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NONMYELOABLATIVE ALLOGENEIC IMMUNOTHERAPY FOR SOLID TUMORS*

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■ **Abstract** Over the past decade, considerable advances have been made in the field of allogeneic hematopoietic stem cell transplantation. Recognition that transplanted donor immune cells can cure patients with leukemia has led to the development of nonmyeloablative or "low-intensity" conditioning regimens, which have expanded the application of allogeneic transplantation to a growing number of hematological malignancies. The improved safety and preliminary success of this transplant approach have justified applying allogeneic immunotherapy to patients with treatment-refractory solid tumors.

INTRODUCTION

Allogeneic bone marrow or peripheral blood cell transplantation (referred to as hematopoietic stem cell transplantation or SCT) was originally developed as a method to rescue bone marrow function following high-dose (myeloablative) therapy in the treatment of hematological malignancies (1). Despite recent advances in systemic therapies, for many patients allogeneic SCT remains the only treatment that offers a chance of cure. Over the past decade, our understanding of the mechanisms by which malignant cells are eradicated following transplantation has evolved considerably. Originally, high-dose conditioning was thought to be the main factor responsible for long-term disease-free survival. More recently, it has become clear that transplanted immune cells are capable of killing malignant cells. This so-called graft-versus-leukemia (GVL) or graft-versus-tumor (GVT) effect is a powerful form of immunotherapy that can eradicate advanced or even chemotherapy-resistant leukemias.

The list of hematological malignancies in which GVL effects have been described now includes not only acute and chronic leukemias but also myelodysplastic syndromes, myelofibrosis, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, and Epstein-Barr virus–related lymphoproliferative disorder. The ability of donor lymphocyte infusions to induce remission in patients with relapsed chronic myelogenous leukemia (CML) has provided indisputable evidence of the curative potential of GVL and impelled the development of nonmyeloablative transplant approaches (2). Furthermore, it has stimulated oncologists to seek similar beneficial allogeneic immune effects in metastatic solid tumors (3). This article reviews the development and early clinical results of allogeneic stem cell transplantation as immunotherapy for solid tumors.

THE IMMUNE SYSTEM AND CANCER

The first documented attempt to use the immune system to treat patients with advanced cancer was reported in the late nineteenth century by W. Coley, who injected bacterial toxins into the tumors of cancer patients (4). However, more than a half a century passed before investigators began systematic efforts to explore immunotherapy as an adjunct to other systemic therapies in the treatment of advanced cancer. Recent interest in the development of immune-based treatments for solid tumors has been motivated by the failure of conventional chemotherapy to cure most patients.

The late twentieth century saw the birth of cytokine therapies designed to stimulate the host's immune system against cancer. Pioneering studies by Rosenberg and colleagues in the 1980s provided some of the first evidence that natural killer (NK) cells and T lymphocytes could induce clinically relevant regression of advanced cancer (4–8). In particular, reports of treatment-refractory disease regressing following interleukin-2 (IL-2) and/or interferon-alpha treatment suggested that immunotherapy-based strategies could complement chemotherapy in some tumors. Remarkably, some patients with metastatic melanoma and renal cell carcinoma (RCC) achieved durable remissions following treatment with IL-2, an immune-enhancing agent with no direct antineoplastic effects. Unfortunately, most immunotherapy regimens using cytokines have generally had low response rates and are sometimes associated with considerable toxicity (9–11). It is generally agreed that the main contribution of cytokine-based treatment has been to establish proof of concept, laying the foundation for future immune-based therapies.

Recently, the characterization of antigens overexpressed or restricted to cancer cells has led to the development of vaccines aimed at enhancing host immunity specifically at the tumor (12, 13). This remains a rapidly developing area of investigation with the potential for improving the safety and specificity of immunotherapy compared to nontargeted cytokine-based approaches. Nevertheless, these strategies are very much in their infancy; only a handful of patients treated with cancer vaccines have yet shown clinical benefit.

Defects in the immune system of the tumor-bearing host may be partially responsible for the low response rates from treatments designed to boost self

(autologous) immunity to cancer (14–18). Prior exposure to chemotherapy or global T-cell anergy to cancer as a consequence of tumors lacking immunostimulatory ligands (e.g., B7.1) may contribute to these abnormalities. Allogeneic SCT, which replaces the recipient's defective immune system with that of the healthy donor, could potentially overcome some of these barriers.

ALLOGENEIC IMMUNOTHERAPY: THE GRAFT-VERSUS-LEUKEMIA EFFECT

Allogeneic SCT offers many patients with hematological malignancies the only chance for a cure. During its early development, it was believed that "mega-dose" conditioning (chemotherapy alone or in combination with total body irradiation) was an absolute requirement for the eradication of all malignant cells (1). However, the advent of highly sensitive molecular techniques to measure minimal residual disease showed that many patients with detectable residual leukemia in the first few months following SCT ultimately became "molecular cures." The realization that high-dose, or myeloablative, conditioning frequently fails to eradicate all leukemic cells and the observation that the risk of leukemic relapse is lower in patients who develop graft-versus-host disease (GVHD) provided the first evidence of a GVL effect following SCT (19–23). The demonstration that patients with relapsed CML following allogeneic SCT could be cured by donor lymphocyte infusions, established beyond doubt both the existence and curative potential of the GVL effect (24, 25). Antimalignancy effects after lymphocyte infusions occur in a wide variety of hematological malignancies (26–31). However, response rates to donor lymphocyte infusion for relapsed malignancy after SCT vary according to stage and type of disease (Table 1). For example, ~80% of patients with CML relapsing in chronic phase can be expected to be cured by donor lymphocyte infusion therapy. In contrast, durable responses to donor lymphocyte infusion are relatively rare in relapsed acute myelogenous leukemia (AML) or CML relapsing into blast crisis.

TABLE 1 Targets for a graft-versus-leukemia effect

Malignancy	Susceptibility to GVL
Chronic myelogenous leukemia (chronic phase)	High
Chronic lymphocytic leukemia	High
Low-grade non-Hodgkin's lymphoma	High
Acute myelogenous leukemia	Intermediate
Myelodysplastic syndrome	Intermediate
Multiple myeloma	Intermediate
Intermediate/high grade non-Hodgkin's lymphoma	Intermediate
Hodgkin's disease	Intermediate
Acute lymphocytic leukemia	Low
Chronic myelogenous leukemia (blast crisis)	Low

The mechanisms that account for variability in susceptibility to GVL have not been defined, although in general, rapidly proliferating leukemias appear to be less responsive to the immune effect.

Although allogeneic NK cells may play a role in GVL in HLA-mismatched transplants, most in vitro and in vivo evidence suggests donor T cells are the dominant immune population mediating disease regression (32–37). Indeed, the risk of relapse of some hematological malignancies (e.g., CML) increases substantially when donor T cells are depleted from the allograft in an effort to prevent GVHD (38).

The antigens that serve as the primary target for GVL are not fully understood. The pattern of tissue distribution dictates whether GVL occurs in the presence or absence of GVHD. The scenario of relapsed disease remitting after donor lymphocyte infusion in the absence of GVHD would imply a response to antigens that are restricted to hematopoietic tissues or specifically to the leukemia (39–42). T cells with leukemia-restricted patterns of cytotoxicity have been expanded in vitro from the blood of responding patients. However, in many patients the GVL effect is accompanied by acute or chronic GVHD, suggesting a broader tissue distribution of target antigens. Such responses are directed against broadly expressed minor histocompatibility antigens (mHa) that are polymorphic between the patient and donor.

GRAFT-VERSUS-TUMOR EFFECTS IN SOLID TUMORS

Rationale

Expression of major histocompatibility complex (MHC) class I, in vitro susceptibility to peptide-specific T-cell killing, and regression of disease after treatment with IL-2 provide the basis for speculation that select solid tumors could be susceptible to a GVT effect following allogeneic SCT (5–13). As discussed, mHa differences between the patient and donor may be the dominant antigens targeted by the donor immune system during GVL effect. It can be hypothesized that cancers originating from tissues that are a target of GVHD (skin, liver, gastrointestinal tract, etc.) would express the same mHa that induce GVHD, thus making them a target of the donor alloresponse. Additionally, antigens restricted to the tumor could stimulate tumor-specific alloresponses from donor T cells in contrast to defective tolerized T cells in the tumor-bearing host. However, despite the theoretical advantages of allogeneic immunotherapy, it should be remembered that solid tumors are apt to evade immune-mediated killing. Tumor-cell downregulation of MHC molecules, secretion of soluble inhibitors of T-cell function (e.g., TGF-β), and expression of membrane-bound Fas ligand are just a few mechanisms that could potentially inhibit both autologous and allogeneic immune responses (3, 17, 18, 43).

Animal Models

Before clinical trials were pursued, animal models were tested for the existence of a graft-versus-solid-tumor effect (44). Among mice inoculated with mammary

adenocarcinoma cells, survival in those that received an allogeneic SCT was superior to survival in recipients of a syngeneic SCT (45). Further studies provided evidence that murine mammary adenocarcinoma cells expressed mHa that could be targeted by alloreactive donor T cells in the setting of allogeneic but not autologous bone marrow transplantation (46). These studies provided valuable insight into the plasticity of the GVL effect, suggesting for the first time that allogeneic immune responses might also be inducible against nonhematological malignancies.

Clinical Data

One of the first studies investigating whether an alloresponse might occur outside of the setting of hematological malignancies was a pilot trial comparing autologous versus allogeneic SCT in children with metastatic neuroblastoma (47).

Although GVT effects were not observed in the allogeneic cohort, this isolated observation was not sufficient to support generalizations about the susceptibility of other solid tumors to GVT.

The earliest evidence supporting the existence of an allogeneic GVT effect in a solid tumor came from patients with metastatic breast carcinoma undergoing fully myeloablative allogeneic SCT. A letter describing the incidental regression of a metastatic breast carcinoma lesion in a patient receiving an allogeneic SCT for relapsed AML raised the possibility that a GVT effect was responsible (48). At the same time, regression of liver metastasis in association with severe acute GVHD was reported in a woman transplanted for metastatic breast carcinoma (49). The ability to kill breast cancer cell lines with alloreactive T cells expanded from the patient during GVHD suggested that disease regression resulted from donor T cells targeting broadly expressed (including on the tumor) mHa. In 1998, a series of 10 patients with metastatic breast cancer treated at a single institution with an allogeneic SCT was reported (50). Although disease regression was mainly attributable to myeloablative conditioning, two patients responded during acute GVHD following the withdrawal of immunosuppression. These reports provided the first evidence that a donor immune-mediated antitumor effect could occur after an allogeneic SCT. Unfortunately, enthusiasm for this approach was tempered by significant and sometimes fatal toxicities associated with the transplant.

NONMYELOABLATIVE CONDITIONING AS A PLATFORM TO EVALUATE ALLOGENEIC SCT IN SOLID TUMORS

The observation of GVL effects following SCT and the demonstration that the immune system could be used to treat some metastatic cancers following cytokine therapy prompted exploration of allogeneic transplantation in patients with nonhematological malignancies. Despite progressive improvements in transplant safety, procedure-related mortality remains near 25%. Without evidence of efficacy, most considered this risk too high to justify studies of allogeneic SCT in patients with nonhematological malignancies.

Morbidity related to intensive conditioning contributes significantly to the risk of myeloablative transplants. Veno-occlusive disease of the liver, pneumonitis, and severe mucositis leading to opportunistic bacterial and fungal sepsis are the main toxicities directly related to high-dose conditioning that can be lethal. In an effort to improve the safety profile of allogeneic SCT, investigators recently developed reduced-intensity or nonmyeloablative conditioning regimens. The key factor motivating nonmyeloablative transplant trials was an increased confidence in the potential of the GVL effect to cure malignant diseases. Nonmyeloablative conditioning regimens use powerful immunosuppressants to allow engraftment of the donor immune system while reducing overall toxicity. Pilot trials of this approach were first evaluated in hematologic malignancies known to be sensitive to GVL (51–57). Although no direct comparisons of myeloablative versus nonmyeloablative regimens have yet been made, preliminary data on the safety of this new approach have been encouraging. Several centers reported transplant-related mortality rates of $<20\%$ in patient cohorts usually precluded from conventional SCT because the risk of procedure-related mortality was considered unacceptable. Nonmyeloablative transplants have already been shown to induce GVL effects sufficient to cure patients with a variety of advanced hematological malignancies, including acute and chronic leukemias. The reduced toxicity of this approach offered investigators a safer transplantation modality through which to test whether GVT effects could be induced in solid tumors.

NONMYELOABLATIVE ALLOGENEIC SCT FOR METASTATIC RENAL CELL CARCINOMA

Trial Design

The possibility that the immune system could control metastatic renal cell carcinoma (RCC) was first entertained in the late 1920s after a case report of a patient who had spontaneous regression of metastatic disease (58). The search for donor-mediated GVT effects in this disease was further encouraged by the observation that many patients with metastatic RCC have dysfunctional immunity, and by other in vitro and in vivo evidence of RCC's susceptibility to immune attack (10, 59):

- Isolation of tumor-infiltrating lymphocytes from metastatic lesions
- In vitro data showing susceptibility to lymphokine-activated killer (LAK) cells
- In vitro data showing susceptibility to killing by antigen-specific T cells
- Response of systemic disease to immunomodulator therapy (e.g., IL-2)

We began pursuing nonmyeloablative SCT in patients with metastatic RCC in late 1997, soon after the favorable results of nonmyeloablative SCT in hematological malignancies (60). Because of the experimental nature of the transplant approach, we restricted our pilot trial to patients with metastatic disease

who had failed cytokine-based immunotherapy. Patients with CNS metastasis were excluded in anticipation of an increased risk of intracranial bleeding from conditioning-related thrombocytopenia. Furthermore, concerns related to GVHD morbidity limited the procedure to those who had either an HLA-identical or single-HLA-antigen–mismatched sibling donor. Our strategy to minimize toxicity and optimize the induction of a GVT effect included reduced-intensity conditioning, early withdrawal of immunosuppression, and the administration of donor lymphocyte infusions or cytokines (interferon-alpha or IL-2) for those with progressing disease.

Toxicity and Engraftment

Preliminary results of pilot trials evaluating nonmyeloablative SCT in patients with advanced RCC have recently been reported (60–65). Although most regimens have been well tolerated, complications associated with nonmyeloablative SCT vary with the type and intensity of conditioning agents. Common toxicities associated with conventional myeloablative SCT, such as severe mucositis and veno-occlusive disease of the liver, are rare in RCC patients undergoing nonmyeloablative SCT (Table 2).

Because nonmyeloablative conditioning does eradicate recipient hematopoiesis, both donor and patient myeloid and lymphoid cells are usually detectable at the time of neutrophil recovery (54). This state, called mixed chimerism, is in contrast to the full donor myeloid and lymphoid chimerism that follows myeloablative SCT. Mixed T-lymphocyte chimerism appears to induce donor tolerance to recipient tissue, decreasing risk of acute GVHD. Donor immune effects do not usually occur until donor lymphocytes predominate in the blood. Patients with a prior history of chemotherapy exposure and those exposed to more immunosuppressive conditioning agents develop full donor chimerism faster than those who are chemotherapy-naive or who receive less intense conditioning. Because most

TABLE 2 Transplant-related toxicities after nonmyeloablative SCT

Toxicity	Incidence (%)
Mucositis	0%–5%
Veno-occlusive disease of the liver	0%–5%
Pneumonitis	0%–10%
Febrile neutropenia	25%–90%
Thrombocytopenia requiring platelet transfusions	0%–30%
Graft rejection	0%–10%
Acute graft-versus-host disease	15%–55%
Cytomegalovirus reactivation	20%–40%
Chronic graft-versus-host disease	30%–70%
Transplant-related mortality (overall)	10%–20%

patients with RCC have not received chemotherapy prior to the transplant, donor T-cell engraftment is delayed compared to patients with hematologic malignancies. As a consequence, the majority of nonmyeloablative SCT regimens incorporate strategies to accelerate the conversion from mixed to full donor chimerism by early discontinuation of GVHD prophylaxis (usually cyclosporine or tacrolimus) or by the infusion of donor lymphocytes.

Evidence That RCC is Susceptible to a GVT Effect

Although the ultimate role of allogeneic immunotherapy in the treatment of advanced kidney cancer is still evolving, preliminary trials of nonmyeloablative SCT in RCC quickly established that this tumor is susceptible to a GVT effect (Table 3). The first patient with cytokine-refractory metastatic RCC treated at the NIH using cyclophosphamide (120 mg/m^2) and fludarabine (125 mg/m^2) conditioning had complete regression of pulmonary and bony metastatic disease four months after the procedure and remains in remission >5 years post-transplant (Figure 1). Subsequently, 10 of the first 19 patients transplanted (all cytokine-therapy failures) had a GVT effect with 7 partial and 3 complete responses (61). Disease responses were observed most commonly in patients with the clear-cell variant of RCC (~80% of all RCC cases) in the setting of isolated pulmonary metastatic disease. However, dramatic responses occasionally occurred in patients with extensive metastatic disease in multiple metastatic sites including the bones, lymph nodes, and liver (Figure 2). Failure to observe disease regression following immunosuppression withdrawal did not always preclude the induction of a GVT effect, as some patients responded to a donor lymphocyte infusion. Remarkably, some patients who had been resistant to interferon-alpha before SCT responded to low doses of this agent given subcutaneously after transplantation.

Investigators from The University of Chicago reported four partial responses in 15 patients who received an allograft from an HLA-identical sibling (62). Notably, one partial responder had regression in the primary kidney tumor, a rare event among responders to cytokine-based therapy. Their initial regimen using low doses of fludarabine (90 mg/m^2) and cyclophosphamide (2 g/m^2) resulted in a 75% graft rejection rate. When the doses of fludarabine and cyclophosphamide were increased to 150 mg/m^2 and 4 g/m^2, respectively, all subsequent patients achieved

TABLE 3 Published results of nonmyeloablative SCT for renal cell carcinoma

Reference	Patients (#)	Conditioning agents	Response rate (PR + CR)
61	19	Fludarabine, cyclophosphamide	53%
62	15	Fludarabine, cyclophosphamide	33%
7	7	Fludarabine, cyclophosphamide	0%
63	7	Thiotepa, fludarabine, cyclophosphamide	71%

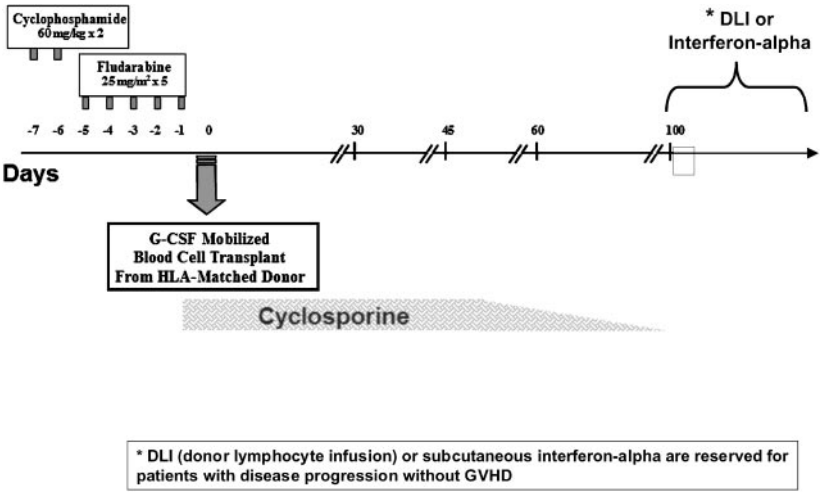

Figure 1 The nonmyeloablative transplant approach used in the pilot trial at the National Institutes of Health for patients with treatment-refractory renal cell carcinoma. Post-transplant immune enhancement through donor lymphocyte infusion or cytokine administration (usually subcutaneous interferon-alpha or IL-2) is reserved for patients with disease progression in the absence of acute or chronic graft-versus-host disease.

sustained donor engraftment. These results highlight how small changes in the doses of conditioning drugs can dramatically influence engraftment. In contrast to the high incidence of GVHD (∼55%) observed following the NIH regimen, only 2 of 12 (17%) patients treated at The University of Chicago experienced grade 2 or greater acute GVHD, perhaps because of a more gradual withdrawal of GVHD prophylaxis. It is of some concern, however, that the lower incidence of GVHD may also be associated with a weaker GVT effect.

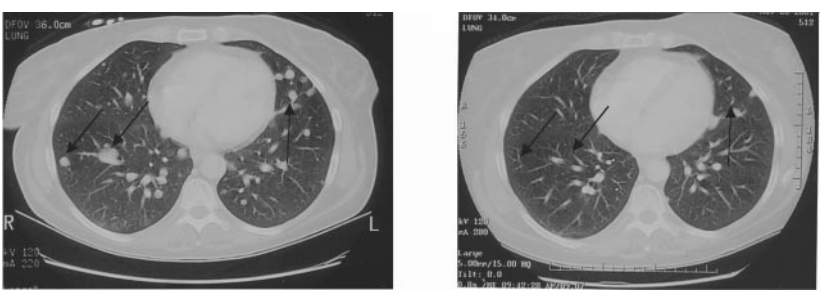

Figure 2 Regression of multiple pulmonary metastases in a patient with IL-2–refractory renal cell carcinoma (clear-cell type) 7.5 months after a nonmyeloablative allogeneic transplant.

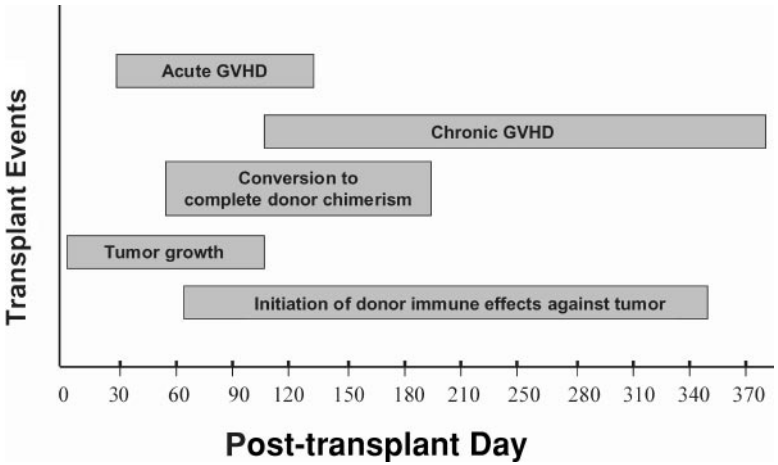

Figure 3 Post-transplant events that provide evidence supporting the involvement of donor T cells in mediating disease regression in renal cell carcinoma events after nonmyeloablative stem cell transplantation.

Another group recently reported partial responses in 4 of 7 (57%) patients with metastatic RCC following treatment with a fludarabine- and thiotepa-based SCT (63). The regimen was associated with minimal toxicity and is now being used in a cooperative European trial investigating GVT effects in patients with a variety of metastatic solid tumors. Regression of metastatic RCC has also been described in nonmyeloablative transplants using 2-chlorodeoxyadenosine (2-CDA), low-dose busulphan, or low-dose total body irradiation (64–66). Trials investigating which nonmyeloablative strategy might be optimal in this malignancy are yet to be developed.

Mechanisms of GVT in RCC

The development of more effective transplant approaches requires a better understanding of the immune cells responsible for the GVT effect. The nonmyeloablative SCT trials described above have all provided indirect evidence that donor immune cells are responsible for the regression of metastatic RCC. The observation that disease regression is delayed four months or more after conditioning and is associated with acute GVHD, immunosuppression withdrawal, donor lymphocyte infusions, and a state of predominantly donor T-cell chimerism strongly suggests that donor T lymphocytes play a central role in mediating disease responses (Figure 3). Furthermore, the observation that tumor regression occurs with or without acute GVHD suggests that both broadly expressed mHa and antigens restricted to the tumor may be target antigens for these allogeneic immune effectors.

Preliminary in vitro data show that RCC cells express a broad range of mHa that could render them susceptible to a GVT effect in the setting of GVHD (67,

68). T-cell clones with tumor-restricted cytotoxicity have been expanded from a few that responded without GVHD (69). These preliminary findings support the hypothesis that distinct T-cell populations recognizing tumor-restricted antigens and/or antigens shared by both the tumor and normal tissues (e.g., mHa) are targets for the GVT effect.

LIMITATION OF ALLOGENEIC SCT IN RENAL CELL CARCINOMA

The susceptibility of RCC to a GVT effect following allogeneic SCT has already provided clinical benefit to patients with advanced treatment-refractory disease. Unfortunately, several factors currently limit the broader application of this approach:

- Allogeneic SCT requires an HLA-matched sibling donor
- There is a 4–6-month delay before the GVT effect occurs
- Patients with rapidly progressive disease are unlikely to benefit
- Risk of regimen related mortality is 10%–20%
- Complete response is rare

Currently, nonmyeloablative SCT is reserved for patients with an HLA-compatible sibling donor, i.e., approximately one third of all patients. Trials evaluating nonmyeloablative SCT using HLA-matched unrelated donors have started, and if effective, could potentially expand the application of allogeneic immunotherapy to the majority of patients with RCC. The regimen-related toxicity of nonmyeloablative SCT is clearly lower than would be expected with a conventional transplant, but life-threatening complications such as GVHD and opportunistic infection still occur. At present, ~10%–15% of patients die as a complication of the procedure. Consequently, most referring oncologists prefer to reserve transplantation for patients failing cytokine therapy. However, because the GVT effect typically takes four months or longer to become established, delaying the transplant increases the risk that the patient will succumb to the tumor before an antitumor response occurs (70). Metastatic RCC is often a rapidly proliferating tumor associated with short survival. It is therefore important to be selective when choosing transplant candidates, as patients with "explosive" metastatic disease will not survive the time required for the generation of a GVT effect.

ALLOGENEIC SCT FOR MELANOMA

Metastatic melanoma has shared a reputation with RCC as an immunoresponsive tumor. Given the positive results of nonmyeloablative SCT in patients with metastatic RCC, it is reasonable to presume that similar GVT effects could be

induced against this tumor. Several groups have attempted to use nonmyeloablative transplantation in patients with advanced treatment-refractory melanoma (54, 71). Surprisingly, preliminary results show allogeneic SCT to have little to no efficacy in this disease. Anecdotal reports of patients with "explosive" metastatic progression in the setting of acute and chronic GVHD are particularly discouraging. A retrospective analysis of 25 patients with metastatic melanoma treated at four different institutions with three different nonmyeloablative regimens showed disappointing results (71). Although 24 of 25 patients achieved sustained donor engraftment and about half developed acute GVHD, only one patient had evidence of a GVT effect. None of the six patients who received a donor lymphocyte infusion responded. Most depressing was the median survival of only 100 days for this patient group. These results may have been due to the inclusion of patients with treatment-refractory, rapidly proliferating tumors, who could not benefit from a delayed GVT effect. Further studies of allogeneic SCT in metastatic melanoma should therefore be reserved for the small subset of patients with slowly growing disease.

ALLOGENEIC PERIPHERAL BLOOD SCT FOR OTHER SOLID TUMORS

Although the number of investigational transplants being conducted for solid tumors has increased substantially over the past few years, insufficient data preclude comment on the efficacy of allogeneic SCT in most solid tumors other than RCC. There are anecdotal reports of GVT effects following nonmyeloablative SCT in patients with metastatic breast carcinoma, colon carcinoma, pancreatic carcinoma, and osteosarcoma (63, 64, 66). A case report and a small case series of tumor responses in patients with metastatic ovarian cancer have also been described recently (72, 73). However, the susceptibility of this tumor to chemotherapy and the proximity of the responses to the transplant conditioning make it difficult to conclude with certainty that disease regression resulted from an immune effect.

Trials designed to systematically investigate nonmyeloablative SCT in a variety of metastatic solid tumors are currently under way in the United States, Japan, and Europe. It will take several years for them to accrue sufficient patients to determine the sensitivity of individual solid tumors to GVT effects.

FUTURE DIRECTIONS

These initial transplant trials have provided proof of principle that an allogeneic GVT effect can be used to treat advanced solid tumors. However, strategies to separate GVT from GVHD are needed to improve the safety and efficacy of this transplant technique. Based on observations described here, it appears that donor T cells recognizing the tumor can be distinct from those causing GVHD. Methods to selectively deplete alloreactive cells that respond to GVHD antigens while

preserving T cells with antiviral and antileukemia effects are currently being investigated in clinical trials (74, 75). If effective, this strategy could provide a useful basis for establishing the donor immune system without a need for post-transplant immunosuppression. Furthermore, it could provide a platform to target allogeneic lymphocytes to the tumor through vaccination strategies or the adoptive transfusion of tumor-specific T cells.

Another promising approach is to exploit the ability of donor NK cells to exert powerful allo-immune cytotoxicity in the setting of mismatched donor-recipient combinations. This effect has recently been illuminated in studies demonstrating heightened NK cell cytotoxicity to HLA-mismatched tumor targets as the consequence of killer IgG-like receptor incompatibility. In this situation, NK cells that are normally inhibited from exerting cytotoxicity by suppressing signals from autologous HLA class I molecules can be cytotoxic to HLA-mismatched targets. In HLA-mismatched transplantation, such incompatibility can result in powerful NK cell–mediated effects in which leukemic relapse is almost completely abrogated (33, 76). Whether solid tumors might be similarly susceptible to alloreactive NK cells is a current area of investigation (77).

Although the use of allogeneic SCT for the treatment of solid tumors is still in its infancy, developments such as these provide a realistic expectation that SCT will be more widely and effectively used in the future.

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