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Treatment of leukemia relapse with recombinant granulocyte-macrophage colony stimulating factor (rhGM-CSF) following unrelated umbilical cord blood transplant: Induction of graft-vs.-leukemia

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Abstract: An infant with congenital leukemia in complete remission (CR1) received an unrelated donor umbilical cord blood cell transplant from a one-HLA disparate donor. The conditioning regimen consisted of thiotepa, busulfan and cyclophosphamide. GVHD prophylaxis consisted of tacrolimus and mini-methotrexate. Engraftment occurred and a bone marrow aspirate obtained on day 28 showed 100% donor cells. The post-transplant course was complicated by skin and liver GVHD, grade III, that responded to therapy with methylprednisolone, anti-thymocyte globulin and daclizumab (Zenapax), in addition to tacrolimus. A bone marrow aspirate obtained on day 187 showed relapse, with 17% blasts. The patient was then treated for 30 days with recombinant human granulocyte-macrophage colony-stimulating factor treatment (rhGM-CSF). A bone marrow aspirate obtained 17 days after the initiation of rhGM-CSF treatment showed 2% blasts. Ascites was the predominant side-effect of the rhGM-CSF treatment. The patient remains in complete remission 24 months after relapse and 30 months after transplantation. This case documents that rhGM-CSF and withdrawal of immunosuppression can induce a durable complete remission after relapse following an unrelated donor cord blood transplant.

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Transplantation with umbilical cord blood cells is being performed with increasing frequency. One reason for this is that less stringent HLA matching can be tolerated because a lower incidence of acute and chronic GVHD (1) is seen than with bone marrow or peripheral blood stem cell transplantation. This is advantageous for patients who lack an HLA-matched related donor. Due to rapid availability, this donor source is also useful for patients who have a narrow time frame for transplantation, such as leukemia patients who are at high risk for early relapse.

A major question about unrelated cord blood transplantation in high-risk hematological malignancies is whether naive lymphocytes in the graft can provide an adequate graft-vs.-leukemia (GVL) effect. This drawback is magnified since donor lymphocyte infusions to re-induce remission are not an option if relapse occurs after transplantation.

We report the case of an infant with acute lymphoblastic leukemia (ALL) whose disease recurred 6 months after she received an umbilical cord blood transplant from an unrelated donor. The early relapse and the mixed chimeric state of

Abbreviations: rhGM-CSF, recombinant human granulocyte-macrophage colony stimulating factor; G-CSF, granulocyte stimulating factor; GVHD, graft-vs.-host disease; GVL, graft-vs.-leukemia.

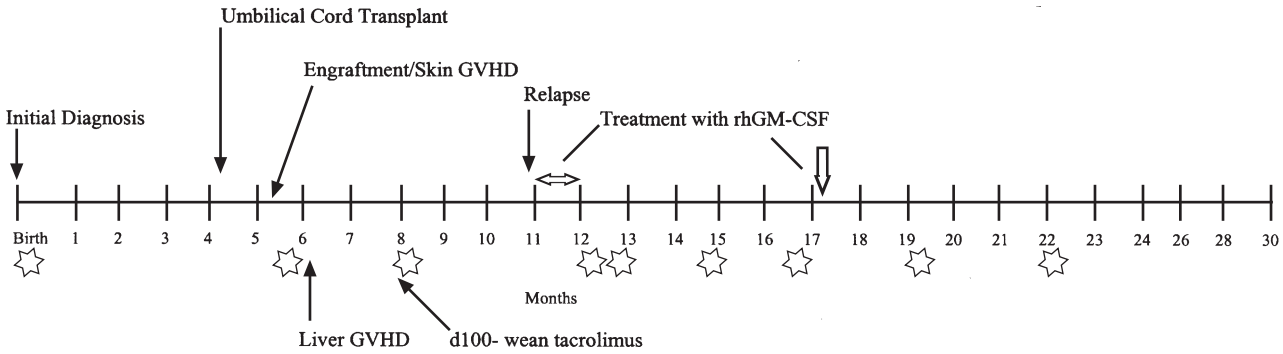

Fig. 1. Treatment schema. Open star (☆): bone marrow aspiration showing complete remission. Open arrow: rhGM-CSF administration.

the bone marrow provided a unique opportunity to stimulate the GVL function of the donor cells with recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) and re-induce remission. This young patient remains in remission 2.5 yr after relapse.

Case report

A female infant with ALL, t(4;11) (q21; q23), CD 10^- blasts was diagnosed at birth. She was treated with dexamethasone, vincristine, daunomycin, methotrexate and triple-agent intrathecal chemotherapy (methotrexate, hydrocortisone, cytarabine hydrochloride) according to the Children's Cancer Group protocol 1953. A bone marrow aspirate obtained on day 28 showed complete remission. By 3 months of age, she was referred for bone marrow transplantation.

The preparative regimen was previously reported (2) and consisted of thiotepa (8.3 mg/kg/day i.v., on days –9 to –7) and busulfan (1.6 mg/kg/dose orally, which was increased to 1.3 mg/kg/dose on the basis of the pharmacokinetic analysis, every 6 h for a total of 16 doses on days –6 to –4). Cyclophosphamide (60 mg/kg/day i.v.) was administered on days –3 to –2. The toxicities of the preparative regimen consisted of grade I stomatitis, nausea and vomiting, and grade 2 diarrhea. On day 0, 0.56×10^8 total nucleated cells/kg from an unrelated-donor umbilical cord blood unit were infused (Table 1).

GVHD prophylaxis consisted of tacrolimus (dose adjusted to maintain serum levels between 5 and 10 ng/mL) and mini-methotrexate (3) (0.17 mg/kg/day on days +1, +3 and +6). Biopsy-proven skin GVHD appeared on day +10, methylprednisolone (2 mg/kg/day) treatment was begun (Fig. 1). The rash disappeared, and the methylprednisolone was changed to oral prednisone on day +23. Biopsy-proven liver GVHD was noted on day +39, and therapy over the next 2 months consisted of tacrolimus, methylprednisolone, daclizumab (Zenapax), and antithymocyte globulin. Her GVHD responded and steroids were completely tapered by day +85. Tacrolimus was tapered beginning on day +100.

A bone marrow specimen obtained on day +113 showed 6% blasts, with some patchy areas of atypical cells and 99.5% chimerism with donor cells as documented by fluorescent *in situ* hybridization (FISH) of the Y chromosome (4). The tacrolimus was abruptly stopped, and the patient's condition monitored. No evidence of GVHD appeared. A bone marrow aspirate obtained on day +187 showed 17% blasts, with the 11q23 rearrangement determined by FISH analysis. These findings were consistent with the relapse of infant leukemia. The peripheral blood smear showed no circulating blast cells. rhGM-CSF (Sargramostim, Immunex, Seattle, WA) treatment was initiated at a dosage of 250 μg/m^2/day s.c. The rhGM-CSF dosage was adjusted to keep the white blood cell count at approximately 20,000/μL, and treatment was continued for 30 days. A bone marrow aspirate 17 days after the initiation of rhGM-CSF showed only 2% blasts and 100% 46,XY karyotype. After completion of therapy, her blood counts returned to normal. The patient tolerated the rhGM-CSF well, except for the development of ascites and abdominal distention, which persisted for approximately 1 month after the completion of rhGM-CSF treatment. The ascites responded moderately to diuresis with albumin and furosemide. Upon completion of rhGM-CSF therapy, bilateral bone marrow aspirates were obtained which showed remission and 100% chimerism with donor cells by FISH analysis. A bone marrow examination on days 335 and 528

Table 1. Donor and patient characteristics.

Characteristics	Patient	Donor
HLA A	2, 11	2, 33
HLA B	44, –	44, 44
DRB1	1301, 1302	1301, 1302
CMV	+	–
ABO	A+	O+
Sex	Female	Male

showed continued complete remission (Fig. 1). Because of reports of late relapse (4), rhGM-CSF treatment was restarted around day +400; however, it was discontinued after 4 days because of the development of respiratory symptoms consistent with an upper respiratory tract infection or capillary leak syndrome. An immunization program was initiated 12 months after the transplantation (6 months after relapse). No GVHD developed during or after therapy with rhGM-CSF. The patient remains in remission 30 months after transplantation and 24 months after relapse.

Discussion

This patient with infant leukemia had poor prognostic indicators: t(4;11) (q21;q23); CD 10^{-} blasts; age <6 months; and a white blood cell count > 100,000/μL at diagnosis. Because of the very high rate of relapse in patients with infant leukemia, she underwent stem cell transplant immediately after attaining remission. Because the patient had neither sibling donors nor a matched unrelated donor, an HLA-mismatched umbilical cord blood transplant from an unrelated donor was given. This decision was based on recent data (personal communication, Dr A. Scaradavou) examining the outcomes of 41 children with infant ALL given umbilical cord blood transplants. Only three patients in that study showed medullary relapse, all approximately 4–5 months after transplantation (16 patients died of causes unrelated to relapse). These results established a role for HLA-mismatched cord blood from an unrelated donor in the treatment of high-risk infant ALL.

Early relapse after allogeneic bone marrow transplant is a poor prognostic indicator. The leukemia that returns is usually resistant to chemotherapy. In addition, early after the transplant, patients have a limited tolerance of chemotherapy. Such a relapse presents a unique opportunity. In the presence of a mixed chimeric state, interventions that directly stimulate the donor cells may induce GVL. For this reason, we abruptly stopped the immunosuppression treatment. Tacrolimus was already being tapered, but we stopped it abruptly. In addition, we started the rhGM-CSF treatment. A complete and prolonged remission was achieved.

There is a precedent for leukemia remission induction by colony-stimulating factors. In one report, a patient with relapsed AML who became neutropenic was given rhGM-CSF for a fungal infection (5). The patient's AML also went into temporary remission. In addition, Giralt et al. (4) reported on the use of G-CSF for the treatment of relapsed ALL and myelodysplasia after allogeneic bone marrow transplantation. Of the seven patients treated with G-CSF, the three who went into remission were those with a low percentage of blasts in the marrow and no circulating blast cells. Relapse occurred in one of these patients 1 yr later. The other two patients continued in remission 10 and 11 months after the G-CSF therapy. More recently, another study investigated the administration of G-CSF during the rapid discontinuation of immunosuppressive therapy. It demonstrated response rates similar to those seen for donor lymphocyte infusions given to treat relapse after allogeneic stem cell transplantation in patients with myeloid leukemias (6). G-CSF given after an unrelated umbilical cord blood transplant for acute leukemia was also seen to induce a response that lasted 4 months (7). Our is the first report of rhGM-CSF being used to induce remission after allogeneic transplantation. It is not clear which of these actions of GM-CSF induced remission in our patient, though rhGM-CSF appears to have a more potent anti-leukemic activity than G-CSF. There have been no reports, however, of rhGM-CSF inducing remission in patients receiving cord blood transplants.

GVHD developed in our patient upon initial engraftment of the donor cells. We therefore had some concerns about reactivation of the GVHD upon rhGM-CSF stimulation of the donor cells. However, we observed only a GVL effect. The main toxicity in our patient was abdominal distention and ascites. Patients who received rhGM-CSF have a higher incidence of abdominal pain compared with a placebo controlled group (8). It has also been reported to cause edema; however, the incidence of edema was equal to that in the placebo control

group. The manufacturers warn that pre-existing edema and the capillary leak syndrome with pleural or pericardial effusion may aggravate fluid retention. However, our patient had no evidence of ascites prior to receiving GM-CSF. It is possible that necrotizing enterocolitis experienced as a newborn predisposed her to this side-effect.

In summary, although the withdrawal of immunosuppression resulted in the progression of disease, the addition of rhGM-CSF successfully induced remission in this patient with infant ALL who suffered a relapse after an allogeneic cord blood transplant. This result further proves that the GVL effect is present in umbilical cord blood from unrelated donors. Based on its mode of action, rhGM-CSF may be a more potent agent for inducing the GVL effect. The optimal setting for rhGM-CSF appears to be in patients who have $< 20\%$ blasts in the bone marrow and no circulating blasts in the peripheral blood. We want to emphasize, however, that this experience is limited, and thus patients treated with rhGM-CSF should be watched closely for side-effects, including a possible activation of their leukemia (4). Certainly, this treatment approach warrants further evaluation.

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