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REGRESSION OF METASTATIC RENAL-CELL CARCINOMA AFTER NONMYELOABLATIVE ALLOGENEIC PERIPHERAL-BLOOD STEM-CELL TRANSPLANTATION

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ABSTRACT

Background Since allogeneic stem-cell transplantation can induce curative graft-versus-leukemia reactions in patients with hematologic cancers, we sought to induce analogous graft-versus-tumor effects in patients with metastatic renal-cell carcinoma by means of nonmyeloablative allogeneic peripheral-blood stem-cell transplantation.

Methods Nineteen consecutive patients with refractory metastatic renal-cell carcinoma who had suitable donors received a preparative regimen of cyclophosphamide and fludarabine, followed by an infusion of a peripheral-blood stem-cell allograft from an HLA-identical sibling or a sibling with a mismatch of a single HLA antigen. Cyclosporine, used to prevent graft-versus-host disease, was withdrawn early in patients with mixed T-cell chimerism or disease progression. Patients with no response received up to three infusions of donor lymphocytes.

Results At the time of the last follow-up, 9 of the 19 patients were alive 287 to 831 days after transplantation (median follow-up, 402 days). Two had died of transplantation-related causes, and eight from progressive disease. In 10 patients (53 percent) metastatic disease regressed; 3 had a complete response, and 7 had a partial response. The patients who had a complete response remained in remission 27, 25, and 16 months after transplantation. Regression of metastases was delayed, occurring a median of 129 days after transplantation, and often followed the withdrawal of cyclosporine and the establishment of complete donor–T-cell chimerism. These results are consistent with a graft-versus-tumor effect.

Conclusions Nonmyeloablative allogeneic stem-cell transplantation can induce sustained regression of metastatic renal-cell carcinoma in patients who have had no response to conventional immunotherapy. (N Engl J Med 2000;343:750-8.)

METASTATIC renal-cell carcinoma has an extremely poor prognosis, with a median survival of less than one year.[1,2] Systemic treatment with cytotoxic chemotherapy is usually ineffective.[3] The introduction of interleukin-2 and interferon alfa for the treatment of metastatic disease provided, for the first time, therapy that induced complete and durable responses.[4,5] Although some patients who have a complete response to such cytokine-based therapy survive for long periods, the overall rate of response to these agents, either alone or in combination, is usually less than 20 percent.[6]

Renal-cell carcinoma is unusual among solid tumors because of its immunogenic properties.[7,8] The response of some patients to immunomodulatory cytokines and the rare spontaneous regressions of metastatic disease provide the rationale for other immunologic approaches.[9,10] Allogeneic bone marrow transplantation can induce powerful graft-versus-leukemia effects in patients with hematologic cancers, including myeloid and lymphoid leukemias, lymphomas, and multiple myeloma.[11-15] There is also anecdotal evidence of graft-versus-tumor effects in patients with metastatic breast carcinoma.[16,17] Because renal-cell carcinoma appears to be susceptible to immunomodulation, we postu-

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lated that a graft-versus-tumor effect, analogous to the graft-versus-leukemia effect in hematologic cancers, might be generated after the transplantation of allogeneic lymphocytes from a healthy donor. Since metastatic disease in renal-cell cancer is typically resistant to chemotherapy, we selected a low-intensity but highly immunosuppressive preparative regimen to reduce transplantation-related complications and mortality while allowing complete engraftment of the donor's immune cells. Such stem-cell transplantations after low-intensity preparation decrease transplantation-related complications while allowing sufficient donor-cell engraftment to generate graft-versus-leukemia effects in hematologic cancers.[18-23] We previously described a patient with metastatic renal-cell carcinoma who had complete regression of metastatic disease after treatment with a nonmyeloablative allogeneic peripheral-blood stem-cell transplantation.[24] We present here the results in 19 patients with metastatic renal-cell carcinoma who were treated in a pilot trial.

METHODS

Patients

Eligible patients were 18 to 75 years of age and had biopsy-confirmed metastatic renal-cell carcinoma that was documented radiographically to be progressive despite prior therapy and that was not amenable to complete surgical resection. Patients were required to have disease that could be evaluated radiographically and to have as a donor an HLA-identical sibling or a sibling with a mismatch at a single HLA locus. Patients were excluded if they had bone metastases alone, active brain metastases, or hypercalcemia or if they had received any treatment for renal-cell carcinoma within 30 days before enrollment.

Study Design

Patients and donors gave written informed consent to participate in this protocol (National Institutes of Health protocol 97-H-0196), which had been approved by the institutional review board of the National Heart, Lung, and Blood Institute. The preparative regimen consisted of intravenous infusions of 60 mg of cyclophosphamide per kilogram of body weight on day 7 and day 6 before transplantation, followed by an intravenous infusion of 25 mg of fludarabine per square meter of body-surface area on each of the last five days before transplantation. The two patients who received a transplant from a donor with a mismatch at a single HLA locus received additional immunosuppression consisting of intravenous infusions of 40 mg of antithymocyte globulin per kilogram on days 5, 4, 3, and 2 before transplantation. Cyclosporine, which is used to prevent rejection of the graft and graft-versus-host disease, was started four days before transplantation, initially as an intravenous infusion at a dose of 3 mg per kilogram daily, with oral cyclosporine (at a dose of 5 mg per kilogram twice daily) substituted as tolerated. On day 0, an allograft from which T cells had not been removed was transfused into the recipient.

Stem-cell donors received 10 μg of granulocyte colony-stimulating factor per kilogram subcutaneously daily for five to six days. Mobilized peripheral-blood stem cells were collected by leukapheresis on day 5, and again on days 6 and 7 if necessary, to obtain a target dose of more than 5×10^6 CD34 cells per kilogram of the recipient's weight.

Decisions regarding post-transplantation cyclosporine withdrawal and lymphocyte infusions were based on the speed and degree of engraftment of donor cells. Because rapid and complete engraftment of donor immune cells is associated with an increased risk of graft-versus-host disease,[20] patients with 100 percent donor–T-cell chimerism in peripheral-blood samples obtained on day 30 after transplantation continued to receive cyclosporine until day 60; thereafter, the dose of cyclosporine was decreased by 25 percent every 10 days and discontinued by day 100 if graft-versus-host disease had not developed. In contrast, mixed donor–recipient lymphoid chimerism is associated with a low risk of graft-versus-host disease but an increased risk of relapse. Therefore, in patients with mixed donor–recipient T-cell chimerism on day 30, the dose of cyclosporine was rapidly tapered over a two-week period. Patients who did not have complete donor–T-cell chimerism after the withdrawal of cyclosporine received up to three monthly escalating doses of donor lymphocytes, with weekly assessment of chimerism, until complete T-cell chimerism, graft-versus-host disease, or disease regression occurred. Also, patients who had stable or progressive disease after the withdrawal of cyclosporine and who had no evidence of severe graft-versus-host disease (i.e., a grade of III or IV) were eligible to receive up to three infusions of donor lymphocytes given monthly in escalating doses (5×10^6, 1×10^7, and 5×10^7 CD3 T cells per kilogram of the recipient's weight). Patients who had no response to treatment with donor lymphocytes and those who were not candidates for additional lymphocyte infusions because they had severe graft-versus-host disease were eligible to receive low-dose subcutaneous interferon alfa or interleukin-2 to enhance a graft-versus-tumor effect.

Response to Treatment

A response was defined as complete if all measurable tumor disappeared and as partial if the sum of the products of the longest perpendicular diameters of metastatic lesions that could be evaluated decreased by at least 50 percent for a period of at least 30 days. All patients underwent computed tomographic (CT) scanning within 30 days before transplantation; 30, 60, and 100 days after transplantation; monthly thereafter for the first year; and then every 3 months.

Assessment of Chimerism and Graft-versus-Host Disease

After the transplant was infused, samples of blood were obtained weekly, and the degree of donor–recipient chimerism in both myeloid and T-cell lineages was assessed by polymerase-chain-reaction assay of minisatellite regions according to published methods.[20,25] The severity of graft-versus-host disease was graded according to the criteria of the International Bone Marrow Transplant Registry.[26]

Statistical Analysis

We calculated the actuarial probability of survival and the cumulative probability of a response according to the method of Kaplan and Meier. We compared differences between outcomes using Wilcoxon's log-rank analysis. The following factors were entered into multivariate analysis: presence or absence of acute graft-versus-host disease, age (mismatched vs. matched), sex, number of CD34 stem cells transfused and the number of donor CD3 T cells in the allograft (more than the median vs. less than the median), the number of metastatic sites (more than two vs. two or fewer), and sex mismatch between donor and recipient (mismatched vs. matched). We used Cox multivariate analysis to evaluate the significance of the results. All data obtained through May 25, 2000, were analyzed.

RESULTS

Patients

Between February 1998 and August 1999, 19 consecutive patients with metastatic renal-cell carcinoma who had suitable donors underwent nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. Of these 19 patients, 17 received a transplant from a molecularly typed, HLA-identical sibling and 2 received a transplant from a sibling donor with a mismatch at a single HLA locus (Table 1). The patients

TABLE 1. CHARACTERISTICS OF THE PATIENTS AND OUTCOME OF TRANSPLANTATION.

PATIENT NO.	AGE (YR)/ SEX	HISTOLOGIC TYPE OF RENAL-CELL CARCINOMA	NO. OF SITES OF METASTASES	NO. OF PRIOR THERAPIES	SEX OF DONOR	EXTENT OF HLA MATCHING	NO. OF CELLS TRANSFUSED/kg		ACUTE GVHD OF GRADE II, III, OR IV*	OUTCOME
							CD34 CELLS $\times 10^{-6}$	CD3 CELLS $\times 10^{-8}$		
1	50/M	Clear cell	2	2†‡	M	6/6	9.1	2.0	No	Complete response; alive on day 831
2	45/M	Clear cell	2	2†§	M	5/6	5.8	1.4	II (gastrointestinal)	Complete response; alive on day 768
3	48/M	Clear and granular	3	3†¶	M	6/6	6.0	1.6	II (skin)	Partial response; alive on day 582
4	55/M	Clear cell	2	2¶‖	M	6/6	5.8	4.8	II (gastrointestinal)	Complete response; alive on day 474
5	64/M	Clear cell	1	2†§	F	6/6	2.2	3.8	IV (gastrointestinal)	Partial response; died of GVHD on day 55*
6	45/F	Clear and papillary	>3	2†§	M	6/6	13.0	4.8	No	Progression; died on day 347
7	42/M	Chromophobe	3	4†§¶‖	F	6/6	2.3	3.0	II (gastrointestinal)	Progression; died on day 93
8	52/M	Clear cell	>3	3†‡¶	F	6/6	11.3	2.4	II (skin, gastrointestinal)	Partial response; alive on day 402
9	40/F	Clear cell	>3	2†¶	F	5/6	8.0	6.5	No	Progression; died on day 244
10	37/M	Clear with sarcomatoid differentiation	3	1†	M	6/6	9.8	4.4	No	Progression; died on day 303
11	56/M	Clear with chromophobic changes	3	2†‖	M	6/6	10.0	2.3	No	Progression; alive on day 351
12	56/F	Clear cell	3	3†¶‖	F	6/6	2.6	4.7	No	Progression; died on day 193
13	53/M	Clear cell	>3	3†¶‖	M	6/6	9.8	7.1	III (skin)	Partial response; died of sepsis on day 164
14	45/F	Clear with sarcomatoid differentiation	>3	4†§¶‖	M	6/6	10.8	6.8	No	Progression; died on day 134
15	47/M	Clear cell	>3	4†§¶‖	F	6/6	10.3	4.2	IV (gastrointestinal)	Partial response; died of progressive disease on day 203
16	47/M	Clear cell	2	1§¶	F	6/6	6.0	4.9	II (skin)	Partial response; alive on day 310
17	44/M	Clear cell	2	3†¶‖	F	6/6	2.2	4.1	No	Stable disease; alive on day 296
18	65/M	Clear and papillary	3	4†§¶‖	M	6/6	13.8	3.6	No	Progression; died on day 117
19	50/M	Clear cell	2	2†§	F	6/6	9.0	5.7	II (skin)	Partial response; alive on day 287

*GVHD denotes graft-versus-host disease. A grade of III or IV indicates severe GVHD.

†Cytokine therapy with interferon alfa, interleukin-2, or both was given.

‡Hormonal therapy was given.

§Chemotherapy was given.

¶An investigational therapy was given.

‖Radiation therapy was given.

ranged in age from 37 to 65 years (median, 48). Although it was not an inclusion criterion, all patients had undergone nephrectomy as part of their previous therapy for the primary tumor. Furthermore, all patients had radiographically documented progressive disease despite prior therapy. Seventeen patients (89 percent) had previously been treated with cytokine-based therapy (interleukin-2, interferon alfa, or both). Most patients had multiple previously defined factors that were associated with a poor outcome, including a short interval between nephrectomy and the development of metastatic disease and the presence of multiple sites of metastatic tumor.

Transplantation and Engraftment

The characteristics of the 19 patients and the outcomes of transplantation are listed in Table 1. The patients received a median of 8.0×10^6 CD34 cells per kilogram (range, 2.2×10^6 to 13.8×10^6) and 4.2×10^8 CD3 T cells per kilogram (range, 1.4×10^8 to 7.1×10^8). The neutrophil count fell to less than 100 per cubic millimeter in all patients and rose to more than 500 per cubic millimeter a median of 10.5 days (range, 7 to 13) after transplantation. It took a median of 8 days (range, 0 to 10) after transplantation for the platelet count to exceed 50,000 per cubic millimeter; 13 of the 19 patients never had platelet counts of less than 20,000 per cubic millimeter. In all 19 patients, engraftment of both T-cell and myeloid lineages from the donor was sustained. At the time of engraftment, myeloid cells were typically of both recipient and donor origin, but recipient cells predominated. In contrast, T cells were predominantly of donor origin.

Clinical Efficacy

Of the 19 patients, 10 had evidence of tumor regression after receiving an allograft. In three patients there was total regression of all metastases (a complete response), and the tumor burden was reduced by at least 50 percent (a partial response) in seven (37 percent). The cumulative probability of a response was 53 percent (95 percent confidence interval, 31 to 75 percent) (Fig. 1A). Regression of metastases was observed at multiple sites, including the lymph nodes, adrenal glands, liver, subcutaneous tissues, bones, and lungs, as well as in abdominal, pelvic, and chest-wall masses (Fig. 2 and 3). The onset of tumor regression was typically delayed, occurring a median of 4 months (range, 1 to 8) after transplantation. Furthermore, disease regression was observed only after all the T cells in the recipient were of donor origin (complete chimerism). In 8 of the 10 patients with a response, metastases regressed only after cyclosporine had been withdrawn.

Radiographic evaluation 30 days after transplantation revealed stable or progressive disease in 18 patients. One patient (Patient 5) had early regression of metastases, first noted on the chest film on day 21, that corresponded with the onset of acute graft-versus-host disease of the gastrointestinal system. Six of the 10 patients who ultimately had a response had initial radiographic evidence of tumor growth; regression followed the discontinuation of cyclosporine, and in Patient 19, an infusion of 1×10^7 CD3 donor T cells per kilogram. Only 1 of the 10 patients who had a response received cytokine therapy (interferon alfa) after transplantation.

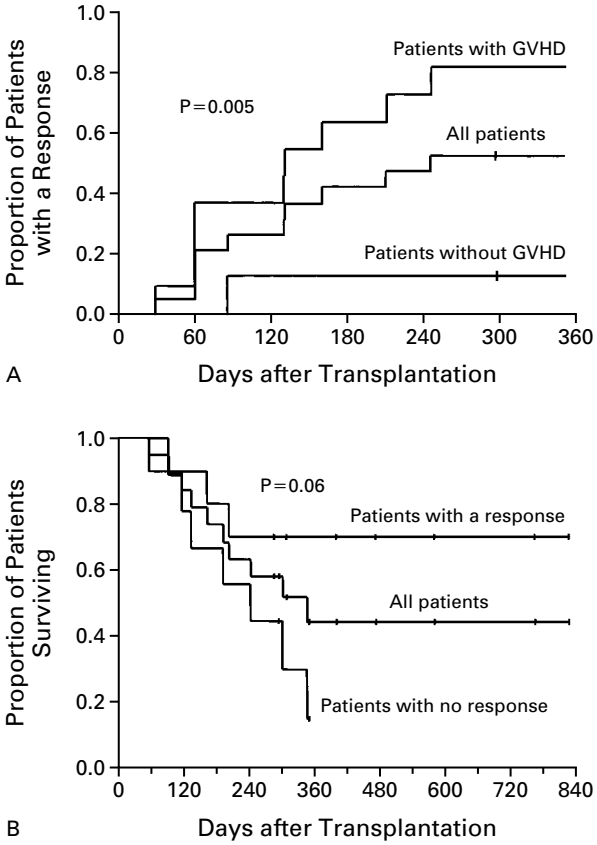


Figure 1. Outcome in 19 Patients with Metastatic Renal-Cell Carcinoma Who Were Treated with Allogeneic Stem-Cell Transplantation.

Panel A shows the Kaplan–Meier estimate of the cumulative probability of a response in all 19 patients and in patients with and those without acute graft-versus-host disease (GVHD) of grade II, III, or IV. Patients in whom acute graft-versus-host disease developed after transplantation had a significantly higher probability of a response (P=0.005). Panel B shows the Kaplan–Meier estimate of survival in all patients and in patients with and those without a response after transplantation. Although not significant (P=0.06), there was a trend toward a survival advantage among patients with a response.

Effects of Infusions of Donor Lymphocytes and Cytokine Treatment after Transplantation

After cyclosporine therapy was discontinued, eight patients received up to 3 escalating doses of donor

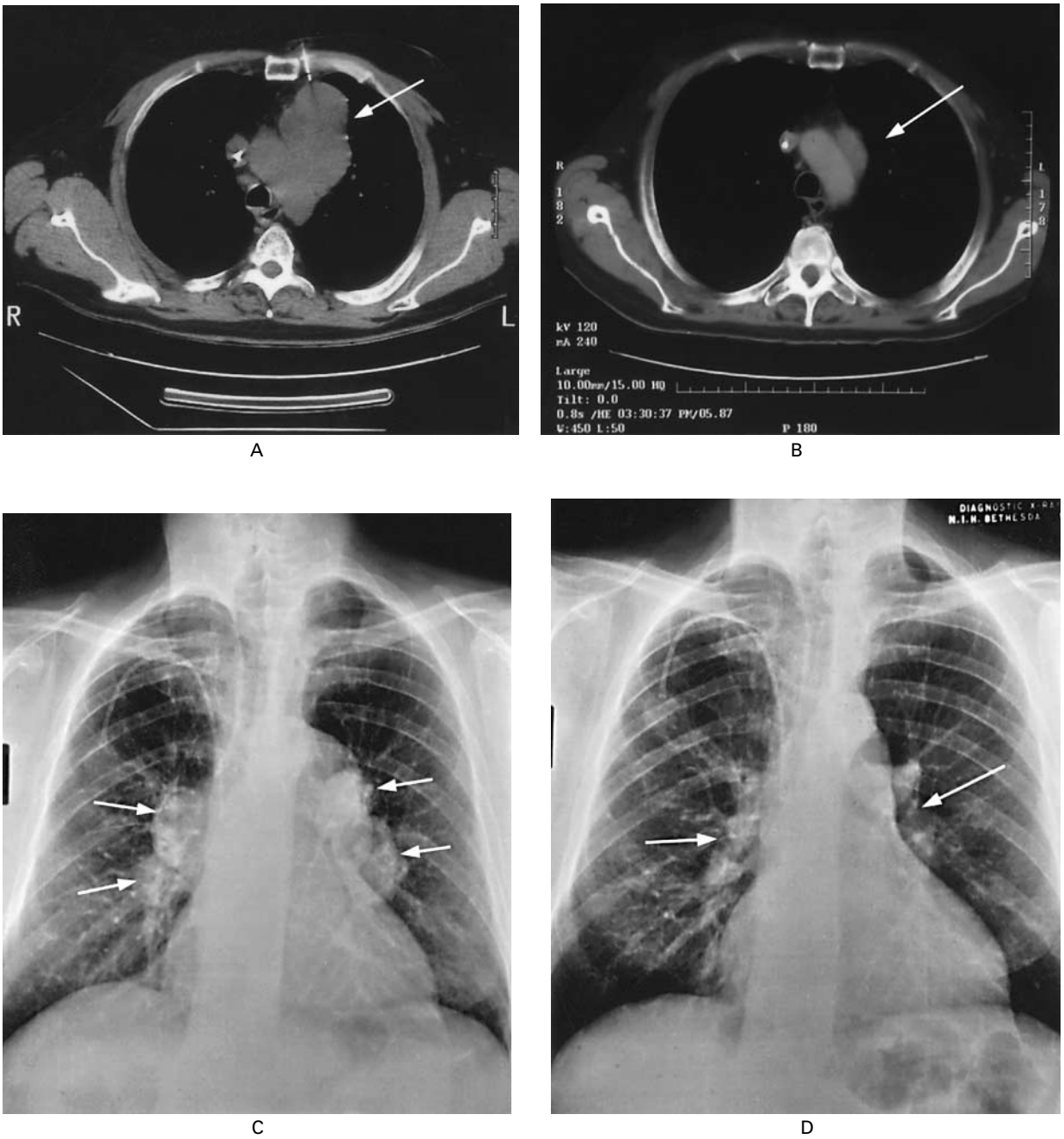
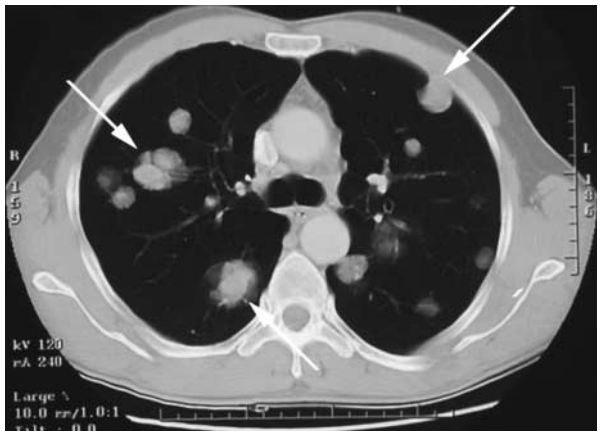


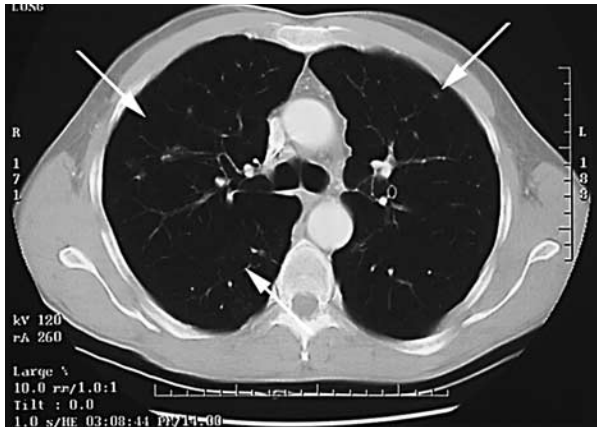
Figure 2. CT and Radiographic Images of Mediastinal and Hilar Adenopathy (Arrows) in Patient 8 before Transplantation (Panels A and C) and 276 Days after Transplantation (Panels B and D).

Regression was concordant with the onset of limited chronic graft-versus-host disease of the skin.

lymphocytes (median number of infusions, 2.5; range, 1 to 3) at 30-day intervals to establish complete T-cell chimerism, treat progressive disease, or both. In two of the three patients with mixed T-cell chimerism, all T cells were of donor origin within 30 days after the donor-lymphocyte infusion (1×10^7 CD3 T cells per kilogram); in the third (Patient 7) mixed T-cell chimerism persisted until his death from progressive disease. Of these eight patients, seven did not have a response to the allograft and were treated with additional infusions of donor lymphocytes; one of these patients (Patient 19) subsequently had a partial response, whereas the disease in the remaining six did not regress despite the infusions of donor lymphocytes.



A



B

Figure 3. CT Images of Pulmonary Metastases (Arrows) 60 Days (Panel A) and 285 Days (Panel B) after Transplantation in Patient 19.

Low-dose subcutaneous interferon alfa or interleukin-2 was given to four patients after transplantation. All had progressive disease; three had no response to donor-lymphocyte infusions, and one was not a candidate for infusions of donor lymphocytes because of the development of grade III graft-versus-host disease. Three of these four patients had no response to the cytokine therapy and died from progressive disease, but the fourth had a dramatic regression of bulky metastatic disease after five doses of interferon alfa. The improvement was temporally related to the onset of grade I graft-versus-host disease confined to the skin. The metastases in this patient had not responded to a three-month trial of interferon alfa therapy given before he received an allograft.

Transplantation-Related Adverse Events

Table 2 lists transplantation-associated adverse events. Acute graft-versus-host disease of grade II, III, or IV — the most serious complication — occurred in 10 patients (53 percent) a median of 55 days (range, 21 to 113) after the procedure; graft-versus-host disease was rated as grade II in 7, grade III in 1, and grade IV in 2. In nine patients the graft-versus-host disease responded to treatment; one patient (Patient 5) died of glucocorticoid-refractory grade IV graft-versus-host disease of the gastrointestinal system. Overall, two patients died of transplantation-related complications (actuarial risk of transplantation-related mortality, 12 percent): Patient 5 of complications associated with acute graft-versus-host disease, and Patient 13 of bacterial sepsis.

Table 2. Transplantation-Related Adverse Events.*

Adverse Event	No. of Patients (%)
Febrile neutropenia	19 (100)
Pneumonitis at engraftment	2 (11)
Pleural effusion	3 (16)
Bradycardia	2 (11)
Bacterial sepsis	1 (5)
Cytomegalovirus	
Reactivation of infection	8 (42)
Esophagitis	1 (5)
Acute GVHD of grade II, III, or IV	10 (53)
Grade II	7 (37)
Grade III	1 (5)
Grade IV	2 (11)
Chronic GVHD	4 (21)
Limited	3 (16)
Extensive	1 (5)
Pure red-cell aplasia	1 (5)
Increase in creatinine†	4 (21)
Nephrotic syndrome	1 (5)
Transplantation-related mortality‡	2 (11)

*No patient had mucositis or venoocclusive disease. GVHD denotes graft-versus-host disease.

†The serum creatinine level was considered to be increased if it was more than 50 percent higher than the level before transplantation.

‡One patient died of graft-versus-host disease, and one died of sepsis.

Progression-free and Overall Survival

As of May 25, 2000, nine patients were alive 287 to 831 days after transplantation (median follow-up, 402 days) (Fig. 1B). The cause of death was progressive metastatic disease in eight patients and transplantation-related complications in two. The three patients who had a complete response remained in remission 27, 25, and 16 months after transplantation. Four of seven patients with a partial response were alive without disease progression 9 to 19 months after transplantation (Fig. 4). The metastases in one patient with a partial response (Patient 19) were still regressing, as

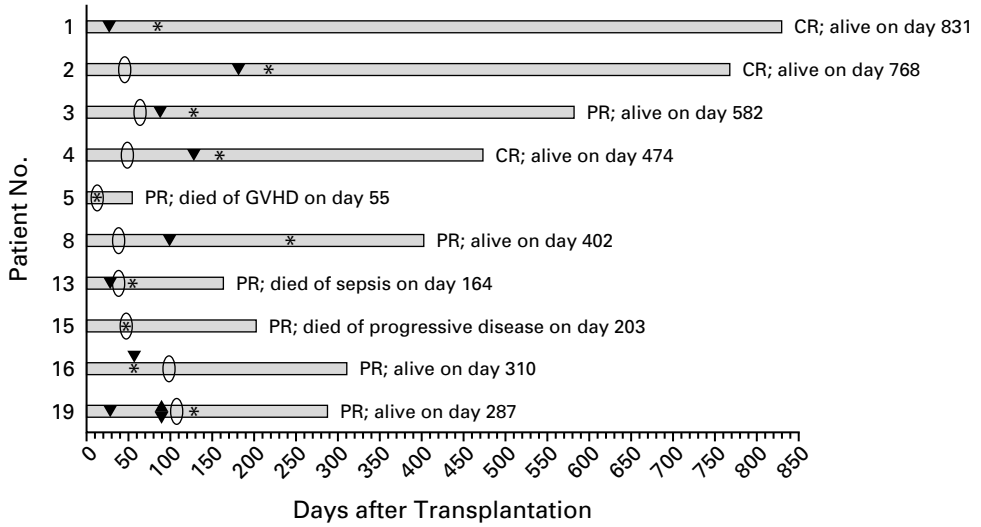


Figure 4. Post-Transplantation Course in the 10 Patients with a Complete Response (CR) or a Partial Response (PR).
The onset of regression (indicated by an asterisk) typically followed the discontinuation of corticosteroid therapy (indicated by a triangle) and the onset of graft-versus-host disease (GVHD, indicated by an oval). In Patients 2 and 8, regression was not noted until more than 200 days after transplantation. Patient 19 had a dramatic regression of bulky pulmonary and bone metastatic disease 41 days after the infusion of 1×10^7 CD3 donor T cells per kilogram (indicated by the diamond).

judged by follow-up CT scanning. Three patients who had a partial response died, two of transplantation-related complications and one of progressive disease. Only two patients who had a response subsequently had progressive disease; in one of them, recurrent disease regressed completely after the abrupt withdrawal of cyclosporine and treatment with three subcutaneous doses of interferon alfa. In this patient the regression of metastases coincided with the onset of chronic graft-versus-host disease limited to the skin.

Factors Affecting the Response to Therapy

Metastatic disease regressed only after T-cell chimerism had become complete; it followed or was concurrent with the withdrawal of cyclosporine in 8 of the 10 patients with a response (Fig. 4). The development of acute graft-versus-host disease was the only factor that predicted a response. Tumor regression occurred more often in patients with acute graft-versus-host disease of grade II, III, or IV (9 of 10 patients) than in those without graft-versus-host disease of grade II, III, or IV (1 of 9) ($P=0.005$) (Fig. 1A). Regression of metastases coincided with the onset of acute graft-versus-host disease in four patients. Five patients with a response had early radiographic evidence of tumor growth in the setting of acute graft-versus-host disease; subsequently, the disease regressed two to six months after the onset of graft-versus-host disease. One patient without acute graft-versus-host disease (Patient 16), in whom regression was first noted on CT scanning 60 days after transplantation, was found to have acute grade II graft-versus-host disease of the skin on day 103, shortly after cyclosporine therapy was discontinued. In only one patient with a response (Patient 1) did acute graft-versus-host disease not develop. In a multivariate analysis, acute graft-versus-host disease was the only factor that predicted a response (relative likelihood of a response, 11.0; 95 percent confidence interval, 1.4 to 88.5). Responses were observed only in patients with clear-cell renal carcinomas.

DISCUSSION

Since renal-cell carcinoma appears to be susceptible to immunologic control, we evaluated the effect of therapy with allogeneic peripheral-blood stem cells on metastatic disease that was refractory to conventional management. And because renal-cell carcinoma does not respond to most chemotherapeutic agents, even at high doses, we used a low-intensity conditioning regimen, which provided sufficient immunosuppression to allow engraftment of the donor's immune cells, while avoiding the substantial side effects of conventional myeloablative regimens. Furthermore, to maximize the opportunity for graft-versus-tumor effects, we sought to establish rapid engraftment of the donor's cells by the early discontinuation of cyclosporine and the administration of additional infusions of donor stem cells to treat disease progression or to bring about complete T-cell chimerism.

We found that despite their advanced refractory disease, more than half our patients ultimately had a response. The regressions of metastases were often striking, occurring at multiple sites in patients who had had no response to prior therapy with interleukin-2, interferon alfa, or both. Remarkably, all disease completely regressed in three patients, and they remained in remission 27, 25, and 16 months after transplantation. Furthermore, only two of seven patients with a partial response have had a relapse; in one of these patients, the subsequent regression of all recurrent metastases was temporally related to the onset of chronic graft-versus-host disease limited to the skin (following the abrupt withdrawal of immunosuppression and treatment with three doses of interferon alfa).

Evidence that regression of metastatic renal-cell carcinoma was mediated by a graft-versus-tumor effect is compelling. First, fludarabine and cyclophosphamide, which were used to establish engraftment of the allogeneic cells, are inactive against renal-cell carcinoma[27,28]; indeed, CT scans obtained within a month after transplantation showed either stable or progressive disease in almost all patients. Second, tumor regression typically occurred shortly after the withdrawal of cyclosporine, and in one patient it followed an infusion of donor lymphocytes. Similar graft-versus-leukemia effects after allogeneic bone marrow transplantation are well documented after a reduction in the dose of cyclosporine and the infusion of donor lymphocytes.[13] Moreover, the median interval of four months from pretransplantation preparative chemotherapy to the first signs of disease regression, the observation that regression occurred only after complete donor T-cell chimerism had been established, and the association of graft-versus-host disease with regression of metastases are all consistent with the occurrence of an antitumor effect that was mediated by the donor's T cells. Remarkably, in two patients the interval from transplantation to regression of metastatic disease was more than 200 days. These delays in responses are similar to the delays of up to a year in patients with relapsed chronic myelogenous leukemia who have a response to infusions of donor lymphocytes.[13,29]

Although the occurrence of acute graft-versus-host disease of grade II, III, or IV was significantly associated with a response, it was not essential for a graft-versus-tumor effect; two patients did not have acute graft-versus-host disease when their disease regressed. Furthermore, regression often occurred months after the onset of graft-versus-host disease, suggesting that the T-cell population that caused tumor regression was distinct from the population that induced graft-versus-host disease. Although only patients with clear-cell carcinomas had responses, these tumors were the predominant subtype. Therefore, additional patients will need to be treated before any possible relation between tumor type and susceptibility to a graft-versus-tumor effect can be established.

The donor cells that mediate the graft-versus-tumor effects we observed and their target antigens are a central focus of investigation. The prolonged interval from transplantation to tumor regression is consistent with the time required for the activation and expansion of antitumor cytotoxic T cells. The finding that patients who had no response to conventional cytokine-based immunotherapy subsequently had a response to transplantation provides evidence that allogeneic immunotherapy may be as effective as strategies designed to enhance autologous antitumor immunity or even more potent than such approaches.

We should emphasize that our study was small and that follow-up has been relatively short. Additional patients and more time will be required to determine the frequency and durability of the responses to allogeneic T cells. Furthermore, it is important to consider the limitations of such therapy. Allogeneic peripheral-blood stem-cell transplantation can cause substantial and sometimes fatal complications, most of which are related to graft-versus-host disease. Although the adverse effects were not life threatening in most of our patients, two died of transplantation-related causes. An equally important limitation is the prolonged time required for the induction of an antitumor effect. Patients with rapidly advancing metastatic disease, who would be unlikely to live long enough for the generation of a graft-versus-tumor effect, would not benefit from such therapy. Because of these limitations, nonmyeloablative allogeneic peripheral-blood stem-cell transplantation should remain an investigational approach for the treatment of metastatic renal-cell carcinoma.

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