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LETTER TO THE EDITOR

Salvage with a mini-allograft after primary engraftment failure following autologous transplant for multiple myeloma

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A 45-year-old patient with IgG myeloma was found to be refractory to five cycles of continuous infusion cyclophosphamide, vincristine, doxorubicin and dexamethasone. Approximately 50% reduction in paraprotein was achieved with 6 months of thalidomide and dexamethasone. An autograft was planned, but in view of the young age and poor response to initial chemotherapy, human leukocyte antigen (HLA) typing was performed for a possible mini-allograft in the event of a poor response to the autograft. A brother was found to be HLA-identical. Autologous stem cells were mobilized with 5 days of granulocyte-colony stimulating factor (G-CSF) (10 μg/kg in two divided doses per day). The total number of cells collected over 2 days of apheresis was 2.56×10^8 mononuclear cells/kg with a CD34+ cell dose of 5×10^6/kg.

Melphalan was administered at the dose of 200 mg/m^2 and unmanipulated stem cells were infused the next day. G-CSF was started on day +7. Neutropenic fever was treated with meropenem, teicoplanin and amphotericin B. He continued to remain pancytopenic on day +18. Bone marrow on day +19 revealed marked hypocellularity with no evidence of myeloma. New parenchymal lung infiltrates developed consistent with a breakthrough fungal infection on a chest computerized tomography scan. As there was no evidence of engraftment by day +21, it was decided to proceed with a mini-allograft from the HLA-identical sibling.

He was conditioned with a combination of fludarabine 90 mg/m^2 over 3 days (days −4 to −2) and a single dose of 200 cGy total body irradiation on day 0. The donor was mobilized with G-CSF and 19.3×10^6 CD34+ cells/kg collected and infused. Cyclosporine and mycophenolate were used as graft-versus-host disease (GVHD) prophylaxis. Antimicrobial therapy was continued and G-CSF was started on day +5 to hasten engraftment. Granulocyte transfusions were given on days +2 and +5. Prompt engraftment was achieved with an absolute neutrophil count of >500/mm^3 on day +8 and an unsupported platelet count of >20 000/mm^3 by day +9. Chimerism analysis using variable number tandem repeats performed on day +30 showed complete donor-type engraftment. He developed grade II acute GVHD involving the gastrointestinal tract, which responded to treatment with steroids.

On day +51, cytomegalovirus (CMV) disease was diagnosed on biopsy and blood polymerase chain reaction (PCR) when diarrhea and vomiting developed. This was initially treated with ganciclovir, but therapy was switched to leflunomide (100 mg daily for 3 days, followed by 20 mg once daily) when ganciclovir-induced pancytopenia developed. On a total of 4 weeks of leflunomide, there was gradual improvement in CMV disease with complete resolution of symptoms and a negative blood PCR. At the last follow-up 16 months after the allograft, he has limited chronic GVHD on cyclosporine and alternate-day corticosteroids. The performance status is normal with no evidence of fungal or CMV infection. Serum immunofixation is negative and there is 100% donor-type chimerism.

Primary engraftment failure following an autologous transplant is very uncommon but has serious consequences.[1–4] Prolonged neutropenia in the setting of graft failure increases the risk of fungal infections that usually respond poorly to therapy because of persistently low counts. Second transplants following graft failure or relapse are generally associated with a poor outcome related mainly to infection and organ toxicity[5], but improved outcome has been reported with the use of reduced-intensity allografts because of lower toxicity.[6,7,8]

Our patient had active fungal infection at the time of the allogeneic transplant, but a combination of antifungal therapy along with granulocyte transfusions and prompt donor engraftment helped in controlling and subsequently curing the fungal infection. The use of leflunomide to treat CMV was based on data from the renal transplant group at our centre[9] and case reports on its use in allograft recipients.[10]

We conclude that a mini-allograft may be a reasonable treatment option in selected patients with failure of autologous engraftment.

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