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Successful reduced-intensity stem cell transplantation from unrelated cord blood in three patients with X-linked severe combined immunodeficiency

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Running title:

RIST from CB in patients with X-SCID

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Abstract

We described three boys with X-linked severe combined immunodeficiency (X-SCID) who were successfully treated by reduced-intensity stem cell transplantation from unrelated cord blood (CB). Mean age at the transplantation was 5.7 months (range, 3-9 months). Pre-transplantation conditioning for all patients consisted of fludarabine (FLU) (30 mg/m²/day) from day -7 to day -2 (total dose 180 mg/m²) and busulfan (BU) 4mg/kg/day from day -3 to day -2 (total dose 8 mg/kg). All of the CB units were serologically matched HLA-A, B, and DR loci. Although two of them had suffered from fungal or bacterial pneumonia before transplantation, there were no other infectious complications during transplantation. All the patients have engrafted and achieved 100% donor chimerism. We also confirmed full donor chimerism of both T and B cells. Only one patient developed acute GVHD grade III, which resolved by increasing the dose of oral corticosteroid. None of the patients have developed chronic GVHD during the follow up for 21 to 77 months. No patients had received intravenous immunoglobulin replacements after the transplantations, or showed delay in psychomotor development. Reduced-intensity conditioning consisting of FLU and BU and transplantation from unrelated CB was effective and safe treatment for patients with X-SCID.

Introduction

The severe combined immunodeficiency (SCID) is the most severe form of primary immunodeficiencies (PID). About a half of the cases is X-linked SCID (X-SCID; T-B+NK-SCID), caused by deficits of cytokine receptor common gamma chain¹. Haematopoietic stem cell transplantation (SCT) is the only curable treatment for these high-risk patients^{2,3}. In the early series, HLA-identical sibling bone marrow transplantation led to a complete immunologic reconstitution without any conditioning regimen^{4,5}. Thereafter transplantations from closely matched unrelated volunteer donor (MUD) transplantations have been performed with better outcome in terms of both survival and immunologic reconstitution than those from haploidentical donors; the majority of the patients after MUD transplantations with myeloablative conditioning required no longer intravenous immunoglobulin replacement^{2,5,6}. However, MUD transplantation requires long time to search for a suitable donor, often over 3 months, and associates with both high frequency and intensity of GVHD. Moreover, immunological reconstitutions are often incomplete in many patients especially with X-SCID after MUD transplantations without any conditioning⁴. Most of these problems could be resolved by the transplantation with already typed umbilical cord blood (CB) with a known number of CD34 cells supplied from CB bank because of its lower incidence of GVHD.⁷⁻⁹ Following the first report of CB stem cell transplantation (CBT) for PID patients from their their sibling donors¹⁰, successful unrelated CBT have been described¹¹⁻¹⁶. Because the overall survival rates are over 70%, CB could be a

promising source when HLA-identical sibling donors are not available.

X-SCID is fatal and required SCT in the first year of life despite possible late complications such as mental and growth retardation after myeloablative transplantation receiving in infancy¹⁷⁻¹⁹. On the other hand, most of them have already suffered from bacterial and/or fungal infection at the diagnosis of X-SCID. Recently developed reduced-intensity conditioning (RIC) regimens have been applied to unrelated SCT for PID patients, because of their intense immune suppression and less myelotoxicity²⁰. Thus, reduced-intensity stem cell transplantation (RIST) from CB could be a choice for the patients with X-SCID but not fully established to date. Here, we report the successful allogeneic RIST from unrelated CB for treatment of X-SCID in our single centre experience.

Patients and Methods

Patients

Three patients with X-SCID received unrelated CBT because they had no HLA-matched sibling donors. As shown in Table, mutations in common gamma chain gene were detected in all of the patients. Patients 1 and 2 had suffered from pneumonia caused aspergillus and bacteria, respectively, at the diagnosis of X-SCID. Patient 3 was diagnosed as having X-SCID at birth because his brother had the same disease. (Table)

Conditioning regimen and graft-versus-host disease prophylaxis

Pretransplant conditioning for all patients consisted of fludarabine (FLU) (30 mg/m²/day) from day -7 to day -2 (total dose 180 mg/m²) and busulfan (BU) 4mg/kg/day (patient 1 and 2; oral;

patient 3; intravenous) from day -3 to day -2 (total dose 8 mg/kg). Neither ATG nor Campath was included in the conditioning regimen.

Prophylaxis for acute graft-versus-host disease (GVHD) included cyclosporine A (3 mg/kg) from day-1 to day +180, and methylprednisolone 0.5 mg/kg/day (day+7-+13), 1 mg/kg/day (day+14-+28), 0.5 mg/kg/day (day+29-+42), 0.3 mg/kg/day (day+43-+56), and 0.2 mg/kg/day (day+57-+72). Cyclosporine A was discontinued by day+180, after confirming the lack of clinical GVHD.

Graft characteristics

As shown in Table, all cord bloods were collected from female donors. All of these cord blood units were serologically well matched at 6/6 (A, B, DR) HLA loci. Infused nucleated cell doses were 11 to 20 x 10⁷/kg (mean, 15 x 10⁷/kg) which contained CD34+ stem cell ranging from 3.2 to 6.7 x10⁵/kg (mean, 5.1 x10⁵/kg).

Supportive cares

Supportive cares for transplantation in our institution have been previously described²¹. Briefly, all the patients received continuous infusions of low molecular weight heparin, 100 unit/kg/day, as prophylaxis against hepatic veno-occlusive disease (VOD) from day -7 to day +30. Oral polymixin B and amphotericin B, inhaled vancomycin, tobramycin and amphotericin B were given as antibacterial and antifungal prophylaxis. Antiviral prophylaxis consisted of oral acyclovir (600 mg/m²/day) from day -7 to day +35 and weekly intravenous γ -globulin (200 mg/kg/2weeks) from day -6 to day +90. Granulocyte colony-stimulating factor (G-CSF) was

given intravenously at 5 µg/kg from day +5 until an absolute neutrophil count (ANC) reached 500/µl or more for 3 consecutive days. Oral mucositis was treated with intravenous pentazocine and parental nutrition.

Acute GVHD was diagnosed and graded according to Seattle criteria²², and treated by prednisolone. CMV infection was diagnosed by CMV antigenemia, and treated with ganciclovir in combination with anti-CMV high titer γ-globulin.

Chimerism studies

Hematological recovery was defined as achieving both an ANC > 500/µl for 3 consecutive days and a platelet count > 50 x10⁹/l for 7 consecutive days without the need for transfusion.

Chimerism was tested by fluorescence in situ hybridization (FISH) of their peripheral mononuclear cells using X and Y chromosome probes. Chimerism of T or B cell lineage was assessed by flow cytometry using an intracytoplasmic staining of common gamma chain together with fluorescein-labelled antibodies against CD3 and CD19.

Immunologic reconstitution studies

Immunologic reconstitution status after transplantation was monitored by serum immunoglobulin levels (IgG, IgA and IgM) and flow cytometry analyses of their peripheral mononuclear cells for CD3, CD4, CD8, CD16, CD19 and CD56.

Results

Engraftment and chimerism

As shown in Figures A, B and C, all the patients have achieved engraftment of ANC > 500/µl

with a mean of 22 days (range, 19-27 days). Mean time to platelet engraftment (platelets > 50x 10⁹/l) was 34 days (range, 28-43 days). 100% donor chimerism was demonstrated by FISH with X and Y chromosome probes at one-year post transplantation. We also confirmed full donor chimerism of both T and B cells. Chimerism has been stable to date with a mean follow-up of 53 months (range, 21– 77 months). The frequencies of transfusions were similar to the other patients with non malignancy such as congenital metabolic disorder receiving RIST in our institute.

Regimen related toxicity

Patient 1: He received anti-fungal treatment by intravenous micafungin 3mg/kg before conditioning until day+90 for the pre-existing lung aspergillosis and showed no exacerbation during the course of CBT. Both clinical and radiological improvement was achieved after cord blood engraftment. Patient 2: Although he had already suffered from bacterial pneumonia on admission, he received appropriate antibiotics treatment and recovered at the beginning of conditioning. He had no additional severe infectious complications until engraftment. Patient 3: He could have received CBT at three months of age without infection. He also had no severe infectious complications until engraftment. Although mild mucositis and increase of serum transaminase were recognized, none had complicated severe regimen related toxicity such as VOD.

Graft-versus-host disease

Only one patient (patient 2) developed acute GVHD grade III, consisting of mild skin rash and diarrhea that resolved by increasing oral corticosteroid. None of the patients have developed chronic GVHD or associated complications during follow-up periods.

Immunologic reconstitution

Peripheral blood lymphocyte subpopulations were gradually reconstituted in all patients after UCB transplantations. As shown in figures, peripheral blood CD3-, CD19-, CD56-positive cells gradually increased up to almost normal age-related levels at one-year post transplantation. We confirmed common gamma chain expression on all of these lymphocyte subpopulations. All the patients had not received any more intravenous immunoglobulin replacements by 5~6 months after the transplantations. Moreover, specific antibodies were produced against influenza, pertussis, and measles following vaccination in all the patients.

Growth and psychomotor development

As shown in Table, all of our patients showed normal psychomotor development and performance status to date. Only one patient, patient 3, accompanied -2.4SD short stature with follow up at 21 months post- transplantation, although the other two patients had normal growth development.

Discussion

We presented here three patients with X-SCID successfully treated by CBT with RIC regimen using FLU/BU. Both FLU/melphalan (LPAM) and FLU/BU regimens with or without some modifications such as additional serotherapy is widely used for RIC regimen in the cases of SCID^{23,24}. Although FLU/LPAM regimen results in satisfactory engraftment²⁰, LPAM has toxicity to both primitive and committed stem cells resulting in early onset and a prolonged duration of neutropenia²⁵. In addition, LPAM containing conditioning regimen has been

identified as a risk factor for VOD²⁶, possibly because LPAM induces severe mucosal injuries in the oral cavity and gastrointestinal tract compared with other agents²⁷⁻²⁹. On the other hand, BU has preferential toxicity to committed stem cells²⁵. Although conditioning regimens including standard-dose BU is associated with a high rate of treatment-related complications due to organ toxicity, reduced-dose of BU in combination with FLU is less myelosuppressive and toxic than FLU/LPAM or standard-dose of BU regimen³⁰. Indeed, our patients achieved full donor T- and B-cell chimerism and clinical cure with minimum complications related to myelotoxicity. To date, none of our patients showed mental or growth delay except for one patient, patient 3, who had short stature of -2.4SD at the 21 months after CBT. Both growth and endocrine functions are commonly affected by standard myeloablative conditioning but has not been reported in BU-based RIC for SCT during infancy and childhood³¹. Our case, patient 3, raises the possibility of growth retardation following the BU-based RIC regimen because he received SCT at three months old. Further studies are necessary to determine the appropriate time for SCT to prevent the late complications such as growth retardation.

Although CBT has greater tolerance to HLA disparity, HLA incompatibility increases the incidence and intensity of GVHD and transplantation-related mortality^{16,32}. Low incidence of severe GVHD in our series patients possibly reflected the well-matched CB units. Since unrelated CB is immediately available from CB banks, it has advantage for the patients with X-SCID who need urgent transplantation.

Pre-existing infections are the principal risk factors for poor outcomes of SCT. Patients 1

and 2 overcame pre-existing fungal and bacterial pneumonia, respectively, and recovered after transplantation. This suggested that, in addition to the appropriate antimicrobial therapy, an early immunological reconstitution with minimum immune suppression by immediate SCT using RIC regimen contributes to the termination of the infections. Detection of fungal antigens or viral nucleotides by PCR-based techniques is critical for the early diagnosis and appropriate treatment of infections. On the other hand, early diagnosis of X-SCID before any infections episodes as shown in patient 3 is necessary for safe SCT particularly in the patients with SCID. Recently developed newborn mass-screening by quantitative assay for T-cell receptor excision circles might be useful for early diagnosis of patients with a wide variety of SCID genotypes^{33,34}.

In conclusion, CBT is a suitable alternative to bone marrow transplantation X-SCID patients requiring SCT with no sibling donors. Reduced-intensity conditioning consisting of FLU and BU is an effective and safe treatment for such cases. Further studies are necessary to determine the appropriate time for SCT to minimize the late complications such as growth retardation.

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Conflict of interest statement

No potential conflicts of interest were disclosed.

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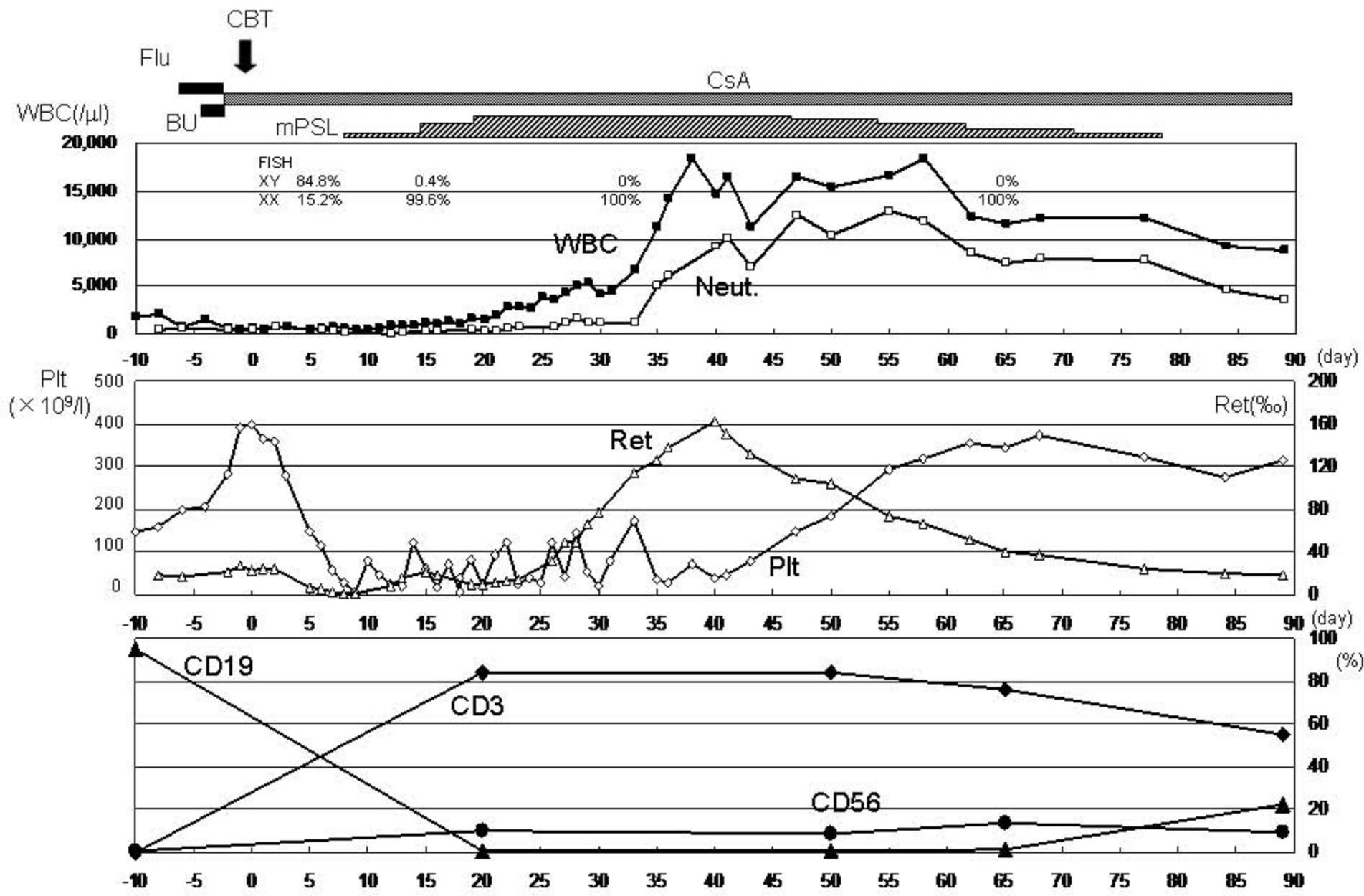
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Title and legend of Figure

Figure. Clinical course of the three patients with X-SCID receiving RIST from CB. **A**, Patient 1; **B**, Patient 2; **C**, Patient 3; ■, WBC; □, Neutrophils (Neut); Δ, Reticulocyte (Ret); ◇, Platelet (Plt); ◆, CD3; ▲, CD19; ●, CD56; respectively. Note that all patients have engrafted and reached > 500/μl neutrophils with day+19, +22, +27, respectively (mean day+22). Platelet engraftment (platelets > 50 x 10⁹/l) was day+28, +43, +31, respectively (mean day+34).

B



C

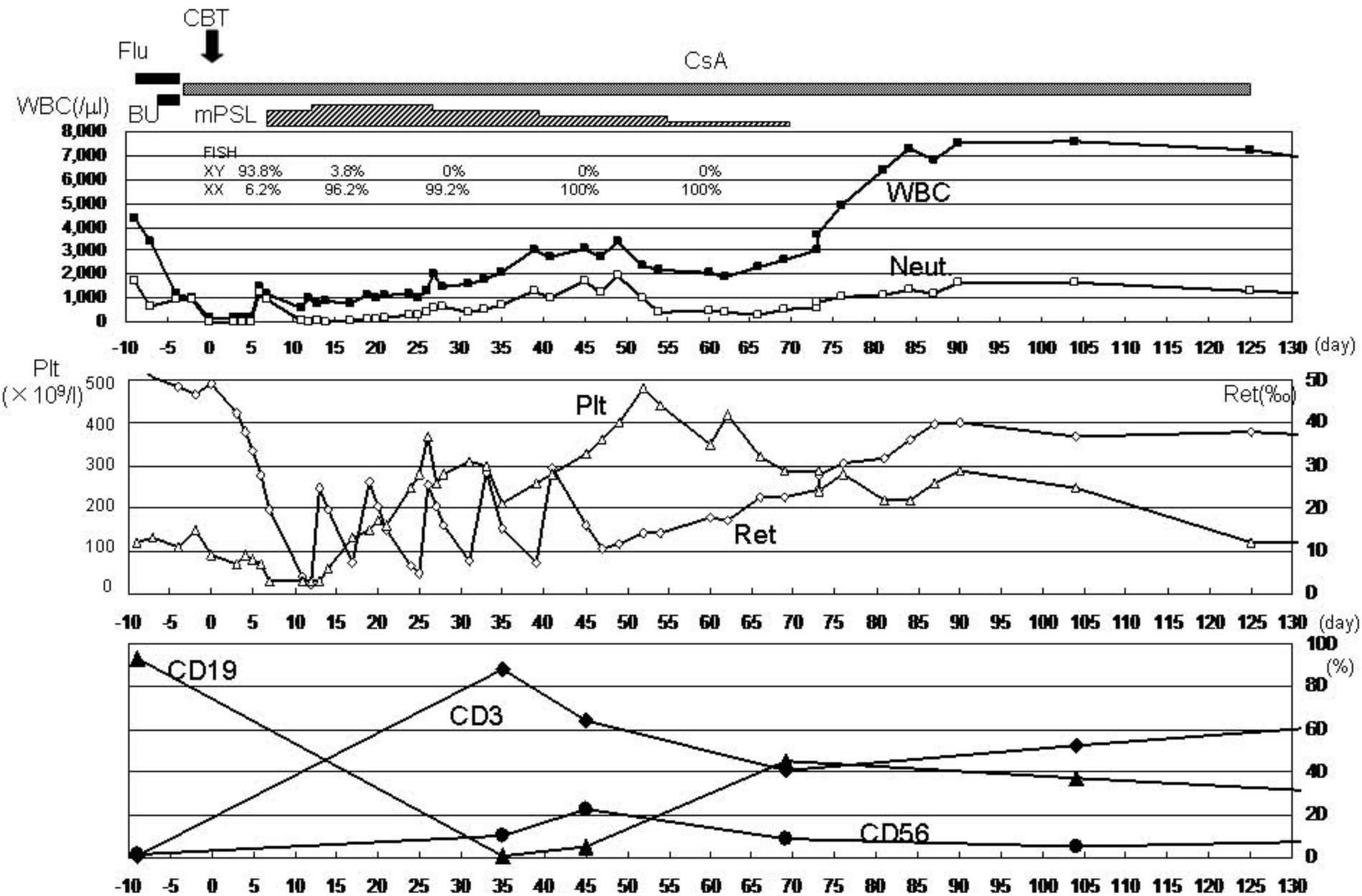


Table. Patients' Characteristics

Patient	1	2	3
Age at diagnosis (months)	8	4	0
Age at CBT(months)	9	5	3
Mutations in common gamma chain	682T>G in exon 5	9_10insA in exon 1	216G>A in exon 2
HLA-identity	6/6	6/6	6/6
Nucleated cell dose (x 10 ⁷ /kg)	11.2	20.4	15.6
CD34+ cell dose (x 10 ⁵ /kg)	6.7	5.3	3.2
Cytomegarovirus serology	positive	positive	positive
Haematological recovery			
Neutrophile>500/ μ l	day+19	day+22	day+27
Platelet>50x10 ⁹ /l	day+28	day+43	day+31
Complications at CBT	aspergillus pneumonia	bacterial pneumonia	none
Additional infections during CBT	none	none	none
GVHD acute(grade)	0	III	0
chronic	-	-	-
Chimerism (donor%)	100	100	100
B cell engrafted(donor%(day))	100(day+120)	100(day+89)	100(day+83)
IVIg replace at present	none	none	none
Performance Status (ECOG, <i>Okenn MM, et al, 1987</i>)			
	PS-0	PS-0	PS-0
Outcome	Alive	Alive	Alive
	+77mo	+69mo	+21 mo
Hight	-0.53SD	-0.49SD	-2.4SD
Body mass index	15.0	16.1	15.6
Mental status	normal	normal	normal

CBT, cord blood transplantation; HLA, human leukocyte antigen; GVHD, graft-versus-host disease; IVIG, intravenous immunoglobulin; ECOG, Eastern Cooperative Oncology Group