Clinical Trial of Low Dose Cytosine Arabinoside in the Treatment of Acute Promyelocytic Leukemia

The purpose of this study is to determine the efficacy of low dose cytosine arabinoside (LD Ara-C) as an alternative treatment to conventional cytotoxic induction chemotherapy in childhood acute promyelocytic leukemia (APL). Four children with APL in poor medical condition prior to chemotherapy were treated with LD Ara-C (10 mg/m^2/12h) for 3 weeks. In three patients, the second course was administered after a resting period of two weeks. Subsequent conventional cytotoxic induction chemotherapy was applied in patients who did not enter complete remission (CR). After induction of CR, maintenance chemotherapy with a conventional monthly multi-drug regimen was applied. CR in one patient and partial remission (PR) in two patients were obtained after two courses of LD Ara-C. Patients who did not enter CR after LD Ara-C entered on subsequent conventional chemotherapy. There were no major complications such as intracranial hemorrhage and sepsis; myelosuppression was not as severe as in conventional chemotherapy; there was clinical and laboratory improvement in coagulopathy. We concluded that LD Ara-C may be an alternative treatment to the conventional chemotherapy in children with APL, especially in whom conventional cytotoxic induction chemotherapy is thought to increase the risk of serious complications and early fatality during induction chemotherapy.
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Key Words : *Low dose cytosine arabinoside, Acute promyelocytic leukemia, Induction chemotherapy*

Ki Woong Sung, M.D., Hyeong Soo Choi, M.D., Eun Sun Yoo, M.D., Kyung Ha Rhu, M.D.*, Hee Young Shin, M.D., Hyo Seop Ahn, M.D.

Division of Hemato-Oncology, Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea
Department of Pediatrics, Ewha Womans University College of Medicine, Seoul, Korea*

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Address for correspondence
Hyo Seop Ahn, M.D., Department of Pediatrics, Seoul National University Children's Hospital, 28 Yeongeon-dong, Jongro-gu, Seoul 110-744, Korea
Tel : (02) 760-3625 / 3570, Fax : (02) 743-3455

INTRODUCTION

The clinical behavior of acute promyelocytic leukemia (APL) is distinguished by fatal coagulopathy at diagnosis and a relatively high mortality rate during remission induction with conventional cytotoxic chemotherapy. The response of APL to conventional cytotoxic chemotherapy differs from those of other subtypes of acute myelocytic leukemia (AML) in that remission induction failures are attributable primarily to early death rather than refractory disease (1, 2, 3). These early fatalities result from hemorrhage, renal and pulmonary complications of disseminated intravascular coagulopathy (DIC), or, more rarely, infection during periods of bone marrow hypoplasia (2). Overly aggressive cytotoxic chemotherapy in APL may contribute to the high mortality rate during the first month of induction therapy, especially in patients who are in poor condition at diagnosis and can not tolerate intensive induction chemotherapy.

As an alternative to conventional cytotoxic induction chemotherapy, we used low dose cytosine arabinoside (LD Ara-C) to treat four newly diagnosed APL children who had severe infection, severe coagulopathy, were in poor condition prior to induction chemotherapy, and in whom it was thought to develop serious complications with death during induction chemotherapy.

PATIENTS AND METHODS

Four previously untreated APL children were treated with two daily subcutaneous or intravenous injections of Ara-C (10 mg/m^2/12h) for 21 days. In three patients (patients 1, 2, 3), a second course of LD Ara-C was administered after a resting period of 14 days, and follow-up bone marrow examination was carried out two weeks after the completion of this second course. Subsequent conventional cytotoxic induction chemotherapy with the Denver induction regimen (4) or a high dose Ara-C regimen (5) was applied in two patients (patients 1, 2) who did not enter complete remission (CR) after two courses of LD Ara-C. In one patient (patient 4), subsequent conventional cytotoxic induction chemotherapy (Denver induction regimen) was applied instead of a

Table 1. Treatment schedules and clinical courses

Patient No.	Age(years) /Sex	Reason for LD Ara-C	Induction Chemotherapy	Further Treatment	Duration of CR and Outcome
1	10/F	DIC, pneumonia	LD Ara-C(x2) → PR → DI(x2) → CR	DM 1/2 Capizzi II	62m BM relapse and death
2	13/F	DIC, sepsis, liver abscess	LD Ara-C(x2) → PR → HD Ara-C(x2) → CR	DM 1/2 Capizzi II	>31m
3	13/F	DIC, perianal abscess	LD Ara-C(x2) → CR	DM 1/2 Capizzi II	>8m lost F/U
4	5/M	DIC, sepsis, pneumonia	LD Ara-C(x1) → DI(x2) → CR	DM 1/2 Capizzi II	5m BM relapse and death

CR : complete remission, PR : partial remission, BM : bone marrow, x2 : two courses, LD Ara-C : low dose Ara-C regimen, HD Ara-C : high dose Ara-C regimen, DI : Denver induction regimen, DM : Denver maintenance regimen, 1/2 Capizzi II : half times of Capizzi II regimen

second course of LD Ara-C. After induction of remission, maintenance chemotherapy with a conventional monthly multi-drug regimen such as the Denver regimen (4) and 1/2 Capizzi II (half times in Ara-C administration) regimen (6) was applied. The treatment schedules in this study are summarized in Table 1.

All patients were suffering from coagulopathy and significant infections at diagnosis and received treatment with gabexate mesilate and fresh frozen plasma for coagulopathy, and with antibiotics for infections.

Complete remission is defined as < 5% blasts plus promyelocytes in normal cellular marrow with a normal peripheral blood count and an absence of signs and symptoms of leukemia on physical examination. Partial remission (PR) is defined as insufficient reduction in blasts plus promyelocytes (5~25%) or inadequate bone marrow recovery.

RESULTS

The results are summarized in Table 1 and 2. CR was achieved after two courses of LD Ara-C in one patient (patient 3) and PR was obtained after two courses of LD Ara-C in two patients (patients 1, 2) who entered CR after other subsequent courses of conventional cytotoxic induction chemotherapy without any significant complication. In one patient (patient 4), subsequent conventional cytotoxic induction chemotherapy was applied without follow-up bone marrow examination after one course of LD Ara-C. Although promyelocytes were still present in the peripheral blood after one course of LD Ara-C in patient 4, coagulopathy disappeared and his general condition improved enough to tolerate intensive chemotherapy. He entered CR after subsequent conventional cytotoxic induction chemotherapy. Follow-up is

Table 2. Characteristics of response to LD Ara-C

Patient No.	Response to LD Ara-C		Bone marrow					Peripheral blood				Nadir of WBC /μl	Duration of DIC (days)
			MB (%)	PMC (%)	MC (%)	NB (%)	Cellularity (%)	Hb g/dl	WBC /μl	Plt 10^3/μl	MB+PMC (%)		
1	PR	at Dx	55	35	5	1	100	4.5	132,800	14	77		
		F/U	2.5	3.5	31.5	46.0	100	9.4	2,300	63	0	1,500	19
2	PR	at Dx	40	17	9	1	100	3.8	32,680	14	61		
		F/U	5.8	3.4	23.0	56.4	50	7.7	4,170	179	0	430	14
3	CR	at Dx	2.8	72.4	20.8	0.8	100	5.6	60,000	13	34		
		F/U	0	1.2	41.2	51.2	60	9.1	6,700	149	0	800	36
4	?*	at Dx	2	70	9	5	100	4.3	3,600	25	36		
		F/U			ND			9.1	1,700	34	5	1,600	21

MB : myeloblast, PMC : promyelocyte, MC : differentiated myeloid cell, NB : normoblast
F/U : Follow-up bone marrow examination was carried out two weeks after the completion of a second course of LD Ara-C.
Duration of DIC : The time during which antithrombotic therapy was needed.
ND : Bone marrow examination was not carried out.
* In patient 4, subsequent conventional cytotoxic chemotherapy was applied after one course of LD Ara-C without bone marrow examination.

depicted in Table 1. After induction of CR, patient 1 maintained CR for 62 months before relapse in the bone marrow and died 6 months later. Patient 2 has maintained CR for 31 months. Patient 3, the only one who entered CR without further cytotoxic chemotherapy, maintained this state for 8 months, but was subsequently not followed up. Patient 4 experienced CR for 5 months, but then relapsed and unfortunately died 3 months later.

Blasts disappeared completely from the peripheral blood of patients who entered CR (patient 3) and PR (patients 1, 2). In patient 4, to whom only one course of LD Ara-C was administered, blast count in the peripheral blood decreased after one course of LD Ara-C.

When bone marrow examination was carried out two weeks after the completion of the second course of LD Ara-C in three patients (patients 1, 2, 3), marrow aplasia was not noted in any of them. Bone marrow cellularities were 100%, 50%, and 60%, respectively. Instead of marrow aplasia, an increase in the proportion of differentiated myeloid cells and normoblasts was noted.

Myelosuppression was significant, requiring transfusions frequently, but was not as severe as in conventional cytotoxic chemotherapy. During and after chemotherapy with LD Ara-C, the nadirs of WBC count in the peripheral blood were 1,500/μl, 430/μl, 800/μl, and 1,600/μl, respectively, in each patient and all patients experienced severe thrombocytopenia (<20,000/μl).

Extrahematologic tolerance was good, and a significant toxic effect other than cytopenia was not observed during chemotherapy with LD Ara-C. Coagulopathy was present in all patients at diagnosis, and there was clinical and laboratory evidence of improvement of coagulopathy during chemotherapy with LD Ara-C. None of our patients showed aggravation of hemorrhagic manifestations; during chemotherapy with LD Ara-C, no newly-developed infection was seen.

DISCUSSION

APL is considered a distinct entity among AML; its pathophysiology, diagnosis, treatment, and behavior are distinct from those of other subtypes (2, 7). The clinical behavior of APL is distinguished by coagulopathy at diagnosis and a relatively high mortality rate during remission induction with conventional cytotoxic chemotherapy. The majority of patients present with ecchymoses or overt bleeding (2, 8). Coagulopathy is the most serious problem in APL and its severity and frequency are often aggravated by cytotoxic chemotherapy.

The clinical response of APL patients treated with conventional cytotoxic chemotherapy is distinct, in that remission induction failures are attributable primarily to early death rather than to refractory disease. These early fatalities result from hemorrhage, renal and pulmonary complications of DIC, or, more rarely, infection during periods of bone marrow hypoplasia (2). Cerebral and pulmonary hemorrhage complicates induction chemotherapy in up to 40% of patients (9). Aggressive chemotherapy destroys leukemic cells and causes the release into the circulation of procoagulant factors from the azurophilic granules (10). Overly aggressive cytotoxic chemotherapy in APL may contribute to the high mortality rate during the first month of induction chemotherapy.

The purpose of conventional treatment is to destroy the leukemic cells by cytotoxic drugs and to allow normal cells to proliferate. The two main drugs used are Ara-C and daunorubicin (11). Used in conventional doses, these drugs kill leukemic cells but are also very toxic to normal cells. This type of therapy is complicated by bone marrow aplasia and may result in early complications and fatality in APL patients during the first month of therapy, especially in patients in poor medical condition, who are - for example - suffering from coagulopathy or infection prior to chemotherapy (12). Some researchers have proposed a more gradual induction regimen (13).

The unusual response of APL to chemotherapy is reflected in the bone marrow. While marrow aplasia is the essential characteristic of therapeutic response in other subtypes of AML, CR in APL can be achieved without marrow aplasia (14, 15). Differentiation of APL cells is present in remission of APL (16) ; these cells have a lower labeling index and longer cell cycle duration. This slow cycling of leukemic promyelocytes in APL may be due to increased expression of transforming growth factor-β (TGF-β). Because TGF-β may inhibit proliferation, APL cells may be primed for maturation rather than proliferation.

The potential of many drugs to induce differentiation of leukemic cells rather than cytotoxicity has been screened *in vitro* (17); in leukemia, various ways have been tested (18, 19), including suppression of proliferative pressure by LD Ara-C, enhancement of differentiation by retinoic acid derivatives or by differentiation factors, modulation of cell metabolism interrupting an autocrine loop (a growth factor and its receptor), and induction of differentiation by many drugs including actinomycin-D, interferons, vitamin D_3, dimethylsulfoxide, phobol esters, dexamethasone, low dose 6-TG, and deferoxamine. Recent approaches to the treatment of leukemia include the use of these differentiation-inducing agents. Among them, all-*trans* retinoic acid which has been known to be a potent inducer of myeloid differentiation, has been tried in the treatment of APL as an alternative agent to conventional

induction chemotherapy, and with some success (10). Ara-C is one of these drugs; based on its ability to induce *in vitro* differentiation of leukemic cells, LD Ara-C has been proposed as an alternative therapy for acute leukemia and MDS. At high concentrations, Ara-C is cytotoxic, but at low concentrations, it can induce differentiation and also possibly cause selective cytotoxity against leukemic cells (20).

Chemotherapy with LD Ara-C was first applied in a patient with RAEB in transformation after the failure of conventional treatment (21) and as initial treatment in an elderly AML patients (22, 23, 24). Using LD Ara-C, it has been possible to obtain CR in all categories of leukemia (23), and chemotherapy with LD Ara-C has been known to be more effective in cases of hypoplastic AML (25, 26).

According to the literature, LD Ara-C has been applied to two main groups of patients in whom conventional cytotoxic chemotherapy was either usually ineffective or contraindicated (26). The first group consisted of patients with a disease unresponsive to conventional treatment, including relapsing AML, resistant AML (27), MDS (17) as well as those with AML that developed after MDS or myeloproliferative disease, or was secondary to cytotoxic treatment (26). The second group consisted mainly of patients who was thought to develop serious complications with death during conventional induction chemotherapy; included were elderly patients and those with severe infections or in poor condition prior to chemotherapy. We used LD Ara-C in childhood APL patients who had a high risk of complications; because we thought that the risk of complications and fatality during induction chemotherapy was much higher in APL patients in poor condition prior to chemotherapy than in patients with other subtypes of AML, LD Ara-C instead of a conventional cytotoxic agent was chosen as a remission inducing agent.

The mechanism of action in LD Ara-C therapy is still controversial. While *in vitro* evidence suggests that Ara-C may act as a differentiation inducing agent (28), its *in vivo* effect may be on the basis of more than a single mechanism. Ara-C is a cytotoxic drug when used at conventionally established doses but at a low dose, a differentiation inducing effect is observed in mouse leukemic cells (28, 29) and in human leukemia cell lines such as HL-60 (30, 31), ML-1 (18), and U-937 (32). The absence of bone marrow aplasia, the continuing existence of marrow cellularity, and the presence of promyelocyte with mature granulocyte, along with decreasing leukemic blasts during treatment with LD Ara-C in AML, seem to favor the differentiating mechanism of LD Ara-C (33). Some authors have regarded the gradual rise in peripheral blood count with LD Ara-C as supportive evidence of its differentiation inducing effect (34). Published data indicate that LD Ara-C induced remission can be achieved without bone marrow hypoplasia (23, 24, 27), and that the induction of hypoplasia by itself does not always result in CR (26). Indeed, while in some patients a hypoplastic phase is obtained prior to the normalization of bone marrow and peripheral blood, in other patients CR is achieved without transitional marrow aplasia (35); this also suggests that LD Ara-C has a differentiation inducing effect. Since differentiated myeloid cells increased with LD Ara-C treatment, our data demonstrate the occurrence of this effect.

Another effect of LD Ara-C is that it is cytotoxic, even at very low doses; in many cases, its administration causes an *in vivo* cytotoxic effect on normoblasts and megakaryocytes in bone marrow and sometimes hypoplasia. Some researchers have concluded that LD Ara-C exerts its effect by halting proliferation through cytotoxic effects, not by differentiation induction (23). Significant cytopenia with mild to moderate bone marrow hypoplasia suggests that the cytotoxic effect of LD Ara-C is more or less sufficient to rid the marrow of a susceptible leukemic clone (34). According to many researchers, however, myelosuppression, though significant in most patients treated with LD Ara-C, was not as serious as in conventional remission induction chemotherapy for AML. Although the action of LD Ara-C *in vivo* also involves toxicity to blasts and to the normal hematopoietic system, this toxicity alone may not be sufficient to obtain CR (26).

Due to wide variations in the results of previous studies, it is difficult to draw conclusions about the mechanism of LD Ara-C. Its action is probably not based on a single mechanism of differentiation induction or cytotoxicity; differentiation induction, cytotoxicity, or both acting together may contribute to the achievement of CR.

The dosage of LD Ara-C and the duration of treatment have varied in different studies. In the majority of series, however, a dose of 10 mg/m^2/12h has been administered for 15~21 days (26). Short-term treatment of less than 5 days has had little effect (36). The optimum duration of treatment has not been established yet. In some studies, only one course of LD Ara-C was administered (34, 37, 38), but we and others administered two or three (23, 27, 39). In our cases, we gave two daily injections of Ara-C (10 mg/m^2/12h) for 21 days; three patients (patients 1, 2, 3) received a second course after resting period of 14 days. Patient 4 received only one course of LD Ara-C, followed by conventional cytotoxic induction chemotherapy. LD Ara-C was given subcutaneously in most series but in a few groups continuous intravenous infusion was also tried (40). Some authors

have concluded that the outcome of LD Ara-C treatment is independent of the mode of administration (41); in our study, it was in most instances given subcutaneously, but IV bolus infusion was sometimes used.

When CR is not obtained after LD Ara-C, some authors have recommended one to two additional courses for remission induction (26). However we used a conventional cytotoxic induction regimen because we believed that the initial poor condition which had urged us to use LD Ara-C, had disappeared, that the risk of complications and fatality had decreased after LD Ara-C administration, and that the patient could tolerate intensive chemotherapy. After the further use of cytotoxic agents, CR was obtained in all patients without any significant complications (patients 1, 2, 4).

There has been much published data concerning the controversial response rate of adult AML to LD Ara-C (23, 24, 38, 42, 43). According to these data, CR rates have ranged from 0 to 100%, with the rate for myeloblastic and promyelocytic leukemia (FAB M1-3) twice as high as those for its monocytic subtypes (FAB M4-5) (41). The reasons for such wide variation, despite the similarity of dose, route of administration, and duration of treatment are not clear. There is no published data concerning the response rate of childhood APL to LD Ara-C, especially in patients in poor medical condition prior to chemotherapy. In our patients, CR was achieved in one patient, and PR was achieved in two after two courses of LD Ara-C treatment. In patient 4, neither CR nor PR was achieved, and promyelocytes were still present in the peripheral blood after one course of LD Ara-C treatment. The promyelocyte count in peripheral blood decreased, however, and coagulopathy and general condition improved enough to tolerate intensive chemotherapy. Subsequent conventional cytotoxic chemotherapy was possible without any significant complications.

Although reports of long-term follow-up in patients treated with LD Ara-C are not yet available, it is apparent that the duration of remission is usually short (20, 34). After CR, some maintenance chemotherapy with or without LD Ara-C may therefore be necessary. Some researchers have used a monthly 7-day cycle of LD Ara-C without significant improvement in survival (25). Others have recommended that a more aggressive treatment should be initiated once remission is obtained. Bone marrow transplantation is a suitable alternative when possible (44). In our cases, we used monthly multi-drug maintenance chemotherapy (Denver and 1/2 Capizzi II regimens).

While many authors have claimed that LD Ara-C is associated with minimal toxicity (23, 24, 38), some have noticed significant cytopenia requiring hospitalization, frequent transfusions, and antibiotics (20). It seems, though, that LD Ara-C, unlike conventional regimens, is not toxic enough to prevent the regeneration of normal hematopoietic elements. Compared with conventional chemotherapy, myelosuppression is reduced, and this results in less need for transfusions and few early deaths due to infection. Extrahematologic tolerance is good. In our cases, nadirs of WBC count in peripheral blood were not as low as in conventional cytotoxic chemotherapy. All patients experienced severe thrombocytopenia but it was not clear whether this was entirely therapy-related, since all patients had coagulopathy at diagnosis and thrombocytopenia was pronounced at the beginning of chemotherapy with LD Ara-C. Marrow aplasia was not noted in any patient; instead of aplasia, there was an increase in the proportion of differentiated myeloid cells and normoblasts. This suggests that aplasia of bone marrow is not a general feature of treatment with LD Ara-C and that CR can be obtained even without bone marrow aplasia.

We concluded that whatever the mechanism of action of LD Ara-C, LD Ara-C may be an alternative to conventional cytotoxic induction chemotherapy in children with APL, especially in those who have severe infection, severe coagulopathy, are in poor condition prior to chemotherapy, or in whom it is thought that serious complications and early fatality may result from conventional cytotoxic induction chemotherapy.

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