Donor Cell–Derived Leukemia and Myelodysplastic Neoplasm

Unique Forms of Leukemia

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Donor cell leukemia (DCL) is an infrequent complication of hematopoietic stem cell transplantation (HCT). DCL represents a unique form of leukemogenesis in which normal donor cells become transformed into an aggressive leukemia or myelodysplastic syndrome (MDS) following engraftment in a foreign host environment. This rapid oncogenic transformation provides an exceptional opportunity to study the effect of reparative and regenerative processes, clonal selection, and external environmental factors on the development of malignancy.

Principles learned from studying DCL should provide insights into the process of leukemogenesis. However, owing to the rare frequency and difficulty of detection, DCLs are challenging to study. The study of DCL not only provides information about pathways that promote leukemogenesis but also has important prognostic and therapeutic implications because prior studies have shown that the majority of DCL cases are difficult to treat and do not usually respond to donor lymphocyte infusion.1 In this issue of the Journal, Wang et al2 present 10 new cases of donor cell–derived leukemia and myelodysplastic neoplasms and compare these with the 74 previously reported cases compiling the largest collection of DCL in the literature. In this editorial we will present a brief review of DCL, focusing on potential contributing factors and comment on the impact of the article by Wang et al.

Detection of DCL

The first report of donor cell–derived leukemia was by Fialkow et al3 in 1971. A 16-year-old girl with acute lymphoblastic leukemia received marrow from her HLA-identical brother. At 62 days after transplantation, she experienced relapse, and cytogenetic studies showed only the male karyotype of donor-type cells. The authors speculated that a host-derived agent or factor had transformed the donor cells.

Early case reports of DCL were limited to sex-mismatched transplants in which the diagnosis was based on cytogenetic studies showing the absence or presence of a Y chromosome. Conventional cytogenetics remains a major technique for detecting host vs donor origin in sex-mismatched transplants. Owing to the ability to monitor larger numbers of interphase cells, the introduction of fluorescence in situ hybridization tests targeting the Y chromosome have increased the sensitivity of DCL detection.4

In cases in which the donor and recipient are sex-matched, most transplant centers monitor chimeric engraftment in the regenerating marrow by polymerase chain reaction (PCR) amplification of tandem repeat sequences targeting variable number of tandem repeats or short tandem repeats (STRs). These polymorphic stretches of DNA are highly variable between individual people and provide a sensitive marker for detecting a minor clone of residual host cells in a background of donor-derived marrow.

Monitoring of chimeric engraftment detects the percentage of donor cells populating the marrow or peripheral blood and is an early indicator of graft failure or relapse. In our institution, the myeloid (CD33), lymphoid (CD3), and blast (CD34) populations are sorted by flow cytometry and analyzed by STR-PCR to determine donor lineage–specific engraftment. Commonly used STR-PCR techniques target polymorphic regions on 12 different chromosomes, are applicable to malignancies with many cytogenetic abnormalities, and can be used in sex-matched transplants. The major...
impediment to DCL detection is routinely testing samples in relapsed cases. Although cytogenetic studies are usually performed on most recurrent leukemias, in many cases the chimeric status of the recurrent leukemias and myelodysplastic disorders is not studied, so reported cases could underestimate the real incidence.

Etiology of DCL

Many reviews have speculated on the etiology of DCL, a unique and scientifically intriguing model of leukemogenesis in which normal cells undergo oncogenic transformation. We briefly describe some of the plausible and/or interesting pathways that may contribute to DCL and refer interested readers to recent comprehensive reviews.1,5 The causes of DCL can be classified into intrinsic features present in the donor stem cells and extrinsic factors provided by the regenerating marrow environment.

Donor Cell Intrinsic Factors

Transplanted malignancies represent a rare form of DCL. We6 and others8 have reported cases in which an undetected malignancy was inadvertently transplanted into the host. Our series included 6 cases of DCL directly transmitted through HCT.6 It is interesting that these 6 transplanted malignancies were all lymphoid-derived, and the enhanced ability to detect abnormal lymphocyte populations in the donor marrow by flow cytometry and IgH PCR gene rearrangement may have facilitated their discovery. However, these are rare cases, and although it is difficult to advocate for extensive screening of all donors to find silent and potential hematologic malignancies, the current use of older people as donors, owing to the trend of transplantation in older patient populations, may warrant selective increased donor screening.

With the field of genomics progressing at high speed, one may envision the future screening of potential donors by whole genome sequencing. However, this screening would likely be helpful for only a handful of patients for whom there may be a known predisposition to hematologic malignancies because the detection of fusion genes and mutations may not be sufficient to predict leukemic transformation. BCR-ABL,7 t(14;18),8 and abnormal B-cell clones have been found present at low levels in healthy adults,9 and translocations characteristic of pediatric leukemias are found in 1% of cord blood, a frequency 100-fold higher than the cumulative risk of the corresponding leukemia.10-12

Similarly, a premalignant donor clone could evolve independently, acquiring additional hits and transforming to leukemia once engrafted in an allogeneic environment. In HCT, a limited number of “normal” hematopoietic cells are mobilized, harvested, and reintroduced into a depleted marrow space that has recently been exposed to intensive chemotherapy and/or radiation to eliminate the prior malignancy. Following transplantation, the marrow undergoes a marked expansion to populate the new environment and provide needed peripheral blood cells. The enhanced proliferative drive (augmented by growth factors) may result in increased replicative errors, mutations, and aging (shortened telomeres). The enormous replicative stress to repopulate an empty marrow space may result in transient dominance of a hematopoietic clone with proliferative advantage. In support of this model, there are several reports of the emergence of a transient dominant clone with cytogenetic abnormalities that disappears with time.1,2

Host Extrinsic Factors

A number of extrinsic factors have been hypothesized to contribute to the rare oncogenic transformation promoting DCL. The best-known example of posttransplantation malignancy is the Epstein-Barr virus–mediated posttransplantation lymphoproliferative disorder (PTLD) that arises in solid organ and HCT recipients.13 In the HCT setting, PTLD frequently occurs in donor cells and is not commonly classified as DCL but may provide clues into the development of DCL. Viral integration and transformation of the new donor cells in an impaired host immune system may contribute to oncogenic transformation, although apart from Epstein-Barr virus–mediated PTLD, evidence of an oncogenic unidentified virus is lacking.

Another potential factor contributing to the transformation of allogeneic cells could be the bone marrow microenvironment. Hematologic diseases can disrupt the marrow environment, resulting in myelofibrosis and osteosclerosis. In a similar manner, there is increasing evidence that implicates the bone marrow stroma in the development of hematopoietic malignancies. First, chromosomal abnormalities have been described in nonhematopoietic cells from the bone marrow of patients with acute myeloblastic leukemia and MDS.14 Second, stromal cells from patients with MDS display altered patterns of cytokine and growth factor expression compared with stroma from healthy donors.15 Third, there are several reports of mouse models in which defects in the microenvironment are capable of inducing and sustaining hematologic diseases.16-20 Most recently, Raaijmakers et al21 showed that Dicer1 deletion in mouse osteoprogenitors disrupts hematopoiesis and induces myelodysplasia and acute myeloblastic leukemia. Subsequent transplantation of normal marrow into the Dicer1 deletion mice results in donor-derived MDS representing a murine model of DCL. Thus, an altered microenvironment permissive of a first malignancy may also promote or support the transformation of donor cells.

The fact that, in most cases, donors for patients with DCL do not develop leukemia also suggests the involvement of a
host factor in promoting DCL. Such host factors may include damaged or regenerating marrow stroma, immunotolerance of the developing leukemia, or potential genetic predisposition to leukemogenesis. As mentioned, a damaged microenvironment following intensive chemotherapy and/or radiotherapy may also be a key factor. Radiation induces a stress response with overproduction of reactive oxygen species and inflammatory markers that are detectable for decades.1

**Donor-Derived Leukemias and Myelodysplastic Neoplasms**

In their article in this issue of the *Journal*, Wang et al2 present a clinicopathologic study of 10 new cases of donor-derived leukemias and myelodysplastic neoplasms from 3 separate institutions and compare these cases with the previously reported 74 cases of DCL. This study demonstrates that DCL is a rare complication of allogeneic HCT with a general risk of between 0.2% and 0.48%. The interval between transplantation and leukemia varies between 1 and 193 months, with a mean of 24 months. Similar to previous reports, the majority of cases occurred within the first few years following transplantation, and the annual incidence of DCL, although low, is considerably higher than the incidence of leukemia in the general population.

The major difficulty in detecting DCL is in determining the donor status of the neoplasm, especially when the abnormal cells represent only a small fraction of the total marrow. Because the majority of reported DCLs involve a large percentage of the marrow, donor status can be inferred by chimerism studies. In the case of minimal disease, the abnormal cells must be isolated by flow cytometric sorting before donor-host determination. Chimerism analysis of cells fractionated into CD15+ and CD3+ populations, as is often done, may not adequately isolate an abnormal immature myeloid population. Therefore, the true incidence of DCL must be greater than is detected and reported in the literature.

Perhaps the most striking feature of the cases in this new series is the preponderance of donor-derived myelodysplastic neoplasms (70%). Until these reports, MDS cases accounted for only 28% of DCLs.2,22 Most of the newly reported cases of DCL have a high frequency of cytogenetic abnormalities (80%), with chromosome 7 abnormalities (monosomy 7 and deletion of 7q) present in 6 of the 10 cases. Furthermore, many of the MDS cases were identified by abnormal clonal cytogenetic changes arising in posttransplantation patients with cytopenias. Many of the donor-derived MDSs described in this series are unusual in that they arise from hypoplastic marrow and do not show morphologic dysplasia or an increased population of myeloid blasts in the bone marrow. Early abnormal clones may not have evolved sufficiently to develop classic morphologic features of MDS. Alternatively, they may represent a unique form of donor-derived myelodysplastic neoplasm in the transplant setting. In contrast, many of the previously reported cases of DCL with MDS were identified based on the presence of abnormal morphologic or immunophenotypic cell populations. Multiple cytogenetic abnormalities and monosomy 7 are usually associated with de novo and treatment-related MDS with a poor prognosis. This suggests that the donor-derived myelodysplastic neoplasms reported in this series may be related to conditioning in the host before transplantation.

However, there are reports of de novo and therapy-related monosomy 7 MDS cases and 1 case of monosomy 7 in donor cells that remitted spontaneously, suggesting that monosomy 7 may be a marker of abnormal clonal dominance in the post-transplantation setting and, in some cases, may not progress to leukemia.23 Case 5 exhibited a transient MDS that underwent spontaneous remission after 18 months. This patient initially underwent transplantation for therapy-associated MDS with a low level of monosomy 7. Cytogenetic studies 6 months after transplantation showed the recurrence of monosomy 7 in 68% of the marrow cells with complete donor chimerism by STR analysis and a normocellular marrow without increased myeloid blasts or significant morphologic dysplasia. After 18 months without further therapy, the abnormal monosomy 7 clone disappeared. This case may represent a transient clonal dominance in which a single abnormal clone initially outgrew the other normal donor cells to preferentially populate the marrow. At 18 months after transplantation, the initial growth advantage was no longer present or the environment had changed and the abnormal clone was replaced by normal donor cells.

The appearance of transient monosomy 7 early after engraftment emphasizes the relevance of early clonal dominance in the regenerating marrow that is responsive to many extrinsic and environmental cues, including growth factors, immunomodulation, and a heavily pretreated marrow microenvironment. It is interesting that 1 study found preferential proliferation of cultured cells with monosomy 7 after granulocyte colony-stimulating factor therapy, with remission in some cases following growth-factor withdrawal.24

The report by Wang et al2 contains the largest collection of DCL and myelodysplastic neoplasms yet compiled; the analysis of this cohort of patients identified several interesting features of DCL. The median interval between HCT and the diagnosis of DCL of 24 months is a short time for the transformation of apparently normal cells into a detectable leukemia. The authors found that in patients who underwent transplantation for prior malignancies, DCL developed with a shorter latency period than in patients who received transplants for benign conditions. Interestingly, DCLs that developed from umbilical cord stem cell transplants that usually
receive a lower cell dose than other stem cell sources developed DCL much more rapidly. This finding may be related to the increased replicative stress that these cells undergo during engraftment and marrow regeneration. Following diagnosis, almost half of the patients died of disease with an 8.5-month median follow-up. Thus, although rare, DCL portends a poor prognosis and warrants further studies to define the factors that promote the rapid transformation of normal donor cells into high-grade leukemias.

Donor cell–derived leukemia and myelodysplastic neoplasms represent a rare but intriguing form of leukemogenesis unique to the hematopoietic transplantation setting. The study of DCL has been hindered by a low incidence and difficulty in diagnosis. As more cases are compiled, it is becoming clear that DCL is multifactorial in etiology and serves as an important model of malignancy depending on the intrinsic features of the normal donor cells and the extrinsic cues provided by the regenerating marrow environment. Continued research into the etiology of DCL will better define the unique cellular and environmental interactions that promote this rare form of leukemogenesis following HCT.

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References


