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Low Dose Cytosine Arabinoside Regimen for Overt Leukemia, Hypoplastic Leukemia and Myelodysplastic Syndromes : Hypoplastic Leukemia Responds Best.

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ABSTRACT : In a series of 38 patients consisting of 13 with overt acute leukemia, 14 with hypoplastic leukemia, and 11 with myelodysplastic asyndromes (MDS), responsiveness to low dose cytosine arabinoside (LDAC) regimen was investigated to clarify the disease type most benefitted. LDAC was continuously administered intravenously at dose 0.2mg/kg/day and continued as long as possible to meet the pre-assigned target point of 5% marrow blasts which was confirmed by weekly marrow aspiration. Overall response rate was 47% ; complete remission (CR) being 31% and partial remission (PR) 16%. CR rate was significantly different between the disease types ; 69% in hypoplastic leukemia, 23% in overt leukemia and 0% in MDS ($p=0.01$). In hypoplastic leukemia the survival time was significantly longer in the LDAC-treated cases compared with 15 historical control cases treated with supportive care only ; median survial being 750 days in the former and 250 days in the latter ($p=0.01$). In overt leukemia only three M2 AML cases obtained CR ; two of them were treated during hypoplastic phase induced by intensive chemotherapy. All CR cases eventually achieved the target point after 20 to 42 days (median 26) of LDAC administration. Substantial toxicity of LDAC was evident, but most cases tolerated well. The present investigation suggests that hypoplastic leukemia is the disease type most sensitive to LDAC regimen. Stratification of the elderly leukemia patients should be considered for this regimen.

INTRODUCTION

Cytosine arabinoside (ara-C) is now widely used for a variety of acute leukemias. Conventional dose of ara-C is a major component of multi-drug induction chemotherapy for acute myeloid leukemias (AML) in most institutions, and high dose of ara-C is mainly used for post-remission chemotherapy or for induction chemotherapy of resistant or refractory leukemias.[1] Low dose of ara-C has been so far used for the treatment of acute leukemia, myelodysplastic syndromes (MDS) or resistant leukemia in the elderly and/or compromized patients.[2~11]

Bolwell *et al* recently reviewed the results of low dose ara-C (LDAC) regimen reported from many institutions.[12] They reported that overall complete remission (CR) rate is around 30% in AML and 18% in MDS. These rather low unsatisfactory response rates indicate that it is

of clinical importance to clarify whether certain type (s) of acute leukemia or MDS show preferential response to LDAC regimen. We analysed the results of LDAC regimen in a series of 38 patients with overt leukemia, hypoplastic leukemia, or MDS and concluded that hypoplastic leukemia responds best and survival time could be durable.

MATERIALS AND METHODS

Of twenty-seven cases of acute leukemias 13 had overt acute leukemia defined by FAB classification and 14 had hypoplastic leukemia defined by histology-proven hypoplastic marrow. Hematological profiles of the patients in each group are summerized in Table 1 and 3, respectively. The reasons of entry to LDAC regimen were old age in 11 patients, compromized host in 12 patients and resistant leukemia in 4 patients.

Diagnosis of hypoplastic leukemia was established when the bone marrow clot and/or Jamshidi's needle biopsy section shows less

Table 1. Hematological Profiles of Patients with Hypoplasetic Leukemias Treated with LDAC Regimen

Case No.	Age	Sex	Peripheral Blood				Bone Marrow			
			Hb(g/dl)	WBC(μl)	Plt(μl)	Blast(%)	Cellularity(%)[1]	Blast(%)	Blast Type[2]	Dysplasia Score[3]
1.	63	M	7.4	2500	42500	1	31	28.0	M1	2
2.	55	F	9.6	3250	244500	0	50	22.4	M4	0
3.	58	M	8.3	2050	2500	1	42	28.6	M2	5
4.	74	M	3.8	1100	47500	5	44	48.2	L	0
5.	70	M	5.9	1700	35500	0	25	18.8	M1	1
6.	78	F	6.4	550	7500	2	41	36.0	M1	4
7.	62	F	7.7	1250	65000	0	26	26.0	M1	0
8.	73	M	6.0	1200	31000	0	22	45.1	L	2
9.	72	M	9.4	1650	70000	0	34	22.8	Null	4
10.	44	M	7.4	800	17500	2	38	56.0	M1	2
11.	76	F	10.7	4500	177500	3	23	20.0	M4	3
12.	64	F	6.9	1550	62500	0	22	15.6	M4	5
13.	66	M	11.2	2100	62500	0	37	17.0	M2	1
14.	56	M	6.4	1300	16000	0	41	42.2	Null	6

LDAC : low dose cytosine arabinoside, 1, 2 and 3 are all defined in the text

Table 2. Treatment Outcome in Patients with Hypoplastic Leukemias Treated with LDAC Regimen

Case No.	LDAC Regimen			BM Blast(%)			PB Neutrophil Count(μl)			Outcome	Consolidation Regimen	CR duration (mo)	Survival (mo)	Remarks
	Dose (mg/day)	Duration (days)	Serum Concentration(ng/ml)	Before	Day14	After[1]	Before	Nadir	After[2]					
1.	10	31	3.96	28.0	16.8	1.6	120	85.5	2686	CR	LDAC	5	28	2nd CR
2.	10	20	5.31	22.4	10.6	2.4	171	15	3080	CR	LDAC	6	26	2nd CR
3.	12	25	4.58	28.6	25.2	1.2	823	6.5	1740	CR	LDAC	4	17	
4.	10	42	ND	95.4	82.8	1.0	148.5	68	2150	CR	—	12	19	
5.	13	28	7.67	18.8	28	—	407	0	—	ED[3]	—	—	2	
6.	10	11	4.21	36.0	22.5	10	346	30	1725	NR	—	—	10	
7.	10	24	2.63	26.0	12.5	3.6	231	48	1733	CR	BHAC DMP	5	42	2nd/3rd CR
8.	10	28	2.75	45.1	12.8	1.8	600	5.5	2525	CR	—	9	17	
9.	10	29	ND	22.8	19.2	3.2	252	31.8	1138.5	NR	—	—	8	
10.	10	33	ND	56.0	33	20.8	248	63	144	NR	—	—	20+	
11.	10	21	ND	20.0	2.8	1.0	270	16	1987	CR	LDAC	24+	24+	
12.	20	28	ND	22.8	9.2	2.0	564	252	780	CR	LDAC	8+	8+	
13.	10	31	ND	17.0	6.8	2.6	546	57	941	CR	LDAC	4	6+	
14.	12	28	ND	42.2	14.9	4.4	101	0	30	NR	—	—	—	

1: bone marrow blast percent just after the cessation of LDAC in each case.
2: neutrophil count three weeks after the cessation of LDAC in each case.
3: early death due to asphyxia.

Table 3. Hematological Profiles and Treatment Outcome in Patients with Overt AML Treated with LDAC Regimen

Case No.	Age	Sex	FAB subtype	Prior chemotherapy	LDAC Regimen		Bone Marrow			Outcome	CR duration (mo)
					Dose (mg/day)	Duration (days)	Before		After		
							Cellularity[1]	Blast(%)	Blast(%)		
1.	68	F	M2	−	10	14	109	53.4	0.4	CR	uncertain
2.	50	M	M6	−	10	16	92	32	4.4	PR	4
3.	68	M	M4	−	10	31	583	58.4	10.4	NR	
4.	73	F	M4	DCMP	10	25	386	62	54	NR	
5.	63	F	M4	DCMP	10	21	84	10.4	41.4	NR	
6.	35	M	M3	DCMP	30	17	10	59	98.6	NR	
7.	69	F	ALL	VCR+PSL	60	11	29	95.8	81.0	NR	
8.	32	M	ALL	VCR+PSL	12	40	5	42.6	12.4	NR	
9.	23	M	M1	−	12	29	39	26.8	22.8	NR	
10.	67	F	M2	DCMP	10	21	19	23.6	0.2	CR	13
11.	59	M	M2	DCMP	10	17	17	17.8	0.2	CR	5
12.	53	M	M4	DCMP	10	24	134	25.7	20.8	NR	
13.	41	F	M2	DCMP HDAC	10	18	187	8.8	32.8	NR	

1: nucleated cell count($\times 10^3$/l)

than 50% cellular marrow and the blast percent exceeds 15% in non-erythroid cells (NEC). Areas of cellular marrow was estimated according to the method of Hartstock *et al.*[13] Cytological types of blast cells in hypoplastic leukemias as well as in overt leukemia were determind by routine cytochemistry and immuno-phenotyping including terminal deoxynucleotidyl transterase (TdT). Types of hypoplastic leukemia was classified according to leukemic cell characters defined as follow; peroxidase(PO)-positive myeloblasts without maturation as M1, PO-positive myeloblasts with maturation beyond promyelocytes as M2, PO-positive as well as non-specific esterase positive blasts and myelomonocytic components as M4, PO-negative/TdT-positive blasts as L and PO-negative/TdT-negative blats as Null. The latter two categories were negative for common ALL antigen.

Since some cases of the above-defined hypoplastic leukemias had tri-lineage dysplasia in mature cell fractions of the bone marrow, the degree of morphological dysplasia was graded into three scores; score 1 for less than 5% dysplastic cells in each cell lineage, score 2 for 5-20% and score 3 for 20% or more. Sum of the scores for three lineages was considered the dysplasia score for a given case.

In order to evaluate clinical benefit from LDAC regimen in patients with hypoplastic leukemia, 16 historical control cases with this disease which were treated with supportive cares only were also analysed. Clinical and hematological features of the hypoplastic leukemia patients totaling 29 cases in number are summarized in **Table 7.**

Eleven cases of FAB-defined MDS were composed of six patients with refractory anemia with excess of blasts in transformation (RAEB-T) and two with RAEB, two with refractory anemia (RA) and one with RA with ringed sideroblasts (RARS). Hematological profile of the patients was summarized in **Table 4.**

Ara-C was continuously administerred at dose 0.2mg/kg/day by using an intravenous infusion pump (Terumo) or via a hyperalimentation catheter. Duration of treatment wes determined primarily by the blast percent in the bone marrow and performance state of individual cases. 5% blast cells was assigned as target point of successful cytoreduction by LDAC. Patients who obtained complete remission (CR) was given two or three courses of 21 days' LDAC regimen or BHAC-DMP[14] (behenoyl ara-C + daunomycin + 6-mercaptepurine and prednisolone) as conslidation therapy. The plasma concentration of ara-C was measured by an redioimmunoassay in seven cases of hypoplastic leukemia on day 4 of LDAC regimen according to the pharmacokinetic results obtained by Kreis *et al.*[15]

In this study CR from leukemias or MDS was

Table 4. Hematological Profils and Treatment Outcome in Patients with MDS Treated with LDAC Regimen

Case No.	Age	Sex	FAB subtype	Peripheral Blood				Bone Marrow			LDAC Regimen		Outcome	Survival (mo)
				Hb (g/dl)	WBC (μl)	Plt (μl)	Blast (%)	Cellularity[1]	Blast (%)	Auer body	Dose (mg/day)	Duration (days)		
1.	64	M	RAEB-T	5.7	3700	3.5	1	105	16.4	+	20	26	NR	7
2.	50	M	RAEB	5.0	2200	0.6	1	101	5.0	−	12	10	PR	24+
3.	81	F	RAEB	7.3	4600	2.9	0	135	9.6	−	10	14	PR	3
4.	77	M	RAEB-T	6.4	1700	3.1	4	165	12.2	+	10	21	AML	7
5.	36	M	RAEB-T	5.8	2350	0.25	6	159	13.8	+	10	28	AML	4
6.	36	F	RAEB-T	5.9	7750	24.5	13	86	24.0	−	10	28	PR→AML	30+
7.	54	M	RAEB-T	5.5	3400	6.0	3	211	21.0	−	12	23	ED	4
8.	42	M	RAEB-T	7.0	2500	15.0	5	440	21.0	−	16	18	NR	5+
9.	71	F	RA	6.2	3800	3.0	0	176	1.0	−	8	15	NR	6+
10.	59	M	RA	5.8	4200	6.0	0	187	2.0	−	10	14	PR	16+
11.	77	F	RARS	6.1	3800	15.0	0	258	1.0	−	10	14	PR	44

1: nucleated cell count ($\times 10^9$/l), ED: early death

defined as the hematological state characterized by normalization of leukocyte count, neutrophil percent and platelet count and less than 5% marrow blasts and partial remission (PR) as the state with normal blood parameters but 5% or more marrow blasts in case of leukemias and 3g or more Hb increment and two-fold or more increment in neutrophil and/or platelet count in case of MDS. Statistical analysis was performed by using Kaplan-Meyer's method and Fischer's exact test.

RESULTS

Response Rates according to Disease Groups

Overall respones rate was 47% in this series; CR being 31% and PR 16%. CR rates were significantly different among disease groups; 69% in hypoplasetic leukemia, 23% in overt leukemia and 0% in MDS ($p=0.01$). PR was obtained in one case of overt leukemias and in five cases (45%) of MDS.

Response in Hypoplastic Leukemia

(a) Response Pattern

All of nine CR cases were treated for 20 days or more (20-42 days). Six of them showed a significant reduction of the blast percentage in day-14 bone marrow by more than 50% of pre-treatment value. In the remaining three cases the blast percent eventually decreased on day-25, 29 and 42, respectively. In all CR cases the final blast percent was below the target point of 5%. Case 5 died of asphyxia when his peripheral blood began to show neutrophil recovery. In Case 11 ara-C was discontinued on day 12 due to pneumonia complicating early induction.

The median nadir neutrophil count was 40/μl. The neutrophil count began to increase before cessation of LDAC regimen in three CR cases and within 14 days after the regimen in six cases.

Seven CR cases received consolidation therapy; LDAC was repeated in six cases, and BHAC-DMP was given in one case. The median CR duration was 6 months. All CR cases eventually relapsed showing again hypoplastic bone marrow manifestation. The second CR was obtained with LDAC regimen again in three cases and the third CR in one.

The median serum ara-C concentration was 4.4 ng/ml in seven cases of MDS measured. Unfortunately ara-C concentration was not measured in cases with overt lenkemia or MDS.

(b) Treatment Outcome in relation to Histological and Cytological Features (**Table 5**)

Cases of hypoplastic leukemia were devided into two groups according to severity of bone marrow hypoplasia; severely hypoplastic group with less than 30% cellular marrow and mildly hypoplastic group with30-50% cellular marrow. CR rate was significantly higher in the former ($p=0.01$).

Cases were also devided into severly dysplastic group with score 4 or more and

Table 5. Treatment Outcome in Relation to Histological and Cytological Features (Hypoplastic Leukemias)

	BM Cellularity		Dysplasia		Blast Types				
	≧30%	30<≦50%	Score 0~3	Score 4~9	M1	M2	M4	Null	Lymphoid
Case No (%)	5(100)	9(100)	7(100)	6(100)	5(100)	2(100)	3(100)	2(100)	2(100)
CR (%)	4(80)	5(56)	6(86)	3(50)	2(40)	2(100)	3(100)	0(0)	2(100)
NR (%)	1(20)	4(44)	1(14)	3(50)	3(60)	0(0)	0(0)	2(100)	0(0)

Table 6. Comparison of Clinical and Hematological Features between Responders and Nonresponders (Hypoplastic Leukemias)

	CR	NR
Case No.	9	4
mean age	65.7	62.5
PB		
WBC (μl)	2005	1075
Hb (g/dl)	80	7.4
Plt ($\times 10^4/\mu$l)	8.4	2.8
lymphocyte (%)	52	63.3
BM		
Blast(%)/ANC	27.7	37.2
Blast(%)/NEC	34.7	46.6
lymphocyte (%)	27.3	19.2
G+E (%)	35.2	38.9
mean survival (mo)	20.7*	10.0*

*: statistically significant($p<0.05$)
case 5 of early death excluded from this table.

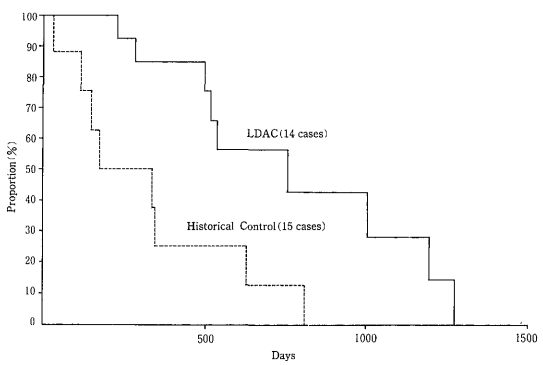

Fig. 1. Comparison of Survival between LDAC-treated Group and Historical Control

minimally dysplastic group with score 0 to 3. Significantly higher CR rate was noted in the minimally dysplastic groups ($p=0.01$).

CR rates in Null type and M1-type cases were lower than those in M2-type, M4-type and L-type cases. These differences were not significant due to the small case number in each type.

(c) Comparison of Clinical and Hematological Parameters between Responders and Non-Responders.

As shown in **Table 6** responders revealed higher leukocyte count, Hb value and platelet count on initial diagnosis. The bone marrow blast percent was lower in the responders. These differences were not statistically significant. Survival time was significantly longer in the former ($p=0.03$).

(d) Comparison of Survival Time between LDAC-treated Group and Historical Control Group.

As shown in **Fig. 1**, survival time was significantly longer in the LDAC-treated group; 50% survival being about 250 days in the historical control group and 750 days in the LDAC-treated group. In the latter group four cases survived for more than two years as the result of continued first CR in one case and repeated achievement of CR in three cases.

Response in Overt Acute Leukemia Group

Three cases obtained CR; all being FAB M2 type AML. In two of them LDAC was started during hypoplastic phase induced by the intensive multi-drug chemotherapy which failed to erradicate leukemic blasts efficiently. CR duration was not so durable. In two ALL cases LDAC was also given during hypoplastic phase after vincristine/prednisolone therapy. However, lymphoblasts which were common ALL antigen positive were resistant to this regimen.

Response in MDS Group

PR was obtained Only in five of 11 cases treated. In Case 2 PR was obtained after a severe bone marrow aplasia induced by a short LDAC course of 10 days. PR in this case was durable for one year and morphological dysplastic chaneges were reduced in degree. PR

states in other cases was brief; soon leading to overt AML in one case.

DISCUSSION

The overall CR rate of 34% in acute leukemia of the present series is very similar to that reviewed by Bolwell.[12] However, we noticed that CR cases were apparently concentrated in the hypoplastic leukemia group; CR rate reaching nearly 70%. Although entry of cases to the present series was not completely sequential, the hypoplastic leukemia seems to be the best candidate for this regimen. Other reports also pointed out the better effect of LDAC on the hypoplastic leukemia.[7,16] Among overt AML cases only three patients with M2 enterred CR in this series. In two of them the regimen was started when the bone marrow was still hypoplastic but with significant number of leukemic blasts remaining after multi-drug induction therapy. Thus the hypoplastic marrow which indicates smaller leukemic cell burden seems to be prerequisite for good outcome by LDAC regimen. It is possible that LDAC cannot exert cytotoxic effect efficiently in cases with overt AML or larger leukemic cell burden. In the present series ara-C was continuously infused intravenously and the median concentration was 4.4ng/ml on day 4. This concentration is apparently within the range of ara-C cytotoxicity measured in vitro on fresh AML cells but such a low concentration cannnot cover whole range of AML blast cell growth. Our study, therefore, suggests that sensitivity to LDAC of leukemic blasts as well as smaller leukemic burden primarily determine the treatment outcome.

The long-term admistration of ara-C may be another important factor determing the outcome. In our series the administration period was determined by serial bone marrow examination (mostly weekly interval) to meet the target point of 5% blasts. In the hypoplastic leukemia this was achieved by the median of 26 days' infusion of ara-C. During this preiod neutrophil count in the peripheral blood declined progressively but never disappeared in most cases. Most patients tolerateted well this neutropenic phase with supportive cares including prophylactic antibiotics, transfusion of red cells and platelets and intravenous hyperalimentation in some compromized hosts. The serial marrow examinations disclosed early or late decline of the blast percent in most CR cases. This decline was absent or inadequate in cases who failed to obtain CR. It was suggested that less than 5% bone marrow blasts is crucial to obtain CR. Although many trials of LDAC used 14 to 21 days as intended duration of treatment, our study suggests that administration of LDAC should be continued long enough to achieve the target in individual cases. As shown in **Table 7** in most cases of hypoplastic leukemia the blast percent is less than 50% and the blast cells usually do not show rapid increase. These biological characteristics suggest rather low growth rate of leukemic cells. LDAC regimen which continues over three to six weeks may cover efficently the cell cycle of slow growing leukemic cells so that eventual cytotoxic effect ensues.

In the present series FAB-defined MDS group

Table 7. Clinical and Hematological Features of 29 Patients with Hypoplastic Leukemias

	mean value (range)
Age	63.5 (44~84)
male/female	18/11
PB	
WBC (μl)	2081 (550~4500)
Hb (g/dl)	7.7 (3.1~13.2)
plt ($\times 10^4/\mu$l)	7.1 (0.75~26.25)
lymphocyte (%)	63.9 (15~94)
Blast(+) Case	14 (48%)
Blast(%) in positive cases	2.0 (1~7)
BM	
Cellularity	
$\leqq$30%	10 cases (42%)
30<<50%	14 cases (58%)
Blast(%)/ANC	29.2 (9.8~56)
Blast(%)/NEC	37.1 (17.9~63.3)
Blast Type (cases)	
M1	13 cases (44%)
M2	6 cases (21%)
M4	4 cases (14%)
Null	4 cases (14%)
Lymphoid	2 cases (7%)
Dysplasia Score	
0~3	18 cases (62%)
4~9	11 cases (38%)
G+E (%)	36.1 (4.8~74)
lymphocyte (%)	28.5 (7.6~55)

showed the worst response rate which is compatible with that in Bolwell's review, although other reports obtained higher CR rate.[17,18] Some cases of the hypoplastic leukemia group have severe tri-lineage dysplasia in the mature bone marrow cells suggesting common biological features shared by MDS group. We compared the response rate between the two morphologically distinguished groups, ie, minimally dysplastic group and severely dysplastic group. The response rate was significantly lower in the severely dysplastic group. However, this rate is still much higher than that in MDS group. Therefore, the marrow hypocellularity seems more important than the mere presence of dysplasia in determining good outcome with LDAC regimen. Howe *et al* also considered that the hypoplastic leukemia is a disease entity distinct from MDS, especially RAEB or RAEB-T, of which marrow is usually normo-or hypercellular.[19]

Although early works with LDAC regimen suggested that ara-C exerted its effect by inducing differentiation of leukemic blast cells,[2,3,20,21,22] later works mostly favoured cytotoxic effect as major mechanism of CR induction based on the regular observation of aplastic bone marrow before CR. In the present series all cases which eventually enterred CR passed through an apparent aplastic phase irrespective of disease group. In a few CR cases granulopoiesis began to recover in the peripheral blood before cessation of LDAC. This can be explaind by clonal change achieved by cytotoxic effects of ara-C on leukemic blasts and relative resistance of residual normal hematopoietic precursors to low serum concentration of ara-C. Several studies including our own using cytogenetic marker and/or in vitro clonal culture confirmend such a clonal change.[18,23,24,25] On the contrary there is few study comfirming the differentiation induction by ara-C that can be seen easily in leukemic cell lines cultured in vitro.[26] The relative resistance of normal myeloid precursors to low ara-C concentration was suggested by our observation that normal CFU-GM persistently developed GM-colonies during consolidation therapy with LDAC (data not shown).

Proportion of the elderly patients among the total acute leukemia patients seems to be expanding these years in most countries. Some reports insist that intensive multi-drug chemotherapy can exert substantial CR rate comparable to that in younger age group.[19,27] However, it is usually difficult to reproduce such a good outcome. Therefore, treatment strategy is still controverial concerning chemotherapy of acute leukemia in the elderly. If we could have a mild chemotherapy regimen which exerts effective and even selective cytotoxicity on leukemic blasts, but maintan patient's condition well, a great improvement in the cutcome of these patients can be obtained. As shown in the present series by comparing the results with historical control cases of hypoplastic leukemia which were treated with supportive cares only, apparent improvement in survival time was observed. The finding that four cases survived for more that two years by obtaining a long CR or repeated CRs with this regimen strongly suggests a real benefit from LDAC regimen for the elderly patients with hypoplastic leukemia. With conventional supportive cares only these patients usually show median survival of around 8 to 10 months.[19,28,29,30] In our instituion this type of leukemia comprises almost 50 percent of the leukemia in the elderly. Unfortunately overt leukemias in the elderly seem less sensitive to this regimen. Therefore, it is of clinical importance to stratify elderly patients with acute leukemia according to the histologically-determined bone marrow cellularity.

In most CR cases the duration of CR induced by LDAC was rather short, around six months in this series as well as in other reports. We are now giving CR cases the same LDAC regimen or multi-drug intensive chemotherapy as consolidation chemotherapy. So far there is no convincing result that these consolidations prolong CR duration (data not shown). Therefore, it is urgently necessary to develop a new combination regimen in order to obtain durable CR by incorporating newer drugs such as mitoxantrone, VP-16 or aclarubicin to LDAC. Such a new approach should be also tested for overt leukemias in the elderly or compromized patients.

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