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Original Article

Retrospective Analysis of Cord Blood Transplantation on 62 Adult Patients with Advanced Hematological Malignancies

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Abstract The Japan Cord Blood Network was established in 1999 and 8 institutions from the Kyushu Hematology Organization Study Group had performed cord blood transplantation (CBT) 67 times on 62 patients with advanced hematological malignancies from 1999 to 2004, which included acute and chronic leukemias in 34 patients, non-Hodgkin's lymphoma in 14, adult T-cell leukemia in 11 and others in 3 patients. The median age was 44 and disease status was no remission on 50 patients prior to CBT. Myeloablative conditioning regimens were used in 27 patients while 35 patients received non-myeloablatives. Engraftment could not be determined in 25 patients and the median survival time was 70 days. Thirteen patients were alive from 288 to 1277 days and 49 had been expired. The causes of death were the underlying disease in 19 patients, severe infection in 14 and graft-versus-host disease in 3 and miscellaneous in the remaining patients. This retrospective study shows that some patients with far-advanced hematological malignances could be successfully treated with CBT at the expense of many early deaths due to early relapse and severe infection. It is of importance that the appropriate indication for CBT should be discussed between transplant experts and patients and their families in each case.

Key words: Cord blood, stem cell transplantation, adult hematological malignancy, engraftment, adult T-cell leukemia

Introduction

The Japan Cord Blood Network was established and began to distribute cord blood to the transplant centers throughout Japan for undertaking unrelated cord blood transplantation (CBT) since February 1999. Up until November 2005, 2704 CBT has been performed and recently 1-2 cases/day is being transplanted to the patients who could find HLA-matched or one to two mismatched cord blood[1].

Here in southwestern district of Japan adult T-cell leukemia/lymphoma (ATL) related to human T-lymphotropic virurs I (HTLV-I) is commonly seen[2], and in further south of Kyushu island like Kagoshima or Okinawa, nearly a half of lymphoid malignancies belong to ATL. ATL is a

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known lymphoid malignancy which is quite resistant to standard treatment for malignant lymphoma, and only some selected patients have experienced a long-term survival after very extensive chemotherapy and/or allogeneic hematopoietic stem cell transplantation (SCT)[3].

The median age of ATL patients is close to 60 years and they rarely enter into a durable remission. Therefore, it is hard to get a good candidate for SCT in ATL patients. However, because of the encouraging SCT results for ATL[3], some institutions have challenged to do CBT on ATL patients who are not in good remission, but otherwise just have to wait for dying of progressing disease.

Many members of Kyushu Hematology Organization for Treatment Study Group (K-HOT-SG) working in the Kyushu Island have performed SCT for years and experienced CBT as well[4].

We decided to do retrospective analysis on CBT to evaluate the treatment results including ATL, since cord blood is a useful stem cell source, but since available cord blood is limited in numbers, it is our task to use them effectively for the proper and indicated patients.

Patients and Methods

Inquiries about age, gender, underlying diseases, disease status at the time of CBT, previous SCT, performance status (PS) before and after CBT, the interval between the onset of underlying disease and CBT, date of CBT, conditioning regimens, either myeloablative or non-myeloablative SCT, the number of nucleated cells and $CD34^+$ cells in the supplied cord blood, success of engraftment, outcome, cause of death, acute and chronic graft-versus-host disease (GVHD) and costs of CBT, were sent to the 23 members of K-HOT-SG.

Since there is a lot of controversy with regard to indications for CBT, the members of K-HOT-SG were also asked to answer the questionnaires on the patients who would be a suitable candidate for CBT, i.e. underlying disease, disease status including remission or relapse, conditioning regimens and prophylaxis for GVHD. They can choose over 2 disease status for indication to do CBT.

Results

The first CBT was performed in this group in December 1999 and the last patient for this analysis was transplanted in October, 2004. The number of patients transplanted had increased as the year passed. Clinical data for a total of 62 adult patients were sent back to the K-HOT office from 8 institutions. A total of 67 CBT was undertaken on 62 patients among whom 5 patients had CBT twice because of poor engraftment in 4 patients and relapse in 1. The treatment results on these 5 patients were analyzed after the second CBT was performed. The median age was 44 years ranging from 16 to 73 with 37 males and 25 females. The underlying disease includes acute myelogenous leukemia (AML) in 18, acute lymphocytic leukemia (ALL) in 11, ATL in 11, non-Hodgkin's lymphoma (NHL) in 14, multiple myeloma in 2, and myelofibrosis in 1 (Table 1).

Out of 62 patients, 12 were in the remission status at the time of CBT. Among patients in no remission, there were 6 patients who had had autologous peripheral blood SCT and 4 patients with allogeneic SCT. The performance status (PS) prior to CBT was PS0-1 in 42 patients, PS2 in 15, PS3 in 4 and PS4 in 1. The median interval from the onset of disease to the time of CBT

Table 1 Background patients' characteristics

Cheracteristics	
No of patients	62
Median age (range)	44 (16～73)
Male/female	37/25
Disorders	
AML	18
ALL	11
CML	5
NHL	14
ATL	11
MM	2
MF	1
Disease status	
CR	12
non-CR	50
Previous SCT	
auto PBSCT	6
Allo-SCT	4
PS prior to CBT	
0-1	42
2	15
3	4
4	1
Median interval between onset of disease and CBT	10 mo

AML: acute myelogenous leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myelogenous leukemia, NHL: non-Hodgkin's lymphoma, HL: Hodgkin lymphoma, ATL: adult T-cell leukemia, MM: multiple myeloma, MF: myelofibrosis, CR: complete remission, SCT: stem cell transplantation, PBSCT: peripheral blood stem cell transplantation, PS: performance status, CBT: cord blood transpalantaiton

Table 2 Results of Cord Blood Transplantation

characteristics	
No of patients	62
Conditioning	
myeloablative	27
non-myeloablative	35
(TBI	42)
No of MNC (median) (range)	2.5×10^7/kg ($1.2\text{-}9.0\times10^7$/kg)
No of engraftment	37
Neutrophil recovery ≧ 500/μl	20 days (9-45)
Thrombocyte recovery ≧ 20 x 10^3/μl	41 days (2-90)
No of death	48
Alive	14
Acute GVHD	
0	18
I	6
II	11
III	3
IV	3
Chromic GVHD	
0	11
Limited	2
PS for 14 surviving patiens after CBT	
0	12
1	2
Cost of CBT	¥350(81～1300) $\times10^4$or $30 (6.9～110) x 10^3

TBI: total body irradiation, MNC: mononucleated cells
GVHD: graft vs host disease, PS: performance status

was 10 months ranging from 4 months to 5 years.

The conditioning regimen for conventional SCT consisted of busulfan and cyclophosphamide (Bu/CY) or CY + total body irradiation (TBI), while fludarabine and CY + TBI were used in most of the non-myeloablative SCT. The prophylaxis for GVHD is short course of methotrexate and cyclosporine A or FK506 as used in SCT from other stem cell sources[3].

The median number of mononucleated cells in CB was 2.5×10^7/kg ranging from 1.2 to 9.0 x 10^7/kg, while that of CD34 positive cells were 1.0×10^5/kg in 16 patients examined.

Engraftment of the cord blood was confirmed on 37 patients. It took 20 and 41

days for neutrophil and thrombocyte counts to become higher than 500/μl and 20x10^3/μl, respectively. The remaining patients suffered from severe complications prior to noticing engraftment or apparent engraftment failure in 2 patients. So far 13 patients had been alive for the median of 339 days ranging from 288 days to over 3 years. The rest of patients had been already expired. The cause of death was uncontrollable underlying malignant disease in 19 patients, but 6 patients died of regimen-related toxicity or veno-occlusive disease (VOD) of the liver. Systemic infection or pneumonia contributed to death in 14 patients. The cause of death was thought to be GVHD in 2 and thrombotic microangiopathy (TMA) in 1 patient. The remaining 7 patients died of multi-organ failure and miscellaneous causes. The overall median survival time was 70 days ranging from 6 to 1470 days after CBT (Fig. 1).

Since K-HOT-SG is working in the endemic area of ATL, eleven ATL patients treated with CBT were analyzed separately. The median age was 56 ranging from 39 to 61 years with 3 females and 9 males. Only 2 patients were in good remission prior to CBT. The myeloablative conditioning regimens were given to 2 patients, while 9 patients received non-myeloablatives. Two patients underwent CBT twice and one of them has been alive for more than 1.5 years. The remaining patients died of underlying disease in 5 patients and infection or other events in 5 patients, respectively.

Acute GVHD was observed in 24 patients at grade of 0-I and 17 at grade $\geqq$2. Limited extension of chronic GVHD was recorded on 2 patients among 29 patients who survived over 100 days. For the 13 surviving patients after CBT, performance status was 0 in 12 patients and 1 in 1 patient (Table 2).

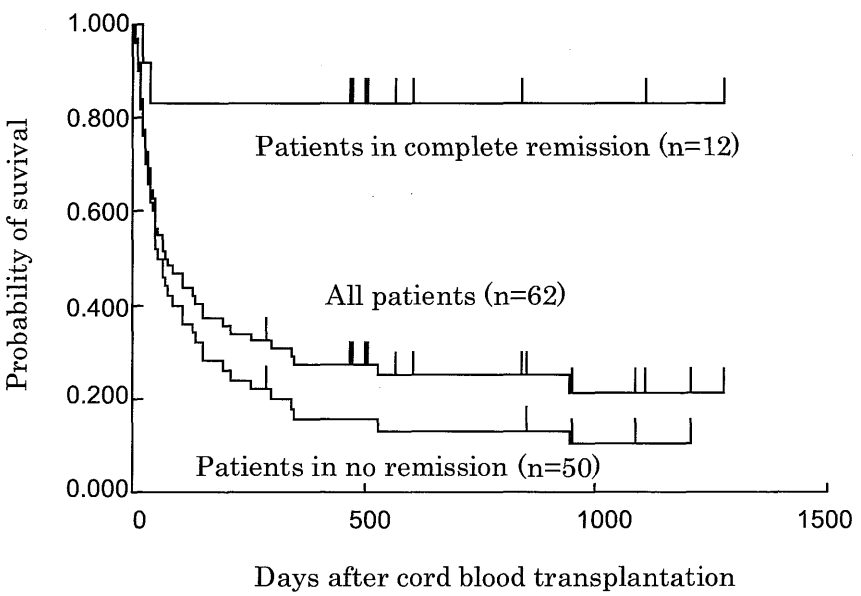

Fig. 1 The survival curve after cord blood transplantation by the Kaplan-Meyer's method.
The median survival time is 70 days for all patients. The 9 out of 12 patients in good complete remission has been alive for over 472 days in good condition up until this survey was performed, and the median survival of those transplanted in no good remission or relapse was only 50 days after cord blood transplantation.

The cost for CBT was recorded on 17 patients, and it cost less than 2 million yen on 11 patients, while the remaining 6 needed more than 4.2 million yen and one patient used 13 million yen to finish one course of CBT.

The questionnaires regarding indications to do CBT were sent to the 21 members of K-HOT-SG and 15 institutions responded to them. The indications were classified according to the risk group among hematological malignancies and underlying disease status including remission status and sensitivity to chemotherapy.

The members of K-HOT-SG consider that CBT is indicated when the patients are in the following conditions; 2nd remission or successive remission in good to moderate risk of acute leukemia, 1st remission in poor-risk acute leukemia. For CML, first chronic phase is considered to be an indication for CBT in 1 institution, CML in transformation in 4, crisis in 4, and second chronic phase in 9 institutions. Myelodysplastic syndrome (MDS) is a wide range of disease. Nine institutions offer CBT for refractory anemia with excess of blasts, 8 do for chronic myelomoncytic leukemia, and transformation into AML is considered for CBT in 13 hospitals. Nine institutions offer CBT for severe aplastic anemia which is dependent on transfusion or refractory to other treatment modalities. Second or successive remission in malignant lymphoma, relapse after autologous SCT for multiple myeloma, and 1st or second remission for ATL is thought to be indication for CBT, but childhood solid tumors are not considered to be suitable for CBT.

Discussion

The members of K-HOT-SG have been engaged in not only conventional SCT but also CBT. The underlying disease status for CBT was usually bad and therefore, 18 patients could not survive early post-transplant complications and died within 30 days. For those who got over 30 days, the follow-up period was still short and it is hard to tell that the surviving patients could make it for the longer period of time. There were, however, 6 patients in relapse or CML in transformation who were alive for over 1 year after CBT.

The patients in relapse were usually resistant to salvage treatment. Although longer follow-up is needed, these patients might have benefited from CBT or otherwise they probably lost their lives for a short period of time. This suggests that there are a small number of patients with relapsed or refractory hematological disorders who may enter into good and durable remission with CBT. This is supported by others' experience. The survival curve in mismatched CBT for leukemia is reported to be comparable to that of mismatched bone marrow transplantation, i.e. 26% survival at 3 years by the International Bone Marrow Transplant Registry (IBMTR) and the National Cord Blood Program (NCBP)[5], and 36% survival at 2 years according to the European Blood and Marrow Transplant Group (EBMT), respectively[6].

Unfortunately a large number of patients in a high risk for relapse suffered from progressive underlying disease leading to early death. In addition, not only early relapse but also repeated aggressive prior treatment for recurrent disease gave rise to developing severe complications like life-threatening infections, VOD or other treatment-related toxicity associated with CBT. Because CBT is associated with a high incidence of engraftment failure and engraftment is much slow in CBT as compared

with SCT from other stem cell sources, there is an inherent problem with developing severe infection which often leads to death.

In the southwestern district of Japan where the hospitals of K-HOT-SG are located, ATL is commonly seen in the hematological department. Eleven ATL patients were enrolled in this study and 1 patient has had durable remission. The number of patients is too small to draw any conclusion, but a portion of ATL patients in good condition could be treated successfully with CBT.

Thus this retrospective analysis on 62 patients with advanced hematological malignancies indicates that a small number of patients would benefit from CBT, but the results have not been as good as expected. Since the number of cord blood reserved in the cord blood banks is limited, indications for CBT should be discussed sincerely with professional staff in one's own institution, patients and their family members, and even transplant physicians in other institutions. We must also realize that cord blood has been collected from volunteered pregnant women and many medical personnel are involved in collecting cord blood from the umbilical vessels with no additional personnel's or financial support regardless of working hours.

Indications for CBT proposed by members of K-HOT-SG appear to be reasonable. Early death due to poor engraftment or regimen-related toxicity should be avoided as much as possible. Absolute resistance to treatment for underlying disease, old age, poor general condition with PS$\geqq$2, liver, kidney, pulmonary and other visceral organ disturbance preclude any aggressive treatment including SCT.

Recently reduced-intensity or non-myeloablative stem cell transplantation (NMSCT) has been introduced to the clinical practice. Miyakoshi et al[7] presented successful engraftment after reduced intensity umbilical cord blood transplantation for adults with advanced hematological diseases. In this setting, conditioning regimen is too mild to kill all the tumor cells, but instead graft-versus tumor (GVT) effect is expected to control the disease. Many patients in the present study were in relapse and carried large tumor burdens. In this case they are not probably a good candidate for NMSCT since tumor would re-grow rapidly before GVT effects are set on. It agrees our treatment results that all the long-term survivors in no remission of the underlying disease prior to CBT had exclusively received extensive conditioning regimens, while mild conditioning was able to maintain complete remission in 4 of 9 surviving patients who had been in remission prior to CBT.

In conclusion, CBT is feasible in patients with advanced hematological malignancies and age of over 70, but only a limited number of patients are able to enjoy long durable remission. Since CBT has been introduced to the clinical practice recently, we need to experience more under a clinical study and learn who is suitable for CBT. It can be undertaken not necessarily within a strict protocol study but in a well-designed practice. However, prospective registry of such patients should be considered in the national groups, e.g. the Japan Society for Hematopoietic Cell Transplantation. When it works and any problem arises in CBT cases, then such information can be distributed to the members and subsequently feedback to the problem cases. Then it is believed that the outcome will be gradually improved with some learning curve.

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(和文抄録)

成人造血器悪性疾患62例に対する臍帯血移植成績の後方視的解析

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日本臍帯血ネットワークが1999年に設立されて以来, 九州の血液専門の8施設において成人造血器悪性疾患62例に対して2004年までに67回の臍帯血移植 (CBT) を実施した結果を後方視的に解析した. 原疾患としては白血病34例, 非ホジキンリンパ腫14例, 成人T細胞白血病11例, その他3例で年齢中央値44歳, 移植時の原疾患の状態は非寛解50例であった. 骨髄破壊的移植が27例で残りは骨髄非破壊的なコンディショニング後の移植であった. 生着は早期死亡などのため25例に確認できず, 生存中央値は70日であった. 13例が288～1277日生存し, 49例はすでに死亡していた. 死因としては基礎疾患の進行が19例と最も多く, 感染症, 移植片対宿主病がそれにつづいた. 早期死亡や重篤な感染症の合併が多いが, 進行した非寛解例でも良好な状態に導入できる例があることから, 今後CBTの適応については1例1例検討し, 患者・家族に十分なインフォームドコンセントをとった上で応用していくことが重要であると考えられた.