transfusions might represent steps forward in the treatment of refractory myelogenous malignancies [15,29].

Realistically, increasing survival to any significant degree in pediatric patients with refractory acute leukemia will require novel approaches to overcoming the intrinsic resistance of leukemia cells to high-dose chemoradiotherapy. The risk factors for mortality and relapse identified in the present study may help guide clinicians in making recommendations for allogeneic SCT in pediatric patients with refractory acute leukemia. Our data suggest that earlier optimal timing of transplantation will be associated with better clinical outcomes in patients with refractory or relapsed acute leukemia, regardless of other factors. Conversely, transplantation might not be indicated for patients with persistent PB blasts after 3 courses of salvage chemotherapy.

ACKNOWLEDGMENTS

This work was supported by a grant from the Ministry of Health, Labor, and Welfare of Japan.

Financial disclosure: The authors have no conflicts of interest to disclose.

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Int J Hematol (2010) 91:630–635
DOI 10.1007/s12185-010-0549-1

ORIGINAL ARTICLE

Mosaic Down syndrome-associated acute myeloid leukemia does not require high-dose cytarabine treatment for induction and consolidation therapy

Kazuko Kudo · Asahito Hama · Seiji Kojima · Ruriko Ishii · Akira Morimoto · Fumio Bessho · Shosuke Sunami · Naoyuki Kobayashi · Akitoshi Kinoshita · Yuri Okimoto · Akio Tawa · Ichiro Tsukimoto

Received: 13 January 2010 / Revised: 11 February 2010 / Accepted: 24 February 2010 / Published online: 18 March 2010

Abstract The present study aimed to identify optimal treatment intensity in children with mosaic Down syndrome (DS) and acute megakaryoblastic leukemia (AMKL). A retrospective review of AMKL patients was undertaken to identify mosaic DS children. Between November 1992 and November 2007, seven children were diagnosed as mosaic DS and AMKL. The median age at diagnosis was 29 months (range 4–34 months). Three patients had a past history of transient abnormal myelopoiesis. UPN1–4 were treated with intermediate-dose cytarabine and UPN4 received additional one course of high-dose cytarabine. All of these patients were remained in first CR. UPN5–7 were treated with high-dose cytarabine according to the AML99 protocol. UPN5 with *GATA1* mutation suffered from acute pneumonia and pancreatitis and discontinued chemotherapy. UPN7 relapsed after cessation of chemotherapy and was rescued with allo-PBSCT. The cumulative doses of cytarabine were 3.5–10.65 g/m^2 in the UPN1–4 and 40.4–78.4 g/m^2 in the UPN5–7. The 8-year overall survival was 100% and the 8-year event-free survival 85.7%, respectively. Our retrospective study reveals that patients with mosaic DS and AMKL have a good prognosis. Reduction in intensity may work in patients with mosaic DS as well as with AML-DS.

Keywords Acute megakaryoblastic leukemia · Mosaic Down syndrome · Cytarabine · *GATA1*

K. Kudo, A. Morimoto, A. Tawa and I. Tsukimoto are members of The Japanese Childhood AML Cooperative Study Group, Japan.

K. Kudo (✉)
Division of Hematology and Oncology, Shizuoka Children's Hospital, 860, Urushiyama, Aoi-ku, Shizuoka 420-8660, Japan
e-mail: kazukok@sch.pref.shizuoka.jp

A. Hama · S. Kojima
Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

R. Ishii
Department of Pediatrics, Kyoto Prefectural University of Medicine, Kyoto, Japan

A. Morimoto
Department of Pediatrics, Jichi Medical University School of Medicine, Shimotsuke, Japan

F. Bessho
Department of Pediatrics, Kyorin University, Mitaka, Japan

S. Sunami
Division of Pediatrics, Narita Red Cross Hospital, Narita, Japan

N. Kobayashi
Division of Pediatrics, Jikei University, Kashiwa, Japan

A. Kinoshita
Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki, Japan

Y. Okimoto
Division of Hematology Oncology, Chiba Children's Hospital, Chiba, Japan

A. Tawa
Department of Pediatrics, National Hospital Organization Osaka Hospital, Osaka, Japan

I. Tsukimoto
Division of Pediatrics, Yokohama Tobu Hospital, Yokohama, Japan

1 Introduction

Acute megakaryoblastic leukemia (AMKL) is rare in the general pediatric population but accounts for one half of acute myeloid leukemia (AML) patients in children with Down syndrome (DS). The association of AML with DS (AML–DS) is well recognized, as is mosaicism of DS. Mosaic trisomy 21 occurs in 3.85% of the DS population [1]. The physical features may be milder in these individuals, particularly if there are a large proportion of normal cells. Therefore, it makes it more difficult to detect mosaic DS patients, which can lead to a late diagnosis.

AMKL was unfavorable in non-DS children. Recent studies showed that children with AML–DS had a favorable outcome with less intensive chemotherapy [2–8]. Simon et al. [9] described a patient with mosaic DS and AML with a favorable response to therapy. To date, only several case reports have reported with mosaic DS and AML. A treatment regimen specifically designed for AML–DS has been used in Japan since the mid-1980s. We analyzed the mosaic DS and AMKL patients who were treated with different protocols, retrospectively. The present study aimed to identify optimal treatment intensity in children with mosaic DS and AMKL.

2 Methods

A retrospective review of AMKL patients who registered in the AML99 trial [10] and the previous multi-center trial was undertaken to identify mosaic DS children. Four patients were identified among 351 patients who registered in the AML99 trial. Three patients, who were treated following to the AT-Down protocol [2], were identified among the previous multi-center trial. Their clinical characteristics are summarized in Table 1.

2.1 Statistical analyses

The event-free survival (EFS) and overall survival (OS) rate with standard error (SE) was estimated using the Kaplan–Meier method [11]. The outcome data were updated in March 2009.

3 Results

Between November 1992 and November 2007, seven children (4 males, 3 females) were diagnosed as mosaic DS and AML at six institutions. The characteristics of all seven patients are summarized in Table 1, and the details of each patient are shown in Table 2. The median age at diagnosis was 29 months (range 4–34 months). Six patients were diagnosed as having AMKL (FAB classification M7) and one was myelodysplastic syndrome (MDS) at initial diagnosis. CD41 and/or CD42 marker were positive in 29.4–96.5% of bone marrow (BM) cells. Three patients had a past history of transient abnormal myelopoiesis (TAM) during the neonatal period (UPN1, 3, 4). Mosaic DS had been diagnosed in UPN1–4 before chemotherapy. In other patients (UPN5–7), the diagnosis of mosaic DS was made during treatment. Three patients had mild mental retardation. Four patients had dysmorphic features such as hypertelorism and epicanthal folds. Cytogenetic analyses of peripheral blood lymphocytes (PBL) or BM cells were done at diagnosis and during complete remission in all patients. In UPN1–3, 5 and 7, initial BM cytogenetics revealed complex chromosomal abnormalities in addition of +21. Fluorescence in situ hybridization (FISH) analyses of any of PBL, BM in complete remission (CR) or skin fibroblasts showed that frequency of trisomy 21 varied from 4 to 30%.

Table 1 Summary of the clinical characteristics of patients with mosaic Down syndrome and acute megakaryoblastic leukemia

No. of patients	7
Age, median (range)	29 months (4–34 months)
Sex, male/female	4 male, 3 female
FAB classification	
M7	6
MDS	1
Preceding TAM	3
Mental retardation	3
Dysmorphic features	4
Frequency of +21 (%)	
PBL	0–23
Skin	8.5–30
Chemotherapy	
AML99 [10]	3
AML99 Down [3]	1
AT-Down [2]	2
AT-Down [2] + high-dose cytarabine	1

FAB French–American–British classification, *MDS* myelodysplastic syndrome, *TAM* transient abnormal myelopoiesis

UPN1 was treated according to the AML99 Down protocol and remained in first CR. UPN2–4 were treated according to the AT-Down protocol and remained in first CR. UPN4 received additional one course of high-dose cytarabine after AT-Down protocol and suffered from acute respiratory distress syndrome (ARDS). The other three patients (UPN5–7) were treated according to the AML99 protocol with increasing cytarabine dose density. UPN5 suffered from acute pneumonia and pancreatitis and discontinued chemotherapy. UPN6 was treated according to the AML99 protocol without any serious complications

Table 2 Detailed characteristics of the patients with mosaic Down syndrome and acute megakaryoblastic leukemia

	UPN1	UPN2	UPN3	UPN4	UPN5	UPN6	UPN7
Age (month)/ gender	31 months/F	20 months/F	29 months/F	34 months/M	29 months/M	24 months/F	4 months/M
WBC ($\times 10^9$/l)	13.8	7.8	4.9	35.8	5.3	21.1	40.3
Hb (g/l)	64	73	82	74	62	80	101
Plt ($\times 10^9$/l)	14	17	91	54	28	97	60
BM blast (%)	39.6	17.6	33.4	64.3	71.5	24.5	41.0
CD41 positive (%)	89.7	ND	78.9	0	14.2	ND	96.5
CD42 positive (%)	ND	44.2	NA	66	33.6	29.4	ND
FAB classification	M7	MDS (CD42+)	M7	M7	M7	M7	M7
Preceding TAM	+	−	+	+	−	−	−
Mental retardation	+	+	−	−	+	−	−
Dysmorphic features	−	+	+	+	+	−	−
Frequency of +21 (FISH) (%)							
In CR PBL/BM	7	23	NA	4 (BM)	12	1.5	0
Skin	21	NA	30	NA	30	8.5	12.5
Chemotherapy	AML99 Down	AT-Down	AT-Down	AT-Down + high-dose cytarabine	AML99	AML99	AML99
Cumulative dose of							
Cytarabine (g/m^2)	3.5	4.2	4.2	10.65	40.4	58.4	78.4
Anthracycline[a] (mg/m^2)	150	250	250	200	210	260	260
Etoposide (mg/m^2)	2,250	2,700	2,700	2,300	2,200	750	3,200
RRT	−	−	−	+	+	−	−
CCR	+	+	+	+	+	+	Second CR after PBSCT
Outcome	Alive	Alive	Alive	Alive	Alive	Alive	Alive
Follow up period (year/mo)	5 years 9 months	16 years 4 months	14 years 9 months	13 years 9 months	6 years 8 months	3 years 5 months	7 years 6 months
GATA1 mutation	ND	ND	ND	ND	+	ND	ND

Table 2 continued

	UPN1	UPN2	UPN3	UPN4	UPN5	UPN6	UPN7
Chromosomal analyses							
BM at diagnosis (G-band)	47, XX, der(2)t(2;11)(q37;q13), der(15)	49, XX, 5q−, 7q+, +8, +13, +21[7]	48, XX, +19, +21[9/20]	47, XY, +21[20/20]	47, XY, del(11)	46, XX[15/20]	47, XY, +21[2/20]47, idem, add(1)(p11)
	t(1;15)(q23;p13), del(20)(q1?), +21[18/20]	47, XX, +21[5]46, XX[14]	48, idem, add(3)(q21), add(7)(q?11)[8/20]		(p?), +21[18/20]	47, XX, +21[5/20]	der(9)add(9)(p13)add (9)(q22), add(10)
	46, XX [2/20]	46, XX[16] 47, XX, +21[4]	46, XX[3/20]		46, XY[2/20]		(q22)[7/20]46XY[11/20]
In CR PBL/BM (G-band)	47, XX, +21[2/30]	ND	BM; 46, XX[20/20]	BM; 46, XY[20/20]	47, XY, +21[0, 4, 1, 1/20]	47, XX, +21[1/20]	47, XY, +21 [2, 6, 3/20]
	46, XX [28/30]				46, XY[20, 16, 19, 19/20]		46, XY[18, 14, 17/20]

WBC white blood cell, *Hb* hemoglobin, *Plt* platelet, *BM* bone marrow, *FAB* French–American–British classification, *MDS* myelodysplastic syndrome, *TAM* transient abnormal myelopoiesis, *PBL* peripheral blood lymphocyte, *RRT* regimen-related toxicity, *CCR* continuous the first complete remission, *ND* not done, *NA* not available, *PBSCT* peripheral blood stem cell transplantation, *FISH* fluorescence in situ hybridization analyses of any of PBL, BM in CR or skin fibroblasts

[a] Anthracycline dose was converted as doxorubicin dose as follows; doxorubicin = 1, daunorubicin = 0.83, idarubicin = 5, mitoxantrone = 4, and pirarubicin = 0.6

except for an anaphylactic reaction to etoposide. She has remained in first CR. UPN7 relapsed in the bone marrow after cessation of chemotherapy and was rescued with allo-peripheral blood stem cell transplantation (PBSCT).

The cumulative doses of cytarabine were 3.5–10.65 g/m^2 in the UPN1–4 and 40.4–78.4 g/m^2 in the UPN5–7. Cytogenetic analysis at diagnosis revealed acquired chromosome changes occurring in addition to the constitutional +21 except UPN4 and 6. The 8-year OS was 100% and the 8-year EFS 85.7%, respectively (Fig. 1).

4 Discussion

The prevalence of mosaic DS was reported to be 3.85% of the DS population, and an accurate clinical diagnosis was made in only 37.5% of mosaic patients [1]. The physical features may be milder in these individuals. About one half of AMKL patients have DS. It is necessary to exclude mosaic DS when AMKL is diagnosed, because sometimes DS individuals are more sensitive to antileukemic agents than non-DS individuals. Our recent report demonstrated that toxicity-related unfavorable events were reduced with less intensive chemotherapy for AML with DS [3]. Simon et al. [9] described a patient with mosaic DS and AML with a favorable response to therapy. The same explanation may apply to the seven patients described in the present series.

A treatment regimen specifically designed for AML with DS has been used in Japan since mid-1980s. The regimen was less intensive and did not include high-dose cytarabine and prophylaxis against CNS leukemia. Remission induction chemotherapy consisted of pirarubicin (25 mg/m^2/day on days 1 and 2), cytarabine (100 mg/m^2/day on days 1–7), and etoposide (150 mg/m^2/day on

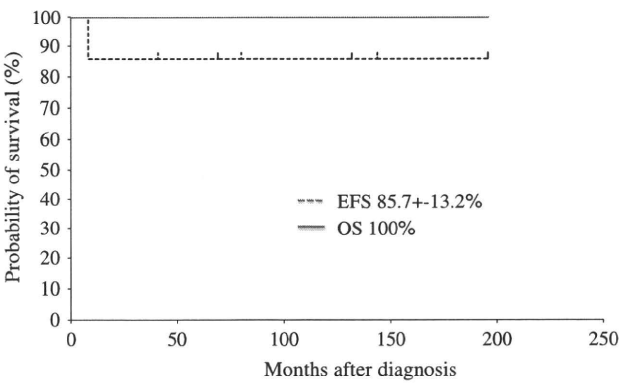

Fig. 1 Actuarial survival rate of seven patients with mosaic Down syndrome and AMKL. All of seven achieved complete remission (CR). One patient relapsed and rescued with allo-PBSCT. The 8-year overall survival (OS) was 100% and the 8-year event-free survival (EFS) 85.7%, respectively

Table 3 Clinical courses of patients with mosaic Down syndrome and acute megakaryoblastic leukemia

UPN	Age (months)/gender	TAM	Dysmorphic features	Frequency of +21[a]		Cytarabine dose	RRT	Outcome	References
				PBL/BM	Skin				
1	31/F	+	−	7%	21%	ID	−	CCR (69 months+)	Present case
2	20/F	−	+	23%	NA	ID	−	CCR (196 months+)	Present case
3	29/F	+	+	NA	30%	ID	−	CCR (177 months+)	Present case
4	34/M	+	+	4%	NA	ID	+	CCR (165 months+)	Present case
5	29/M	−	+	12%	30%	HD	+	CCR (80 months+)	Present case
6	24/F	−	−	1.5%	8.5%	HD	−	CCR (41 months+)	Present case
7	4/M	−	−	0%	12.5%	HD	−	2nd CR after PBSCT	Present case
8	10/M	−	+	50%	50%	LD	−	CCR (24 months+)	[12]
9	24/M	+	+	NA	NA	LD	−	CCR(12mo +)	[13]
10	23/F	−	+	50%	NA	NA	+	CCR (24 months+)	[9]
11	16/M	+	−	13%	6%	NA	−	CCR (24 months+)	[14]
12	14/F	−	+	+r(21); 79%		NA	−	CCR (24 months+)	[15]
13	32/M	−	−	0–6%	NA	HD	+	Dead (7 months)	[16]

TAM transient abnormal myelopoiesis, *PBL* peripheral blood lymphocyte, *CCR* continuous the first complete remission, *NA* not available, *ID* intermediate dose, *HD* high dose, *LD* low dose, *RRT* regimen-related toxicity, *PBSCT* peripheral blood stem cell transplantation

[a] Fluorescence in situ hybridization (FISH) analyses of any of PBL, BM in complete remission or skin fibroblasts

days 3–5). Pirarubicin was used in the above protocol instead of daunorubicin, which was originally used in the previous AT-Down protocol [2], to reduce the cardiotoxicity. Patients who achieved CR received four courses of intensification therapy of the same regimen. On the other hand, the AML99 protocol for non-DS patients with AML included a repetitive high-dose cytarabine course [10]. In the AML99 protocol, three or four high-dose cytarabine courses administered at 12-h intervals and cumulative dose of cytarabine was 59.4–78.4 g during total six courses of chemotherapy.

The clinical courses of the seven patients in this series and the six patients in the literature [9, 12–16] are summarized in Table 3. The median age at diagnosis was 24 months (range 4–34 months). Five patients (UPN1, 3, 4, 9, 11) had a past history of TAM during the neonatal period. Eight patients (UPN2–5, 8–10, 12) had dysmorphic features and the majority of them were found the frequency of +21 over 20%. Presence of either TAM or dysmorphic features was found in 10 patients among 13 patients. Five patients (UPN1, 6–7, 11, 13) were phenotypically normal, whose levels of +21 varied from 8.5 to 21%, mostly below 20%. UPN5–7 and 13 were treated with high-dose cytarabine. UPN6, 7 and 13 were well tolerable to repetitive high-dose cytarabine regimen. On the other hand, UPN5 suffered from acute pneumonia and pancreatitis and discontinued chemotherapy. UPN4 received one course of high-dose cytarabine in addition to intermediate-dose cytarabine, resulting in the development of ARDS. Three patients (UPN1–3) who were treated with intermediate-dose cytarabine and two patients (UPN8–9) who received low-dose cytarabine [12, 13] had no serious therapy-related complication.

Recent studies showed that children with AML–DS had a favorable outcome with an approximately 80% cure rate [2–8]. The 8-year EFS of the seven patients was 85.7%. UPN7 relapsed after cessation of chemotherapy and was rescued with allo-PBSCT. In the Western literature, UPN13, whose age at diagnosis was 3 years or younger, relapsed and died despite chemotherapy with idarubicin and high-dose cytarabine [16]. Hasle et al. [17] analyzed *GATA1* mutation in ten children 4 years or older and proposed that *GATA1* mutation might be a good prognostic marker of the ML-DS rather than age, blast count or FAB type. This is retrospective study and *GATA1* mutation was analyzed in only one patient. As *GATA1* mutation was identified in UPN5, he was considered to possess typical DS characteristics. Intensified chemotherapy might be unnecessary for him to achieve and continue first CR. Unfortunately, clinical samples were not obtained except UPN5; we could not reveal the correlation between the presence of *GATA1* mutations and the good prognosis in our series. Sandoval et al. [18] reported a patient of TAM with *GATA1* mutation in a mosaic DS. The same interpretations would be made concerning *GATA1* mutations in mosaic DS and AMKL.

In conclusion, our recent report demonstrated that toxicity-related unfavorable events were reduced with less intensive chemotherapy of AML-DS. Reduction in intensity may also work in mosaic DS patients. On the basis of the retrospective observation, we have designed a treatment protocol for AML–DS that is less intensive than that

for non-DS. AML should include AML patients with mosaic DS.

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