Interleukin-2-induced Graft-Versus-Leukemia for the Treatment of AML in a BRCA2 Fanconi Anemia Patient

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**BACKGROUND**

Fanconi anemia (FA) is characterized by congenital malformations, bone marrow (BM) failure, and increased risk of hematological and epithelial malignancies.1,2 Of the 15 complementation groups, which have now been identified, biallelic BRCA2 mutations occur in only 2% of FA patients3 and are associated with an exceptionally high risk of acute leukemia at an early age, a poor prognosis, and resistance to standard therapy.4

We used interleukin-2 (IL-2) to successfully stimulate a graft-versus-leukemia effect (GVL) in a biallelic BRCA2 FA patient with acute myelogenous leukemia (AML), which was previously refractory to nonmyeloablative conditioning chemotherapy and matched sibling donor BM transplant. Although IL-2-induced GVL has been reported in AML patients, our observations are noteworthy for 2 reasons. Firstly, to our knowledge, this is the first time IL-2-induced GVL has been reported in FA patients. Secondly, there are few reports in the literature on FA patients with BRCA2 mutations, which are associated with a high risk of malignancy and refractory leukemia. We believe that it is important to share our experience, which suggests the potential of immunotherapy in this setting, with the pediatric hematology/oncology community.

**CASE HISTORY**

A 2-year-old girl with FA due to compound heterozygous BRCA2 mutations developed AML with a 5q deletion (5q−). While awaiting admission for transplant, she was given a single dose of fludarabine, as her white blood cell count was doubling daily and had reached 35,000/mm³. Her white blood cell count fell by 50% the next day. She then began a nonmyeloablative conditioning regimen including fludarabine 5 mg/kg, cytarabine 20 mg/kg, and cytoxan 20 mg/kg (all total doses).

She received a transplant from her HLA-identical brother who did not have FA. She was given tacrolimus for graft-versus-host disease (GVHD) prophylaxis. She tolerated the transplant well and had no organ toxicity or GVHD. Her blood counts recovered and there were no peripheral blood (PB) blasts. However, she had cytogenetic evidence of rapid autologous marrow recovery and progression of leukemia. Fluorescence in situ hybridization (FISH) for X and Y probes and a probe for 5q− on PB showed 14% XX (recipient) cells and 3% 5q− cells, 2 weeks after the transplant. Four weeks after the transplant, PB had 58% XX cells and 8% 5q− cells and BM had 58% recipient cells and 4% 5q− cells (Fig. 1).

She was admitted for a second nonmyeloablative conditioning regimen identical to the first, except for escalation of both the cytoxan dose and the cytarabine dose from 20 to 40 mg/kg (all total doses). On day 35 posttransplant, she was given a BM boost from her HLA-identical brother. She again received GVHD prophylaxis with tacrolimus, but her levels were maintained lower and it was stopped 3 weeks after the boost. She had no GVHD. She remained in hematological remission with slower recovery of normal counts. One month later, there was cytogenetic evidence of autologous marrow recovery and progression of leukemia with 18% XX cells and 3% 5q− cells in PB and 30% XX cells and 3% 5q− cells in BM.

On day 85 posttransplant (50 days after the BM boost), she was treated with IL-2 (9 million IU/m²/d) by continuous infusion for 4 days to induce GVL in order to eradicate residual leukemia that was refractory to chemotherapy. This IL-2 dose had been used for patients who received chemotherapy in a Children’s Oncology Group study for AML.5 Although the dose was higher than that used in a study after allogeneic transplant,6 it was chosen based on leukoreduction of GVHD, despite a brief course of tacrolimus after her BM boost and her good clinical condition. Her complications from the high-dose IL-2 therapy were fever, anorexia, rash, emesis, and diarrhea and capillary leak. After stopping IL-2, she still had a rash and mild capillary leak syndrome. She was treated with prednisone for a few days for possible GVHD and had a rapid and complete response 6 days after the completion of IL-2 therapy. She did not receive planned maintenance IL-2 therapy because of the toxicity associated with the induction dose. Performing FISH, it was observed that she did well for three months with FISH studies showing >99% donor cells and <0.1% 5q−. She had a normal performance status and excellent quality of life. On day 155 post-transplant, her minimal residual disease by 5q− FISH started to increase.

On day 240 posttransplant, she was administered IL-2 (3 million IU/m²/d). A lower dose was used to avoid the complications, which she experienced with the higher dose. IL-2 was tolerated fairly well, and she achieved complete remission by 15 days after the start of IL-2 therapy. However, she developed edema and wheezing toward the end of a 10-day period with a maintenance dose of 1 million IU/m²/d. Computed tomography scan showed extensive mediastinal soft tissue encasing her pulmonary veins that was consistent with fibrosing mediastinitis. Before IL-2 therapy, she required placement of a tunneled central venous catheter. The fibrosing mediastinitis was postulated to be due to catheter...
placement followed by IL-2 therapy because of previous suggestions that idiopathic fibroinflammatory disorders may be due to immune reactions to blood vessel wall abnormalities. The patient was previously tested negative for histoplasmosis. She was sent to the operating room for a biopsy of the mass, but this could not be performed as she had a cardiac arrest with the induction of anesthesia.

After the procedure, she required inotropic support for severe bradycardia and she was kept on a ventilator. She was treated with prednisone and cyclosporine, as the severe bradycardia was thought to be due to GVHD. She was administered fludarabine because of the good response of her leukemia to fludarabine at diagnosis and because of the risk of prednisone and cyclosporine inhibiting the GVL, enabling her minimal residual disease to progress. Her bradycardia resolved rapidly with immunosuppression. Unfortunately, she had a morphological relapse of her AML within 3 weeks of starting immunosuppression. She was sent home on palliative care at her parents’ request and passed away soon after.

CONCLUSIONS

We describe a single case in which the patient with FA and AML responded to IL2 infusion, ultimately achieving a complete remission for months. The IL-2 was associated with significant infusion-related toxicity. The higher dose of IL-2 used during the first time was associated with more infusion-related toxicity due to a more intense immune response. There was also a better and more prolonged leukemia response supporting the importance of the IL-2-generated immune response.

Unfortunately, the patient had a rare complication of fibrosing mediastinitis after her second IL-2 treatment that required immunosuppression. Her leukemia progressed rapidly after the start of immunosuppression, suggesting that remission was being maintained by a GVL effect.

Others have reported the use of donor lymphocyte infusion and IL-2 to induce remission in patients with hematologic malignancies who had relapsed after stem cell transplantation. Our experience suggests that further research in prophylactic IL-2 therapy after transplant or preemptive therapy for cytogenetic relapse may be helpful in patients with BRCA2 FA and AML, who often have chemotherapy-resistant disease.

REFERENCES


