Acta Med. Okayama, 2019
Vol. 73, No. 2, pp. 181–188

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Exchange Transfusion and Cytarabine for Transient Abnormal Myelopoiesis in Hydrops Fetalis

Tomoka Okamura[a], Yousuke Washio[a], Junko Yoshimoto[a], Kazumasa Tani[b], Hirokazu Tsukahara[a], and Akira Shimada[c]*

[a]Department of Pediatrics, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Departments of [b]Obstetrics and Gynecology, [c]Pediatric Hematology/Oncology, Okayama University Hospital, Okayama 700-8558, Japan

Most cases of transient abnormal myelopoiesis (TAM) in neonates with Down syndrome (DS) resolve spontaneously; however, DS-TAM neonates with hydrops fetalis (HF) show poor clinical outcomes. We report three infants with DS-TAM and HF who were treated with exchange transfusion (ET) followed by low-dose cytarabine (LD-CA). All of them survived without developing liver failure, acute leukemia, or other serious adverse events. Our results suggest that this combination treatment with ET and LD-CA would be safe, tolerable and effective as an novel approach for DS-TAM patients with HF.

Key words: cytarabine, Down syndrome, exchange transfusion, hydrops fetalis, transient abnormal myelopoiesis

About 10% of infants with Down syndrome (DS) are estimated to develop transient abnormal myelopoiesis (TAM), which is characterized by an increased number of blasts in the peripheral blood at the time of birth [1]. In most infants, TAM resolves spontaneously; however, cytokine production and hyperviscosity due to increased blasts and sustained immunological dysfunction cause various pathological conditions, and about 20-30% of these infants die due to cardiopulmonary or liver failure [2]. For example, liver failure is occasionally lethal, and all patients with DS-TAM may develop liver disease, irrespective of the absence or presence of symptoms; liver failure is also considered to be a risk factor for early death [3]. These conditions are estimated to start *in utero* and subsequently cause hydrops fetalis (HF), which is strongly associated with a poor prognosis [4,5]. HF is a serious fetal condition defined as an abnormal accumulation of fluid in two or more fetal compartments, and it includes ascites, pleural effusion, pericardial effusion, and skin edema [6]. In general, HF shows poor clinical outcomes, and mortality rates for this condition are greater than 50% [7,8].

The treatment strategy for HF due to DS-TAM is not clearly defined, and several lethal cases have been reported with no treatment [3,9]. For cardiopulmonary failure due to severe TAM, exchange transfusion (ET) might be effective; however, ET alone is not always curative for HF infants with TAM [3]. As an adjunct, low-dose cytarabine (LD-CA) treatment is recommended for patients with clinical impairments associated with TAM, especially high white blood cell (WBC) or blast counts [4,9,10]. A few reports have suggested that LD-CA treatment is also effective in infants with HF secondary to TAM [9,11].

In this report, we describe three severe cases of TAM in infants with HF who required intensive care.

Received August 16, 2018; accepted December 11, 2018.
*Corresponding author. Phone: +81-86-235-7249; Fax: +81-86-221-4745
E-mail: pajj236e@okayama-u.ac.jp (A. Shimada)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

All three cases were successfully treated with LD-CA after ET, and all were alive after the treatments. We discuss this combined therapy for HF due to DS-TAM and review the relevant literature.

Case Reports

Case 1. A girl was born to a 33-year-old gravida 4 para 3 woman. Antenatal ultrasound at 38 weeks detected pleural effusion, pericardial effusion, and ascites, and she was diagnosed with HF. On the same day, the patient was delivered by cesarean section due to fetal distress. Immediately after birth, she was intubated and underwent drainage of pleural and pericardial effusion. Diagnosis of trisomy 21 was made by G-band staining of the peripheral blood. At birth, the WBC count was 213,000/μL, and 68.5% of the WBC were blast cells (Table 1). She was diagnosed with persistent pulmonary hypertension of the newborn (PPHN), and inhalation of nitric oxide was initiated. Catecholamine and hydrocortisone were also required. Because the patient's respiratory and circulatory failure further deteriorated, ET was performed on days 2 and 3. Rasburicase was administered for hyperuricemia (6.4 mg/dL). The WBC count was reduced after ET on day 2, but was restored on day 3. LD-CA therapy (0.9 mg/kg/day) was started after ET on day 3 and stopped on day 8 because of pancytopenia. Her general condition improved after ET and CA. Because of pancytopenia, she needed a blood transfusion on day 26 and administrations of granulocyte-colony stimulating factor (G-CSF 4 μg/kg) on days 25 and 26. She was discharged on day 48. Currently, she is 3 years old and has not developed acute myeloid leukemia or distinct liver dysfunction (Fig. 1).

Case 2. A girl was born to a 34-year-old gravida 0 para 0 woman. Antenatal ultrasound at 30 weeks detected hydrops (pericardial effusion, ascites), hepatomegaly, and ventricular septal defects (VSDs). Hydrops did not deteriorate, and the girl was delivered by cesarean section due to fetal distress at 38 weeks. At birth, she was intubated. Diagnosis of trisomy 21 was made by G-band staining of the peripheral blood. The WBC count was 61,380/μL, and 46.0% of the WBC were blast cells. VSD was identified. She was diagnosed with PPHN; consequently, inhalation of nitric oxide and continuous injection of prostaglandin I2 were initiated. Catecholamine and hydrocortisone were required. ET was performed on days 1 and 2. Because of the persistence of disseminated intravascular coagulation, LD-CA therapy (0.9 mg/kg/day) was started on day 3 and continued for 7 days. After the combination therapy, her respiratory distress and circulatory failure gradually improved. She received G-CSF (4 μg/kg) on day 28 and repeated blood transfusion because of pancytopenia. Aminotransferase (AST) (peak 373 IU/L on day 20), alanine aminotransferase (ALT) (peak 437 IU/L on day 20), and direct bilirubin (peak 4.6 mg/dL on day 26) levels were elevated starting from the 2nd week of her life, but they decreased gradually and finally returned to the normal range on day 70. Pulmonary artery banding was performed on day 121, and she was discharged in the 4th month of her life. Currently, she is 2 years and 9 months old, and has not developed acute myeloid leukemia or distinct liver dysfunction (Fig. 2).

Case 3. A boy was born to a 33-year-old gravida 2 para 2 woman. Prenatal ultrasound at 33 weeks detected fetal hepatosplenomegaly, cardiomegaly, and fetal pericardial effusion. He was delivered by cesarean section the next day. At birth, he was intubated. Trisomy 21 was detected by G-band staining of the peripheral blood. The WBC count was 237,420/μL, and 55.0% of the WBC were blast cells. He was diag-

Table 1 Clinical and laboratory findings at birth in three cases

Case	Male/ Female	gestational age (week)	birth weight (g)	APGAR score	Karyotype	WBC ($\times 10^6$/ml)	Blast (%)	Hgb (g/dl)	Plt ($\times 10^6$/ml)	LDH (U/l)	AST (U/l)	ALT (U/l)
1	Female	38	2,717	2/5	47, XX, +21	213	68.5	14.6	149	2,442	52	22
2	Female	38	2,932	4/8	47, XX, +21	61.4	46.0	14.1	224	1,207	47	78
3	Male	33	2,651	3/6	47, XY, +21	237.4	55.0	11.6	147	6,048	148	363

WBC, white blood cell count; Hgb, hemoglobine; Plt, platelet; LDH, lactate dehydrogenase; AST, aspartate transaminase; ALT, alanine transaminase.

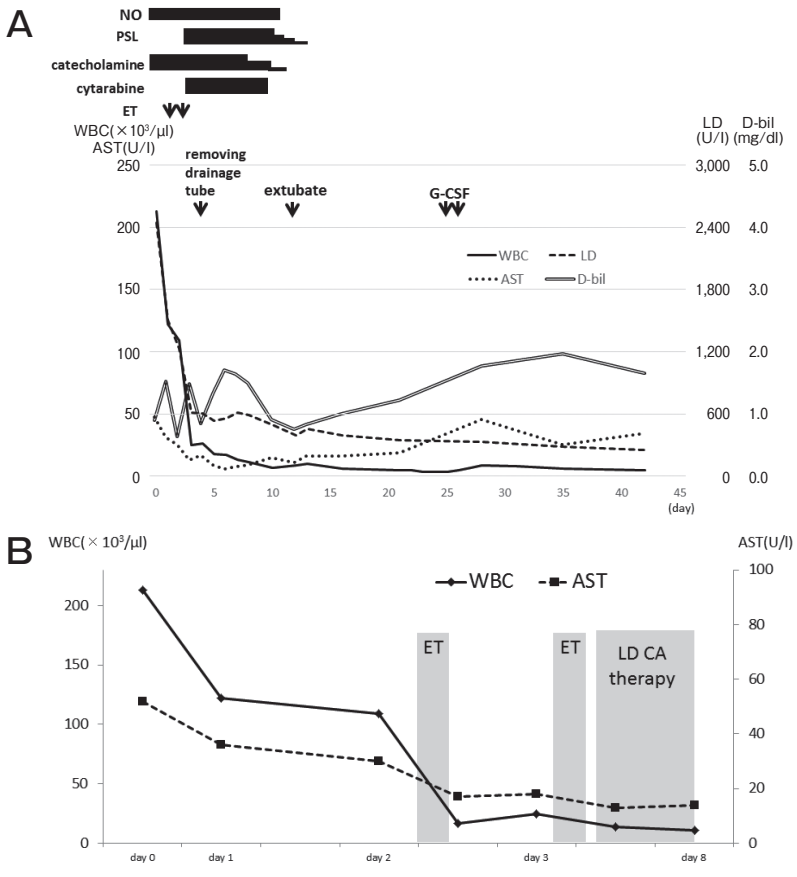

Fig. 1 (A) Clinical course of case 1. NO, inhalation of nitric oxide; PSL, prednisolone; ET, exchange transfusion; G-CSF, granulocyte-colony stimulating factor; WBC, white blood cell; D-bil, direct bilirubin. (B) Relation of WBC, AST, and therapies.

nosed with PPHN, and inhalation of nitric oxide therapy was initiated. Catecholamine and hydrocortisone were required. ET was performed on day 1. Because of the elevation of AST and ALT, LD-CA therapy (0.5 mg/kg/day) was initiated on day 3 and performed for 7 days. His general condition improved after ET and CA. Rasburicase was administered because his serum uric acid level was elevated (11.3 mg/dL) before starting chemotherapy. AST (peak 169 U/L on day 22), ALT (peak 117 IU/L on day 22), and direct bilirubin (peak 6.3 mg/dL on day 18) levels were elevated starting from the 2nd week of his life, but they decreased gradually and returned to the normal range at 6 months of age. He received G-CSF (4 μg/kg) on day 30 and blood transfusions on days 20 and 25 because of pancytopenia. He was discharged on day 47. Currently, he is 1 year and 4 months old and has not developed AML or distinct liver dysfunction (Fig. 3).

Written informed consent was obtained from each parent before beginning treatment.

Literature Review

We reviewed Japanese and English case reports from Ichushi Web and Pubmed using key words *TAM*, *HF* and *systemic edema*. Reports with no records of treatment were excluded. A total of 25 (9 Japanese and 16 English [3,9,11-17]) DS-TAM cases with HF were reported from 2002 to 2016 (Table 2). There was no differences in the overall survival among the different treatment protocols (Table 3).

Discussion

Blast cells start to proliferate in the liver and spleen *in utero*, in a process known as extramedullary hematopoiesis, and shift to the bone marrow after birth [18]. The cases of patients with severe TAM are often compli-

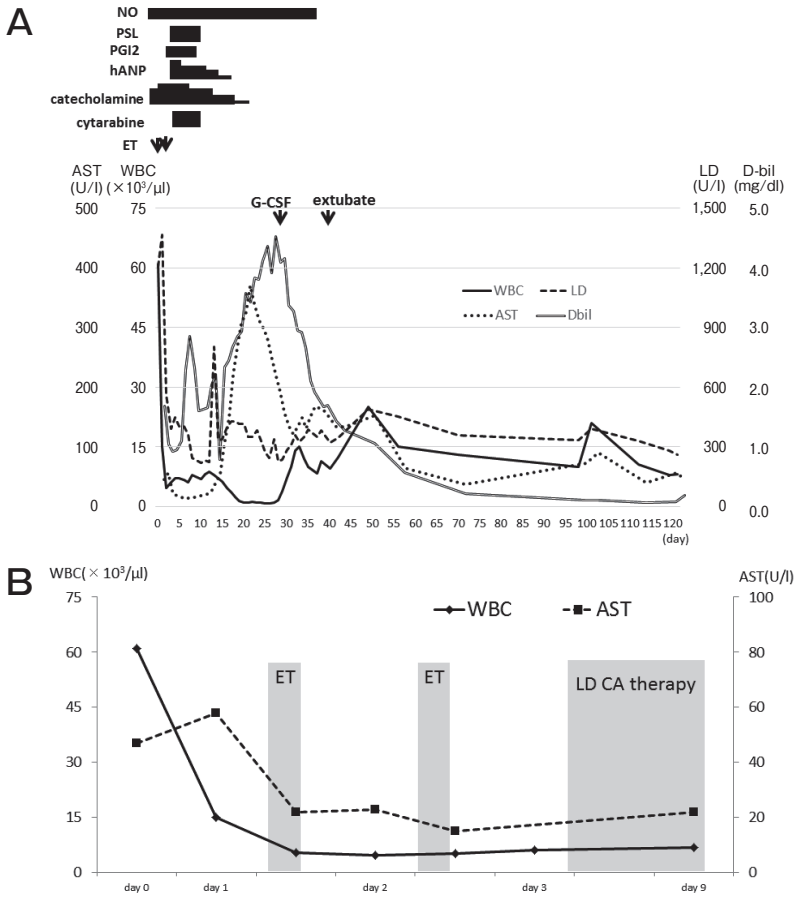

Fig. 2 (A) Clinical course of case 2. NO, inhalation of nitric oxide; PSL, prednisolone; PGI2, prostaglandin I2; hANP, carperitide; ET, exchange transfusion; G-CSF, granulocyte-colony stimulating factor; WBC, white blood cell; D-bil, direct bilirubin. (B) Relation of WBC, AST, and therapies.

cated by fetal death, hydrops, and liver failure *in utero*. Hydrops is a manifestation related to poor clinical outcomes [4,5]. Klusmann *et al.* reported that the early death rate of TAM babies with hydrops is 71% (5 out of 7 patients) with any treatment [4].

Recent reports indicate that ET is effective in controlling cardiopulmonary failure accompanied by hydrops in DS-TAM [4,17] because pulmonary hypertension in TAM patients is presumably caused by hyperviscosity and embolism of blast cells [17]. Indeed, obvious reduction of the blast cells by ET results in the improvement of pulmonary hypertension [17].

In the present cases, ET markedly decreased the number of blast cells and prevented respiratory and circulatory failure. Several studies have suggested that cytokines produced by blast cells contribute to the pathogenesis of TAM [2,19-21]. Our previous study revealed that abnormal cytokinemia might play an important role in the pathophysiology of TAM [22]. Shitara reported that the abnormal production of cytokines such as interleukin (IL)-6, IL-8, and IL-13 was related to TAM and pericardial effusion [21]. Hattori *et al.* reported that TGF-β was strongly associated with liver fibrosis [20]. Therefore, reducing the number of blast cells and the serum levels of inflammatory cytokines by ET would presumably improve the pathological conditions in patients.

The LD-CA treatment has been highly effective in several severe DS-TAM cases. The Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) recommends that TAM patients who have WBC counts of over 100,000/μL receive LD-CA treatment. JPLSG also recommends that infants with WBC counts < 100,000/μL be treated with LD-CA if they present with symp-

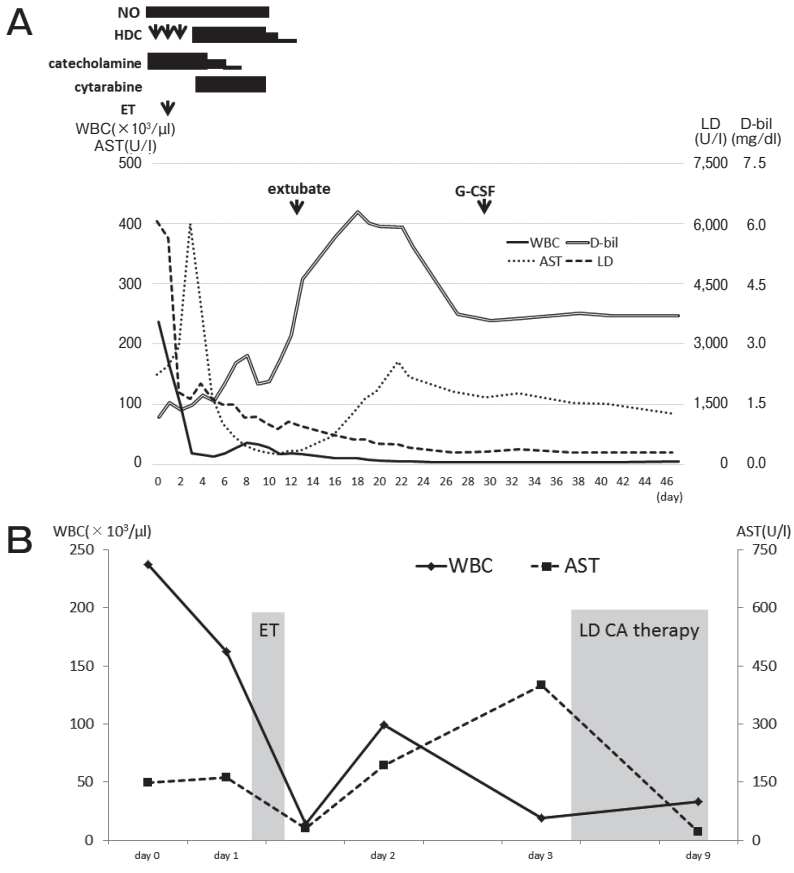

Fig. 3 (A) Clinical course of case 3. NO, inhalation of nitric oxide; HDC, hydrocortisone; ET, exchange transfusion; G-CSF, granulocyte-colony stimulating factor; WBC, white blood cell; D-bil, direct bilirubin. (B) Relation of WBC, AST, and therapies.

toms related to poor outcomes such as elevated direct bilirubin, effusions (pleural, peritoneal, or pericardinal), and systemic edema [23]. The German BFM group reported the following patient data in TAM patients who were treated with 0.5-1.5 mg/kg LD-CA for 3-12 days: WBC count > 50,000/μL, platelet count < 100,000/μL, cholestasis (direct bilirubin > 15 mg/dL), and deterioration of the general condition due to liver failure [4]. There are no defined criteria for initiating LD-CA treatment; therefore, it is difficult to determine when chemotherapy should be initiated in critically ill patients without an increase in WBC counts. WBC counts do not always correlate with the severity of TAM, and a few reports have described patients with poor outcomes whose WBC counts were < 100,000/μL [9].

Moreover, it was likely that ET successfully removed blast cells and abnormal cytokines; if so, however, the effect was transient, and ET could not completely eliminate the residual blasts. Therefore, a sustained immune attack could cause liver failure. TAM blasts start to proliferate *in utero*, and thus a few severe TAM cases with HF are lethal at birth [1]. Moreover, irreversible liver fibrosis could develop due to sustained abnormal cytokinemia with or without TAM blasts [3,20]. Therefore, the timing of ET and LD-CA is also important, and they should be performed in the early period, because a few reports have shown that patients

Table 2 Therapies and survival rates in previous reports

Therapy	Number of case	Number of survivor	Survival rate
no therapy or steroid alone	10	3	30%
LD-CA without ET	4	3	75%
ET without LD-CA	6	2	33%
combine therapy	5	2	40%

Table 3

No.	Ref	Symptom	Preterm or term	WBC ($\times 10^6$/ml)	ET	Therapy CA	Steroid	Outcome
1	9	SE PIE PeE	term	231	○	○		Died
2	9	Hydrops	preterm	57				Died 48 h
3	11	Hydrops	preterm	13		○		Alive
4	11	Hydrops	preterm	16		○		Alive
5	12	SE PeE As	preterm	57				Died at day 16
6	13	Hydrops	preterm	77				Alive
7	14	Hydrops	preterm					Died 11 min
8	15	Hydrops	preterm	221		○		Alive
9	16	SE PeE As	term	287	○	○		Died 2 months
10	3	SE	preterm	21				Died at day 1
11	3	SE	term	13	○	○	○	Alive
12	3	SE	preterm	26				Died
13	3	SE	preterm	114	○			Died at day 44
14	3	SE	preterm	46	○		○	Died at day 55
15	17	SE PIE PeE	preterm	143	○	○		Alive
16	17	PIE PeE As	preterm	165	○			Died at day 5
17	J1	Hydrops	preterm	232			○	Died at day 37
18	J2	Hydrops	term	139	○			Died at day 16
19	J3	Hydrops	preterm	342				Died at day 15
20	J4	Hydrops	preterm	146			○	Alive
21	J4	Hydrops	preterm	144	○		○	Died at day 14
22	J4	Hydrops	preterm	45		○	○	Died at day 37
23	J4	Hydrops	preterm	144	○	○	○	Alive
24	J5	Hydrops	preterm	34	○		○	Alive
25	J6	SE As	preterm	42			○	Alive
26		Hydrops	term	213	○	○	○	Alive
27		Hydrops	term	61	○	○	○	Alive
28		Hydrops	preterm	237	○	○	○	Alive

Case 17–25 are from reports written in Japanese. Reference of J1–J6 shown below. Case 26–28 are present cases. Ref, reference; SE, systemic edema; PIE, pleural effusion; PeE, pericardial effusion; As, ascites.

J1) Imai K, Toyoshima K, Kotani M, Nagasawa M, Shibasaki J, Hoshino R, Ohyama M, Kawataki M and Y Itani: The pathological examinations of liver specimens of three infants with transient abnormal myelopoiesis (TAM) accompanying hepatic fibrosis. Jornal of Japan Society for Premature and Newborn medicine (2010) 22: 70–76 (in Japanese).

J2) Aiba K, Sugiura T, Ninchoji T, Nomura T, Kouwaki M and Koyama N: Transient abnormal myelopoiesis with pseudohyperkalemia cause by extreme leukocytosis: a case report. J Jpn Pediatr Soc (2010) 114: 515–518 (in Japanese).

J3) Mashiyama F, Imamura T, Satou M, Maeda H, Kanai Y, Ogasawara K, Haneda K, Honda Y and Ohto H: A severe case of transient abnormal myelopoiesis in Down syndrome with hydrops fetalis. Jpn J Obstet Gynecol Neonatal Hematol (2014) 24: 22–23 (in Japanese).

J4) Ohzeki K, Iida A, Matsui S, Okabashi A, Shimamura N, Ogino H, Okada M, Kouge A, Oohashi S, Fujinaka Y, Masunaga K and Takigawa I: Four cases of premature infants with Down syndrome who presented with TAM and antenatally identified hydrops fetalis. J Jpn Soc Perin Neon Med (2014) 50: 1104–1109 (in Japanese).

J5) Suenaga H, Uchiyama A, Okamura T, Ohno H, Sugita E, Imai K, Masumoto K, Titsu S, Nakanishi H and Kusuda S: Efficacy of Rasburicase for the treatment of hyperuricemia due to transient abnormal myelopoiesis in a preterm infant with Down syndrome. Journal of Japan Society for neonatal health and development (2016) 28: 67–71 (in Japanese).

J6) Nakayama M, Matsushima M, Fukagawa Y, Kaneda Y, Tanaka K, Yamada K, Izawa T, Furukawa S, Kobayashi Y and Iwashita M: A case of transient abnormal myelopoiesis with hydrops. Tokyo J Ob-Gyn (2016) 65: 547–551 (in Japanese).

died due to liver failure at 1-2 months after birth even if their symptoms temporarily improved as a result of ET after birth [2]. Thus, the results of our study suggest that the combination of ET followed by LD-CA in the early period after birth might be safe and might prevent the development of liver failure. Further studies with larger samples are needed to verify these results.

When administering LD-CA treatment to infants with severe TAM, it is important to consider the potential side effects. Even though LD-CA treatment can sometimes cause myelosuppression (anemia, thrombocytopenia, and leukopenia) and tumor lysis syndrome (renal dysfunction, electrolyte disturbance, and hyperuricemia), only a few reports have demonstrated that LD-CA treatment followed by ET rescued patients, even in cases with hydrops [11]. In the present three cases, blood transfusion was required to treat anemia and thrombopenia and G-CSF to treat leukopenia. G-CSF administration in older patients with myelodysplastic syndrome occasionally increases the number of blast cells [24]. Indeed, G-CSF administration in TAM patients could increase blast cells and accelerate leukemogenesis. In the present cases, the number of blast cells did not increase, and AML did not occur; however, a shorter period of LD-CA therapy may have reduced the risk of leukopenia. The optimal treatment period should be investigated in future studies. In addition, none of our 3 present cases were complicated with tumor lysis syndrome. Hayasaka *et al.* [17] reported that ET may reduce the risk of tumor lysis syndrome by decreasing the number of blast cells. Our cases also indicated that ET could be a suitable pretreatment for chemotherapy to avoid tumor lysis syndrome.

Liver fibrosis is one of the most severe complications of TAM. Previous reports suggest that inflammatory cytokines produced by megakaryoblasts in the liver, such as TGF-β1 and platelet-derived growth factor, promote liver fibrosis by facilitating the synthesis of extracellular matrix [2, 19, 20]. In the present study, cases 2 and 3 had liver dysfunction, but it improved with supportive therapy. Moreover, all 3 patients survived without lethal liver failure. Thus, it is possible that LD-CA with ET prevents the progression of lethal liver fibrosis by reducing the number of blast cells, which produce inflammatory cytokines.

In conclusion, our 3 patients with hydrops and severe TAM were rescued from respiratory and circulatory failure by reducing their numbers of blast cells using a safe combination therapy of ET and LD-CA. Further large-scale studies will be needed to clarify the efficacy of LD-CA after ET therapy.

References

1. Brink DS: Transient leukemia (transient myeloproliferative disorder, transient abnormal myelopoiesis) of Down syndrome. Adv Anat Pathol (2006) 13: 5: 256–262.
2. Maeda H, Go H, Imamura T, Sato M, Momoi N and Hosoya M: Plasma TGF-β1 levels are elevated in Down syndrome infants with transient abnormal myelopoiesis. Tohoku J Med (2016) 240: 1–5.
3. Park MJ, Sotomatsu M, Ohki K, Arai K, Maruyama K, Kobayashi T, Nishi A, Sameshima K, Takagi T and Hayashi Y: Liver disease is frequently observed in Down syndrome patients with transient abnormal myelopoiesis. Int J Hematol (2014) 99: 154–161.
4. Klusmann JH, Creutzig U, Zimmermann M, Dworzak M, Jorch N, Langebrake C, Pekrun A, Macakova-Reinhardt K and Reinhardt D: Treatment and prognostic impact of transient leukemia in neonates with Down syndrome. Blood (2008) 111: 2991–2998.
5. Smrcek JM, Baschat AA, Germer U, Gloeckner-Hofmann K and Gembruch U: Fetal hydrops and hepatosplenomegaly in the second half of pregnancy: a sign of myeloproliferative disorder in fetuses with trisomy 21. Ultrasound Obstet Gynecol (2001) 17: 403–409.
6. Bellini C, Hennekam RC, Fulcheri E, Rutigliani M, Morcaldi G, Boccardo F and Bonioli E: Etiology of nonimmune hydrops fetalis: a systematic review. Am J Med Genet A (2009) 149: 844–851.
7. Heinonen S, Ryynanen M and Kirkinen P: Etiology and outcome of second trimester non-immunologic fetal hydrops. Acta Obstet Gynecol Scand (2000) 79: 15–18.
8. Swain S, Cameron AD, McNay MB and Howatson AG: Prenatal diagnosis and management of nonimmune hydrops fetalis. Aust NZ J Obstet Gynaecol (1999) 39: 285–290.
9. Hoskote A, Chessells J and Pierce C: Transient abnormal myelopoiesis (TAM) causing multiple organ failure. Intensive Care Med (2002) 28: 758–762.
10. Gamis AS, Alonzo TA, Gerbing RB, Hilden JM, Sorrell AD, Sharma M, Loew TW, Arceci RJ, Barnard D, Doyle J, Massey G, Perentesis J, Ravindranath Y, Taub J and Smith FO: Natural history of transient myeloproliferative disorder clinically diagnosed in Down syndrome neonates: a report from the Children's Oncology Group Study A2971. Blood (2011) 118: 26: 6752–6759.
11. Dormann S, Kruger M, Hentschel R, Rasenack R, Strahm B, Kontny U and Niemeyer C: Life-threatening complications of transient abnormal myelopoiesis in neonates with Down syndrome. Eur J Pediatr (2004) 163: 374–377.
12. Anuk D, Tarcan A, Alioglu B, Avci Z, Haberal N, Ozyurek E and Ozbek N: Hydrops fetalis in a neonate with Down syndrome, transient myeloproliferative disorder and hepatic fibrosis. Fetal Pediatr Pathol (2007) 26: 223–228.
13. Akdag A, Tunc B, Oguz S, Dilli D and Dilmen U: A newborn with Down syndrome-transient myeloproliferative disorder. J Perinat Med (2010) 38: 445–447.
14. Malin GL, Kilby MD and Velangi M: Transient abnormal myelopoiesis associated with Down syndrome presenting as severe hydrops fetalis: a case report. Fetal Diagn Ther (2010) 27: 171–173.
15. Takeyama M, Uchida Y, Arai I, Kamamoto T, Nishikubo T, Kanehiro H, Sado T, Kunishima S and Takahashi Y: Efficacy of inchinkoto for a patient with liver fibrosis complicated with tran-

sient abnormal myelopoiesis in Down's syndrome. Pediatr Int (2011) 53: 1093–1096.
16. Koga H, Miyako K, Suga N, Hidaka T and Takahashi N: Improving circulatory disturbance in transient abnormal myelopoiesis. J Pediatr Hematol Oncol (2012) 34: 149–151.
17. Hayasaka I, Cho K, Morioka K, Kaneshi Y, Akimoto T, Furuse Y, Moriichi A, Iguchi A, Cho Y, Minakami H and Ariga T: Exchange transfusion in patients with Down syndrome and severe transient leukemia. Pediatr Int (2015) 57: 620–625.
18. Bonifer C, Faust N, Geiger H and Muller AM: Developmental changes in the differentiation capacity of hematopoietic stem cells. Immunol Today (1998) 19: 236–241.
19. Minakata S, Sakata N, Wada N, Konishi S, Marutani S, Enya T, Nakagawa H, Wada H and Takemura T: Liver fibrosis with hypereosinophilia causing transient abnormal myelopoeisis. Pediatr Int (2016) 58: 1222–1225.
20. Hattori H, Matsuzaki A, Suminoe A, Ihara K, Nakayama H and Hara T: High expression of platelet-derived growth factor and transforming growth factor-β1 in blast cells from patients with Down syndrome suffering from transient myeloproliferative disorder and organ fibrosis. Br J Haematol (2001) 115: 472–475.
21. Shitara Y, Takahashi N, Aoki Y, Kato M, Nishimura R, Tsuchida S and Oka A: Cytokine profiles in pericardial effusion in Down syndrome infant with transient abnormal myelopoiesis. Tohoku J Exp Med (2017) 241: 149–153.
22. Shimada A, Hayashi Y, Ogasawara M, Park MJ, Katoh M, Minakami H, Kitoh T, Kojima S, Kawa K and Kimura H: Pro-inflammatory cytokinemia is frequently found in Down syndrome patients with hematological disorders. Leuk Res (2007) 31: 1199–1203.
23. Muramatsu H and Kikuchi A: The treatment strategy for transient abnormal myelopoiesis. (2011) 25: 179–184. (in Japanese)
24. Negrin RS, Haeuber DH, Nagler A, Olds LC, Donlon T, Souza LM and Greenberg PL: Treatment of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor: a phase I-II trial. Ann Intern Med (1989) 110: 976–984.