Graft-Versus-Myeloma Effect: Proof of Principle

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The presence of a graft-versus-tumor effect has been well established in leukemia but not in multiple myeloma. A 40-year-old patient with myeloma refractory to standard chemotherapy and autologous transplantation received a matched unrelated T-cell-depleted transplant after conditioning with fractionated total-body irradiation, thiotepa, and cyclophosphamide. This procedure resulted in a transient and incomplete response with evidence of rapidly progressive disease within 2.5 months posttransplantation. The patient then received a small number of donor peripheral blood (PB) mononuclear cells (CD3 cells 1.2 × 10^6/kg) without any further cytotoxic therapy. A complete remission was attained, lasting now for more than 14 months. The procedure was associated with severe acute and subsequently limited chronic graft-versus-host disease (GVHD). This report provides the first direct evidence of a graft-versus-myeloma effect after allogeneic transplantation.

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CD34, 0.08 \times 10^9/kg. Eight days after infusion of fresh donor cells (day +124 post-bone marrow transplant [BMT]), the patient developed bilateral retroperitoneal, axillary, and inguinal adenopathy, and splenomegaly (3 cm below left costal margin). Fine-needle aspiration showed reactive lymphadenopathy, and vancomycin and piperacillin were started. Four days later, a fever of 101°F and a rash developed. Antibiotics were discontinued and daily prednisone 60 mg was started for 4 days, resulting in complete disappearance of rash, splenomegaly, and adenopathy. Upon prednisone tapering, diffuse erythema recurred, prompting reinitiation of prednisone at 60 mg. A skin biopsy was diagnostic of GVHD grade IV. The patient was admitted 28 days after the second infusion of donor buffy coat cells because of progressive skin GVHD with blister formation, worsening of diarrhea (500 mL), and mild elevation of alanine aminotransferase to 78 U/L. Daily methylprednisolone at 2 mg/kg was started. Because of progressive skin desquamation, intravenous cyclosporin at a dose of 5 mg/kg was administered on alternating days with dose adjustment according to serum levels. Diarrhea increased to a maximum of 1,100 mL/day. Liver-function tests remained normal; direct bilirubin was 1.1 mg/dL, alanine aminotransferase 78 U/L, and aspartate ami- notransferase and alkaline phosphatase remained normal. The skin lesions improved slowly, and the patient was discharged 56 days after infusion of fresh donor buffy coat cells.

M protein level was 3.9 g/dL at the time of fresh donor buffy coat infusion, but was no longer detectable 2 weeks after admission for acute GVHD (42 days after second buffy coat). Immunofixation analysis showed no evidence of monoclonal protein. The bone mar- row biopsy was normocellular (50%) with normal trilineage hematopoiesis without evidence of residual multiple myeloma. DNA fingerprinting indicated the presence of donor cells and less than 10%, if any, recipient cells.

CMV antigenemia recurred during acute GVHD (63 days after fresh buffy coat). Persistent thrombocytopenia necessitated platelet transfusions until 18 weeks after infusion of donor cells. All immunosuppressive therapy was discontinued on day 230 posttransplantation (106 days after infusion of fresh donor cells). On day 55 after transplantation, the patient developed chronic GVHD involving the mouth, eyes, and liver, which improved upon institution of oral prednisone at 1 mg/kg/d along with cyclosporin 5 mg/kg every other day. Prednisone has since been slowly tapered to a current dose of 5 mg/d. Abnormal laboratory tests include alkaline phosphatase elevation to 777 U/L, aspartate aminotransferase 83 U/L, alanine aminotransferase 139 U/L. The patient has not required red blood cell or platelet transfusions for 12 months, maintaining an almost normal hemogram with a hemoglobin level of 14.3 g/dL, a WBC count of 6.5 \times 10^9/L, and a platelet count of 137 \times 10^9/L. Her Karnofsky score is more than 90%.

**DISCUSSION**

This patient’s clinical course provides direct evidence that a graft-versus-myeloma effect exists. There was only a transient antitumor effect to total-body irradiation, thiotaepa, and cyclophosphamide, and in fact progressive disease was clearly documented before day +70 posttransplantation. Cryopreserved donor PB cells had no apparent effect on myeloma parameters; fresh donor mononuclear cells obtained from 100 mL PB resulted in complete disappearance of all evidence of disease, based on morphology, flow cytometry to detect aneuploidy within the plasma cells with the same light-chain restriction as the myeloma cells, and M protein measurements in blood and urine on immunofixation. The lack of efficacy of cryopreserved donor cells might have been the consequence of excessive cell death during freezing and thawing or the presence of inadequate numbers of donor cells.

The antimyeloma effect in this patient was associated with severe GVHD requiring aggressive therapy with high-dose glucocorticosteroids and cyclosporin A without abrogation of the antitumor effect. The patient remains in complete remission 14 months after the fresh donor PB infusion with limited chronic GVHD and persistent mild thrombocytopenia (137 \times 10^9/L).

It is extremely unlikely that the antitumor effect in this patient resulted from corticosteroid treatment for GVHD. The patient had been resistant to two cycles of high-dose dexamethasone before transplantation and remained in complete remission during 6 months of discontinuation of all steroid therapy after the donor cell infusion.

It is a humbling experience for BMT physicians to appreciate a profound antitumor effect exerted by donor PB cells after failure of myeloablative chemoradiotherapy. Our findings and recent results with donor buffy coat infusions in patients with relapsed CML strongly argue in favor of a major contribution of a graft-versus-tumor effect in the eradication of hematologic malignancies. In CML, donor buffy coat cells effect tumor cytoreduction exceeding 6 logs. Our findings appear to be different from those reported in CML in at least three aspects. (1) Whereas control of CML seems to require large quantities of PB mononuclear cells, with no responses seen with less than 10^7 T cells/kg, the complete response in our myeloma patient required 10 to 500 times fewer donor cells. It is unknown whether the same effect would have been seen if HLA-matched sibling donor cells had been infused. (2) While the best results in CML are seen in patients treated either in stable chronic phase or in early relapse (cytogenetic or molecular, before hematologic relapse), our patient achieved a lasting complete response upon administration of donor cells in fulminating relapse. Our result is similar to observations reported by Drobyski et al., who reported cytogenetic remissions in six patients with accelerated-phase CML. (3) Whereas in CML, GVL-associated cytogenetic (median, 2 to 4 months) and molecular (median, 6 to 10 months) remissions are attained slowly, the graft-versus-myeloma effect in our patient was brisk, with disappearance of myeloma...
protein and resolution of bone marrow plasmacytosis in less than 1 month. Although it is unlikely, we cannot exclude the possibility that the cryopreserved donor PB cells may have undergone a rapid expansion following the infusion of fresh donor cells and thus may have contributed to this remarkable response. Occasionally, cytogenetic and molecular remissions in CML have been documented as early as 40 days postinfusion. Complete cytogenetic or molecular responses were reported by Van Rhee et al in all five patients receiving unrelated donor cell infusions, as compared with five of nine in the sibling donor group.

Since the half-life of normal IgG is approximately 23 days, it can be assumed that the entire antitumor effect in our patient was accomplished within the first 2 weeks after donor cell infusion, which is in keeping with data in murine models. It is likely that future progress in cancer therapy will depend on judicious and safe manipulation of the immune system, rather than on further intensification of cytotoxic agents.

ACKNOWLEDGMENT

The authors gratefully acknowledge the dedicated secretarial assistance of Christina Bewley and the excellent technical assistance of Dwayne Bracy.

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