laboratory data of 8 APL relapsed patients at presentation.

Group	Patient	Sex/Age	Hb (g/dL)	WBC (x10⁹/L)	PLT (x10⁹/L)	t(15;17)	PML-RARα
A	PM	F/30	8	2	29	+	ND
A	AA	F/49	12.2	1.1	100	+	ND
A	SS	F/17	10.1	1.9	5	+	ND
A	GL	M/35	6.2	1.4	30	+	+
A	GM	M/17	14	1	66	+	+
B	DCC	F/22	9.6	2.2	48	+	+
B	SB	M/62	10.8	0.4	28	+	+
B	AR	F/41	7.8	34.6	17	+	+

Abbreviation: ND, not done.

Table 2. Induction and consolidation chemotherapy at the onset of 8 APL relapsed patients.

Group	Patient	CR-Induction	Consolidation
A	PM	DNR	DNR+ARA-C (2 courses)
A	AA	DNR	DNR+ARA-C (2 courses); HD-ARA-C(2 course)
A	SS	IDA+ARA-C	IDA+ARA-C; MTZ+VP; IDA+ARA-C+6TG
A	GL	IDA+ARA-C	IDA+ARA-C; MTZ+VP; IDA+ARA-C+6TG
A	GM	DNR	DNR+ARA-C+6TG
B	DCC	ATRA+IDA	IDA+ARA-C; MTZ+VP; IDA+ARA-C+6TG
B	SB	ATRA+IDA	IDA+ARA-C; MTZ+VP; IDA+ARA-C+6TG
B	AR	ATRA+IDA	IDA+ARA-C; MTZ+VP; IDA+ARA-C+6TG

Abbreviations: DNR, daunorubicin; ARA-C, cytosine arabinoside; HD, high dose; IDA, idarubicin; MTZ, mitoxantrone; VP, etoposide; 6TG, 6 thioguanine.

anthracyclines alone or in combination with cytosine arabinoside (Ara-C) in 5 patients (group A) and the association of idarubicin and ATRA according to the AIDA protocol in 3 patients (group B) (Table 2). All patients obtained a first complete remission (CR) and then relapsed after 6, 32, 33, 59 and 63 months (group A) and 8, 32 and 34 months (group B) (Table 3). Seven patients had both clinical and molecular relapses, 1 patient (patient AR, group B) had only a molecular relapse (presence of the PML/RARα transcript).

All relapsed patients were treated with ATRA 45 mg/m²/d given orally in two doses until CR, associated with mitoxantrone 6 mg/m²/d for 6 days (30-minute infusion) and Ara-C 1 g/m²/d for 6 days.

Complete remission (CR) was defined as the patient being in normal health with hemoglobin > 10 g/dL, neutrophils > 1×10^9/L and with fewer than 5% of leukemic promyelocytes in a normal cellular marrow. Non response (NR) was defined as more than 30% of blasts in bone marrow after treatment.

Table 3. First and second CR duration of 8 APL relapsed patients.

Group	Patient	I CR duration (months)	II CR duration (months)
A	PM	6	NR
A	AA	63	62+
A	SS	32	56+
A	GL	59	43+
A	GM	33	21
B	DCC	34	10
B	SB	32	12
B	AR	8	5

Chromosome analysis was performed at diagnosis using Q-banding techniques and karyotype abnormalities were described according to the *International Society for Human Cytogenetic Nomenclature* criteria.[4]

RT-PCR analysis for the PML/RARα rearrangement was performed after induction chemotherapy and to monitor patients in remission. Since this technique was not available at the beginning of this study, its results are not given for all patients.

Results

Second CR was achieved in 7 out of 8 patients (87.5%), 1 patient of group A did not respond and died within two months because of progression of the disease (Table 4). No patient had serious hemorrhagic or infectious complications during second induction chemotherapy.

Second CR duration for patients of group A was 21, 43+, 56+, 62+ months (Table 3). One of these patients (GM) underwent an autologous bone marrow transplantation during second PCR negative CR, but relapsed after 15 months. He gained a third remission with a second course of mitoxantrone plus Ara-C and he is still in CR.

In group B second CR duration was 5, 10 and 12+ (Table 3). One patient (AR) was treated after a molecular relapse and obtained only a clinical remission. Five months after chemotherapy she had a cytological and molecular relapse. The patient DCC relapsed after a three year period of maintainance therapy with ATRA. She gained a second CR and then received an autologous bone marrow transplantation. She relapsed 7 months later. At present she is in her third CR after treatment with idarubicin and ATRA.

PCR analysis for PML/RARα was performed after chemotherapy in 7 patients (Table 4). It was negative in 6 patients and positive in 1 patient (AR, group B)

Table 4. Molecular and clinical results of 8 patients in APL relapse.

Group	Patient	II CR	PCR to II CR	II cytological relapse	Update	PCR
A	PM	N	ND			
A	AA	Y	–	N	II CR	–
A	SS	Y	–	N	II CR	–
A	GL	Y	–	N	II CR	–
A	GM	Y	–	Y	III CR	–
B	DCC	Y	–	Y	III CR	–
B	SB	Y	–	N	molecular relapse	+
B	AR	Y	+	Y	III relapse	+

Abbreviations: ND, not done.

who had a cytological relapse after 5 months. One patient (SB, group B) with negative PCR following induction chemotherapy converted to having a positive PCR after 11 months.

Discussion

Until some years ago, APL relapses were studied together with the other AML subtypes. No difference, in fact, had been shown between APL and the other AMLs as far as achievement of second remission was concerned. This was obtained in about 40% of cases.[5,6] The advent of ATRA modified therapeutic possibilities both in de novo and in recurrent-refractory APL.[2,7] It has been appreciated that a combination of ATRA and chemotherapy confers significant improvement in CR rates and reduces the incidence of hemorrhagic syndrome in newly diagnosed APL patients.[8] This approach is now adopted as standard treatment of the disease with impressive results. In particular, using a combination of ATRA and idarubicin as induction therapy, Mandelli *et al.*[9] gained a 95% of hematological remissions. In a more recent update, the same group demonstrated that estimated actuarial event free-survival at 3 years was 70%.[10]

Huang *et al.*[2] found that ATRA was also effective in APL relapsed patients; however, Frankel *et al.*[11] showed that only 3 out of 19 patients, who had relapsed from a remission induced by all-trans retinoic acid, could be brought into remission again using the same drug.

Our relapsed APL patients were divided in 2 groups on the basis of their previous treatment. The patients previously treated with conventional chemotherapy formed group A, whilst group B comprised patients entered in the AIDA scheme. The re-induction schedule was identical in both groups: ATRA associated with mitoxantrone and Ara-C. Seven out of 8 patients entered a second CR, showing that the protocol was effective in both groups of patients. We did not observe a significant increase of bleeding diatheses, which were usually exacerbated by chemotherapy before the advent of ATRA. There was, however, a great difference between the behavior of two groups during follow-up. Group A patients had a longer second CR than group B patients. Three out of 5 group A patients, in fact, are still in molecular remission after a minimum follow-up of 43 months. Out of the group B patients, 2 experienced an overt relapse and, after 11 months, one had a molecular relapse, which has been demonstrated to be predictive of clinical relapse.[12,13] This behavior is consistent with a lower efficacy of ATRA, probably due to a sharper selection of high-risk patients with the first induction treatment. This, together with the possibility of new additional chromosome aberrations in relapse, could make the disease more resistant to chemotherapy. On the basis of our results (Table 3) there is no relation between first and second CR duration in the two groups. The duration of second CR in the group B patients is compatible with the data reported for relapsed AML patients.[5] In contrast, group A patients behave differently, having a much longer second CR.

In conclusion, the combination of ATRA and chemotherapy must be considered the treatment of choice in patients not previously treated with retinoids. In contrast, although ATRA decreases the life-threatening hemorrhage and allows a second CR, patients already treated with ATRA as induction therapy usually obtain only very short remissions. Since conventional chemotherapy seems not to be sufficient, more intensive schedules, including bone marrow transplantation, are probably required for this group of patients.

Contributions and Acknowledgments

CC, MLu, AC and MLa were responsible for the design of the study. CB was responsible for the conception of the study. MT, PZ and MD contributed to execution of the study and data collection. All the authors contributed to the analysis and writing the paper.

Disclosure

Conflict of interest: none.

Redundant publications: no substantialm overlapping with previous papers.

Manuscript processing

Manuscript received February 2, 1998; accepted April 28, 1998.

References

1. Warrell RP Jr, de The' H, Wang Z-Y, et al. Acute promyelocytic leukemia. N Engl J Med 1993; 329:177-89.
2. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic

leukemia. Blood 1988; 72:567-76.
3. Fenaux P, Chomienne C, Degos L. Acute promyelocytic leukemia: biology and treatment. Semin Oncol 1997; 24:92-102.
4. Third International Workshop on chromosome in leukemia. Cancer Genet Cytogenet 1980; 4:95-142.
5. Davis CL, Rohatiner ZS, Lim J, et al. The management of recurrent acute myelogenous leukemia at a single centre over a fifteen-year period. Br J Haematol 1993; 83:404-11.
6. Castagnola C, Nozza A, Bonfichi M, et al. Leucemia mieloide acuta in ricaduta: analisi di 70 pazienti [abstract]. 35° Congresso nazionale Società Italiana di Ematologia 1995; p. 170.
7. Ohno R, Ohnishi K, Takeshita A, et al. All-trans retinoic acid therapy in relapsed/refractory or newly diagnosed acute promyelocytic leukemia (APL) in Japan. Leukemia 1994; 8(Suppl.3):S64-S69.
8. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans retinoic acid in acute promyelocytic leukemia. N Engl J Med 1977; 337:1021-8.
9. Mandelli F, Diverio D, Avvisati G, et al. Molecular Remission in PML/RARα-positive acute promyelocytic leukemia by combined all-trans retinoic acid and Idarubicin (AIDA) protocol. Blood 1977; 90:1014-21.
10. Avvisati G. Treatment of acute promyelocytic leukemia in Italy: updated results of the AIDA protocol [abstract]. 2nd International Symposium on *Acute promyelocytic leukemia a curable disease*, 1997, p. 15.
11. Frankel SR, Eardley A, Heller G, et al. All-trans retinoic acid for acute promyelocytic leukemia. Results of the New York Study. Ann Intern Med 1994; 120:278-86.
12. Korninger L, Knobl P, Laczika K, et al. PML-RARα positivity PCR in the bone marrow of patients with APL precedes haematological relapse by 2-3 months. Br J Haematol 1994; 88:427-31.
13. Diverio D, Riccioni R, Mandelli F, et al. The PML-RARα fusion gene in the diagnosis and monitoring of acute promyelocytic leukemia. Haematologica 1995; 80: 155-60.