

Allogeneic Hematopoietic Stem Cell Transplantation for Solid Tumors

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Abstract:

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiation therapy. Stem cells may be obtained from the transplant recipient (autologous HSCT) or can be harvested from a donor (allogeneic HSCT). Stem cells may be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

The perception of the mechanisms through which malignant cells are eradicated following allogeneic hematopoietic cell transplantation (HCT) has evolved substantially over the past four decades. No longer merely thought of as a means to rescue hematopoietic function following myeloablative conditioning, allogeneic transplantation is now known to be a powerful type of immunotherapy capable of curing patients with other-wise fatal malignant diseases. This conceptual evolution has translated into a diversification of the indications for allotransplants and led to the development of reduced intensity transplant approaches whose beneficial antineoplastic effects occur as a consequence of the transplanted donor immune system. Recently, investigators have begun to test whether non-hematologic malignancies might likewise be susceptible to allogeneic immune attack.

Keywords: Cancer, Solid Tumors, Stem Cell Transplantation

Introduction:

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiation therapy.

Stem cells may be obtained from the transplant recipient (autologous HSCT) or can be harvested from a donor (allogeneic HSCT).

Stem cells may be harvested from:

1. Bone marrow,
2. Peripheral blood,
3. Umbilical cord blood shortly after delivery of neonates.

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Although myeloablative conditioning can cytoreduce or debulk malignancies, the curative antitumor effects of allogeneic hematopoietic stem cell transplantation (HCT) are mostly mediated by transplanted donor immune cells. A heightened awareness and appreciation of the immune-mediated anticancer effects that occur after allogeneic transplantation has led to the increasing use of reduced-intensity stem cell transplantation (RIST) approaches to treat advanced malignancies. The graft-versus-leukemia effects that occur against hematologic cancers after RIST have recently attracted oncologists to explore the therapeutic potential of allogeneic HCT for treatment-refractory solid tumors. Delayed tumor regression after RIST in a subset of patients with metastatic renal cell, breast, ovarian, pancreatic, and colon carcinoma has recently been reported, confirming the existence of a graft-versus-tumor effect in solid tumors. Advanced disease states, rapidly growing tumors, and accrual of patients with extremely short survival are factors that have been identified to limit the efficacy of allogeneic immunotherapy. This review discusses

results of allogeneic HCT for solid tumors and the development of newer transplant strategies to optimize the potential of the graft-versus-tumor effect. 1

The field of bone marrow transplantation has undergone dramatic changes over the past few decades. Not only has the terminology changed (e.g., hematopoietic stem-cell transplantation), but the role of allogeneic transplantation has been modified from supportive to immunotherapeutic and the applications have expanded from hematologic malignancies to solid tumors. The development of non-myeloablative conditioning regimen has greatly increased the number of patients eligible for this kind of treatment. Use of hematopoietic stem-cell transplantation as a form of adoptive immunotherapy in the treatment of cancer depends on advances in tumor immunology, particularly the identification of tumor antigens and mechanisms of immunotherapy. The earliest use of allogeneic transplantation of immunogenic cells for the treatment of solid tumors in the late 1960s and early 1970s produced no definite graft-versus-tumor effects. However, as conventional allogeneic hematopoietic stem-cell transplantation methods for the treatment of hematologic malignancies have matured, these methods have reestablished the foundation for expanding their application to solid tumors. From the first case reports on medulloblastoma and breast cancer to subsequent case series reports on breast cancer and renal cell carcinoma, allogeneic hematopoietic stem-cell transplants have demonstrated graft-versus-tumor effect. At present, the most common solid tumor for which this treatment is used is advanced renal cell carcinoma, but allogeneic hematopoietic stem-cell transplants have proven feasible for other solid tumors as well. 2

Autologous HSCT takes advantage of the steep dose-response relationship observed with many chemotherapeutic agents and allows for escalation of chemotherapy doses above those limited by myeloablation. 3

The use of allogeneic HSCT for solid tumors relies on a graft-versus-tumor effect. Allogeneic HSCT is uncommonly used in solid tumors, and may be used if an autologous source cannot be cleared of tumor cells or cannot be harvested. 4

Our perception of the mechanisms through which malignant cells are eradicated following allogeneic hematopoietic cell transplantation (HCT) has evolved substantially over the past four decades. No longer merely thought of as a means to rescue hematopoietic function following myeloablative conditioning, allogeneic transplantation is now known to be a powerful type of immunotherapy capable of curing patients with other-wise fatal malignant diseases. 5

This conceptual evolution has translated into a diversification of the indications for allotransplants and led to the development of reduced intensity transplant approaches whose beneficial antineoplastic effects occur as a consequence of the transplanted donor immune system. Recently, investigators have begun to test whether non-hematologic malignancies might likewise be susceptible to allogeneic immune attack. 5

Early clinical data suggesting graft vs solid tumor effects

in humans

The first report suggesting a possible GVT effect against a tumor of epithelial origin noted the incidental regression of a metastatic breast adenocarcinoma lesion following allogeneic HCT for relapsed acute myelogenous leukemia. 6

Use of non-myeloablative conditioning in allogeneic transplantation for solid tumors:

By the late 1990s, there was sufficient interest in investigating for GVT effects against solid tumors based on available preclinical and clinical data. The major factor limiting the initiation of pilot trials was the significant morbidity and mortality associated with conventional allogeneic HCT. 5

Dose-intensive conditioning used to provide both tumor cytoreduction and a means to allow donor engraftment contributed in part to the morbidity and mortality associated with HCT. Subsequently, it was recognized that reducing the intensity of the conditioning regimen might translate to a reduction in the risk of procedure-related morbidity and mortality.

In the late 1990s, transplant regimens using non-myeloablative or reduced intensity conditioning were designed by a number of investigators and were evaluated for their engraftment potential and toxicity profile. 5

Two major factors impacted on the design and development of these dose-reduced conditioning regimens.

First, the recognition that GVL effects alone may be sufficient to eradicate some hematologic malignancies in the absence of dose-intensive therapy.

Second, the realization that the primary role of the conditioning regimen could be limited to preparing the recipient for engraftment by inducing adequate host immunosuppression. 5

Thus, non-myeloablative conditioning regimens were designed using agents that would induce adequate immunosuppression to facilitate donor immune engraftment while maintaining a low toxicity profile. 5

Pilot trials utilizing non-myeloablative HCT (NMHCT) demonstrated that such regimens were generally well-tolerated, having a decreased incidence of transplant-related morbidity and mortality while achieving sufficient donor immune engraftment to induce sustained remissions of some hematologic malignancies. 5

Characteristics of solid tumors that might predict for susceptibility to an allogeneic graft versus tumor effect: 7

1. High degrees of MHC class I expression
2. Genetic mutations resulting in expression of immunogenic tumor antigen(s)
3. Susceptible to immunomodulatory therapy (ie, cytokines, vaccines)
4. Data showing in vitro susceptibility of tumor to T-cell attack
5. Normal tissue from which tumor originated is a target for acute or chronic GVHD
6. Tumor kinetics show a slow to moderate proliferative capacity

Clinical results of NMHCT in solid tumors

The current worldwide clinical experience of NMHCT for solid tumors is limited, with <200 cases reported in the literature. Because there existed no convincing evidence to support the existence of a GVT effect in solid tumors, pilot trials have been restricted primarily to terminally ill patients with advanced treatment-refractory metastatic disease. 5

Renal Cell Carcinoma

At present, RCC remains the solid tumor in which allogeneic antitumor responses have been best characterized. The following factors provided an incentive to study the susceptibility of this malignancy to a GVT effect. 5

First, metastatic RCC is a uniformly fatal cancer in which the majority of patients succumb to disease within a year of diagnosis.

Second, therapeutic options are extremely limited, with conventional chemotherapy and radiotherapy being largely ineffective

Third, RCC is considered an “immune-responsive” tumor based on its susceptibility to cytokine therapy, history of occasional spontaneous regression and existence of tumor-infiltrating T lymphocytes in regressing metastatic lesions. 5

These considerations led to the development of a clinical protocol at the National Institutes of Health (NIH) that sought to test the safety and efficacy of NMHCT in patients with cytokine-refractory metastatic RCC. 5

At present, more than 55 patients have undergone NMHCT for RCC at the NIH. Of the 50 patients who are currently evaluable for outcome, 49 engrafted fully and achieved 100% donor T-cell chimerism by day 100 post-transplant. Twenty-two of 50 (44%) patients have had a disease response including four CRs (complete remission) and 18 PRs (partial remission). Five patients who were deemed “non-responders” had radiographic evidence for a mixed response. 5

Disease regression was associated with acute and chronic GVHD and was typically delayed in onset and did not occur until CSP was tapered, consistent with an alloimmune-mediated GVT effect. 5

Several patients have proven to have a durable disease response including the first complete responder who remains without evidence of metastatic disease nearly 5 years post-transplant. 5

Regression of disease in multiple metastatic foci has been observed although pulmonary responses appear to occur most frequently. On occasion, disease responses have been dramatic and have included complete resolution of large pulmonary metastases with bulky adenopathy. 5

Colorectal Carcinoma

Aglietta and colleagues reported their experience with 39 patients with metastatic colorectal cancer who underwent reduced-intensity conditioning (RIC) allogeneic HSCT between 1999 and 2004 at 9 European Group for Blood and Marrow Transplantation (EBMT) centers. 8

Endpoints that were assessed were achievement of mixed chimerism, incidence of graft-versus-host disease (GVH), treatment-related mortality and toxicities, overall survival

(OS), and time to treatment failure (in patients who responded to the therapy). 8

Patient population characteristics were heterogeneous; pre-transplant disease status was partial response in 2 patients, stable disease in 6 patients, and progressive disease in 31. Thirty-eight patients (97%) had been previously treated, some with only chemotherapy and others with surgery and/or chemotherapy. 8

After transplant, tumor responses were complete in 2% of patients; partial in 18%, and 26% of patients had stable disease, for overall disease control in 46% of patients. Transplant-related mortality was 10%. Median overall follow-up was 202 days (range: 6–1,020 days), after which time 33 patients had died and 6 were still alive. Tumor progression was the cause of death in 74% of patients. 8

Achievement of response after transplantation was associated with a difference in OS, with the 18 patients who had a response having a median OS of approximately 400 days versus approximately 120 days for those who had no response ($p=0.00018$). 8

Pancreatic Cancer

Kanda and colleagues reported on the efficacy of RIC (reduced intensity conditioning) allogeneic HSCT against advanced pancreatic cancer in 22 patients from 3 transplantation centers in Japan. 9

The RIC regimens differed among the centers, and the patient population was fairly heterogeneous, with 15 patients having metastatic disease and 7 locally advanced disease. 9

After HSCT, 1 patient achieved complete response, 2 patients had partial response, 2 had minor response, and 8 had stable disease, with an overall response rate of 23%. 9

Median survival was 139 days, and the major cause of death was tumor progression (median duration of survival in advanced pancreatic cancer in the non-transplant setting is less than 6 months, even in patients treated with gemcitabine). 9

Only 1 patient survived longer than 1 year after transplantation. The authors concluded that a tumor response was observed in one fourth of patients with advanced pancreatic cancer who underwent HSCT and that the response was not durable. 9

Abe and colleagues reported the outcomes for 5 patients with chemotherapy-resistant, unresectable pancreatic adenocarcinoma who received a non-myeloablative allogeneic peripheral blood HSCT. The median patient age was 54 years (range: 44–62 years). All patients had advanced disease, either with metastases or peritonitis, and had received at least 1 course of chemotherapy including gemcitabine. After HSCT, tumor response was only observed in 2 patients—1 had complete disappearance of the primary tumor and 1 had a 20% reduction in tumor size; the remaining patients had progressive disease ($n=2$) or stable disease ($n=1$). 10

The authors concluded that their study showed a graft-versus-tumor effect but that in order to obtain durable responses, an improved conditioning regimen and new strategies to control tumor growth after non-myeloablative allogeneic HSCT are needed. 10

Breast Cancer

The high prevalence of breast carcinoma in the general population as well as the recent disappointing results of autologous transplantation trials has inspired a number of investigators to explore NMHCT in patients with this malignancy. 11

Bregni et al. treated six patients with metastatic breast cancer with NMHCT following conditioning with cyclophosphamide, fludarabine and thiotepa. 11

Two patients had a partial response that was delayed and did not occur until several months following transplantation. In both cases, responses were preceded by DLIs and GVHD, consistent with a GVT effect. 11

Graft-versus-tumor effect in non-small-cell lung cancer

Moscardo et al reported a complete and durable regression of a stage IB non-small-cell lung carcinoma in a patient who had received an allogeneic peripheral blood hematopoietic stem cell transplant for acute myeloblastic leukemia in first complete remission. Disappearance of the tumor coincided with development of graft-vs.-host disease. This suggests that simultaneous generation of cytotoxic T lymphocytes against lung carcinoma cells could have been responsible for the regression. 12

Malignant melanoma:

Our initial experience treating metastatic melanoma highlights some of the potential problems involved in evaluating allogeneic transplantation in other solid tumors. Death from rapid disease progression occurred before day 100 in five of the first 11 patients with metastatic melanoma who were transplanted. Although three patients had partial regression of their melanoma, these responses occurred early in the course of the transplant, were short-lived, and probably reflect chemotherapy effects related to the conditioning regimen rather than an allogeneic, immune-mediated antitumor response. One patient had delayed regression of several subcutaneous metastatic nodules in the setting of progressive CNS disease. 13

Ovarian cancer

Bay et al. studied five patients with refractory ovarian cancers who underwent allogeneic transplantation. Among these patients, four tumor regressions were observed during acute or chronic GVHD. Furthermore, in one patient the use of methylprednisolone for chronic GVHD was correlated with relapse. 14

The EBMT STWP subsequently reported results from its database concerning 17 patients heavily pretreated for ovarian cancer (including the 5 cases mentioned above). 60 Most patients received a non-myeloablative conditioning regimen (n = 15) and allogeneic stem cells from an HLA identical sibling donor (n = 16). Among these patients, 3 died soon after the allograft because of disease progression, and 14 were evaluable for engraftment and chimerism. All patients except one achieved complete chimerism 60 days after allograft with full hematological recovery. In total, eight patients developed a more than grade 2 acute GVHD. At a median follow-up of 296 days (range 5–1,599 days), 6 patients were alive and 11 had died (3 of non-progression mortality and 8 of tumor progression). Overall, seven patients had a PR co incident with the development of GVHD. Among the 17 patients studied, 3 received DLIs, with 1 patient showing tumor regression after DLI. The regression of metastatic cancer in seven patients (41%) supports the existence of a graft-versus-ovarian-cancer effect, and the results indicate a strong correlation between the occurrence and persistence of GVHD and the antitumor effect. The GVHD rate was 47%, and non-progression mortality was 17%. Future strategies are aimed at enhancing the antitumor effect of GVHD. 15

Soft-tissue sarcoma

An immune-mediated effect against sarcoma has been shown in experimental animal models of allogeneic transplantation. 16,17 Only single case reports and small series of patients with soft-tissue sarcoma (STS), however, have been treated with allogeneic transplantation from HLA-matched sibling donors. The largest series, including nine patients with various histotypes, 18 has shown no evidence of cancer regression following allografting, while other authors have reported evidence of a graft-versus-sarcoma effect. 19,20

A retrospective analysis of patients registered on the EBMT database was not able to draw firm conclusions about the possible usefulness of allogeneic transplantation in advanced STS, mainly because of the heterogeneity of the patient population. 21 Indeed; STS represent an extremely heterogeneous group of diseases, both in terms of histology and biological and clinical behavior. For this reason it is likely that any immune-mediated GVT effect will vary considerably among patients owing to a number of, as yet undefined, factors. In this setting, prospective studies are required.

Limitations of non-myeloablative hematopoietic cell transplantation (NMHCT) in solid tumors. 5

	(%) Incidence
HLA-matched sibling donor available	30– 25
Acute GVHD	60–30
Chronic GVHD	70– 40
CMV reactivation	40–20
Graft rejection	10– 5
TRM	20– 10

Patient characteristics likely to predict a favorable outcome after non-myeloablative hematopoietic cell transplantation (NMHCT) for solid tumors. 5

- Good performance status (ECOG=0–1)
- Younger patient age (< 65 years)
- Small tumor volume
- Slow tumor growth kinetics
- Absence of CNS metastatic disease
- Evidence (clinical or in vitro) that tumor is susceptible to immune-mediated attack

KEY POINTS 22

■ Allogeneic stem-cell transplantation from a HLA-compatible sibling donor or from a matched unrelated donor is a beneficial treatment for patients with relapsed and high-risk hematological malignancies

■ Radiotherapy and/or chemotherapy are administered before allotransplant for cytoreduction of the disease and for ablation of the patient's immune system, thus allowing engraftment of infused cells; the newly introduced non-my-

eloablative or reduced intensity regimens are purely immunosuppressive

■ T cells in the infused transplant facilitate engraftment and exert an immune attack on the patient's leukemia/tumor cells, the so-called "graft-versus-leukemia/tumor" effect

■ Retrospective analyses and prospective pilot studies demonstrate a graft-versus-tumor effect in solid tumors, particularly in advanced, clear cell renal cancer, but also in breast, ovarian, colorectal and pancreatic carcinoma, and soft-tissue sarcoma

■ The mechanisms of the graft-versus-tumor effect are still poorly understood: an immune reaction by donor T cells against minor histocompatibility antigens or tumor-associated antigens is most probably involved

■ Allogeneic transplantation in renal cancer and other solid tumors should be considered a developmental therapy until definitive proof of a clinical benefit is achieved by current studies.

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زرع الخلايا الجذعية المكونة للدم الخيفي لعلاج الأورام السرطانية الصلبة

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الخلاصة:

تعني عملية زرع الخلايا الجذعية المكونة للدم الإجراء الذي يتم من خلاله نقل الخلايا الجذعية المكونة للدم لاستعادة وظيفة نخاع العظام لدى مرضى السرطان الذين يتلقون جرعات عالية من الأدوية الكيميائية قاتلة لنخاع العظم، مع أو بدون العلاج الإشعاعي لكامل الجسم. ويمكن الحصول على الخلايا الجذعية من المستلم (زرع ذاتي) أو من متبرع آخر. قد تحصد الخلايا الجذعية من نخاع العظام أو الدم المحيطي أو دم الحبل السري بعد فترة قصيرة من الولادة لحديثي الولادة. وقد تطورت النظرة إلى الآليات التي من خلالها يتم القضاء على الخلايا الخبيثة بعد زرع الخلايا الجذعية المكونة للدم من شخص آخر إلى حد كبير على مدى العقود الأربعة الماضية. لم يعد التفكير فيه باعتباره مجرد وسيلة لانقاذ وظيفة نخاع العظم بعد العلاج الكيميائي بل يعتبر الآن نوع قوي من العلاج المناعي قادر على علاج المرضى الذين يعانون من أمراض سرطانية قاتلة. وقد أدى تطور هذا المفهوم إلى تنويع موجبات الزرع الذاتي و تطوير العلاج التحضيري لعملية الزرع منخفض الشدة. بدأ الباحثون مؤخرًا باختبار ما إذا الأورام الخبيثة غير الدموية قد تكون أيضا عرضة للهجوم المناعي.