Mislabeled units of umbilical cord blood detected by a quality assurance program at the transplantation center

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We instituted procedures to check the identity of cord blood unit provided for transplantation by carrying out ABO and human leukocyte antigen (HLA) typing of the thawed units before transplantation. ABO typing is done using standard techniques. Rapid HLA class I serology is with monoclonal antibody trays (One Lambda Inc) using standard incubations. One mislabeled umbilical cord blood (UCB) unit was detected on the day of intended transplantation by repeat ABO typing of the thawed unit at our transplantation center. Because ABO typing will not detect all labeling errors, the rapid serologic class I HLA typing procedure was done on thawed units just before transplantation for all units without an attached segment. This procedure identified a second mislabeled unit. In a 6-year period, 2 of 871 (0.2%) cord blood units sent to us for transplantation were mislabeled and potentially would have been transplanted incorrectly. This error rate of 1 per 249 (0.4%) patients could have potentially devastating consequences. (Blood. 2009; 114:1684-1688)

Introduction

Transplantation of umbilical cord blood (UCB) stem cells for hematopoietic reconstitution is increasing.[1-5] As a result of the promising results with UCB, the US Congress has appropriated funds to substantially increase the number of UCB units collected and stored. UCB banking has now transitioned from research and development[6-10] to a routine operation.[11-20] The emphasis is now on increasing collections at the lowest possible cost to develop large numbers of banked units and to increase the ethnic diversity of the banked units to make transplantations available to more patients. The operation of UCB banks is becoming standardized, partly the result of the American Association of Blood Banks (AABB) and the Foundation for Accreditation of Cellular Therapy (FACT-NETCORD) standards for the collection, testing, processing, and banking of UCB for transplantation.[21,22] The AABB and FACT-NETCORD standards are similar to current Good Manufacturing Practices and Good Tissue Practices promulgated by the Food and Drug Administration (FDA).[23,24] The FDA has also considered the establishment of a regulatory framework for UCB publishing a recent guidance on licensure.[25]

Despite progress with UCB bank standardization, some shortcomings remain. Some banks are not yet accredited; and standards, although vigorous in many ways, leave considerable room for interpretation and variability.[20] Thus, the overall quality of UCB banks throughout the world is not really known. As the largest UCB transplantation center using UCB from multiple banks, we have observed considerable variability in the quality and consistency of UCB that is provided to us for transplantation.[20]

Here we report 2 cases of mislabeled UCB from highly reputable UCB banks (1 in the United States and 1 in Europe) and the effectiveness of ABO and rapid human leukocyte antigen (HLA) typing for verifying unit identity for UCB units without a physically attached segment.

Methods

At the University of Minnesota, all somatic cell and tissue products for hematopoietic transplantation and immunotherapy are prepared in the University of Minnesota Medical Center Clinical Cell Therapy Laboratory. Cellular products, such as UCB obtained from an outside supplier, are received in the Clinical Cell Therapy Laboratory where they are inspected and systematically assessed in preparation for clinical use.

Preparation of UCB units for transplantation

The UCB unit is removed from the liquid nitrogen storage tank manually, the cassette opened, and the UCB bag placed inside an overwrap bag. This overwrap bag containing the UCB unit is placed in a 37°C sterile saline bath during which it is gently kneaded to assist the thawing process. The unit is then washed by adding 10% dextran 5% human serum albumin (HSA) and centrifuging it at 400*g* for 15 minutes at 10°C twice. The unit is then held at room temperature for up to 4 hours until ABO and HLA confirmatory testing is completed. For units shipped to us without an attached segment, ABO and Rh typing, and more recently HLA-A and B typing, are done.

ABO typing

Approximately 1.0 mL red cells is removed after the wash step. A cell pellet is made by centrifugation and resuspended in 0.9% saline for ABO and Rh(D) typing of the red cells. ABO and Rh(D) typing is done using standard techniques and commercial reagents.[19]

HLA typing

HLA type of UCB units is confirmed as part of the quality control measures for UCB for transplantation. Whenever possible, this confirmation typing is performed on DNA recovered from a contiguous attached segment of the cord blood unit (CBU) bag detached before shipment by the source UCB. When confirmatory typing is done from an attached segment at the

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Table 1. ABO and HLA types of patient 1 and involved cord blood units

		HLA class I				HLA class II		
	ABO	A1	A2	B1	B2	DRB1-1	DRB1-2	Match
Patient	0+	03	11	35	51	14	BL	—
Original unit (as ordered)	0+	03	11	35	51	14	0701	5/6
Original unit*	A+	—	—	—	—	—	—	—
Original unit (serologic typing)	A+	01	28	08	52	—	—	0/4
Original unit (molecular typing)	—	01	68	08	52	02	03	0/6
Transplanted unit	—	03XX	11XX	4901	51XX	1401	0301	4/6

— indicates not done.

*These typing results are from the original unit after it was thawed and do not correlate with the type of that unit provided on records from the CBB: TNC recovery, 31% (laboratory average, ~ 60%-80%).

University of Minnesota, DNA is isolated from thawed UCB using QIAamp96 kits (QIAGEN). Confirmatory typing consists of low-resolution HLA-A, -B, -C, -DRB1, 3, 4, 5, and DQB1 typing by rSSO (LABType; One Lambda Inc) followed by high-resolution DRB1, 3, 4, 5; DQB1 typing by PCR-SSP using appropriate allele-specific trays (Invitrogen) selected on the basis of low-resolution type. The procedure is as described by the manufacturer except that DNA when in short supply is diluted to 20 ng/μL.

In cases where confirmatory HLA typing could not be performed on cells derived from an attached segment, the identity of the thawed component was established before infusion by rapid serologic HLA class I typing. For this quality control procedure, HLA typing was performed on immunomagnetically selected T lymphocytes (Dynal Dynabeads CD2 PanT) isolated either from a thawed contiguous segment or from cell residue obtained from dextran-albumin product washes from thawing. HLA class I serology is determined with monoclonal antibody trays (One Lambda Inc) using standard incubations. Close coordination with the cell-processing laboratory staff on anticipated infusion date and expected time of sample arrival ensures prompt availability of HLA results, typically within 3 hours of receipt of the sample.

Case reports

Case 1

A 14-year-old boy with adrenoleukodystrophy underwent allogeneic bone marrow transplantation in November 2001. Unfortunately, the graft was lost in March 2002, and the patient experienced progressive disease. The patient was evaluated for a second transplantation June 2002 and a UCB unit with a 5/6 antigen match was identified (Table 1). The patient was admitted for transplantation July 2002 with the transplantation scheduled for August 5th. The UCB unit arrived with no attached segments at our laboratory on July 24th (transplantation day 12), and the preparative regimen was begun on July 27th (transplantation day 9).

On the day of transplantation, as part of our usual quality control program, we carried out ABO/Rh(D) typing of the thawed UCB unit. The blood from the thawed unit typed as A^+, but records received with that unit indicated that the type was O^+ (Table 1). In addition, the cell recovery (calculation based on the number of cells specified in the accompanying records) was 31%, considerably less than the usual recovery in our laboratory. These 2 findings prompted us to obtain rapid serologic class I HLA typing. After confirming that the unit was mislabeled (Table 1), a second unit was secured. The new UCB unit successfully engrafted at 15 days. Subsequent investigation established that the labels had been incorrectly placed on 2 UCB units and their nonintegrally attached samples at the time of processing.[26]

Case 2

The patient was a 51-year-old woman with acute myelogenous leukemia who was to undergo an UCB using 2 partially HLA-matched units. The ABO, Rh(D), and HLA type of the patient and the 2 units selected for transplantation are shown in Table 2. Confirmatory typing was performed on segments provided by the UCB bank and the results verified the HLA match as originally listed. However, because one of the units did not have an integrally attached segment, rapid ABO and serologic HLA typing were performed at the time the unit was thawed. The ABO and Rh type matched that of the records for both units (Table 2). The results of the HLA testing, however, were different from those expected based on the original and confirmatory HLA typing, which were not done on attached segments. The unit was not transfused and the transplantation was carried out using a different second unit (Table 2). Engraftment occurred on day 30 and the patient continues to do well.

Results

Assessment of red cell and rapid HLA typing screening program

Between January 1, 2002 and December 31, 2007, a total of 871 CBU were received for transplantation to 499 patients. Using the ABO, Rh, and HLA typing methods described, 2 units (0.23%) were found to be mislabeled. The first mislabeled unit was detected

Table 2. HLA types of patient 2 and involved cord blood units

	ABO and Rh	A	B	C	DRB1	DQB1	Match
Patient	A positive	0201, 3001	4901, 5101	0701, 1402	0404, 1501	0302, 0602	—
Unit 1 from bank	A positive	0201, 3002	0702, 5101	0702, 1502	0404, 1501	0302, 0602	4/6
Unit 2 from bank	A positive	0201, 1101	4001, 5101	0304, 1402	0404, 1501	0302, 0602	4/6
Unit 2 transplantation day	A positive	2*, 29*	51*, 44*	—	13†, 14†	05†, 06†	2/6
Substitute for unit 2	O positive	0206, 3001	4201, 5101	1502, 1701	0302, 0404	0302, 0402	4/6

— indicates not applicable.

*Rapid serologic test results.

†Follow-up molecular typing.

by ABO and Rh typing, but this would be expected to detect only a portion of the random population. Thus, the rapid HLA serologic typing was added and that method identified the second mislabeled unit, although it would not be expected to detect all labeling errors.

CBU for transplantation are thawed and washed twice with dextran/HSA in our clinical Cell Therapy Laboratory, and so samples are available for the red cell and HLA typing. There have been no problems recovering an adequate sample of either red cells or DNA from residue in thawed units. During the first 10 months of 2008, rapid HLA typing was required because of the absence of an integral attached segment for 47 of 133 (35%) UCB units scheduled for transplantation. One of those 47 was found to be incorrect.

The wash procedure reduces the dimethyl sulfoxide to approximately 5% of initial levels; thus, the thawed cells can be stored for several hours before transplantation.[27-29] Results of the HLA typing are available within 3 hours, and there is no indication that this brief interval between thawing and transplantation has interfered with engraftment.

UCB bank responses to unit/segment mislabeling

Follow-up with the UCB that provided the first mislabeled unit revealed that several units of cord blood were processed at the same time on the same laboratory bench. In the process, the specimens and cord blood bag labels were mixed up between 2 different donations, thus leading to HLA typing results being attributed to the wrong CBU. As a result, this bank changed their operating procedures to prevent multiple CBU from being processed at the same time on the same laboratory bench or hood. Because the samples had been mislabeled at the time of the original processing and because there were no attached segments, the confirmatory typing did not detect the labeling error.

The second labeling error occurred during the original HLA typing of the unit in the laboratory providing the HLA typing for the cord blood bank (CBB). Samples from the UCB units prepared for HLA typing were labeled at the CBB with the same identifier as the bag but were then relabeled for HLA typing. Usually, this relabeling was done in the UCB bank; however, on that day, the relabeling was done in the HLA laboratory. Two UCB units were processed the same day, and the samples for HLA typing were reversed between the 2 units when they were relabeled in the HLA laboratory. As a result of this error, the process of relabeling in the HLA laboratory was discontinued.

Discussion

For marrow and blood stem cell transplantations, blood samples for testing are obtained directly from the donors or the stem cell product, but this direct testing of cord blood is not standard. These cases illustrate the need for comprehensive and stringent quality assurance programs for UCB banks and transplantation centers. Mislabeling can occur and is a potentially disastrous situation. In the receipt of 871 units of UCB in 6 years, we have identified 2 (0.2%) units that were mislabeled, and 2 of 499 (0.4%) of our patients would have received the incorrect CBU if not for this quality assurance program. In the white population, the chance of 2 persons having the same ABO and Rh type is 28% and HLA-A and B serologic type is less than 5%. Thus, the typing approach we have used could be expected to identify virtually all mislabeled units (72% ABO/Rh and $>$ 95% HLA-A and -B).

Because most transplantation centers do not carry out the quality control testing we describe here, it seems possible that other mislabeled UCB units may have been transplanted without ever being detected. The first case of mislabeling occurred because of processing multiple units simultaneously in the same workspace, whereas the second illustrates the need for attention to detail when labeling specimens. Our experiences also illustrate the importance of having a quality control program at the transplantation center to ensure that the UCB being transplanted is that which is reported on the associated records. This has implications for both the patient and the UCB.

Patient consequences

Of course, the worst consequence for a patient would be failure of engraftment from a mislabeled unit. First, it may be difficult to locate an alternative CBU or the alternate may have a less desirable cell content or HLA match. For instance, for patient 2, one unfortunate result of this labeling error was that the dose of cells given was less than planned. The dose expected in the unit originally selected was 5.3×10^7 nucleated cells (NC)/kg, but the replacement unit contained 3.7×10^7 NC/kg. HLA matching and cell dose are very important in successful UCB,[30,31] and so errors that necessitate rapid decisions, leading to compromises in these UCB characteristics, jeopardize patient care. In addition, there is an increased cost because of rapid HLA typing and for identifying backup CBU. The HLA typing delays the transplantation, but we have no evidence that this has interfered with engraftment. A thorough study of storage of these cells for up to 8 hours has recently been initiated under the sponsorship of the National Marrow Donor Program.

Bank consequences

Receipt of a mislabeled unit creates mistrust about the CBB by the transplantation center and may lead to decreased use of that CBB. At the least, the transplantation center may wish to conduct some kind of external audit of the CBB.

The FDA has recently published a guidance for licensure of UCB.[24] We previously reported that 151 (56%) of 268 units of UCB shipped to us for transplantation during a 3-year period, 151 (56%) had one or more issues potentially related to quality that required evaluation before a final decision regarding their suitability for use.[20] We think that approximately 10% of these issues probably affected the quality of the unit, although none of our patients was adversely affected by these quality failures. These were primarily the result of quality control issues, such as transmissible disease test results, potential bacterial contamination, storage conditions during shipping, and processing methods. However, approximately 6% were related to record keeping, which was the major problem that led to our receipt of 2 mislabeled units. Thus, despite quality programs for UCB promulgated by the AABB and FACT-NETCORD, there is considerable variation in how banks select, process, and control the quality of units they place into the bank. Some UCB units in inventories available for patients do not meet current AABB/FACT-NETCORD standards. Some standards are not specific, and there is a lack of consensus about several issues related to quality. Communication between banks and transplantation centers often is not sufficiently timely or effective to allow effective decision-making regarding the suitability of a specific CBU for a specific patient.

Because of the issues we have observed, including 2 potentially disastrous labeling errors, we urge that a major study be initiated to determine the accuracy of data and quality of the existing cord

blood inventory. This information could also help to harmonize the standards of the AABB and FACT-NETCORD because each set of standards may have certain strengths.

Considerable variation can also occur even when banks follow applicable standards and quality control programs, because there are some differences between standards (AABB and FACT-NETCORD), many standards are not specific, standards have changed over time, and each bank may decide to place individual units into their useable inventory despite failure to meet that bank's own criteria.

As a result of this experience, we have the following proposals:

UCB banks. Banks should become accredited and adhere to standards and pertinent regulations. During processing of UCB, there should be segregation of units so that one product is prepared at a time. Bar code labels should be used, and labeling should be done according to strict standard operating procedures one unit at a time. Clear and complete communication with the transplantation center is important. Information about the CBU should be complete and provided well in advance of the transplantation.

UCB bag manufacturers. UCB containers should be manufactured with enough attached tubing to allow several segments to be prepared and to remain attached to the bag. The configuration should be such that the bags with the attached segments can be placed and stored in the cassette for freezing and preservation. Tubing should be manufactured such that, when segments are prepared, they will be prenumbered.

Transplantation centers. Effective communication with the UCB bank is essential. When a unit is tentatively selected for transplantation, the transplantation center should verify that confirmatory HLA typing has been or is being done on an attached segment. If not, the transplantation center should specify that HLA confirmatory testing be done on an attached segment. If there is no attached segment, an alternative or back-up UCB should be selected and available at the transplantation center within 24 hours. Arrangements should be made to carry out ABO and Rh typing and rapid serologic HLA typing of the thawed CBU to assure the accuracy of the HLA type of the CBU.

HLA typing technology is shifting to the use of DNA methods, and many typing laboratories no longer use serologic methods. The HLA laboratories supporting cord blood transplantation programs should be urged to retain the ability to do the simple screening serology for A and B locus testing until the quality and accuracy of test results of CBU that lack attached segments can be assured.

Red cell antigen typing is more simple and readily available, but typing of CBU for red cell antigens other than ABO and Rh(D) is not done. Thus, a more extensive red cell antigen typing battery cannot be used to confirm the identity of CBU.

Two other factors may affect the ability to do rapid HLA serologic typing. The first is that thawing the CBU at the patient's bedside and immediate transplantation do not allow for specimen collection or the time to carry out the testing. The second is that some centers are replacing washing the thawed CBU with a dextran albumin dilution step. With dilution, the dimethyl sulfoxide cryopreservative is not removed, and it is possible that the stem cells might be damaged while HLA typing is being done. We think that a rate of one mislabeled CBU per 299 patients is a sufficiently important problem to warrant continuing ABO, Rh, and HLA typing of thawed CBU before transplantation. Following these recommendations will minimize the chance of error in UCB banking and thus provide the best chance of an accurate HLA match between donor and patient.

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Authorship

Contribution: J.M. designed the project, analyzed data, and wrote the manuscript; D. McKenna designed the project, analyzed data, and contributed to the manuscript; D.K. supervised collection of data and provided input on manuscript and review drafts; D. Maurer supervised HLA typing, provided data, and contributed to the manuscript; H.J.N. supervised collection of data and contributed to the manuscript; K.F. managed the cord blood unit selection process, communicated with cord blood banks, sought substitute cord blood units, contributed information for the manuscript, reviewed drafts of the manuscript, and provided suggestions; C.B. cared for patients, made transplantation decisions, approved selection of units for transplantation, provided clinical data, and contributed to the writing of the manuscript; and J.E.W. provided overall supervision of cord blood unit selection, transplantation process, and strategy in response to erroneous labeled unit, suggested data to be obtained, and contributed to the writing of the manuscript.

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