1083-8791/07/1301-0001$32.00/0
doi:10.1016/j.bbmt.2006.10.022

ASBMT
American Society for Blood and Marrow Transplantation

# Allogeneic Stem Cell Transplantation for Solid Tumors: Which Way Forward?

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## ABSTRACT

**The patients presenting with metastatic solid tumors remains with poor prognosis. Despite advances in treatment and better understanding of the biological pathway during the past two decades, outcome remains often very poor. On the other hand, allogeneic stem cell transplantation has been established as a potent antitumoral immunotherapy in various hematological malignancies. Preliminary results confirm that graft versus tumor effect does exist. The main challenge is now to transform this biological and clinical effect into a real clinical benefit in term of curability and survival.**


## INTRODUCTION

At the conclusion of a recent meeting in Stresa, Italy that gathered medical oncologists and investigators worldwide involved in allogeneic stem cell transplantation (allo-SCT) for nonhematologic malignancies [1], Marco Bregni highlighted the following points:

1. Allografting in solid tumors is feasible with limited toxicities and transplant-related mortality (TRM). However, further improvement of toxicities and TRM is needed if the procedure is to become accepted by the oncology community, particularly in diseases for which many therapeutic options exist (eg, breast cancer and renal cell carcinoma).
2. A graft-versus-tumor (GVT) effect can be documented in various solid tumors. Further research is needed to translate the GVT effect into meaningful clinical benefits.
3. Advanced renal cancer appears to be the most promising solid tumor for allografting. Other tumors with promising response rates are breast cancer and ovarian cancer.
4. There is some evidence that small-volume disease achieved by tumor debulking before transplantation or by cytoreduction with chemotherapy with or without autologous transplantation may be of benefit.
5. Targeting the immune response to the tumor with specific immune lymphocytes, natural killer (NK) cells, or vaccines, is a promising area of research.
6. Unrelated or haploidentical donor transplantation for solid tumors remains in the developmental phase.
7. The search for target antigens of the immune response should be a translational research endpoint included in every clinical trial.

These conclusions were promulgated after a 2-day meeting during which medical oncologists and allo-SCT investigators exchanged their experiences with biological and clinical aspects of tumor development and treatment. These exchanges facilitated a comprehensive overview of achievements and unanswered questions in the field and provided a basis for future directions. Three diseases were discussed in detail: renal cell carcinoma (RCC), breast cancer (BRC), and ovarian carcinoma (OVC). These were chosen because high numbers of patients have been transplanted for these indications, and because consistent evidence of tumor response is documented.

## RENAL CELL CARCINOMA

The initial pioneering study by Childs et al [2] achieved response rates of up to 53% in patients who had failed other forms of immunotherapy (mainly recombinant interleukin-2 and/or interferon [INF]-α) and who received allo-SCT after reduced-intensity conditioning including cyclophosphamide and fludarabine, from an HLA-identical sibling. Childs et al recently updated their results; currently, 75 patients with a median of 2 metastatic sites have undergone transplantation. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A, given alone in the initial cohort and later in combination with mycophenolate mofetil or mini-dose methotrexate. Tumor responses (frequently preceded by tumor progression) were delayed in onset (130-160 days after transplantation), sometimes occurring after the administration of posttransplantation INF-α, even in patients who had previously failed this treatment. In a

few cases, responses were durable. Overall, sustained engraftment was achieved in 74 of 75 patients. Acute and chronic GVHD were observed in approximately 50% of the patients. Death from TRM occurred in 8% of the patients, half of whom died from complications related to GVHD. To date, 38% of the patients have exhibited radiographic evidence of tumor regression (27% partial remission [PR]; 9% complete remission [CR]), with responses occurring at a median of day 160 after transplantation (range, days 30-425). Several prognostic factors are associated with response, including a limited number of metastatic sites, exclusive lung metastases, clear cell histology, and "slow" progressive disease. Liver metastases appear to be a negative prognostic factor (an 11% response rate in those who underwent transplantation for liver metastasis), whereas lung metastasis was a positive factor (a 55% response rate). Responses in nonclear histology, including papillary tumors, were not observed. Artz et al [3] reviewed the literature and the Chicago experience and found that in 14 reported studies, a total of 163 evaluable patients had 32 PRs and 7 CRs, with an overall response rate of 24%.

## BREAST CARCINOMA

The first cases of tumor regression after allo-SCT were observed in patients treated for metastatic breast cancer [4,5]. The first series of patients was reported by Ueno et al [6] from the M.D. Anderson Cancer Center. Ten patients with liver or bone marrow metastases received a standard conditioning regimen (cyclophosphamide, BCNU, and thiotepa). Three objective responses after tapering of immunosuppression (1 CR, 2 PRs) were documented. This finding was later confirmed by other investigators [7-10]. The largest unpublished series was presented by Ueno and Niederwieser on behalf of the Center for International Blood and Marrow Transplantation Research (CIBMTR) and the European Group for Blood and Marrow Transplantation (EBMT).[1] A total of 75 patients who received an allograft between 1992 and 2000 from a HLA-identical or unrelated donor from 16 centers were included. A GVT effect was suggested by disease response according to a preliminary data analysis.

## OVARIAN CARCINOMA

Although the first patient receiving an allo-SCT was reported almost 50 years ago [11], the first patient series documenting a GVT effect was reported only recently [12]. On behalf of the EBMT, Bay et al [12] described 24 patients who had undergone allo-SCT (with 2 receiving 2 allo-SCTs), 2 with a myeloablative regimen (cytoxan + busulfan) and 22 with 1 of 3 nonmyeloablative fludarabine-based regimens. Median age was 51 years. Patients received allo-SCT at a median of 41 months from diagnosis; disease status at time of transplantation was progressive disease (PD) in 9 patients, stable disease (SD) in 10 patients, PR in 6 patients, and CR in 1 patient. The graft source was bone marrow in 5 (19%) and peripheral blood stem cells in the other 21 (81%). Engraftment and full donor chimerism were rapid and complete, irrespective of the conditioning. Acute GVHD was observed in 15 patients (≥ grade 2 in 11 cases [44%]), correlated with tumor response in 8 cases. Chronic GVHD occurred in 8 patients, in 3 after donor lymphocyte infusion (DLI). Seven patients received DLI for PD, and 3 achieved PR associated with chronic GVHD. Responses were as follow: 0 CR, 13 PR, 7 SD, and 4 PD. TRM was relatively high (6 patients; 28%), and 16 patients died from disease progression. The median survival time was 10 months.

## MELANOMA

Metastatic melanoma was initially a favored area of investigation for allo-SCT, due mainly to the positive results obtained after nonallogeneic immunotherapy based on cytokine [13] or vaccine approaches [14]. However, the absence of tumor response has consistently been reported [15]. Melanoma is now considered a contraindication for allo-SCT.

## OTHER TUMORS

Although other tumors are of interest, reports on these remain anecdotal. However, preliminary clinical evidence of a GVT effect has been described in soft tissue sarcoma, pancreatic cancer, prostate cancer, and colon cancer [1,16].

## CURRENT DIFFICULTIES

It is reasonable to conclude that GVT effects occur in diverse metastatic solid tumors. Nevertheless, the number of patients with solid tumors referred for allo-SCT remains low for several reasons, which must be taken into consideration if recruitment is to be improved [17].

First, most ST patients receiving allo-SCT are not included in clinical trials. In 2004, published series accounted for only 200 patients, whereas almost 1000 allo-SCT patients were reported to the EBMT alone. This has reduced the impact of allo-SCT data and has promoted a "last-chance" transplantation approach for end-stage patients already nonresponsive to other treatments. Besides being of no benefit to the patients, this strategy reinforces the perception that allo-SCT is unsuccessful, discouraging clinical trials in more appropriate disease settings.

Second, there are multiple failures of communication between medical oncologists and the transplantation community. The failure of autologous transplantation to prolong survival in women with breast

cancer has had a deleterious impact on the referral of patients with solid tumors for investigational allo-SCT trials. Many practicing oncologists who could refer patients for allo-SCT do not understand the immunotherapeutic nature of the allograft. In addition, new targeted therapies are becoming available to oncologists, notably for RCC. There is an unproven assumption that these agents will be as spectacular as imatinib has been in treating chronic myeloid leukemia. Although patients may fail targeted treatments, these new drugs remain attractive because they are less toxic than allo-SCT. Furthermore, outside of the transplantation community, the continuing trend toward decreased TRM is little known and underestimated. Response rates of patients after allo-SCT remain within the range of 15%–25%. Although this finding is encouraging considering the disease status of most patients, there are very few CRs, and although survival is sometimes prolonged, most patients eventually die from progressive disease. Clearly, medical oncologists would refer more patients if the results were better. Improved outcome could be anticipated if fewer patients in advanced-stage disease were referred, given the anticipated improved therapeutic effect and lower transplant-related toxicity [5].

Despite its limitations, however, allo-SCT adds a unique immunotherapeutic component with the promise of cure. Our challenge is both to transform allo-SCT into an efficient therapy and to communicate our optimism to the oncologic community.

## THE WAY FORWARD

### Patient Selection

Adequate selection of patients with poor prognosis at an early stage of disease is mandatory to achieve better tumor control and reduce toxicity, and it is the only likely way to achieve cure. Better markers of disease prognosis and treatment response are needed to identify those patients most likely to benefit from allo-SCT.

### Debulking

Optimal strategies for decreasing tumor load at the time of transplantation by surgical or chemotherapy debulking should be defined. Targeted therapies may also be valuable, but such treatment must be selected according to the precise molecular pathology.

### Cell Therapy

NK cells, T-regulatory cells, and $CD8^+$ cytotoxic T cells are potential candidates in complementary strategies to achieve better antitumor effects.

### Improved Understanding of Target Antigens and Immune Mechanisms

Identification of the antigens mediating GVT could lead to vaccine or adoptive cell transfer strategies that could significantly improve the antitumor effect.

### Widening of the Donor Repertoire

Because most patients do not have an HLA-identical sibling donor, transplants from alternative donors should be incorporated into clinical trials of allo-SCT to treat solid tumors.

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