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Original Article

Comparison of Direct Costs for Allogeneic Bone Marrow Transplantation from Unrelated Donors and Umbilical Cord Blood Transplantation for Childhood Acute Lymphoblastic Leukemia in Japan

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ABSTRACT

Background: The 5-year disease-free survival rate for childhood acute lymphoblastic leukemia has improved due to improvements in the regimen. Hematopoietic stem cell transplantation (HSCT) is performed for patients at very high risk. There are 2 types of HSCT that use bank donors: allogeneic bone marrow transplantation from unrelated donors (U-BMT) and umbilical cord blood transplantation from unrelated donors (U-CBT). We compared the costs of U-BMT and U-CBT.

Methods: A standard recipient model was developed based on the publically available clinical path and a literature survey. The period for which costs were calculated was set at 116 days. We analyzed 3 age groups, namely, patients aged 1 to 4 years, 5 to 9 years, and 10 to 14 years. Seven adverse events associated with transplantation were analyzed: severe bacterial infection, severe fungal infection, cytomegalovirus infection, herpes virus infection, graft failure, sinusoidal obstruction syndrome, and acute graft-versus-host disease. Sensitivity analyses were done to confirm the robustness of the calculations.

Results: Total cost, including adverse event costs, was 10.3 million yen for U-BMT and 10.9 million yen for U-CBT, and average per diem cost was 87600 yen and 94200 yen, respectively. Sensitivity analysis showed that the total cost of U-CBT was higher than that of U-BMT in all age groups except age group 10 to 14 years.

Conclusions: Cost minimization analysis indicated that the total cost of U-CBT, including adverse event costs, for 116 days was 7.4% higher than that of U-BMT. However, recent improvements in U-CBT appear to have substantially reduced the cost of this treatment.

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KEYWORDS: cost, U-BMT, U-CBT, acute lymphoblastic leukemia, childhood

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The 5-year disease-free survival rate for childhood acute lymphoblastic leukemia (ALL) has recently improved due to improvements in the regimen, and an event-free survival rate of 75% to 80% was reported.[1] Chemotherapy with anticancer drugs is the primary treatment, but hematopoietic stem cell transplantation (HSCT) is performed in patients at very high risk, including those with Philadelphia chromosome-positive ALL, T-cell ALL, infant ALL with mixed-lineage leukemia rearrangements, or hypodiploid ALL with less than 44 chromosomes, as well as those who have primary induction failure or relapse.[2]

When choosing donors, factors such as human leukocyte antigen (HLA) typing, rate of graft survival, wait time for transplant, CD34+ cell count, and frequency of acute graft-versus-host disease (aGVHD) must be considered. In Japan, the universal public insurance system ensures that cost is not an important factor in choosing treatment.[3] Allogeneic bone marrow transplantation between siblings (Sib-BMT) is the first choice for transplants in children because survival is good if an appropriate donor is available. The second choice is fully HLA-matched allogeneic bone marrow transplantation from unrelated donors (U-BMT) using a donor from a bone marrow bank, since the survival rate almost equals that of Sib-BMT.[4–6] Umbilical cord blood transplantation from unrelated donors (U-CBT) using a donor from a cord blood bank is the third choice.[7]

U-CBT is regarded as inferior to U-BMT because the survival rate after U-CBT is 10% lower than that of U-BMT. In addition, as compared with U-BMT, recovery of neutrophil count and platelet count takes 10 to 15 days longer after U-CBT, which increases the risk of infection among U-CBT patients.[8–12] However, U-CBT has advantages over U-BMT, namely, lower risk of severe aGVHD, ease of locating donors (it takes 10 days on average to find a donor for U-CBT, as compared with 119 days for U-BMT),[13] and low infestation to donors. U-CBT outcomes have improved, and several studies reported that there was no difference in event-free or overall survival between U-BMT and U-CBT for childhood ALL.[14–16] In Japan, a case series study found that U-CBT was superior to U-BMT.[17]

If outcomes do not significantly differ between U-CBT and U-BMT, differences in waiting time, quality of life, and cost between the 2 treatments would then be the main issues in selecting a treatment strategy. Few studies have compared the costs of Sib-BMT, U-BMT, and U-CBT. Majhail et al. compared actual medical expenses during the 100-day period after treatment with Sib-BMT, U-BMT, and U-CBT.[18] The costs of U-BMT (US$4050 per day) and U-CBT (US$4522 per day) were similar, but the least expensive treatment was Sib-BMT (US$3446 per day). In addition, Sib-BMT resulted in fewer complications and lower costs as compared with U-CBT and U-BMT. In Japan, Inoue et al.[19] used reimbursement data to compare costs at several centers. Total medical cost was 13.5 million yen (11400 yen per day) for Sib-BMT, 10.3 million yen (11500 yen per day) for U-BMT, and 20.0 million yen (15600 yen per day) for U-CBT. Interestingly, this order was identical to that reported by Majhail et al. Nevertheless, it is difficult to compare costs at different centers because institutes use different protocols, *e.g.*, for supportive care [inclusion of an antimicrobial agent, an antiviral drug, anticoagulant therapy, and granulocyte colony-stimulating factor (G-CSF)]. Moreover, recent advances in U-CBT have reduced hospital stays and complication rates, and these improvements may not have been reflected in the study by Inoue et al.

To compare the direct medical costs of U-BMT and U-CBT, we developed a model of the standard recipient in which standard supportive care was included and recent clinical and administrative data were considered.

Methods

A standard recipient model was developed based on the publicly accessible clinical path and a literature survey. The period for cost calculation was set at 116 days (15 days before transplantation and 100 days after transplantation). The payer's perspective was adopted, and direct medical cost was calculated using the 2010 national tariff of hospital charges, images, examination/pathology, radiotherapy, surgery/anesthesia, injections, and drugs.[20, 21]

In developing the model, drug dose varied according to age, body weight (BW), and body surface area (BSA). Patients were grouped into 3 age groups: those aged 1 to 4 years (BW: 12.5 kg, BSA: 0.6 m^2), 5 to 9 years (BW: 25 kg, BSA: 0.8 m^2), and 10 to 14 years (BW: 40 kg, BSA: 1.2 m^2). Seven hypothetical adverse events occurring during transplant treatment were analyzed: severe bacterial infection, severe fungal infection, cytomegalovirus (CMV) infection, herpes virus infection, survival deficiency, sinusoidal obstruction syndrome (SOS), and aGVHD. Total body irradiation (TBI) + etoposide (VP-16) + cyclophosphamide (CPA),[3] was used as transplant pretreatment. We assumed pretreatment periods as follows: 15 days for administration of antibiotics and antifungal agents, 5 days for

Table 1 Treatment model: Transplant pretreatment (day -15) to 100 days after transplant (day 100)

Standard pretreatment (TCCSG 04-16 guideline)		
Total body irradiation (TBI)	12 Gy divided into 6 fractions over 3 days	Days -8, -7, -6
Cyclophosphamide (CPA)	60 mg/kg/day for 2 days	Days -3, -2
Etoposide (VP-16)	Body weight (BW) 30 kg > 60 mg/kg/day BW 30 kg < 1800 mg/m^2/day	Day -5
Infection prevention		
Bacterial infection prevention	cefmetazole (CMZ) div. 100 mg/kg/day	Day 15 to neutrophil count recovery
Fungal infection prevention	micafungin (MCFG) p.o. 50 mg/kg/day	Day 15 to day 100
	trimetoprim (INN) + sulfamethoxazole (SMZ) p.o. 0.05 g/kg/day	Day 15 to day 100 (3 per weekday)
Herpes infection prophylaxis	Aciclovir (ACV) p.o. 20 mg/kg/day	Day 5 to day 30
Marrow survival promotion		
	Granulocyte colony-stimulating factor (G-CSF) 400 μg/m^2/day	Day 3 to neutrophil count recovery
Transfusion		
Red blood cell transfusion		To recovery of hemoglobin U-BMT every 10 days, U-CBT every 6 days
Platelet transfusion		To recovery of platelet count U-BMT every 8 days, U-CBT every 7 days
Treatment		
Central venous catheter insertion		Once
Hematopoietic stem cell transplantation		Day 0
Examination		
	Blood count, hemogram, reticulocyte, biochemistry (TP, Alb ,GOT, GPT, LDH, ALP, γGTP, ChE, BUN, Cr, Na, K, Cl, T-Bil, D-Bil, CRP)	Daily (day 15 to neutrophil count recovery) 3 per weekday (after marrow recovery)
	PT, APTT, AT III, D-dimer, Fbg, CMV antigenemia, β-D-glucan, chest XP	Once a week
	Urinary sediment, urine qualitative analysis	Twice a week
	IgG, IgA, IgM, TAT, tPA/PAI-1, TM, protein C, haptoglobin	Every other week
Hospital charges		
	Regular hospital charges	Day -15 to day -3, neutrophil count recovery to day 100
	Sterile room hospital charges	Day 2 to neutrophil count recovery
	Diet charges	Day 15 to day 100

Treatment model is based on the clinical practice guideline and clinical path of the Tokyo Children's Cancer Study Group (TCCSG). The central venous catheter was assumed to be inserted under general anesthesia.
U-BMT: allogenic bone marrow transplantation from unrelated donors, U-CBT: umbilical cord blood transplantation from unrelated donors, div.: divide, p.o.: per os

administration of anti-varicella virus medication, and 2 days for a stay in a sterile room (recipients were assumed to have been transferred 2 days before surgery). After transplantation, treatment was assumed to be (1) sterile room, G-CSF, and antibiotic administration until recovery of neutrophil count, (2) antifungal administration until discharge, (3) administration of anti-varicella virus medication for 30 days (Table 1), (4) packed red blood cell transfusion once every 6 days (for U-CBT) or 10 days (for U-BMT), and (5) platelet transfusion once every 7 days (for U-CBT) or 8 days (for U-BMT).

Treatments for the 7 investigated adverse events are

Table 2 Treatment of adverse events

(1) Severe bacterial infection	meropenem (MEPN) div.	100 mg/kg/day	For 14 days
	vancomycin (VCM) div.	40 mg/kg/day	For 14 days
	Blood culture		Twice
(2) Severe fungal infection	amphotericin b (AMPH-B) div.	5 mg/kg/day	For 14 days
	β-D-glucan		Twice
(3) Cytomegalovirus (CMV) infection	Ganciclovir	10 mg/kg/day	For 21 days
		5 mg/kg/day	For 95 days
(4) Herpes simplex virus/varicella zoster virus (HSV/VZV) infection	Aciclovir (ACV) div.	30 mg/kg/day	For 20 days
(5) Sinusoidal obstruction syndrome (SOS)	Low-molecular-weight heparin (LMWH)	75 IU/kg/24 h	For 86 days
	Prostaglandin I_2 (PGI_2) div.	0.15 μg/kg/day	For 10 days
	Fbg, TAT, D-dimer, protein C, tPA, PT, APTT, AT3, TM		10 times
(6) Acute graft-versus-host disease (aGVHD)	Dexamethasone (DEX)	2 mg/kg/day	For 5 days
		1.5 mg/kg/day	For 5 days
		1 mg/kg/day	For 5 days
	Antithymocyte globulin (ATG)	30 mg (BW 12.5 kg)	For 10 days
	(used in 30% of cases)	625 mg (BW 25 kg)	For 10 days
		1250 mg (BW 50 kg)	For 10 days
(7) Graft failure	Granulocyte colony-stimulating factor (G-CSF)	400 μg/m^2/day	For 100 days
	Complete blood count		70 times
	Sterile room hospital charges		For 100 days

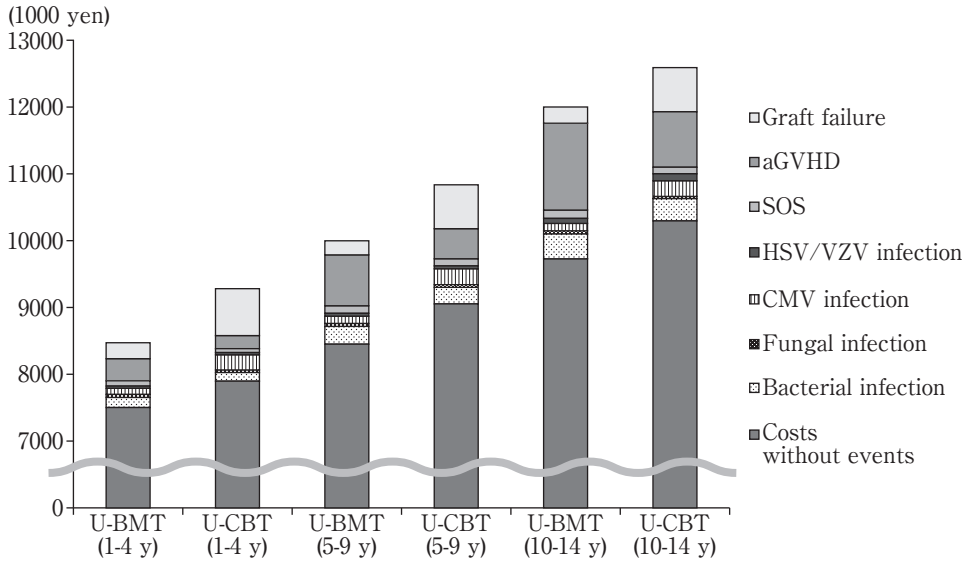
div.: divide, BW: body weight

Table 3 Assumed frequency and timing of adverse events

	U-BMT	U-CBT	Onset day (Day)	References
Neutrophil recovery day, median (Day)	18 th (17 th-18 th)	27 th (23 th-35 th)		4-6, 8
Platelet recovery day, median (Day)	30 th (29 th-31 th)	69 th (56 th-81 th)		
Survival deficiency incidence, median (%)	6.4	16.5 (7.3-25.7)		4-7
Severe bacterial infection, average (times)	1.4	1.3	10 th	5, 18
Severe fungal infection (%)	13.5	8.3	10 th	
CMV infection (%)	9.6	21.7	20 th	
HSV/VZV infection (%)	15.4	18.3	10 th	
SOS (%)	10.0	8.0	14 th	5, 19
aGVHD (%)	52.0	33.0	26 th	4, 5, 7
Median (%)	(45.9-58.0)	(30.8-35.0)		

U-BMT: allogenic bone marrow transplantation from unrelated donors, U-CBT: umbilical cord blood transplantation from unrelated donors, CMV: cytomegalovirus, HSV/VZV: herpes simplex virus/varicella zoster virus, SOS: sinusoidal obstruction syndrome, aGVHD: acute graft-versus-host disease

shown in Table 2. In the model, we assumed that antithymocyte globulin was used in 30% of patients with aGVHD. If graft failure occurred, administration of G-CSF and use of a sterile room were assumed to continue until day 100. The assumed timing and probabilities of events are shown in Table 3. The range of probabilities for the events was investigated by literature survey, and median probabilities were used in the calculations. We assumed that neutrophil count recovery would occur on day 18 for U-BMT and day 30 for U-CBT. The date of platelet count recovery was assumed to be day 31 for U-BMT and day 71 for U-CBT. Graft failure was assumed to occur in 6.4% of U-BMT pa-



	1-4 y U-BMT	1-4 y U-CBT	5-9 y U-BMT	5-9 y U-CBT	10-14 y U-BMT	10-14 y U-CBT
Costs per day (yen/day)	73100	80000	86360	93190	103450	109050

Fig. 1 Total costs, including event costs, of U-BMT and U-CBT, by age.
y: years, U-BMT: allogenic bone marrow transplantation from unrelated donors, U-CBT: umbilical cord blood transplantation from unrelated donors, aGVHD: acute graft-versus-host disease, SOS: sinusoidal obstruction syndrome, HSV/VZV: herpes simplex virus/varicella zoster virus, CMV: cytomegalovirus

tients and 16.5% (7.3-25.7%) of U-CBT patients.[8–11)]

We made the following assumptions regarding the occurrence of adverse events within 100 days after transplantation: (1) on average, severe bacterial infections occurred on day 10,[9)] and each patient with U-BMT experienced 1.4 infections and each patient with U-CBT experienced 1.3 infections most patients had at least 1 sereous infection,[22)] (2) severe fungal infections occurred on day 10, and the incidence of such infections was 13.5% for U-BMT and 8.3% for U-CBT,[9, 23)] (3) CMV infection occurred on day 20, and the incidence was 9.6% for U-BMT and 21.7% for U-CBT,[9, 24)] (4) the incidence of herpes simplex virus/varicella zoster virus (HSV/VZV) infection was 15.4% for U-BMT and 18.3% for U-CBT,[9, 24)] (5) the incidence of SOS was 10% for U-BMT and 8% for U-CBT,[9, 25)] and (6) aGVHD occurred on day 26, and the incidence was 52% (45.9-58.0%) for U-BMT and 33% (30.8-35.0%) for U-CBT.[8, 9, 11)] Sensitivity analyses were performed to ensure that the results were robust. The total costs of U-BMT and U-CBT were calculated using the minimum, median, and maximum probabilities for each event, and thresholds were identified.

Results

In our analysis, average transplant cost, including adverse event costs, was 10.3 million yen for U-BMT and 10.9 million yen for U-CBT, and average cost per diem was 87600 yen for U-BMT and 94200 yen for U-CBT. The total costs, without adverse event costs, of U-BMT and U-CBT are shown in Fig. 1. The total cost of U-CBT was 7.9 to 10.3 million yen, which was higher than that of U-BMT (7.5-9.7 million yen) for all age groups. Hospitalization costs made up more than 50% of the total costs for both U-BMT and U-CBT. In the older age groups, medication and injection costs were proportionally higher because drug doses were determined by age or body weight.

The total costs, including adverse event costs, increased in relation to age, and the total cost of U-CBT (9.3-12.6 million yen) was higher than that of U-BMT (8.5-12.0 million yen) in all age groups. The unit costs (cost/event) of severe bacterial infection, fungal infection, CMV infection, HSV/VZV infection, and SOS were the same for U-CBT and U-BMT and increased with age because drug doses increased in relation to BW and BSA (Fig. 1). As for graft failure, the cost for U-CBT was higher because the longer

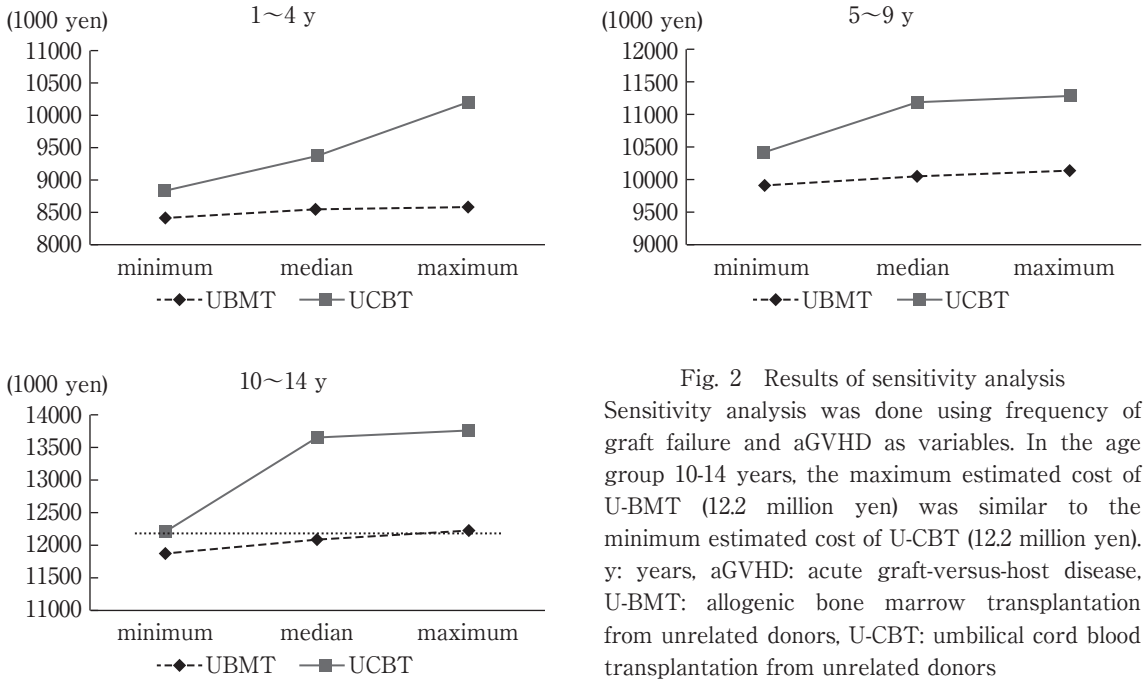


Fig. 2 Results of sensitivity analysis
Sensitivity analysis was done using frequency of graft failure and aGVHD as variables. In the age group 10-14 years, the maximum estimated cost of U-BMT (12.2 million yen) was similar to the minimum estimated cost of U-CBT (12.2 million yen). y: years, aGVHD: acute graft-versus-host disease, U-BMT: allogenic bone marrow transplantation from unrelated donors, U-CBT: umbilical cord blood transplantation from unrelated donors

neutrophil count recovery time required a greater amount of G-CSF.

We conducted sensitivity analyses using frequency of graft failure and aGVHD as variables. The results are shown in Fig. 2. The minimum and maximum values for each variable were used. The total cost ranged from 8.4 to 12.2 million yen for U-BMT and from 8.8 to 13.8 million yen for U-CBT. In the age groups 1 to 4 years and 5 to 9 years, the maximum estimate of the total cost of U-BMT was lower than the minimum estimate of the total cost of U-CBT. In the age group 10 to 14 years, the maximum estimated cost of U-BMT (12.2 million yen) was almost equal to the minimum estimated cost of U-CBT (12.2 million yen).

Discussion

The results of our analysis showed that the average transplant cost of U-BMT was lower than that of U-CBT. Our results are consistent with those of previous studies[14, 15]; however, the total cost of U-CBT in our study was about half that reported in previous studies, perhaps because improved patient management in U-CBT may have resulted in shorter hospital stays and fewer adverse events, because previous studies might have analyzed data from patients with more severe disease, and/or because health care systems might have differed. In a study using multivariate analysis Majhail et al. reported that 5 factors were related to total cost: respirator use, dialysis, Lansky score at transplant, graft failure, and hepatic veno-occlusive disease. Severe cases in which these factors were present were likely to be costlier than the cases included in our model.[14] Severity may be related to the functions of transplant centers and the applicability of technology. Patients with disease of greater severity are more likely to be referred to teaching hospitals, and if only a few centers are able to provide U-CBT, more-severe patients are likely to be priority recipients. In our cost minimization analysis, it was necessary to assume that the severity of U-CBT and U-BMT patients was identical. The appropriateness of incidences of adverse events, which reflect disease severity, should be considered. The total cost of U-CBT without event costs was 6.3% higher than that of U-BMT, and the total cost of U-CBT with event costs was 7.4% higher than that of U-BMT. Costs of adverse events made up 16.5% of the cost of U-BMT and 15.3% of the cost of U-CBT. Most of the total costs (85%) were related to hospitalization and medication, which were not influenced by events. Although disease severity in the present study could differ from that in previous studies, it is unlikely that our finding that U-BMT is less expensive than U-CBT would be affected, assuming that disease severity, as reflected by incidences of adverse events in the 2 groups, is identical.

Among the 3 age groups, the age group 1 to 4 years had the lowest total cost. Because hospitalization cost was the

same for all age groups, the cost difference was due to the fact that drug and injection doses were determined by age and BW.

Among the investigated adverse events, the costs of graft failure and aGVHD were high because graft failure necessitates continuation of expensive G-CSF until recovery and because aGVHD requires expensive antithymocyte globulin therapy. The incidence rate of aGVHD was higher for U-BMT, and the incidence rate of graft failure was higher for U-CBT. The cost of all events was higher for U-CBT than for U-BMT in the age group 1 to 4 years. However, the cost of all events was higher for U-BMT than for U-CBT in the age group 10 to 14 years because of the costs of aGVHD. Since the difference in the incidences of complications is not large, it is unlikely to affect the difference in total costs.

To calculate cost, we used the price listed in the national tariff. In Japan, hospital reimbursement is based on the biennially revised national tariff used by the universal public insurance system. The tariff was revised in 2012, but prices increased by only 0.04% on average. The results of our analysis were almost identical to those produced when the 2012 figures were substituted in the analysis. In Japan, the Bone Marrow Bank (Japan Marrow Donor Program: JMDP, a nonprofit foundation that has the legal responsibility of allocating bone marrow) charges 189000 yen on average to recipients. This cost includes donor identification, HLA typing, marrow extraction and processing, insurance for unexpected events in donors, and administration. In cases of U-CBT, the cord blood bank charges only a handling fee. The parent organizations of cord blood banks are Japanese Red Cross Society Blood Centers, teaching hospitals, and other nonprofit organizations, which are subsidized by the Japanese government. These expenses were not considered in our analysis.

In conclusion, cost minimization analysis showed that the total cost, including adverse event costs, for 116 days of treatment was 7.4% higher for U-CBT as compared with U-BMT. Most of the costs were for hospitalization and medication, which are not influenced by adverse events or disease severity. Our finding that U-BMT was less expensive than U-CBT is consistent with the results of previous studies. However, the cost of U-CBT has decreased by half, and the present difference in cost between U-CBT and U-BMT is now small. Recent improvements in U-CBT appear to have contributed to the cost reduction. Thus, close monitoring and economic evaluation of treatment options for children with acute lymphoblastic leukemia is now warranted. Treatment should be chosen based on cost as well as waiting time and patient preference.

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日本の小児急性リンパ性白血病における非血縁骨髄移植と非血縁臍帯血移植の直接費用の比較

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要約

背景：近年，小児期急性リンパ性白血病（acute lymphoblastic leukemia：ALL）の5年無病生存率は化学療法の発展により改善された．造血幹細胞移植（hematopoietic stem cell transplantation：HSCT）はリスクの高い患者に施行されている．非血縁ドナーからの移植には，非血縁骨髄移植（allogeneic bone marrow transplantatation from unrelated donors：U-BMT）と非血縁臍帯血移植（umbilical cord blood transplantation from unrelated donors：U-CBT）が行われている．われわれは，U-BMT と U-CBT の移植に要される直接費用を比較検討した．

対象と方法：標準患者モデルを公表されたクリニカルパスと文献に基づいて作成した．直接費用の算出期間を移植前処置から退院までの116日に設定した．3つの年齢群（1〜4，5〜9，10〜14歳）に区分し，分析した．移植中イベントを7つ［重症細菌感染症，重症真菌感染，cytomegalovirus（CMV）感染症，ヘルペスウイルス感染症，生着不全，類洞閉塞症候群（sinusoidal obstruction syndrome：SOS），急性移植片対宿主病（acute graft-versus-host disease：aGVHD）］に設定した．解析は感度分析を行った．

結果：直接費用は U-BMT 1030万円，U-CBT 1090万円であった．1日あたりの直接費用は，それぞれ87600円と94200円であった．感度分析により，U-BMT が U-CBT よりも高額になる場合が10〜14歳の群にのみ認められたが，他の年齢群において U-CBT の直接費用は，U-BMT よりも常に高かった．

結論：コスト最小化分析により移植中116日間の U-CBT のイベント・コストを含む直接費用は U-BMT より7.4% 高いことが示唆された．U-CBT の成績の改善は，コスト削減にも関与すると考えられる．

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