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Same sibling marrow following cord allogeneic transplantation as therapy for second relapse acute promyelocytic leukemia in a pediatric patient

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Abstract: Optimal therapy for relapsed APL in pediatric patients is controversial. Allogeneic HSCT is an alternative, with event-free survival of 70–75%. We report a pediatric patient with APL who relapsed 28 months after CBT from her sibling and then was treated with BMT from the same donor. Bone marrow was selected for higher cell dose, donor availability, and partial donor chimerism. Persistent molecular remission was achieved, currently at 65 months after BMT. This case suggests the potential role of GVL activity in APL and illustrates the use of different cell sources from the same donor in allogeneic transplantation for pediatric patients.

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Acute promyelocytic leukemia (APL) in the USA constitutes about 4–8% of AML in the pediatric population, with patients achieving remission rates of 90–96%, five-yr event-free survival of 76–80%, and five-yr overall survival of 89–90% (1–4). Once considered fatal, relapsed APL, which occurs in 15–25% of the cases, has been successfully treated with chemotherapy only (5, 6), autologous or allogeneic HSCT (7–9), with the standard of care still controversial. More recently, a few publications have suggested that HSCT may be a more effective consolidation for refractory or relapsed APL (10, 11).

Second HSCT for relapsed AML have been attempted based on responses achieved by DLIs (12–14) and evidence of strong GVL effect against AML (15), including cases with BM and peripheral blood stem cell grafts from the same donor (14, 16).

We report for the first time a pediatric patient with relapsed APL who was successfully treated with a BMT from her HLA-matched sibling after relapsing 28 months post-CBT from the same donor.

Abbreviations: AML, acute myeloid leukemias; APL, acute promyelocytic leukemia; ATO, arsenic trioxide; ATRA, all-trans-retinoic acid; BM, bone marrow; BMT, bone marrow transplant; CBT, cord blood transplant; CMV, cytomegalovirus; CSA, cyclosporine; CSF, cerebrospinal fluid; DLI, donor lymphocyte infusions; FISH, fluorescence *in situ* hybridization; FK, tacrolimus; GVHD, graft-versus-host disease; GVL, graft-versus-leukemia; HSCT, hematopoietic stem cell transplantation; MMF, mycophenolate mofetil; Pr, prednisone; TBI, total body irradiation; TNC, total nucleated cells.

Case report

A female Caucasian child was diagnosed with hypergranular APL at 22 months of age with history of one month of fatigue, bruising, gum bleeding, and upper respiratory tract infection. Peripheral blood examination showed anemia,

thrombocytopenia, and normal leukocyte count with myeloid blasts; BM aspirate documented hypercellularity with blasts presenting translocations t(2,9) and t(15;17). CSF was negative for blasts. Induction chemotherapy consisted of ATRA, cytarabine, and daunorubicin, and complications were disseminated intravascular coagulation and febrile neutropenia, without need of mechanical ventilation or surgical procedures other than central venous catheter placement. Consolidation with doxorubicin and ATRA was then administered, without complications.

After four months of therapy, BM relapse was diagnosed at presentation of fever and bruising, with similar morphology and cytogenetics. Reinduction chemotherapy was instituted with high-dose cytarabine and ATRA, and consolidation chemotherapy was instituted with ATO 0.15 mg/kg × 5 days/wk for two months to bridge transition during gestation of a male sibling. A fully matched cord blood from the sibling was transplanted (CBT) with the patient in morphological remission (Table 1, Fig. 1) using myeloablative conditioning with busulfan 4 mg/kg/day × 4 days and cyclophosphamide 60 mg/kg/day × 4 days, and CSA for GVHD prophylaxis. Both recipient and donor were CMV negative, with mismatched blood type recipient O+ and donor A+. Cell dose was 7.7×10^8 TNCs, 5.88×10^7 TNC/kg or 3×10^5 CD34+ cells/kg of recipient weight.

With neutrophil engraftment on day +22, discharge was possible on day +28. Day +26 BM showed 77% of female cells and 23% of male cells by FISH. Cyclosporine wean was started on day +109 and discontinued on day +151, without active GVHD. Day +165 BM showed 76.9% of male cells and cytogenetic remission. Normal immunological reconstitution was documented with lymphocyte subset counts and proliferation assays, and inactivated immunizations were given.

Twenty-eight months after CBT, the patient developed fatigue, fever, weight loss, pallor, and bone pain, and BM aspirate showed 31.7% of APL blasts. CSF was again negative. Reinduction therapy was started with intravenous ATO 0.15 mg/kg × 5 days/wk for four wk. Follow-up BM after one month of reinduction documented 16.7% of blasts. A second cycle of ATO was administered, achieving complete BM morphological remission, which had 95% male cells and 1.3% of residual t(15:17) by FISH. During the second cycle, the patient developed a right atrial thrombus associated with a central venous catheter, for which she received enoxaparin therapy for six months.

Bone marrow transplant (BMT) from the same matched sibling was performed 32 months post-CBT, when the patient was 61 months of age and still CMV negative, using myeloablative conditioning with TBI 12 Gy over four days, cytarabine 500 mg/m^2/dose × 4 doses and cyclophosphamide 60 mg/kg/day × 2 days, and low-level CSA prophylaxis (target level of 200–300 ng/mL). At BM harvest, the donor was 34 months of age, with up-to-date immunizations, and CMV negative. TNC dose was 46.7×10^8, equivalent to 2.8×10^8 TNC/kg and 4.1×10^6 CD34+ cells/kg of recipient weight. To induce GVL, CSA wean was started immediately after engraftment and stopped on day +54, when the patient presented with only mild skin erythema (acute skin GVHD stage 1). On day +82 oral Pr was started at 1 mg/kg/day due to worsening of the acute skin GVHD to stage 2 and elevated liver enzymes (Fig. 1), with total bilirubin <2 mg/dL (acute liver GVHD stage 1, Glucksberg grade II). On day +109 with new worsening of the GVHD with skin erythema (stage 2) and persistently elevated liver enzymes (score 3 of chronic GVHD), CSA was restarted at immunosuppressive doses, resulting in resolution of skin and liver GVHD and allowing partial Pr wean. A new attempt to discontinue CSA around day +260 was followed by new recrudescence of skin erythema (chronic skin GVHD score 2) and elevated liver enzymes (chronic liver GVHD score 3), and oral FK 0.05 mg/kg q12 h was started in place of CSA (Fig. 1). MMF was added on day

Table 1. Patient description and graft characteristics: patient characteristics described at the moment of the UCBT and BMT, along with the grafts used

	Patient at UCBT	Umbilical cord blood TNC dose 7.7×10^8 TNC/kg 5.8×10^7 CD34+/kg 3.0×10^5	Patient at BMT	10/10 matched sibling donor TNC dose 46.7×10^8 TNC/kg 2.8×10^8 CD34+/kg 4.1×10^6
Age	2 y 6 mo		5 y 2 mo	2 y 9 mo
CMV status	Negative	Negative	Negative	Negative
HSV status	Negative	Negative	Negative	Negative
Blood type	O+	A+	A+	A+

UCBT, umbilical cord blood transplant; HSV, herpes simplex virus; y, year(s); mo, month(s).

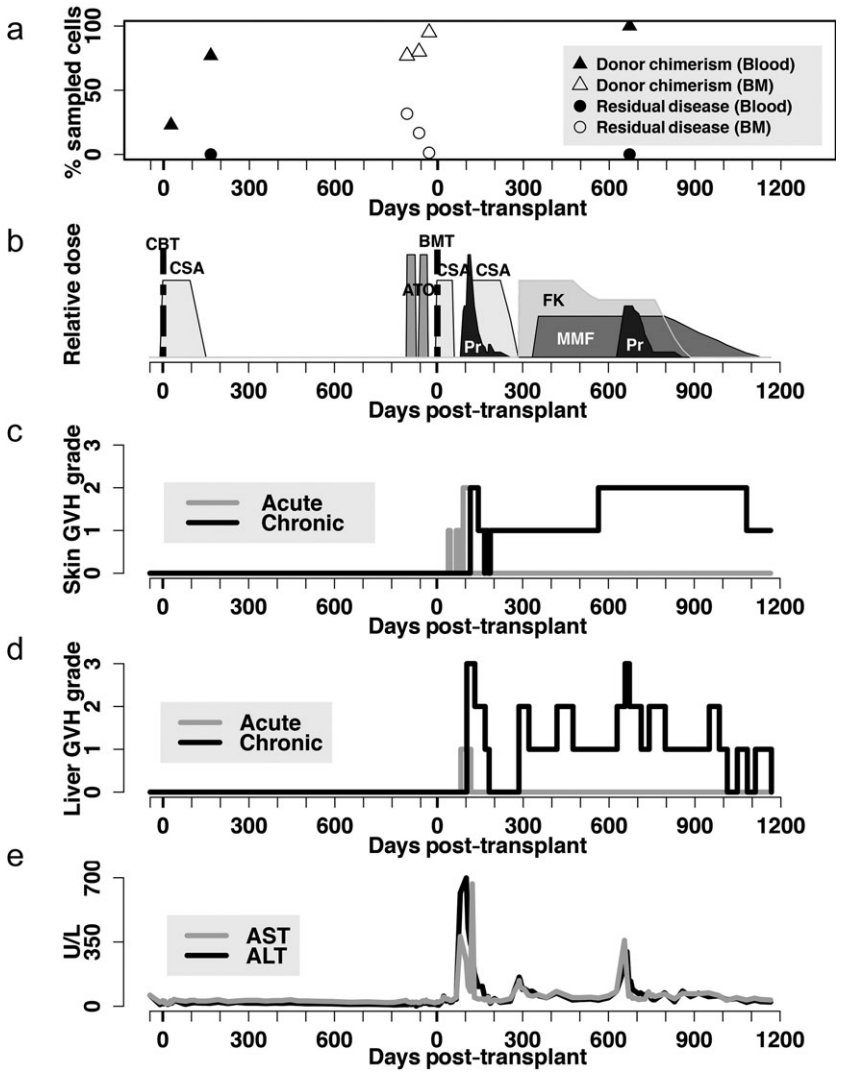

Fig. 1. Therapy, laboratory results, and engraftment timeline. Timeline of the patent's clinical course between first transplant and six yr of follow-up. Disease detection and donor chimerism as determined by FISH (a), therapeutic interventions (b), skin (c) and gut (d) GVHD grade, and aminotransferase levels (e) are plotted over time.

+672 for progressive sclerotic-type chronic GVHD limiting range of motion of arms and trunk, characterizing mild-to-moderate chronic GVHD. As the skin erythema and liver function tests became normal, FK was discontinued on day +887. The patient never had respiratory symptoms or severe infections, and responded well to MMF and physical therapy, with resolution of the scleroderma and normal range of motion of hands and arms, allowing MMF discontinuation by day +1130.

This child currently attends regular school and does not present with developmental delay, with persistent molecular remission at 65 months post-BMT and chronic GVHD score 1 for skin and performance, more than eight yr from diagnosis.

Discussion

Despite very high complete remission rates in patients with APL, relapses still occur in 15–25% of patients. A second complete remission is achievable for most patients (1, 2, 5), and alternatives for consolidation therapy include chemotherapy only, autologous or allogeneic HSCT (11).

Favorable post-HSCT outcomes of patients with AML are generally attributed to GVL (15). Immune responses against AML have been demonstrated by the role of NK cytotoxicity and antigen-specific antibodies and T-cell clones (17, 18). Considering the importance of the allo-response for GVL, the use of a different stem cell source for the second HSCT is usually preferred, but no evidence has been published to support that assumption (19, 20).

In this patient, the malignancy was responsive to chemotherapy, and cytogenetic remission was achieved more than once with standard therapy, even at a late relapse post-CBT, increasing the chances of successful consolidation with HSCT. Her good clinical condition leading to BMT, young age (five yr of age), good organ function,

and absence of infections allowed myeloablative conditioning regimen with the addition of TBI and decreased immunosuppression to allow mild GVHD, fundamental modifications in the second transplantation. The BM chimerism showed good donor cell engraftment from the CBT with residual leukemia and recipient's cells, ensuring the presence of functional donor-derived antigen-presenting cells to favor a better GVL response. Considering that APL is a well-known target for GVL (7–10) with easy and sensitive determination of minimal residual disease, and the fact that this patient had limited disease burden at the second relapse, which happened late post-CBT (28 months), we have decided to perform a BMT from the same donor. The BMT graft would favor engraftment due to higher stem cell dose, allowing the TBI-containing full-myeloablative conditioning regimen. In comparison with the CBT graft, the BMT graft contains higher numbers of mature CD45-RO+ T cells and promotes faster immune reconstitution of T- and B-cell compartments, favoring significant immunity against leukemia and infections (21–23). Finally, in the absence of any other siblings, the same donor was healthy and readily available, with the additional possibility of sequential DLI if necessary.

The management post-BMT was focused on allowing mild GVHD to optimize GVL. As standard practice in our institution, single drug CSA was used for GVHD prophylaxis for a matched sibling HSCT. Lower target levels were maintained, and evidence of mild skin erythema during intensive follow-up was surrogate for therapy titration during the first 100 days post-BMT. Despite mild liver GVHD and the development of scleroderma that required increased and prolonged immunosuppression, and physical and occupational therapies, the child is currently thriving well with no developmental delay, no scleroderma, and no immunosuppressive therapy.

This case demonstrates the role of GVL in APL and the complexity of balancing the development of GVL and GVHD. Our case also illustrates how different stem cell sources from same donor in allogeneic transplantation for pediatric patients can be used to induce a GVL effect.

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Conflict of interest

No conflicts to disclose.

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