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Short Report

Allogeneic Stem Cell Transplantation for Metastatic Renal Cell Cancer (RCC)

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Abstract

A variety of therapeutic options are now available for advanced renal cell cancer, including antiangiogenic and anti-mTOR agents. Allogeneic hematopoietic stem cell transplantation, through its graft-versus-tumor effect, can induce clinical responses and prolonged survival in selected cytokine-refractory patients. However, the still relevant transplant-related mortality due to toxicity and graft-versus-host disease is an obstacle to its widespread use.

Key words: Allogeneic hematopoietic stem cell transplantation, advanced renal cell cancer, graft-versus-tumor.

Allogeneic hematopoietic stem cell transplantation from a compatible donor has been utilized as adoptive immunotherapy in metastatic, cytokine-refractory renal cell cancer (RCC). Since 2000, several investigators have established that RCC is susceptible to a graft-versus-tumor effect: they reported that patients with renal cancer may have partial or complete disease responses, in the 20-40% range, after allogeneic transplantation following a reduced-intensity regimen (Table 1).

Table 1. Major series of allografting for RCC

	No. Patients	TRM %	Response rate %	aGvHD %	Prognostic factors
NIH (2)	75	8	38	50	Limited number of metastatic sites Exclusive lung metastases Clear-cell histology Slow progressive disease
Marseille (3)	32	6	16	-	Non-progressive disease at transplant
Milano (4)	25	16	20	45	C-Reactive Protein Number of CD34+ infused Non progressive disease at +90 after transplant

In the seminal study[1], 19 patients who had failed other forms of immunotherapy (mainly recombinant interleukin-2 and/or interferon-alpha) received allo-SCT from an HLA identical sibling after reduced intensity conditioning (RIC) including cyclophosphamide and fludarabine. The response rate was 53% in these previously treated patients. Childs et al. later updated their results[2]: 74 patients with a median of two metastatic sites have been transplanted. Sustained engraftment was achieved in 74/75 patients. Overall, 38% of patients have had radiographic evidence of tumor regression (27% PR, 9% CR) with responses occurring at a median of day +160 from transplant (range 30-425). Tumor responses (frequently preceded by tumor progression) occurred sometimes after the administration of post transplant interferon-alpha, even in patients who had previously failed this treatment. In a few cases, responses were durable. Acute and chronic graft-versus-host disease (GVHD) were observed in approximately 50% of patients. Death from TRM occurred in 8% of patients, half of whom died from complications related to GVHD. Several prognostic factors were associated with response, including: a limited number of metastatic sites, exclusive lung metastases, clear cell histology and "slow" progressive disease. Liver metastases appeared to be a negative prognostic factor (11% response rate in those transplanted with liver metastasis), while lung metastasis was a positive factor (55% response rate). Responses in non-clear histology, including papillary tumors were not observed.

The group of Institut Paoli Calmettes reported thirty-two cytokine-refractory patients (age: 45 [17-61]), who received the same reduced intensity conditioning [Fludarabine (150mg/msq), Busulfan (8mg/kg) and Thymoglobulin (2,5mg/kg) or TLI (1Cgy)] from a HLA-identical sibling (BM: 9%; PBSC: 91%) followed by Cyclosporine as post-transplant immunosuppression[3]. Prior to allo-SCT a median of 2 lines of treatment (1-3) were administered over a period of 650 days (164-6964). At time of transplant, all pts had measurable disease with a median of 2 metastatic sites (1-4) (lung: 87%; bone: 41%; liver: 12 % and lymph node involvement: 28%): according to RECIST criteria, 21 pts (66%) had progressive disease (PD) and 11 pt (34%) had non progressive disease (NPD) (10 stable, 1 partial remission [PR]). Two of the 32 pts (6%) died from treatment related complications. Four of them achieved PR at days 90-180, 1 pt achieved complete remission (CR) at day 270, with an objective response (OR) rate of 16%. Twenty seven pts finally died of disease progression for a 2-year overall survival (OS) rate of 21% (11-39). Results are dramatically different according to pts disease status at time of transplant. While outcome is uniformly poor for pts with PD, pts with NPD achieved a 36% OR rate with 5 pts (55%) surviving more than 2 years and 3 pts (27%) surviving more than 3 years. This analysis confirms the low treatment-related mortality after RIC-based allo-SCT. However, patients with rapidly progressive RCC do not benefit from this approach, emphasizing the need for selecting pts with slow disease progression kinetics or even less advanced disease to further improve transplant outcome.

Recently, the Milano group published a long-term follow-up of patients who have undergone allograft for cytokine-refractory RCC: Twenty-five patients received a reduced-intensity allograft from an HLA-identical sibling donor after a thiotepa, fludarabine and cyclophosphamide conditioning regimen, and a cyclosporine-based GVHD prophylaxis. One-year overall survival was 48%, and five-year OS was 20%. At a median observation time of 65 months, five patients are alive, one in CR, one in PR and three with stable disease. Survival of patients at favorable/intermediate-risk according to the MSKCC score that underwent allografting was better in comparison to the survival predicted by historical controls. They concluded that 20% of cytokine-refractory RCC patients are alive long-term after allografting, and that transplantation is able to induce long-term disease control in a fraction of relapsed RCC patients[4].

The introduction in the clinic of molecularly targeted agents that interfere with neoangiogenesis, both monoclonal antibodies and small tyrosine-kinase inhibitor molecules (e.g., sunitinib, sorafenib, bevacizumab), has considerably decreased the use of allogeneic transplantation. After the clinical experience of the last ten years, there are still a number of open questions on this therapeutic procedure:

1) Is the GVT effect still occurring after anti-angiogenic (i.e., TKI, VEGF) and/or mTOR inhibition therapies?

2) Is there a therapeutic window for allograft after first- or second-line therapies for RCC?

3) Can we envisage clinical strategies for adoptive immunotherapy in RCC?

Much of the future clinical work in this area will depend on the answers to these questions.

Antigen discovery is an intriguing output of allograft in RCC, that can have therapeutic implications. Experimental evidence suggests that donor-derived T cells and NK cells are the main mediators of the graft-versus-RCC effect upon allogeneic HSCT. Isolation of CD8+ CTL clones recognizing several target antigens of graft-versus-RCC effect (minor histocom-

patibility antigens on RCC cells; a peptide epitope derived from human endogenous retrovirus type E; the tumor-associated antigen encoded by the Wilms tumor 1 gene) has increased our knowledge of the disease biology, and has opened the possibility of antigen-specific adoptive cell therapy. Though not curative, novel targeted agents may be combined with allogeneic transplantation or with adoptive cell therapy to maximize the chances of cure of RCC.

Conflict of Interest

The authors have declared that no conflict of interest exists.

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