Donor Cell-Derived Leukemias/Myelodysplastic Neoplasms in Allogeneic Hematopoietic Stem Cell Transplant Recipients

A Clinicopathologic Study of 10 Cases and a Comprehensive Review of the Literature

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Abstract

We report 10 cases of donor cell leukemia (DCL). All cases except the case of chronic lymphocytic leukemia had anemia, neutropenia, and/or thrombocytopenia when DCL was diagnosed. Eight cases with sex-mismatched hematopoietic stem cell transplant (HCT) showed donor gonosomal complements, suggesting DCL. Clonal cytogenetic abnormalities were detected in 8 cases: 6 were monosomy 7/del(7q). In all 10 cases, engraftment studies confirmed donor cell origin. Retrospective fluorescence in situ hybridization in archived donor cells in 4 cases showed a low level of abnormalities in 2. Of 7 patients with clinical follow-up of 5 months or more, 1 (with acute myeloid leukemia) died of disease; 6 are alive, including 1 with myelodysplastic syndrome with spontaneous remission. Similar to reported cases, we found disproportional sex-mismatched HCTs, suggesting probable underdetection of DCL in sex-matched HCTs. The latency between HCT and DCL ranged from 1 to 193 months (median, 24 months), in keeping with the literature. Analyzing our cases, pooled with reported cases, with survival models showed much shorter latency for malignancy as primary disease, for T-cell large granular lymphocyte leukemia as type of DCL, and for umbilical cord blood as stem cell source.

Allogeneic bone marrow (BM) or hematopoietic stem cell (HSC) transplantation is a main treatment modality for curing some hematologic diseases. The treatment has been applied mainly to acute leukemia and myelodysplastic syndrome (MDS) for the past 2 decades, although a few other hematologic disorders have also been treated with allogeneic BM/HSC transplantation. Posttransplantation relapse of leukemia is frequently seen with varied incidence depending on the type of primary neoplasm. For example, relapse in transplant recipients for acute myeloid leukemia (AML)/MDS occurs in at least 33% of the cases.1,2 Some cases demonstrate progression of disease, and occasional cases develop host cell–derived therapy-related secondary acute leukemia or MDS resulting from a complication of pretransplantation chemotherapy and/or conditioning treatment.3,4 In rare cases, secondary leukemia/MDS is derived from donor cells, thus being designated donor cell leukemia (DCL).5-6 First described in 1971 by Fialkow et al,34 DCL has been reported mostly as case reports. While a few case series have been published and possible mechanisms have been postulated, the clinicopathologic features of DCL have not been well characterized, and the underlying pathogenesis remains unknown since its first description. We analyzed 10 cases of DCL and performed a comprehensive literature review to study the clinicopathologic features of this rare clinical entity.

Materials and Methods

Case Selection

We identified 10 cases of DCL from our BM biopsy database using the search phrases “donor cell leukemia,” “donor cell origin,” and “donor cell–derived.” These included 4 cases from
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Duke University Medical Center, Durham, NC (totally 841 allogeneic HSC transplantsations since 1995), 2 cases from the University of California at San Francisco (731 allogeneic HSC transplants since mid 1986), and 4 cases from the City of Hope National Medical Center, Duarte, CA (4,028 allogeneic HSC transplants since 1975). The diagnoses of secondary leukemia or MDS were confirmed according to the 2008 World Health Organization classification. The primary diagnosis, transplant history, treatment for secondary leukemia/MDS, and other clinical data were obtained from corresponding clinical notes.

Cytomorphologic and Histologic Evaluation

Peripheral blood smears were stained with Wright stain, BM aspirate smears and biopsy touch imprints were stained with Wright-Giemsa, and BM core biopsy specimens and clot sections were stained with H&E. The cases were reviewed independently by 3 hematopathologists (E.W., Q.H., and C.M.L.). Morphologic dysplasia and blast count were evaluated on peripheral blood smears and aspirate smears. BM cellularity was evaluated on core biopsy specimens or on clot sections in cases in which the biopsy quality was suboptimal. The presence of dysplastic changes in the erythroid, granulocytic, and megakaryocytic lineages was determined according to the description in the 2008 World Health Organization classification. BM cellularity was defined as hypercellular when it was more than 1 SD above the age-adjusted mean, as hypocellular when lower than 1 SD, and as normocellular when within 1 SD.

Flow Cytometric Analysis

Flow cytometric immunophenotyping was performed on fresh tissue specimens collected in RPMI 1640 culture medium. Specimens were processed routinely to generate single-cell suspensions, which were then stained with pre-mixed 4-fluorochrome–conjugated antibodies (fluorescein isothiocyanate, phycoerythrin, peridinin chlorophyll protein, and allophycocyanin) per the leukemia/lymphoma panel protocol routinely used in our flow cytometry laboratories. The antibodies in the panel include those against leukocyte common antigen (CD45), B-cell antigens (CD19, CD20, CD22, and κ and λ light chains), T-cell antigens (CD2, CD3, CD4, CD5, CD7, and CD8), myeloid antigens (CD11c, CD13, CD14, CD15, CD33, and CD117), stem cell antigens (CD34 and CD123), and CD10, CD16, CD25, CD38, CD56, CD103, and HLA-DR (Becton Dickinson Biosciences, San Diego, CA). Approximately 10,000 events per tube were acquired on a flow cytometer (dual-laser FACSCalibur, Becton Dickinson Biosciences) and analyzed using the CellQuest computer software program (Becton Dickinson Biosciences).

Conventional Cytogenetic Studies

Cytogenetic analysis was performed on 2 to 4 mL of BM aspirate from each case. Two cultures from each specimen were initiated from the fresh, anticoagulated specimen in complete tissue culture medium. For all but the sample from chronic lymphocytic leukemia (CLL; case 10), the cells were incubated for 24 and 48 hours without mitogen stimulation. For the CLL sample, B-cell stimulated and unstimulated cultures were initiated and examined. Chromosome preparations, including harvesting and GTW banding, were made using standard methods. Cytogenetic abnormalities were classified according to the International System for Human Cytogenetic Nomenclature.

Interphase Fluorescence In Situ Hybridization

For Detecting MLL Rearrangement

An interphase fluorescence in situ hybridization (FISH) analysis was performed on the air-dried slides of aspirate smear using the Vysis (Abbott Molecular, Downers Grove, IL) dual-color, break-apart rearrangement probe specific for the MLL locus (11q23). This probe detects chromosomal separation within the MLL locus associated with translocations involving a variety of other loci. For the analysis, 200 interphase nuclei were examined by 2 different technologists, and the percentage of positive cells was reported.

For Detecting BCR/ABL1

An interphase FISH analysis was performed using the Vysis dual-color dual-fusion BCR/ABL1 translocation probe. This probe is designed to detect the juxtaposition of the BCR locus and ABL1 gene sequences. The translocation involving BCR at 22q11.2 and ABL1 at 9q34, t(9;22)(q34;q11.2), is visible by fusion of the red probe and green probe. In total, 200 interphase nuclei were evaluated by 2 different technologists, and the percentage of positive cells was reported.

For Detecting Monosomy 7 or Interstitial Deletion of the Long Arm of Chromosome 7

FISH analysis was performed using the dual-color Vysis probe specific for the chromosome 7 centromere (CEP 7) and a locus on the long arm (LSI D7S486) at band 7q31. The LSI D7S486 probe was used to identify interstitial deletions, and the CEP 7 (centromeric) probe serves to determine the number of copies of chromosome 7. A total of 200 interphase nuclei per probe set were examined, and the percentage of cells with a single copy of chromosome 7 or interstitial deletion of the long arm of chromosome 7 was calculated.

For Detecting Interstitial Deletion of the Long Arm of Chromosome 5

FISH analysis was performed using the dual-color Vysis probe specific for chromosome 5 at a locus on the short arm (LSI DD5S23/DD5S721) at band 5p15.2 and on the long arm (EGR1) at band 5q31. The EGR1 probe was used to identify interstitial deletions, and the LSI DD5S23/DD5S721 probe
serves to determine the number of copies of chromosome 5. A total of 200 interphase nuclei per probe set were examined, and the percentage of cells with 5q deletion was calculated.

For Detecting Interstitial Deletion of the Long Arm of Chromosome 20

FISH analysis was performed using the dual-color Vysis probe specific for the chromosome 20 centromere (CEP 20) and a locus on the long arm (LSI D20S108) at band 20q12. The LSI D20S108 probe was used to identify interstitial deletions, and the CEP 20 (centromeric) probe serves to determine the number of copies of chromosome 20. A total of 200 interphase nuclei per probe set were examined, and the percentage of cells with deletion of 20q was calculated.

For Detecting Sex Chromosomes

The description for detecting sex chromosomes is given in the next section, “BM engraftment studies.”

BM Engraftment Studies

Donor engraftment was determined by 2 methods. FISH analysis was used to detect donor gonosomal complement if the recipient and donor had sex chromosomes mismatched. Alternatively, polymerase chain reaction (PCR)-based analysis of autosomal and gonosomal short tandem repeats (STRs) was applied to assess donor/recipient genomic chimerism, particularly in cases of sex-matched transplantation.

FISH Analysis of Sex Chromosomes

A dual-color interphase FISH analysis was performed using the X centromere (CEP X) and Y centromere (CEP Y) probe set (Vysis) to detect the number of male (XY) donor or recipient cells and/or female (XX) donor or recipient cells present in a patient BM specimen. A total of 200 to 500 interphase nuclei were evaluated by 2 different technologists, and the percentage of nuclei with a donor’s gonosomal complement was calculated.

STR Analysis

Highly purified genomic DNA was extracted from the pretransplantation, donor, and posttransplantation samples following routine laboratory methods. For positive selection of lymphocytes or granulocytes from posttransplantation samples, magnetically labeled antihuman CD3 or CD15 antibodies (isotype, mouse IgG1 and IgM \(\kappa\), respectively) and the RoboSep automated cell separator (StemCell Technologies, Vancouver, Canada) were used. The extracted sample genomic DNA was subjected to multiplexed PCR-mediated amplification targeting a total of 15 autosomal STR markers and 1 STR marker on the pseudo-autosomal region of the X and Y chromosomes (PowerPlex 16 System, Promega, Madison, WI). Following PCR amplification, the fluorescently labeled PCR products were resolved by capillary electrophoresis on the ABI 3130xl Genetic Analyzer and analyzed by GeneMapper software (Applied Biosystems, Foster City, CA) to resolve the number of repeats and relative abundance of each repeat for each STR locus. These data were then used to calculate the percentage of donor and/or recipient cells in the posttransplantation sample using the donor and pretransplantation recipient STR profiles.

Literature Review

The cases of DCL reported in the literature were identified by a search in PubMed using the key words “donor cell leukemia,” “donor cell origin,” and “donor cell–derived” present in title words. We identified 74 cases in the English literature.5-65

Statistical Analysis

The statistical analyses were performed with SAS, version 9 (SAS Institute, Cary, NC). The Student t test, Wilcoxon-Mann-Whitney test, and Kaplan-Meier survival analysis were used to test the statistical significance in differences between the groups. The latency of each stratified group was analyzed using the Kaplan-Meier survival model and measured from the day of hematopoietic stem cell transplantation until the diagnosis of DCL.

Results

Table 1, Table 2, and Table 3 summarize the clinicopathologic features in 10 cases of donor cell–derived leukemia/MDS. Case 1 has been previously reported.70

Clinical Information

In a total of 10 cases of DCL, 6 patients were male and 4 were female. Ages at diagnosis of secondary DCL ranged from 3 to 70 years, with a median of 54 years. The patients received allogeneic BM/stem cell transplants (HCTs) between 1991 and 2009. Regarding primary diseases, 3 patients were treated with HCT for chronic myelogenous leukemia, 2 for AML, 2 for therapy-related MDS, 2 for B-lymphoblastic leukemia/lymphoma, and 1 for advanced stage of mantle cell lymphoma.

Pretransplantation conditioning included myeloablative treatment in 8 cases and nonmyeloablative treatment in the remaining 2 cases. Among the donors, 6 were males and 4 were females. Of 10 cases, 8 (80%) received transplants from donors of the opposite sex, including 4 male recipients with female donors and 4 female recipients with male donors. Only 2 patients received transplants with sex-matched HSC donation (cases 3 and 5). Of note, 5 recipients received allogeneic transplantation from blood-related donors, whereas donors for the other 5 were unrelated, including all 3 umbilical cord blood transplants. Sources of donation included BM in 4 cases, mobilized peripheral blood HSCs (BHSCs) in 3 cases,
### Table 1
Clinicopathologic Features of Primary Diseases and Transplant Information in 10 Cases of Donor Cell–Derived Leukemia/Myelodysplastic Neoplasms

<table>
<thead>
<tr>
<th>Case No./ Sex/Age (y)</th>
<th>Primary Disease</th>
<th>Primary Cytogenetics</th>
<th>HCT Year</th>
<th>Condition</th>
<th>Donor*</th>
<th>Sources</th>
<th>GVHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/3†</td>
<td>AML-M5a</td>
<td>46,XX(t11;19)(q23;p13.3)</td>
<td>2006</td>
<td>MA</td>
<td>M, U</td>
<td>UBC</td>
<td>–</td>
</tr>
<tr>
<td>2/M/58</td>
<td>CML</td>
<td>46,XY(t9;22)(q34;q11.2)</td>
<td>1994</td>
<td>MA</td>
<td>F, U</td>
<td>BHSC</td>
<td>ND</td>
</tr>
<tr>
<td>3/M/53</td>
<td>ALCL–t-MDS</td>
<td>46,XY</td>
<td>2003</td>
<td>NMA</td>
<td>M, S</td>
<td>BHSC</td>
<td>–</td>
</tr>
<tr>
<td>4/M/58</td>
<td>Blastoid MCL</td>
<td>46,XY(t11;14)(q13;p32)</td>
<td>2008</td>
<td>MA</td>
<td>F, S</td>
<td>BHSC</td>
<td>ND</td>
</tr>
<tr>
<td>5/M/55</td>
<td>CLL–t-MDS</td>
<td>45,XY,–7//46,XY(9.5% –7 by FISH)</td>
<td>2007</td>
<td>MA</td>
<td>M, U</td>
<td>UBC</td>
<td>–</td>
</tr>
<tr>
<td>6/F/66</td>
<td>CML</td>
<td>46,XX(t9;22)(q34;q11.2)</td>
<td>1995</td>
<td>MA</td>
<td>M, S</td>
<td>BM</td>
<td>+</td>
</tr>
<tr>
<td>7/M/44</td>
<td>B-ALL</td>
<td>46,XY(t17;19)</td>
<td>2007</td>
<td>MA</td>
<td>F, M</td>
<td>BM</td>
<td>+</td>
</tr>
<tr>
<td>8/F/22</td>
<td>45–49,XY,add(12p),del(13q),i(17q),+21,others</td>
<td>2009</td>
<td>MA</td>
<td>M, U</td>
<td>UCB</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>9/M/70</td>
<td>AML/MD5</td>
<td>46,XY,inv(7)(q22q34)</td>
<td>2009</td>
<td>NMA</td>
<td>F, S</td>
<td>BM</td>
<td>–</td>
</tr>
<tr>
<td>10/F/19</td>
<td>CML</td>
<td>46,XX(t9;22)(q34.1;q11.2)</td>
<td>1991</td>
<td>MA</td>
<td>M, U</td>
<td>BM</td>
<td>–</td>
</tr>
</tbody>
</table>

ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; AML/MD5, AML arising from MDS; B-ALL, B-lymphoblastic leukemia/lymphoma; BHSC, blood hematopoietic stem cells; BM, bone marrow; CML, chronic myelogenous leukemia; GVHD, graft-vs-host disease; HCT, hematopoietic stem cell transplantation; MA, myeloablative conditioning; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; ND, not done; NMA, nonmyeloablative conditioning; t-MDS, therapy-related MDS; UBC, umbilical cord blood; –, present; -, absent.

* Donor data are given as sex (M or F) followed by maternal (M), sibling (S), or unrelated (U).
† The case has been previously reported.70

### Table 2
Clinicopathologic Features of the Secondary Neoplasms in 10 Cases of Donor Cell–Derived Leukemia/Myelodysplastic Neoplasms

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Interval (mo)</th>
<th>Secondary Neoplasm</th>
<th>CBC*</th>
<th>Blood/Marrow Biopsy</th>
<th>Phenotype</th>
<th>Cytogenetics</th>
<th>FISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.5</td>
<td>AML</td>
<td>7.3/11/2.4/45</td>
<td>Blasts in blood, 5%; marrow, 25%-30% blasts, mild/moderate dysplasia</td>
<td>CD13/CD33/CD117/CD34/HLA-DR/CD7/CD4</td>
<td>45,XY,–7//46,XY(18)</td>
<td>–7 in 81.5% of cells; no rearranged MLL (11q23)</td>
</tr>
<tr>
<td>2</td>
<td>193</td>
<td>AML</td>
<td>11.2/101/0.25/84</td>
<td>Blasts in blood, 21%; marrow, 60%-70% blasts, mild dysplasia</td>
<td>CD45/CD13/CD34/CD117/HLA-DR/partial CD33/CD4</td>
<td>46,XX(30)</td>
<td>No BCR/ABL1</td>
</tr>
<tr>
<td>3</td>
<td>82</td>
<td>MDS-RCMD</td>
<td>9.5/100/0.9/126</td>
<td>Hypercellular marrow, moderate/marked dysplasia, 4% blasts</td>
<td>No increased blasts</td>
<td>46,XX(del20)(q11.2q13.1)(8)/46,XX(12)</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>MDS-U</td>
<td>13/102/3.9/94</td>
<td>Mildly hypocellular marrow; no significant dysplasia</td>
<td>No increased blasts</td>
<td>46,XX(del20)(q11.2q13.1)(8)/46,XX(12)</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>MDS-U</td>
<td>10.3/103/3.2/26</td>
<td>Normocellular; no dysplasia; no increased blasts</td>
<td>No increased blasts</td>
<td>ND</td>
<td>–7 in 68% of cells</td>
</tr>
<tr>
<td>6</td>
<td>166</td>
<td>MDS-U</td>
<td>13.3/107/0.5/107</td>
<td>Normocellular marrow; no significant dysplasia; no increased blasts</td>
<td>No increased blasts</td>
<td>45,XY,–7//46,XY(19)</td>
<td>–7 in 55.5% of cells; no BCR/ABL1</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>MDS-RA</td>
<td>10/107/4/157</td>
<td>Hypocellular, erythroid hyperplasia; no dysplasia; no increased blasts</td>
<td>No increased blasts</td>
<td>46,XX(del7)(q22q22)(2)/46,XX(27)</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>MDS-U</td>
<td>9.5/103/1.2/105</td>
<td>Hypocellular; erythroid hyperplasia; no dysplasia or increased blasts</td>
<td>No increased blasts</td>
<td>45,XY,–7//46,XY(13)</td>
<td>–7 in 42.5%-60.4% of cells; no previous abnormalities (+12, +17, +21)</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>MDS-RA</td>
<td>8.2/97/6/206</td>
<td>Hypocellular; erythroid hyperplasia; no dysplasia or increased blasts</td>
<td>No increased blasts</td>
<td>46,XX(del5)(q13q31)(4)/46,XX(15)</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>166</td>
<td>CLL/SLL</td>
<td>13.4/93/19/209</td>
<td>Lymphocytosis with small round lymphocytes with clumped chromatin</td>
<td>CD19/CD20/CD5/CD23/CD19 light chain</td>
<td>46,XY(del20)(q11.2q13.1)(1)</td>
<td>del(20q) in 7.4% of cells; no BCR/ABL1, +12, +11q, +13q, to –17p</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndrome; MDS-RA, MDS-refractory anemia; MDS-RCMD, MDS-refractory cytopenia with multilineage dysplasia; MDS-U, myelodysplastic syndrome, unclassifiable.
* Values represent hemoglobin/mean corpuscular volume (MCV)/neutrophil/platelets. Values for hemoglobin, MCV, and platelets are given in conventional units (g/dL, μm3, and x 103/μL, respectively); conversions to Système International (SI) units are as follows: hemoglobin (g/L), multiply by 10; MCV (fL), multiply by 1; and platelets (× 109/L), multiply by 1. Neutrophil values are given in SI units (× 109/L); to convert to conventional units (/μL), divide by 0.001.
of MDS, BM hypercellularity was noted in 1 case of refractory cytopenia with multilineage dysplasia, 2 cases demonstrating monosomy 7 in 68% of the interphase nuclei on FISH analysis performed, but instead had FISH analysis demonstrating approximately 54% of the total lymphoid population. Case 10, flow cytometric analysis of the peripheral blood specimen demonstrated a monoclonal B-cell population (CD19+/CD22+/partial CD20+), which constituted approximately 54% of the total lymphoid population. Among these 8 cases with clonal cytogenetic abnormalities, 7 demonstrated clonal cytogenetic abnormalities with 2 to 19 metaphase cells displaying karyotypic abnormalities, whereas 1 case showed a normal female karyotype (donor’s; case 2) and 1 case showed a normal male karyotype with nonclonal change of chromosome 20 in 1 metaphase cell (case 10). Case 5 did not have karyotype analysis performed, but instead had FISH analysis demonstrating monosomy 7 in 68% of the interphase nuclei on an aspirate smear. Among these 8 cases with clonal cytogenetic abnormalities, monosomy 7 was seen in 5 cases (cases 1, 3, 5, 6, and 8), interstitial deletion of the long arm of chromosome 7 in 1 case (case 7), interstitial deletion of the long arm of chromosome 5 in 1 case (case 9), and interstitial deletion of the long arm of chromosome 20 in 1 case (case 4). In addition to case 5, FISH was also performed on DCL cells in 6 other cases. These tests confirmed monosomy 7 in 4 cases (cases 1, 3, 6, and 8).

**Engraftment Studies, Donor Cell Evaluation, Treatment, and Follow-up Data for 10 Cases of Donor Cell–Derived Leukemia/Myelodysplastic Neoplasms**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Engraftment</th>
<th>Donor Cell Evaluation</th>
<th>Treatment</th>
<th>Follow-up (mo)/Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Donor (STR)</td>
<td>No –7 by FISH; interval normal male karyotype [2]</td>
<td>FLAG-IDA</td>
<td>11/DOD</td>
</tr>
<tr>
<td>2</td>
<td>Donor (FISH)</td>
<td>ND</td>
<td>Induction</td>
<td>1/AWD</td>
</tr>
<tr>
<td>3</td>
<td>Donor (STR)</td>
<td>ND; interval normal male karyotype [4]</td>
<td>Gemtuzumab ozogamicin, DLI</td>
<td>5/AWD</td>
</tr>
<tr>
<td>4</td>
<td>Donor (FISH)</td>
<td>ND</td>
<td>ND</td>
<td>2/AWD</td>
</tr>
<tr>
<td>5</td>
<td>Donor (STR)</td>
<td>ND</td>
<td>No</td>
<td>28–7 in 3% of cells in 6 mo, negative in 18 mo</td>
</tr>
<tr>
<td>6</td>
<td>Donor (FISH)</td>
<td>del(7q) in 1.8%-4% of cells; interval normal female karyotype [4]</td>
<td>DLI</td>
<td>6/AWD</td>
</tr>
<tr>
<td>7</td>
<td>Donor (FISH)</td>
<td>del(5q) in 1.8%-4% of cells; interval normal male karyotype [1]</td>
<td>Transfusion; observe</td>
<td>1/AWD</td>
</tr>
<tr>
<td>8</td>
<td>Donor (FISH)</td>
<td>No –7 by FISH; interval normal male karyotype [1]</td>
<td>Transfusion; observe</td>
<td>9/AWD</td>
</tr>
<tr>
<td>9</td>
<td>Donor (FISH)</td>
<td>del(5q) in 6.3%-10% of cells</td>
<td>Lenalidomide [6]</td>
<td>8/AWD</td>
</tr>
<tr>
<td>10</td>
<td>Donor (FISH)</td>
<td>ND</td>
<td>Observe</td>
<td>6B/AWD</td>
</tr>
</tbody>
</table>

* AWD, alive with disease; DLI, donor lymphocyte infusion; DOD, died of disease; FISH, fluorescence in situ hybridization; FLAG-IDA, fludarabine, cytarabine, idarubicin, and granulocyte colony-stimulating factor; ND, not done; STR, short tandem repeat.

* Numbers in bracket “[1]” indicate frequencies.

and umbilical cord blood (UCB) in 3 cases. Secondary donor cell–derived leukemias included 2 cases of AML (20%), 7 cases of MDS (70%), and 1 case (10%) of CLL. The interval between transplantation and diagnosis of DCL ranged from 1 to 193 months, with a median of 24 months (mean ± SD, 68.2 ± 77.5 months). All cases except for the case of CLL had anemia, neutropenia, and/or thrombocytopenia, when the diagnosis of DCL was established.

**Cytomorphologic and Histologic Evaluation**

Both cases of donor cell–derived AML had circulating blasts in the peripheral blood smear, accounting for 6% and 21% of total leukocytes, respectively. Both cases demonstrated mild to moderate dysplasia, in addition to more than 20% of blasts fulfilling the diagnosis of acute leukemia in BM aspirate examination. The 7 cases of MDS included 1 case of refractory cytopenia with multilineage dysplasia, 2 cases of refractory anemia, and 4 cases of MDS, unclassifiable. Of 7 MDS cases, BM hypercellularity was noted in 1 case (case 3) showing normal cellularity in 2 cases, and hypocellularity in 4 cases; dysplasia was observed only in 1 case (case 3; Image 1B), while the other 6 cases did not display significant morphologic dysplasia. Of note, case 3 was the only case demonstrating morphologic features suggestive of myelodysplasia, including hyperplastic BM, morphologic dysplasia, and a marginal increase in blasts (3%-4%). Of 7 MDS cases, 6 did not show morphologic evidence of a myelodysplastic neoplasm. Case 10 showed moderate to marked lymphocytosis in the peripheral blood smear and BM infiltration by small, mature-appearing lymphocytes.

**Flow Cytometric Analysis**

Both cases of AML (cases 1 and 2) demonstrated increased blasts with a myeloid immunophenotype in BM samples. Case 3 showed 3% to 4% myeloblasts in the BM sample, whereas no evidence of increased blasts was noted in cases 4 through 9. In case 10, flow cytometric analysis of the peripheral blood specimen demonstrated a monoclonal B-cell population (CD19+/CD22+/partial CD20+), which constituted approximately 54% of the total lymphoid population. This abnormal B-cell population was restricted to a λ light-chain isotype and aberrantly expressed CD5. CD23 was partially expressed in monoclonal B cells.

**Cytogenetic and Molecular Cytogenetic Studies**

Conventional cytogenetic analyses were performed on BM specimens from 9 cases of DCL. Of these, 8 cases with sex-mismatched HCTs showed donors’ gonosomal karyotype. Among these 8 cases, 7 demonstrated clonal cytogenetic abnormalities with 2 to 19 metaphase cells displaying karyotypic abnormalities, whereas 1 case showed a normal female karyotype (donor’s; case 2) and 1 case showed a normal male karyotype with nonclonal change of chromosome 20 in 1 metaphase cell (case 10). Case 5 did not have karyotype analysis performed, but instead had FISH analysis demonstrating monosomy 7 in 68% of the interphase nuclei on an aspirate smear. Among these 8 cases with clonal cytogenetic abnormalities, monosomy 7 was seen in 5 cases (cases 1, 3, 5, 6, and 8), interstitial deletion of the long arm of chromosome 7 in 1 case (case 7), interstitial deletion of the long arm of chromosome 5 in 1 case (case 9), and interstitial deletion of the long arm of chromosome 20 in 1 case (case 4).

In addition to case 5, FISH was also performed on DCL cells in 6 other cases. These tests confirmed monosomy 7 in 4 cases (cases 1, 3, 6, and 8) and excluded previous
A (Case 2), Donor cell–derived acute myeloid leukemia. Note apparently increased blasts on the aspirate smear (Wright-Giemsa, ×1,000). B (Case 3), Donor cell–derived myelodysplastic syndrome. Note the hyperplastic bone marrow with dysplastic megakaryocytic hyperplasia on the biopsy section (H&E, ×200). C (Case 10), Donor cell–derived chronic lymphocytic leukemia. Note 3 abnormal lymphocytes with clumped chromatin in the peripheral blood smear (Wright, ×1,000).

Image 2l (Case 10) Detection of monoclonal B-cell population by flow cytometric analysis. Note the λ light chain restriction in B cells (CD19+; cluster of green events in the upper panels) and coexpression of CD5 in B cells (lower right panel; green events). CD23 is partially expressed in a monoclonal B-cell population (lower left panel). ECD, phycoerythrin–Texas red; FITC, fluorescein isothiocyanate; PE, phycoerythrin.
cytogenetic abnormalities, such as BCR/ABL1 (cases 2, 6, and 10), MLL rearrangement (case 1), and complex trisomy (case 8), which were detected in primary neoplasms, in 5 cases. In all cases with additional FISH tests, the novel changes in conventional cytogenetics observed in secondary leukemia were confirmed and the primary cytogenetic abnormalities were absent, ruling out the possibility of relapsed disease or clonal evolution. Of note, case 5 had a low level of nuclei with monosomy 7 detected in the pretransplantation sample by karyotyping and FISH. While detection of monosomy 7 in 68% of the interphase nuclei 6 months after HCT raised a possibility of relapsed MDS or progression of disease, the engraftment analysis confirmed the donor cell origin of the abnormal clone (see the next section).

**BM Engraftment Analysis**

All 10 cases had engraftment studies performed on a BM sample by STR analysis (cases 1, 3, 5, and 6) or FISH analysis for donor gonosomal complement (cases 2, 4, and 7-10). In 9 cases (cases 1-8 and 10), in addition, engraftment studies or cytogenetic analysis were performed periodically after the HCT to test the donor cell engraftment. In all of these cases, donor cell engraftment was confirmed after transplantation and the graft was maintained during the course, judged by peripheral blood cell counts. There was no evidence of graft loss during the course. The fractions of donor cells ranged from 98% to 100% of total marrow nucleated cells or CD15+ cells when the secondary leukemia was identified, suggesting a continued donor cell engraftment. Of note, STR analysis demonstrated complete donor cell engraftment in case 5, excluding the possibility of relapsed MDS of host cell origin.

**Subsequent Donor Cell Evaluation**

FISH analysis was retrospectively performed in archived donor cells in 4 cases (cases 1 and 7-9) to test the genomic
(Case 5) Bone marrow engraftment study demonstrating donor cell engraftment in a sex-matched umbilical cord blood transplant recipient when monosomy 7 was detected by fluorescence in situ hybridization analysis (68%). A, Short tandem repeat (STR) genotypic profile of pretransplantation recipient. B, STR genotypic profile of donor. C, STR profile of posttransplantation CD15+ cells. Note the match of all 4 loci between C and B, while 15 loci were actually tested and all were matched.

(Case 2) Engraftment study by fluorescence in situ hybridization for X and Y chromosomes. Note that each of the 3 nuclei contains 2 green signals (X chromosome) without a red signal (Y chromosome). While only 3 cells are present in this image, 500 interphase nuclei were evaluated in this case, of which 498 nuclei were noted to contain green signals without red signals. Therefore, 99.6% of cells had a female gonosomal complement, consistent with donor origin.
simply observed or received supportive therapy, such as blood transfusion. Case 10 with CLL was simply observed owing to relatively stable RBC and platelet counts. In 7 cases, there was clinical follow-up of 5 months or longer. The remaining 3 cases were recently diagnosed and did not have a sufficient length of follow-up (cases 2, 4, and 7). Of the 7 cases with clinical follow-up, only 1 patient died of disease (case 1). In 5 cases, including 4 MDSs and 1 CLL, there was a relatively stable clinical course and patients were alive with disease up to the time when this article was prepared. Case 5 (MDS) demonstrated a spontaneous remission that was evident by normalized blood cell counts and disappearance of the clone with monosomy 7 without pertinent treatment.

### Summary of Pooled Data, Including Current and Reported Cases

We performed a comprehensive literature review and identified 74 cases of DCL reported in the English literature. Of 84 cases in total, 77 (92%) received HCT for integrity of the donor cells when clonal cytogenetic abnormalities were identified in DCL. These include testing for monosomy 7 in cases 1 and 8, interstitial deletion of the long arm of chromosome 7 in case 7, and interstitial deletion of the long arm of chromosome 5 in case 9. No abnormalities were identified in the preserved donor cells for cases 1 and 8, in which high fractions of monosomy 7, 81.5% and 42.5% to 60.4%, respectively, were detected in BM samples with donor cell–derived leukemia/MDS. It is interesting that cases 7 and 9 showed low levels of abnormalities in preserved donor cells, ie, del(7q) in 1.8% to 4% of cells for case 7 and del(5q) in 6.3% to 10% of cells for case 9.

### Treatment for DCL

Both cases of AML (cases 1 and 2) were treated with chemotherapy. Of 7 MDS cases, 1 was treated with gemtuzumab ozogamicin (anti-CD33) and donor lymphocyte infusion (case 3), 1 with donor lymphocyte infusion (case 6), and 1 with 6 cycles of lenalidomide. The remaining 4 MDS cases were simply observed or received supportive therapy, such as blood transfusion. Case 10 with CLL was simply observed owing to relatively stable RBC and platelet counts. In 7 cases, there was clinical follow-up of 5 months or longer. The remaining 3 cases were recently diagnosed and did not have a sufficient length of follow-up (cases 2, 4, and 7). Of the 7 cases with clinical follow-up, only 1 patient died of disease (case 1). In 5 cases, including 4 MDSs and 1 CLL, there was a relatively stable clinical course and patients were alive with disease up to the time when this article was prepared. Case 5 (MDS) demonstrated a spontaneous remission that was evident by normalized blood cell counts and disappearance of the clone with monosomy 7 without pertinent treatment.

### Summary of DCL Cases, Including the Current Series and Reported Cases

<table>
<thead>
<tr>
<th>Total (n = 84)</th>
<th>Reported Cases (n = 74)</th>
<th>Current Cases (n = 10)</th>
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<tr>
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ALL, acute lymphoblastic leukemia (including B-cell and T-cell ALL); AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; DCL, donor cell leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; T-LGL, T-cell large granular lymphocyte leukemia.

* Data are given as number (percentage) or number/total (percentage) unless otherwise indicated. All the numbers represent the cases with data available.
† One case of myeloproliferative neoplasm is included in this category.
‡ The percentages are calculated using number of total cytogenetic abnormalities in each column as the denominator.
neoplastic diseases and 7 (8%) for benign diseases, including severe aplastic anemia in 6 cases and thalassemia in 1 case. Approximately 64% of cases (53/83) received transplants from a donor of the opposite sex, and donor cell origins were thus identified initially by donor gonosomal complements in the secondary leukemia. Stem cell sources included about 62% BM (48/77), 21% BHSC (16/77), and 17% UCB (13/77).

Types of DCL included AML in 31 (37%) cases, MDS/myeloproliferative neoplasm in 28 cases (33%), acute lymphoblastic leukemia (ALL) in 20 cases (24%), T-cell large granular lymphocyte leukemia (T-LGL) in 4 cases (5%), and CLL in 1 case (1%). In 72% of cases (55/76), clonal cytogenetic abnormalities were detected, with monosomy 7 or deletion 7q being the most frequent changes (16/76 [29%]). When stratified by types of DCL, all chromosome 7 abnormalities occurred in myeloid neoplasms (AML or MDS).

The interval between HCT and diagnosis of DCL ranged from 1 to 312 months, with median of 24 months, which is similar to that observed in the current series (median, 24 months; range, 1~193 months). When the pooled cases were stratified by types of primary disease and analyzed by using a cumulative event-free survival model, the disease interval of the neoplastic group was much shorter than that of the benign group (23/1~216 vs 60/9~312; *P* = .06) [Figure 2A](#). When stratified by types of DCL, the T-LGL group demonstrated manifestations of DCL significantly earlier than those of the other groups (4.5/2~8 vs 21/5~216 in AML, 28.5/1~312 in MDS and 24/2~164 in ALL; *P* < .0001) [Figure 2B](#). When stratified by stem cell source, the DCLs with UCB transplants tended to occur earlier than in the group with BM transplants or with BHSC transplants (10/2.7~40 vs 28/1~312 in the BM and 24/5~193 in the BHSC group; *P* < .001 and *P* < .01, respectively).

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**Figure 2** Kaplan-Meier event-free survival analysis of latency periods from transplantation to occurrence of donor cell leukemia (DCL). **A**, Primary benign disease (60/9~151) vs malignant disease (23/15~34) (*P* = .06). **B**, Effects of DCL types (acute myeloid leukemia [AML], 21/15~39; myelodysplastic syndrome [MDS], 29/9~48; acute lymphoblastic leukemia [ALL], 24/12~36; T-cell large granular lymphocyte leukemia [T-LGL], 4.5/2~8) (*P* < .0001, T-LGL in comparison with other groups). **C**, Effects of stem cell sources (BM, 28/20~45; BHSC, 24/7~36; UCB, 10/6~15) (*P* < .001 for UCB vs BM and *P* < .01 for UCB vs BHSC). **D**, Effects of stem cell sources analyzed with censored data (excluding all cases with an interval of >40 months) (*P* < .005 for UCB vs BM and *P* < .05 for UCB vs BHSC). The numbers following each category in parentheses indicate the median of latency/95% confidence interval. BHSC, blood hematopoietic stem cell; BM, bone marrow; UCB, umbilical cord blood.
respectively) \textbf{Figure 2C}. To exclude the possible effect of sequential introduction of the stem cell sources, the cases with an interval more than 40 months were censored, and analysis was performed on the remainder of the cases, with similar statistical differences between the UCB and the other 2 groups \textbf{Figure 2D}. Almost half (29/62 [47%]) of the patients died of disease with an 8.5-month median follow up with the majority (22/29 [76%]) being the cases of acute leukemia.

**Discussion**

The incidence of DCL in allogeneic HCT recipients is unclear, although a recent report suggested an incidence as high as 5% of transplant recipients.\textsuperscript{55} This estimate was, however, based on a survey of a small population of HCT recipients. Hertenstein et al\textsuperscript{61} reported a large survey by the European Group for Blood and Marrow Transplantation, which identified 14 cases of DCL among a total of 10,489 allogeneic HCTs during a period of 21 years and included 91 European Group for Blood and Marrow Transplantation centers. They projected a rate of 124 per 100,000 transplant recipients based on the results of their survey. Of 10 cases of DCL described in the current series, 4 (cases 1, 3, 5, and 6) were identified in a pool of 841 allogeneic HCTs performed at Duke University Medical Center from 1995 to 2010, a 15-year period. This results in a rate of 476 per 100,000, a rate somewhat higher than that found by Hertenstein et al.\textsuperscript{61}

Nevertheless, the observations of Hertenstein et al\textsuperscript{61} and our observations could possibly underestimate the incidence of this transplant complication. While, by statistics, sex-matched to sex-mismatched donations should be close to 1:1, the ratios are markedly skewed toward sex-mismatched transplants in both series, 8 of 10 in ours and 11 of 14 in the series by Hertenstein et al.\textsuperscript{61} This disproportional detection of DCL in sex-mismatched HCTs was also noted in the pooled reported cases (64%; Table 4) and is likely due to direct recognition of donor cell origin by donor gonosomal karyotype.

Historically, the methods used to demonstrate donor origins of recurrent leukemia or secondary leukemia evolved in several phases.\textsuperscript{8,23,30,61,71} From the early 1970s to the late 1980s, donor karyotype was unexpectedly identified in secondary leukemia in recipients with sex-mismatched transplants, and a fluorescent stain with quinacrine (Q stain) for the Y chromosome body was used to confirm the cytogenetic findings. From the late 1980s to the early 1990s, Southern blot analysis for restriction fragment length polymorphism was introduced to test donors’ and recipients’ specific genomic variations. The assay was poorly quantitative and, thus, neither sensitive nor specific for defining the origin of leukemic cells. During this period, FISH techniques were also introduced for detecting X and Y chromosomes in cases of sex-mismatched transplants. More recently, approximately at the end of the last century, more quantitative methods, including PCR-based variable number of tandem repeats and STR analysis, were invented and routinely used in clinical laboratories to assess the engraftment status of donor cells in HCT.

The STR analysis used at Duke University Medical Center (cases 1, 3, 5, and 6) has a sensitivity of detecting approximately 1% of mixed recipient’s cellular components in the background of donor cells or vice versa. Theoretically, increased use of this PCR-based test would certainly enhance the detection of DCL, particularly in cases of sex-matched transplants. Nevertheless, a predominance of sex-mismatched transplants in our series and the reported cases of DCL strongly suggests a continued underdetection of this rare complication of HCTs and shows that a gonosomal karyotype is still the preferred marker for recognition of donor cell origin. In cases of sex-mismatched transplants, it would certainly warrant the attention of cytogeneticists if a complete donor’s gonosomal karyotype was detected when an overt leukemia was identified by a hematopathologist or a clonal cytogenetic abnormality was detected with a donor’s sex chromosomes.

A possible factor in the underdetection of DCL in sex-matched transplants may be related to inadequate communication among hematopathologists, cytogeneticists, and molecular diagnosticians. As an alternative, the cases of DCL could potentially be underreported owing to the uncertainty of cell origin in sex-matched transplants or uncertainty of the neoplastic nature in cases without overt leukemia or clonal cytogenetic changes. For example, a clonal cytogenetic abnormality in fully engrafted donor BM cells should raise a possibility of donor cell–derived myelodysplasia in a recipient with sustained or progressive cytopenia, even though no significant dysplasia is observed; however, a similar patient with a normal donor’s karyotype would make a definitive diagnosis of myelodysplasia impossible because it is common to have a certain extent of cytopenia in transplant recipients due to multiple medications or other causes.

While enhanced communication among hematopathologists, cytogeneticists, and molecular diagnosticians would facilitate the identification of DCL, awareness of the existence of this rare entity by each party involved in making the diagnosis is the key for effective communication and definitive recognition of the disease. As such, we propose an algorithm for a diagnostic approach to DCL in HCT recipients \textbf{Figure 3}. In this working algorithm, overt leukemia or a clonal cytogenetic abnormality in a transplant recipient is subjected to evaluation of leukemic cell origin. Donor cell gonosomal karyotype in a sex-mismatched transplant would suggest a donor cell–derived leukemia or myelodysplastic neoplasm (DCL) unless proved otherwise by FISH or molecular tests. In a case of a sex-matched transplant, evidence of donor cell engraftment by STR or variable number of tandem repeats...
The latency period between a procedure and the occurrence of a secondary disease is an important parameter for study of risk, cause, and pathogenesis of the disease. In our small series, the interval between HCT and DCL ranged from 1 to 193 months with median of 24 months, findings similar to those for the pooled cases (Table 4) and close to the findings reported by Hertenstein et al\(^6\) (median, 17 months; range 4–164 months). It is interesting that when pooled cases are stratified by types of primary disease and analyzed using the Kaplan-Meier survival model, the interval of the malignant group is much shorter than that of the benign group (Figure 2A). Given the fact that patients who received transplants for benign diseases, such as aplastic anemia or thalassemia, were usually younger (median, 20 [range, 10–43 years] vs 37 years [range, 3–70 years]), analysis was performed with age adjustment. The age-adjusted hazard ratio for the malignant group was 2.65 with a 95% confidence interval of 1.12 to 6.25. This shorter latency period for patients with malignancies may imply a contributory role of pretransplantation treatment in the pathogenesis of DCL because this group of patients often receives intense chemotherapy and/or total body irradiation before HCT, whereas patients with primary benign diseases do not.

When stratified by type of DCL, the T-LGL group had occurrence of DCL significantly earlier than other groups (4.5/3–8 vs 21/5–216 months in AML, 28.5/1–312 months in MDS, and 24/2–164 months in ALL; \(P < .0001\); Figure 2B), indicating the pathogenesis of T-LGL may involve a pathway distinct from the others. Owing to the short latency, a question is raised about whether neoplastic T-LGL clones were incidentally transferred from donors to recipients. This is unlikely, however, because in at least 2 of 4 cases reported, donors were retrospectively evaluated and neither showed evidence of T-LGL by morphologic and molecular tests.\(^18\) Polyclonal T-cell large granular lymphocytosis has been reported in recipients with allogeneic organ or BM transplants and has been related to long-term stimulation due to host antigens or viral infection.\(^72,73\) Additional changes, genetic or epigenetic, promoted by decreased immune surveillance or a disturbed hematopoietic microenvironment may place selected clones at a growth advantage, which eventually evolve into T-LGL. The curves for cumulative event-free rate for AML, MDS, and ALL are substantially overlapped, implying that a similar mechanism may govern the process of donor cell transformation in these groups.

The current series seems to comprise a disproportionately higher number of MDS cases (7/10) in comparison with previous reports (28.4%). This may be explained by preferential reports of overt leukemia cases more than the cases with clonal cytogenetic abnormalities but without overt leukemia. In the current series, 9 of 10 were myeloid neoplasms (2 AMLs and 7 MDSs). Of these, 6 cases had monosomy 7. In contrast, the pooled cases included 28 cases of AML and 28 cases of MDS.
in which cytogenetic analysis was performed in DCLs. Of these 56 cases with donor cell–derived AML/MDS, 44 (79%) had clonal cytogenetic abnormalities, with more than one third (16/44 [36.4%]) harboring monosomy 7 or deletion of 7q. Although the rate is closer to that detected in therapy-related AML/MDS (~90% abnormality, with ~50% being –7/–7q)\(^7\)\(^4\) than in de novo AML/MDS (~50% abnormality with ~10% being –7/–7q),\(^7\)\(^3\) the number may overlook some donor cell–derived MDSs undetected owing to normal karyotype.

The single case of CLL in the current series is the only case of mature B-cell neoplasm of donor cell origin reported in HCTs so far in the English literature, excluding rare cases apparently transferred from donors.\(^6\)\(^0\) Of interest, this young woman received a BM transplant for chronic myelogenous leukemia at the age of 5 years. Peripheral lymphocytosis developed and was confirmed to be mature B-cell leukemia about 14 years after allogeneic BM transplantation from a male donor. Donor origin of the B-cell leukemia was confirmed by the donor gonosomal karyotype and FISH-based engraftment analysis. CLL is known to have a high incidence in the elderly population, and occurrence in young people, such as this patient, is extremely rare. Unfortunately, the age of the donor was unknown in this case.

UCB was initially introduced as an HSC source for transplants in the 1990s, and its use has become widespread during the last decade because of the positive outcome in a few early clinical studies.\(^7\)\(^6\) Since the first case of DCL after UCB transplantation reported by Fraser et al,\(^1\)\(^9\) about 10 additional cases have been described in the recent literature.\(^1\)\(^7\),\(^2\)\(^6\),\(^2\)\(^8\),\(^5\)\(^7\),\(^5\)\(^9\)

Based on the data from the Tokyo Cord Blood Bank,\(^5\)\(^8\) DCL occurred in 4 patients among 478 UCB units being used, giving a prevalence of 837 per 100,000 units. However, this rate should be higher, if the denominator were converted to “per transplant,” considering that a single unit is often insufficient for many adult transplant recipients.

Nevertheless, the rate of DCL in UCB transplant recipients seems to be higher than the risk of pooled DCL estimated by the European Group for Blood and Marrow Transplantation survey or by our series. Of 10 cases in our series, 3 (cases 1, 5, and 8) are UCB transplant recipients, including AML in 1 case and MDS in 2. Two of these cases are from a pool of 156 total UCB transplants performed since 1996 at Duke University Medical Center. These are projected to a rate of 1.3% or 1,282 per 100,000 UCB transplants, in contrast with 0.3% or 292 per 100,000 BM/BHSC transplants (2 of 685 at Duke University Medical Center). This rate of DCL in UCB transplants is slightly higher than the rate estimated by Nagamura-Inoue et al\(^5\)\(^8\) based on the data from the Tokyo Cord Blood Bank but would be close to the latter if per transplant were used as the denominator.

Furthermore, the pooled data in our Kaplan-Meier event-free survival analysis include 13 cases of DCL occurring after UCB transplantation. The results of this analysis seem to support the hypothesis that UCB transplantation may bear a potentially higher risk for DCL than other stem cell sources,\(^7\)\(^7\) given the significantly shorter latency in the group (Figures 2C and 2D; \(P < .001\) in comparison with the BM group and \(P < .01\) in comparison with the BHSC group). A low level of genetic abnormalities, such as \(TEL/AML1\), has been reported in samples of UCB.\(^7\)\(^9\) However, transfer of occult leukemia in donor UCB is unlikely because no congenital leukemia has been identified in any donor in the reported cases.\(^1\)\(^9\),\(^2\)\(^8\),\(^3\)\(^0\),\(^5\)\(^7\)

In addition, of 13 cases of DCL after UCB transplantation, 7 were AML, 5 were MDS, and 1 was T-LGL, all of which are more prevalent in adults but rare in childhood leukemia. Of interest, there is no ALL reported in UCB transplants, whereas it comprises 25% in BHSC and 31% in BM transplants. However, composition of DCL types may not be attributed to the shortened latency in UCB transplantation because there is no difference in the intervals among the AML, ALL, and MDS groups by statistical analysis (Figure 2B). Whether the higher risk or shortened latency in UCB is due to the intrinsic immune naive?e in cord blood stem cells or to a different intensity of conditioning or lower HLA matching criteria remains to be further investigated.

Multiple mechanisms of DCL have been proposed, including sustained antigenic stimulation, an impaired hematopoietic microenvironment in the host BM, defective immune surveillance, genomic fusion of residual leukemia with grafted donor cells, transfer of occult leukemia in the donor stem cell source, replication stress due to proliferative demand, acquired “second hit” on susceptible donor cells with an intrinsic defect in the host microenvironment, and many more.\(^7\)\(^1\),\(^7\)\(^9\) Two of the current cases had low levels of cytogenetic abnormalities detected in preserved donor cells (cases 7 and 9). Neither was a UCB donor. One of the cases (case 7) had multiple conventional cytogenetic analyses (4) performed after transplantation that did not show a clonal cytogenetic abnormality until the latest BM biopsy performed 26 months after transplantation identified deletion 7q in 2 of 29 metaphase cells. These findings, along with longer latency in the benign group, support a hypothesis that donor cells with an intrinsic defect may predispose to additional genetic or epigenetic changes facilitated by a disturbed microenvironment of the host BM and eventually evolve into DCL.\(^7\)\(^9\) However, given the diversified types of DCL and varied latency periods in the reported cases, the pathogenesis of DCL may involve more than a single pathway.

Owing to lack of sufficient follow-up information in our case series and the majority of the reported cases, it is difficult to assess the prognosis of DCL in comparison with de novo leukemia or therapy-related counterparts. In the 10 cases in our series, 1 patient (with AML) died of disease progression; the other case of AML (case 2) had been recently diagnosed, and follow-up was insufficient. The remaining 8 cases, including 7...
MDs and 1 CLL, apparently had an indolent clinical course, but only 1 case of MDS (case 5) and the case of CLL (case 10) had sufficient clinical follow-up. In the pooled cases, patients in the majority of AML cases (14/20 [70%]) and ALL cases (8/12 [67%]) died of disease or disease-related complications with relatively short follow-up (median, 6 months for AML and 9 months for ALL), while approximately 80% (18/23) of patients with MDS were alive with disease or without disease progression at a median follow-up of 11 months.

Of particular interest, case 5 (MDS) in the current series seemed to undergo a spontaneous remission with gradually normalized CBCs and disappearance of monosomy 7 (by karyotyping and FISH) 1.5 years after the diagnosis of donor cell–derived MDS. This reversible or transient feature of MDS has been described in the literature in rare cases of de novo MDS, therapy-related MDS, and donor cell–derived MDS in an allogeneic HCT setting. The underlying mechanism and clinical significance of this reversible phenomenon remain unclear. Hypothetically, more cases of transient MDS may be identified with longer clinical follow-up to facilitate its investigation. Based on this limited information, the clinical outcome for donor cell–derived AML or ALL would be at least equal to relapsed acute leukemia, whereas the prognosis for donor cell–derived MDS may be similar to its de novo counterpart. Nevertheless, the biologic behavior, treatment modality, and prognosis of DCL need to be determined by more well-designed clinical studies.

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References


