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CASE REPORT

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Donor cell-derived acute promyelocytic leukemia after allogeneic hematopoietic stem cell transplantation

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Abstract

Donor cell leukemia (DCL) is an infrequent complication after allogeneic hematopoietic stem cell transplantation (HSCT). Its true incidence is difficult to assess, although improvements in chimerism studies contributed to a better diagnosis of DCL. We report two rare cases of donor cell-derived acute promyelocytic leukemia (APL). To our knowledge, only two cases have been described in the literature. Here, we report one male and one female patients with acute myeloid leukemia (AML), who developed an APL in donor cells after HSCT. The latency between HSCT and DCL was 279 and 43 months, respectively. Fluorescent in situ hybridation and chimerism monitoring analysis proved the donor origin of APL. Surprisingly, donor lymphocyte infusion provided a hematological response during 19 months in the female patient. The mechanisms associated with pathogenesis of DCL are unclear and seem to be multifactorial. Increasing worldwide allogeneic hematopoietic stem cell transplantation activity and potentially the age of donor could explain the increasing incidence of DCL in the future. It is highlighted that long-term follow up of recipients will allow to report all cases of DCL, to clarify the genetic landscape and factors which contribute to DCL, to understand the response to DLI.

KEYWORDS

acute myeloid leukemia, bone marrow transplantation

1 | INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is the one of treatment known to cure acute myeloid leukemia (AML). Relapse of AML remains the major cause of treatment failure in patients after HSCT. In rare cases, secondary leukemia is derived from donor cells, designated as donor cell leukemia (DCL). The true incidence is difficult to establish, but a large survey from the European Bone Marrow Transplantation registry reported 14 cases of DCL from more than 10 000 graft procedures.[1] Donor cell-derived acute promyelocytic leukemia (APL) is exceptional: until today only two cases have been reported in the literature.[1,2] We reported here two others cases.

Anne Bouvier and Bénédicte Ribourtout should be considered both as first co-authors with similar implication in the study.

2 | CASE REPORT

2.1 | First patient

A 25-year-old man was diagnosed in December 1984 with normal karyotype AML-M2. He was successfully treated with chemotherapy

(cytarabine, rubidazone, and methotrexate) followed by an allogeneic HSCT from his HLA-identical sister. Conditioning regimen consisted in total body irradiation and cyclophosphamide. In 1992, the patient developed posttransfusion hepatitis C virus. He presented active hepatitis infection until 2003, treated by the combination interferon and ribavirin. Twenty-three years later, in 2008, the patient developed a pancytopenia with a leukocyte count of 0.47 10^9/L, hemoglobin 10 g/dL, and platelet count of 68 10^9/L. Bone marrow aspirate showed

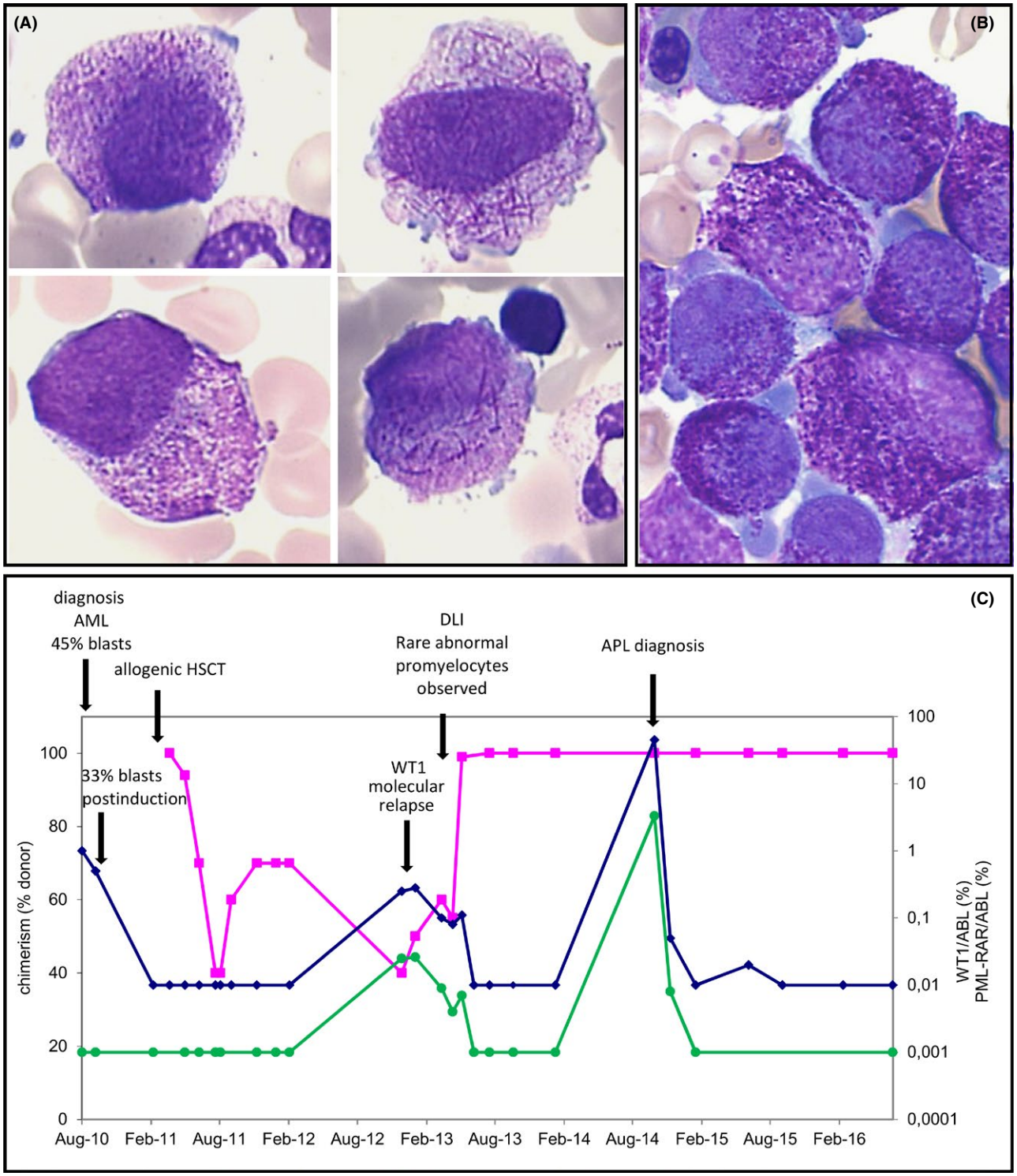

FIGURE 1 Biological data during the clinical course of the patient 2 before and after allo-HSCT. A, MMG stain of blasts in bone marrow the day before DLI. The rare blasts (<1 cell/1000) presented Auer bodies (MGG, ×63). B, Medullary exploration of pancytopenia revealed massive blastic infiltration: hypergranular cells, leading to the diagnosis of promyelocytic leukemia. C, WT1 expression (blue line), chimerism analysis on CD3 cells (pink line), PML-RARA quantification (green line)

promyelocytic blasts, the karyotype was 47,XX,+ 8,t(15;17)(q24;q21) [24]. Molecular analysis found a bcr1 subtype of *PML-RARA* transcript. The pathological karyotype was exclusively present on female donor cells, thus confirming DCL. The patient was treated by chemotherapy and ATRA and remained in complete remission (CR) since. The development of DCL appeared more than 23 years after transplantation. There was no detectable HCV RNA at DCL diagnosis. During this prolonged latency, the patient remained in CR. The donor's samples at the time of graft have been destroyed and no sample has been cryopreserved since, thus no retrospective molecular analyses could be performed. Therefore, the sister could not be tested to detect *PML-RARA*, but she has not developed AML until today, 33 years after donation.

2.2 | Second patient

A 50-year-old woman was diagnosed with normal karyotype AML-M2 in August 2010. Molecular study at diagnosis showed no mutation of *FLT3* or *CEBPA* genes but an atypical *NPM1* mutation and a *WT1* overexpression. Due to refractory leukemia, the patient received salvage chemotherapy and underwent allogeneic HSCT in March 2011 in first CR, with a HLA-locus matched unrelated female donor. The patient received a sequential intensified conditioning regimen combining fludarabine, cytosine arabinoside, amsacrine, busulfan, and thymoglobulin. Graft-vs-host disease (GVHD) prophylaxis consisted of mycophenolate mofetil and cyclosporine.

Measurable residual disease was investigated by *WT1* expression and engraftment status was monitored by serial quantitative chimerism based on real-time PCR of CD3 cells. The patient stayed in mixed chimerism, until molecular relapse in December 2012. She received DLI with 10^7 $CD3^+$ cells/kg in March 2013. Bone marrow examination performed the day before the DLI did not show excess blasts but very rare promyelocytes, containing bundles of Auer rods (<1 for 1000 cells) suggesting blasts of APL (Figure 1A). Her peripheral blood count was normal except for a moderate thrombocytopenia (128 10^9/L). Conventional karyotyping was normal and fluorescent in situ hybridization did not show *PML-RARA* rearrangement. The DLI allowed a molecular remission and a complete donor chimerism on CD3 cells. In October 2013, the patient received 1 Gy of thoracoabdominal irradiation (TAI) for a refractory GVHD. In October 2014, the blood count deteriorated with the reappearance of cytopenias. The bone marrow aspirate showed a massive infiltration by promyelocytes with numerous primary azurophilic granules, but without Auer rods (Figure 1B). Karyotype was 46,XX,t(15;17)(q24;q21)[4]/46,idem,del(9)(q12q32)[5]/46,XX[15], and molecular analysis revealed a bcr3 isoform *PML-RARA* transcript. Diagnosis of DCL was established by chimerism analysis at relapse showing a full donor chimerism on mononuclear cells. The patient received ATRA and arsenic, and reached complete and persistent remission. However, she suffered from extensive chronic GVHD, with major cutaneous, pulmonary, and ocular damages. Further investigations performed a posteriori on cryopreserved

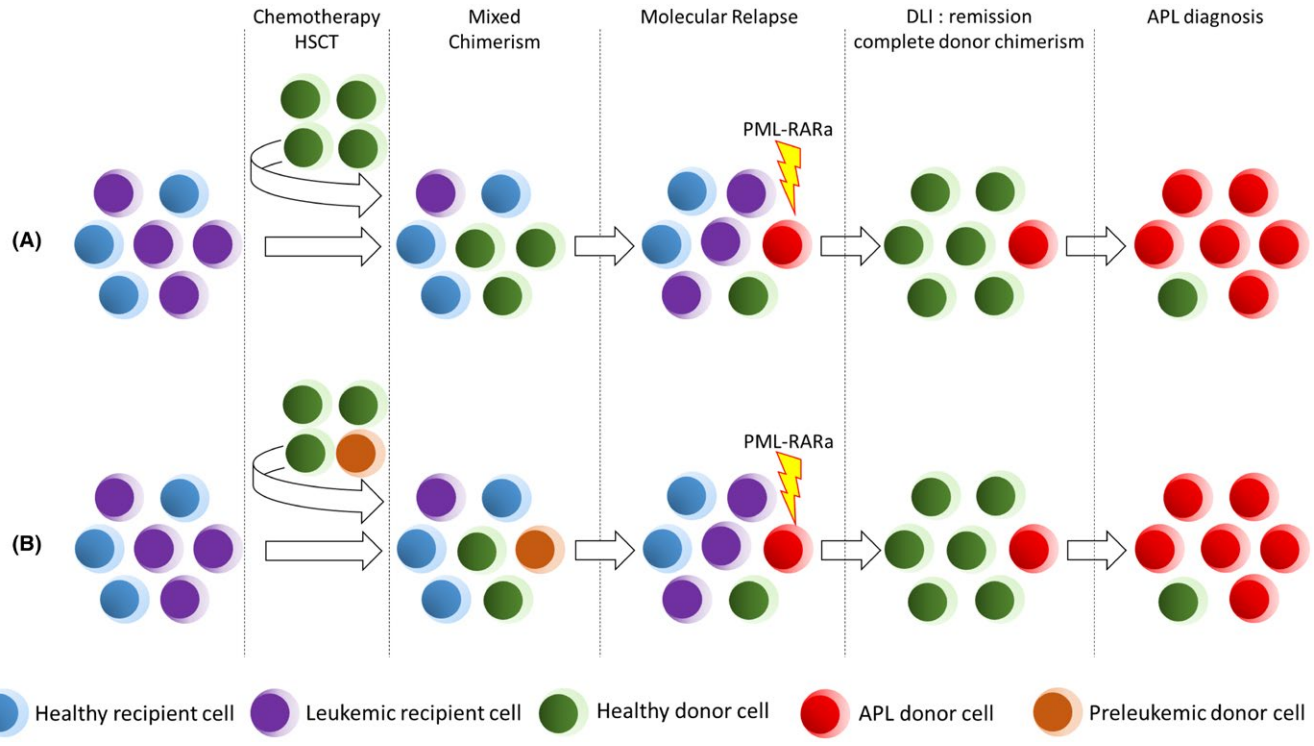

FIGURE 2 Different mechanisms of leukemia development in donor cell. A, Donor cells acquired after allo-HSCT the *PML-RARA* somatic fusion transcript which caused the transformation of donor cells to leukemic cells in impaired host microenvironment (damage by irradiation or cytotoxic chemotherapy) leading to overt leukemic transformation. B, Healthy donor cells may contain premalignant clone at time of transplantation. The infusion of preleukemic clone to the recipient could be the "first hit" of leukemogenesis and "a second hit" could lead to the development of DCL

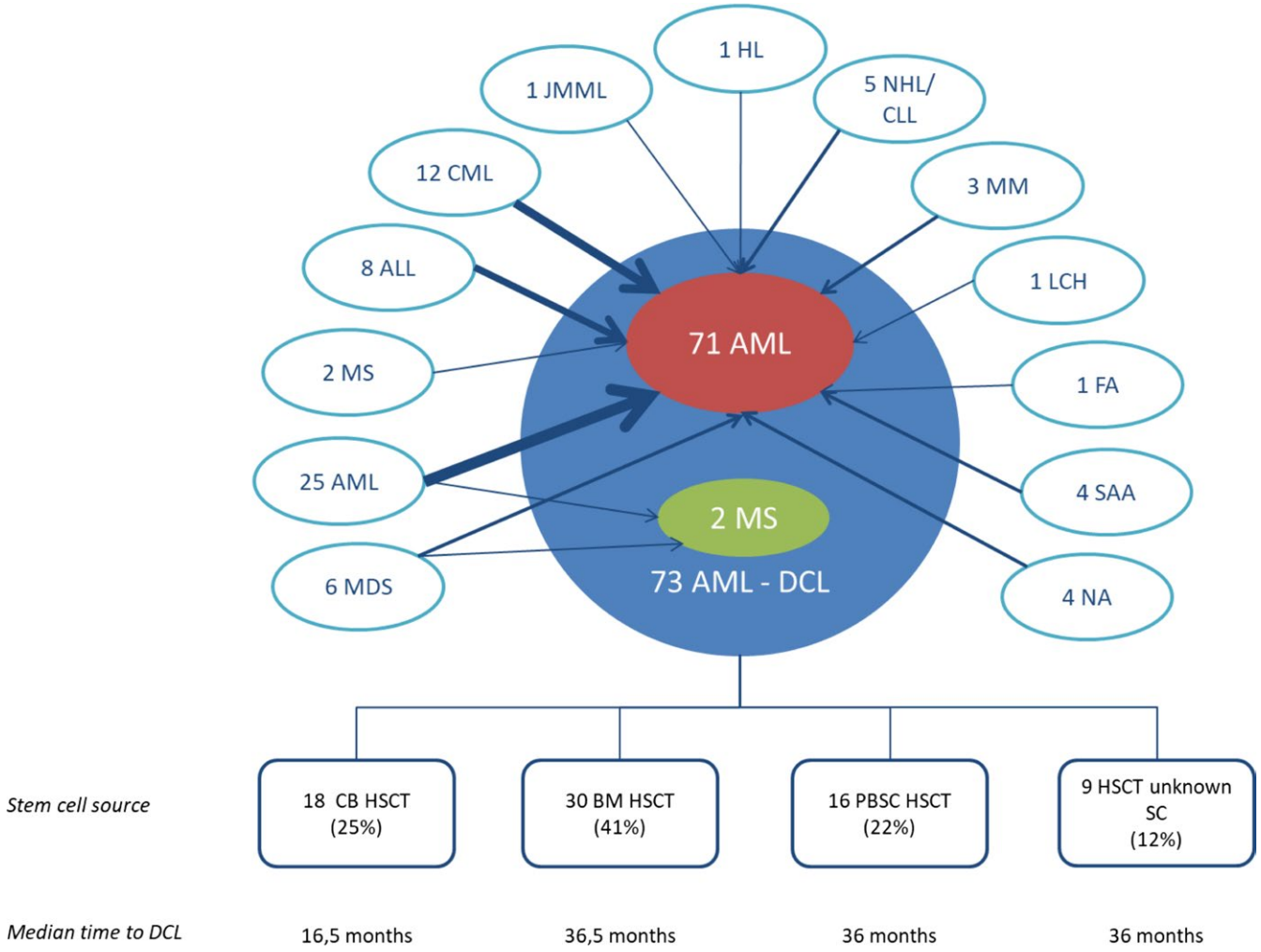

FIGURE 3 Description of primary disease and relationship between time of occurrence DCL and stem cell source. The major primary disease was AML (n = 25), CML in chronic or blastic phase (n = 12), ALL (n = 8), NHL and CLL (n = 5) and MDS (n = 6). In these 73 cases, stem cell source was BM in most cases (41%), PBSC (22%) and CB (25%). The duration between allogenic HSCT and DCL diagnosis was statistically different between the stem cell source (Kruskal-Wallis and Dunn test, $P < 0.05$). MDS, myelodysplastic syndrome; MS, myeloid sarcoma; AML, acute myeloid leukemia; ALL, lymphoblastic leukemia; CML, chronic myelogenous leukemia; JMML, juvenile myelomonocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; LCH, Langerhans cell histiocytosis; FA, fanconi anemia; SAA, severe aplastic anemia; NA, not available; BM, bone marrow; PBSC, peripheral blood stem cell; CB, cord blood; SC, stem cell

samples revealed *PML-RARA* transcript detectable at 0.009% *PML-RARA/ABL1* in March 2013, when rare promyelocytic blasts were observed, but also at the time of WT1 molecular relapse (Figure 1C). No rearrangement was detected in donor cells pregraft. We have no direct information about the donor, but the donor is considered healthy as no alert has been performed on biovigilance registry.

3 | DISCUSSION

DCL is very rare with a frequency near to 0.1% of HSCT cases, but it seems to be steadily increasing. The cases of donor cell-derived APL are exceptional.[1,2] Several scenarios have been proposed to explain the physiopathology of DCL, but the mechanisms remain largely unknown. Defective recipient microenvironment induced by chemotherapy or radiation damages, defective immune surveillance, viral transfection, telomere shortening, occult leukemia in the donor cells, preleukemic mutations in donor cells has been implicated in malignant transformation.[3]

In our patients, the transfer of occult leukemia in the donor stem cell source can be excluded in absence of leukemia development in donors since the donation. Mutations in donor HSC, as somatic fusion gene *PML-RARA*, could be acquired de novo after transplantation and could play a major role in development of DCL in context of replicative stress, defect immune surveillance, host microenvironment damage. Indeed, the effects of cytotoxic treatment and irradiation exposure could contribute to bone marrow injury. Recently, the use of next-generation sequencing has depicted the evolutionary processes from clonal hematopoiesis of indeterminate potential to overt leukemia. Additional mutations on preleukemic donor contribute to

leukemia transformation after graft.[4,5] After allogeneic HSCT, the cells acquired a "second hit" including *PML-RARA* fusion transcript in impaired host microenvironment that lead to the APL (Figure 2).

In addition, case 2 is an atypical presentation of APL because not only the leukemia derived from donor cells (2 years after allogeneic HSCT), but overt APL was diagnosed more than 19 months after the first morphologic suspicion of APL. This latency period is not easily explained. DLI from original donor has induced a surprising a good response enabling complete chimerism for a 19 months period. This transient efficiency of DLI could involve an autoimmune effect. The transformed malignant donor clone could have acquired novel leukemia-associated antigens, recognizable by donor lymphocytes.[6] Low dose TAI was used to control the refractory extensive chronic GVHD appearing after DLI. It could be effective on minority leukemic blasts; however, its relative hematotoxicity may lead to the emergence of APL. Antitumoral immune response became insufficient to control this proliferation in presence of impaired marrow function. The other explanation could simply be the natural latency of APL. APL development in mouse models requires a long period of 6-14 months, suggesting that additional genetic events are necessary to leukemia transformation.[7]

Review of the literature identified more than 70 cases of AML DCL (Table S1).[8] The median time between allogenic HSCT and occurrence of AML DCL was 30 months (range 1-279). The 23 years interval in our case 1 is the longest reported. The median time was different depending on stem cell source, 16.5 months for cord blood (CB), 36.5 months for bone marrow (BM), and 36 months for peripheral blood stem cell (PBSC) after allogenic HSCT. The difference was statistically significant (Kruskal-Wallis, Dunn test, and Hochberg correction, $P < 0.05$) (CB vs BM, $P = 0.0048$; CB vs PBSC, $P = 0.025$) (Figure 3). Another study reported that DCL appears earlier in patients transplanted with CB.[9]

With increasing donor age, the donor-derived clonal hematopoiesis may lead to increased risk of leukemia development in recipient. The screening for frequent malignancies could be recommended in older donors, especially in haploidentical transplantation where parents are used as donors for their children. The use of posttransplantation cyclophosphamide (PTCy) in the haploidentical setting could contribute to increase DCL incidence, but no increase in AML DCL has been reported after PTCy.[10] DCL is an interesting model to understand mechanisms of leukemogenesis, likely multifactorial, and is an uncommon leukemia which should not be ignored in the selection of the best available donor.

CONFLICT OF INTEREST

The authors declare no competing interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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