Profound graft-versus-tumor response in metastatic breast cancer with nonmyeloablative allografting

Introduction

Allogeneic transplants from human leukocyte antigen (HLA)-compatible donors can cure hematologic malignancies which cannot be cured with chemotherapy alone. This technique was first applied to metastatic breast cancer in 1996 [1], where response in lymph node and bone metastases was attributed to an immune response induced by myeloablative allogeneic transplant. This report demonstrated that breast cancer cell lines expressed class I antigen-restricted major histocompatibility complex molecules and that cytotoxic minor histocompatibility antigen-specific T cells recognizing breast cancer cells were present in the patient after transplant. Subsequently, a series of 10 patients receiving ablative allogeneic transplant for advanced breast cancer indicated response in 50% with post-transplant immune response induced by withdrawal of immune suppressive drugs [2]. In the same year, immune response induced by interleukin-2-activated T-lymphocytes following autologous transplantation was reported [3]. The use of infusions of sibling-derived HLA-matched lymphocytes as immunotherapy have been reported to produce tumor responses in breast cancer [4].

The high treatment-related morbidity and mortality associated with myeloablative conditioning regimens led to the introduction of reduced intensity regimens in the late 1990s, which relied on a graft-versus-leukemia effect to achieve response. With suggestion that there is a graft-versus-tumor effect possible in breast cancer, we pioneered a protocol in 1997 which combined the antitumor effect of high-dose chemotherapy and autologous stem-cell infusion with reduced intensity allogeneic stem-cell transplant for patients with HLA-matched sibling donors. The results in 17 patients with
resistant metastastic breast cancer have been published [5]. Three patients had partial remissions after autologous stem-cell transplant and complete remissions after allogeneic transplants; they achieved full chimerism and all developed graft-versus-host disease before regression of cancer. All three are still alive at 82+, 87+ and 118+ months, one having relapsed at 67 months in the colon. Another patient showed no response to autologous stem-cell transplant but had partial remission after allografting. Five patients had grade II or higher acute graft-versus-host disease and five had extensive chronic graft-versus-host disease. No nonrelapse-related deaths occurred during the first 100 days.

In this article, we report a subsequent patient transplanted from her HLA-identical sister. Disappearance of liver, adrenal, mediastinal, pleural and diffuse nodes metastases observed simultaneously with clinical chronic Graft versus host disease (GVHD) 5 months after reduced intensity conditioning transplant suggest a profound graft-versus-tumor effect.

**case report**

A 55-year-woman with Estrogen Receptors (ER) / Progesteron Receptors (PR)-negative inflammatory ductal breast cancer stage III, underwent mastectomy in 1997; subsequently she was treated with radiotherapy and adjuvant cyclophosphamide/epirubicin for 4 months which ended in November 1997. She remained well until 2005 when the disease relapsed in several bones and in bone marrow. Despite two further chemotherapy regimens (taxol- and vinorelbine based), the disease progressed to involve liver, pleura, adrenals, mediastinal and abdominal nodes and further bones. In September 2006, she received autografting conditioned by mitoxantrone 45 mg/m² on day −5 and thiotapec 10 mg/kg on day −4 followed by infusion on day 0 of 7.2 × 10⁶ CD34+ cells/kg, previously collected after cyclophosphamide (3 g/m²) and filgrastim. Subsequent positron emission tomography (PET) Computerized axial tomography (CAT) scan (November 2006) showed no change in metastases. In November 2006 she underwent conditioning for allogeneic transplant with fludarabine (30 mg/m²/day on days −4, −3, −2) and melphalan (70 mg/m²/day on day −2). On day 0, 2.12 × 10⁶ donor CD34+ cells/kg were infused. Immunosuppression was with methotrexate 8 mg/m² on days 1, 3 and 5 after transplantation, and cyclosporine 1 mg/kg/24 h from day −1 through day +15, subsequently 5 mg/kg orally. Sustained hematopoiesis was achieved on day +16 and the patient was discharged on day +17. Complete hematopoietic chimerism was documented 4 weeks after allografting by isoenzyme analysis in peripheral blood mononuclear cells. The further post-transplant course was uneventful until day +50 when acute graft-versus-host disease grade II of the skin developed. Treatment with methylprednisolone was started which was discontinued after graft-versus-host disease had resolved. On day +130, chronic graft-versus-host disease of the skin developed. One week later (20 April 2007), PET-CAT scan documented the total resolution of metastases in the liver, nodes, pleura, mediastinum and adrenal gland. Also bone metastases showed a significant reduction of PET positivity (Figures 1–3). Nine months after Reduced-intensity conditioning for transplant (RICT), the patient is in complete remission under mild immunosuppressive treatment for limited Chronic graft versus host disease (cGVHD).

![Pre-Allografting](image1.png) ![Five months after Allografting](image2.png)

**Figure 1.** Positron emission tomography/CAT of the core—pre- and postallografting.
Figure 2. Positron emission tomography/CAT of the liver—pre- and post-allografting.

Pre-Allografting

Five months after Allografting

Figure 3. Positron emission tomography/CAT of the sternum and vertebral—pre- and post-allografting.

Pre-Allografting

Five months after Allografting
discussion

It was not until 2002 that the first pilot study of nonmyeloablative intensity conditioning transplants for advanced breast cancer was published and in subsequent years a few more have followed [4–7]. These results confirmed that reduced intensity conditioning allogeneic transplants may be safe but in advanced stage disease remission cannot be sustained and survival is not significantly prolonged and, therefore, this treatment is not justified. Less intensive conditioning for allogeneic transplant reduces the risk of the transplant, which might make it suitable in the adjuvant setting.

The response in this case, heavily pretreated and with no other options for cure, supports the possibility of a graft-versus-tumor effect. Complete resolution of metastases in nodes and in several organs concomitant with full chimerism and chronic GVHD was observed 5 months after reduced intensity conditioning transplantation. This response cannot be ascribed to conventional doses of fludarabine and melphalan. Nine months after RICT, the patient is in good health and in complete remission. She is receiving mild immunosuppressive treatment for limited cGVHD.

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references


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