Current role of allogeneic stem cell transplantation in breast cancer

The majority of patients with metastatic breast cancer will relapse and will die of their disease. Allogeneic stem cell transplantation (AlloSCT) with myeloablative conditioning regimens may provide cytotherapy and eradication of disease with two advantages: a cancer free-graft and an immunemediated graft-versus-tumor (GVT) effect mediated by the donor’s immune cells. The first report of an AlloSCT in solid tumors has been published in 1996 [1]. Since then, several small series have been published, especially in renal cell and breast cancer [2, 3–11]. With reduced-intensity conditioning regimens (RIC), the goal of transplantation is the achievement of a full donor engraftment and the induction of a GVT effect, rather than chemotherapy-related cytotherapy. Clinical responses suggestive of a GVT effects have been reported, and more than 1000 patients with refractory and advanced solid tumors, to date, have undergone RICT in EBMT centers.

Graft-versus-breast cancer effect

In 1996, Eibl et al. reported a single patient with metastatic breast cancer who achieved a complete remission after a matched-sibling allogeneic donor transplant. They were also able to isolate from the blood of the patient minor histocompatible antigen-specific and major histocompatibility complex I antigen-restricted cytotoxic T lymphocytes recognizing breast carcinoma target cells [1]. Subsequently, Ben-Yosef et al. provided evidence of breast cancer response following allogeneic transplantation for acute leukemia [12]. In 1998, Ueno et al. published a series of 10 patients with breast cancer who received a myeloablative conditioning and a matched sibling bone marrow donor transplant, observing two responses concurrently with acute graft-versus-host disease. However, the high toxicity of the conditioning and the heavy pretreatment of these patients, associated with a high tumor burden, precluded a meaningful evaluation of the effects of allogeneic transplantation [2].

A clear direct evidence of GVT in hematological malignancies came from the observation that donor lymphocyte infusions can induce remissions of malignant diseases without cytotoxic therapy in patients who relapse after AlloSCT [13]. The GVT effect is strongly associated with GVHD; the responses occur after withdrawal of immunosuppression and after establishment of complete donor chimerism; moreover, the time to response is delayed following transplant.

Spontaneous GVT effects against solid tumors were first documented in the 1980s in mouse models following allogeneic transplantation. Most of the available data on animal models of allografting in solid tumors came from Shimon Slavin and his group in Jerusalem. They demonstrated that naive or immune donor cells, sensitized with either tumor or normal mismatched splenocytes, were able to mediate an effective anti-tumor activity in mice inoculated with a minimal dose of mammary carcinoma cells [14, 15]. Findings indicate that a class of these antigens, called minor histocompatibility antigens (mHags), are peptides derived from cellular proteins and presented to T-cells by MHC molecules in the same way as are viral antigens. Many mHags are expressed on normal hematopoietic (e.g. progenitors, B and T lymphocytes, monocytes), epithelial (e.g. keratinocytes, fibroblasts, gut, liver), and malignant hematopoietic cells. The Leiden group has described a mHag called HA-1, which is expressed by cells of the hematopoietic lineage; the emergence of HA-1-specific cytotoxic T lymphocytes (CTLs) coincided with the remission of chronic myeloid leukemia or of multiple myeloma after allogeneic transplantation [16].

Reduced-intensity conditioning regimens for AlloSCT

It is based on the concept that the reduction in dose and intensity of the conditioning gives a chance also to patients in advanced age and with comorbidities to be eligible to allografting. Since the median age of occurrence of sporadic breast cancer in the general population is 45–49 years, a sizable proportion of these patients would be eligible to AlloSCT. Different drugs are used for this purpose: fludarabine is almost invariably present in all associations; however, its dosage varies considerably from a regimen to another (75–200 mg/m²). Several drugs are currently associated with fludarabine: low-dose (2 Gy) total body irradiation (TBI), conventional drugs known for their immunosuppressive capacity (cyclophosphamide), low-dose myeloablative drugs (busulfan, thiothepta) and/or other potent immunosuppressive compounds (anti-T immunoglobulins or monoclonal antibodies). Although the feasibility has been demonstrated in almost all situations, it does not appear that one of them is superior to the others.

Usually, these regimens are followed by peripheral blood stem cell, rather than by bone marrow transplantation; although this represents a universal trend in AlloSCT, this shift from bone marrow transplant may cause an increased rate of extensive chronic GVHD.
Results of RICT in breast cancer have been recently published [2, 3–11]. In these reports, transplant-related mortality (TRM) has been registered in 0–22% of the patients; a disease response attributable to a GVT effect has been observed in 16–37% of patients and some responses are long-lasting. The EBMT and the CIBMTR reviewed data of patients transplanted in 15 centers between 1992 and 2000 (Ueno et al., manuscript submitted). Sixty-six patients with poor-risk disease were identified; median age at transplantation was 41 years (range, 23–60). Median follow-up time for survivors was 40 months (range, 3–64). Thirty-nine patients (59%) received myeloablative and 27 (41%) received RICT. More patients in the RICT group had poor pre-transplant performance status. More patients in the myeloablative group developed acute (44 versus 34% at 100 days) and chronic (36 versus 8% at 1 year)GVHD. TRM was lower with RICT (29 versus 7% at 100 days). Overall (complete plus partial) response rates were 31% in the myeloablative group and 29% in the RICT group. Nine of 33 patients (27%) who underwent immune manipulation for persistent or progressive disease after AlloSCT had disease control (stable disease or response), suggesting a GVT effect. Overall probability of survival at 2 years was 21% (12–32%) for all patients. Patients who developed acute GVHD after a RICT had lower risks of relapse or progression than those who did not (RR 3.05, P = 0.03).

Carella et al. utilized autografting to achieve maximum tumor reduction before proceeding to RICT. This strategy could provide the benefit of a conventional allograft, but with reductions in the typical acute toxicities and associated mortality of myeloablative conditionings. Between September 1997 and April 2004, they enrolled 17 patients with metastatic breast carcinoma [17]. Median age was 41 years. At the time of autografting, the patients had received a median of 3 (range, 2–5) previous chemotherapy lines; 14 patients had received hormone therapy, and seven patients had undergone radiotherapy on bone lesions. The primary endpoint of this study was the decrease of non-relapse mortality (NRM) from the current 20–35% noted after myeloablative allografting. Patients received autografting at a median of 53 months (range, 14–152) from the diagnosis of breast cancer. No patient died after transplants. One patient who had been in complete remission and two who had been in partial remission before autografting remained in complete or partial remission. No non-relapse mortality was noted in the first 100 days after RICT. Thirteen patients achieved full chimerism. Five patients (29%) developed grade II–III acute GVHD, while six patients developed chronic GVHD (five patients with extensive disease) and needed intensive immunosuppressive therapy. We have recently reported a subsequent patient transplanted from her HLA-identical sister. Disappearance of liver, adrenal, mediastinal, pleural, and diffuse nodes and bone metastases, observed simultaneously with clinical chronic GVHD 5 months after RICT, suggested a profound graft-versus-tumor effect (A. M. Carella, submitted).

Bishop et al. transplanted 16 patients with metastatic breast cancer that had progressed after treatment with anthracyclines, taxanes, hormonal agents and trastuzumab [9]. To distinguish an immunological GVT effect from any anti-tumor effect of cytotoxic chemotherapy in the transplant-conditioning regimen, allogeneic T lymphocytes were removed from the stem-cell graft and were subsequently administered late post-allogeneic transplant. Allogeneic lymphocytes at escalating doses were infused on days +42, +70 and +98 post-allogeneic transplant, respectively. Objective tumor regressions occurred after day +28 post-allografting in six patients and were attributed to allogeneic lymphocyte infusions. Tumor regressions occurred concomitantly with the establishment of complete donor T-lymphoid engraftment, were associated with the development of GVHD and were abrogated by subsequent systemic immunosuppression.

will allografting have a place in the busy therapeutic armamentarium of breast cancer?

Chemoresistant disease, high tumor burden, rapid progression are unfavorable conditions for immune-based therapies like AlloSCT. It has been mostly utilized so far in patients who have failed multiple lines of conventional chemotherapy, often with a rapidly progressing disease. On the other hand, a risk/benefit balance should take into account the transplant-related mortality associated with AlloSCT; even in its non-myeloablative form. Possible solutions are: the selection of patients known to have poor prognosis for upfront transplantation [3]; the adoption of a cytoreductive strategy, either surgical or chemotherapy-based, prior to transplantation [17]; the selection of patients with non-rapidly progressing disease [8]. Targeted therapies are changing the scenario of treatment of breast cancer, and in selected cases, such as trastuzumab, they are being introduced in the adjuvant treatment of high-risk disease [18]; it should be noticed, however, that AlloSCT is itself an immunotherapeutic strategy, and that both strategies can powerfully complement each other if appropriately combined.

These data suggest that a GVT effect exists against metastatic breast cancer. As with hematological malignancies, larger numbers of patients in earlier phase of breast cancer receiving RICT alone or after autografting would be required to determine whether a GVT effect can produce a more clinically relevant response.

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references


