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Allogeneic Hematopoietic Cell Transplantation for Renal Cell Carcinoma: Ten Years After

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Abstract

Introduction—The first series of patients with metastatic renal cell carcinoma (RCC) treated by nonmyeloablative allogeneic hematopoietic cell transplantation (HCT) was reported in 2000 and demonstrated an allogeneic graft-versus-tumor (GVT) effect that encouraged further investigation of this approach. However, the past 10 years have also witnessed profound changes in the medical management of metastatic RCC with the introduction of targeted therapies directed against vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) signaling pathways creating uncertainty about a continued role for allogeneic HCT in the treatment of RCC.

Areas covered—Twenty-one published reports describing clinical outcomes for 398 patients with metastatic RCC treated by allogeneic HCT compiled herein provide a composite overview of the world wide experience for key efficacy and toxicity outcomes. Review of correlative studies that identify donor-derived T cells as mediators of RCC-specific GVT effects offers insight into both the potential as well as the technical barriers to the delivery of antigen-specific posttransplant cellular therapy or vaccination designed to augment the allogeneic GVT effect.

Expert opinion—The future development of nonmyeloablative allogeneic HCT for metastatic RCC will require novel treatment protocols designed to augment and sustain posttransplant GVT effects against RCC to generate renewed enthusiasm for this approach.

Keywords

Renal cell carcinoma; Allogeneic hematopoietic cell transplantation; Graft-versus-tumor effect; Cytotoxic T lymphocyte; Minor histocompatibility antigen

1. Introduction

Renal cell carcinoma (RCC) accounts for 3-4% of new cancer diagnoses in the United States and the majority of patients either present with metastatic disease or relapse following surgical resection [1, 2]. Systemic chemotherapy has minimal activity against metastatic RCC and single- or multi-agent regimens have never been established as a recognized standard approach for this disease [3]. In contrast, RCC has proven to be sensitive to immunotherapies. With the commercial availability of interferon-alpha after 1986 and FDA approval of interleukin-2 for treatment of RCC in 1992, front-line treatment of metastatic RCC with systemic cytokine therapies was widely adopted and demonstrated incremental benefit in overall patient survival despite modest objective response rates around 20% [4-6]. Of great interest, 5 to 7% of patients responding to high dose IL-2 have been observed to achieve durable complete remission of their disease [7]. The mechanism for the anti-tumor effect of cytokine therapies for RCC remains incompletely defined. However, both animal models and human studies have suggested that cytokine therapies could augment host cellular immune responses capable of recognizing RCC tumor [8-13]. The widespread application of immune therapies for RCC with occasional striking success has provided strong encouragement for the development of novel immunologic approaches to treatment including allogeneic hematopoietic cell transplantation (HCT).

The retrospective analysis of leukemic patients treated by myeloablative allogeneic HCT observed that the risk of relapse was lower in patients who developed acute and/or chronic graft-versus-host disease (GVHD), lower in recipients of allogeneic compared with syngeneic marrow, and higher in recipients of T cell-depleted compared with unmodified marrow [14]. Such data first suggested that a graft-versus-tumor (GVT) effect mediated by T lymphocytes derived from the transplant donor was a key component of the anti-tumor properties of allogeneic HCT. Direct evidence for a role for donor T cells in the GVT effect was further provided by studies of donor lymphocyte infusions (DLI) to treat posttransplant relapse that demonstrated anti-leukemic activity in the absence of any conditioning chemotherapies [15, 16].

Recognition that the GVT effect made a major contribution to eradicating leukemia following conventional myeloablative allogeneic HCT provided the conceptual foundation for the development of reduced-intensity, nonmyeloablative conditioning regimens causing little organ toxicity, but suppressing the recipient immune system sufficiently to allow the engraftment of donor cells [17]. The demonstration that nonmyeloablative allogeneic HCT could be successfully applied to the treatment of hematologic malignancies encouraged the examination of nonmyeloablative allogeneic HCT as a novel form of immunotherapy for tumors not historically treated by allogeneic HCT including advanced RCC.

In 2000, Childs and coworkers at the National Cancer Institute (NCI) in Bethesda, Maryland, reported the first case series of 19 patients with metastatic RCC who had failed prior cytokine (17/19) or other therapies and were treated by nonmyeloablative conditioning therapy with cyclophosphamide and fludarabine followed by allogeneic peripheral blood stem cell transplantation received from an HLA-matched (N=17) or single antigen mismatched (N=2) sibling donor. Cyclosporine was used for posttransplant immunosuppression. All patients achieved donor engraftment of both myeloid and lymphoid lineages. Of great interest, objective responses were observed in 10/19 (53%) patients and included 3 complete responders. These observations first suggested that advanced RCC was sensitive to an allogeneic GVT effect. Toxicities were comparable to outcomes reported in patients with hematologic malignancies treated by similar transplant protocols and included two treatment-related deaths (11%), and the development of acute (grade II to IV) or chronic graft-versus-host disease in 53% and 21% of patients, respectively [18].

2. Clinical Outcomes of Allogeneic HCT for RCC

Following the initial report by Childs and coworkers, nonmyeloablative allogeneic HCT treatment protocols for advanced RCC have been further examined by investigators at several US and international transplant centers. Twenty-one reports describing clinical outcomes for 17 separate case series of >3 RCC patients treated by nonmyeloablative conditioning and allogeneic HCT were identified and summarized in Table 1 [18-38]. Confirmatory evidence for an allogeneic GVT effect against advanced RCC was reported in 13 of the 17 case series. Responses were observed following transplants received from sibling donors, as well as from HLA-identical unrelated donors, or from unrelated cord blood stem cells [25, 38]. However, in contrast to a 53% overall response rate first reported by Childs and co-workers [18], the response rates among the 17 case series were highly variable (range 0 to 57%) with a median response rate of only 14% (Table 1). Similarly, the aggregate response rate for 398 patients compiled from 21 reports listed in Table 1 (allowing that some patients could be counted twice within the EBMT retrospective analysis of 124 patients [36] and smaller reported case series from European centers) was 89/398, or 22%; also substantially lower than observed by Childs and coworkers. In addition, complete responses were rare with most responding patients achieving only transient partial remissions and suffering subsequent disease progression. Many of the objective responses also occurred only after the application of posttransplant therapies to manage disease progression. For example, in 6 of 13 reports describing objective responses of metastatic RCC following allogeneic HCT, the response(s) of one or more patients followed the application of posttransplant DLI or interferon (IFN)- α (Table 1) [18, 23, 25, 26, 29, 33, 36]. Treatment by nonmyeloablative conditioning and allogeneic HCT also exposed patients to morbidity and mortality risks inherent to this style of adoptive immunotherapy. Transplant-related deaths were reported in 14 of the 17 series (range 0-43%) with a median rate of 14%. Additionally, rates of acute and chronic GVHD (median of 44% and 47% respectively) generally reflected treatment-associated norms established by the broader use of nonmyeloablative conditioning and allogeneic HCT for patients with hematologic malignancies [39].

2.1 Prognostic Factors

Based on the initial evidence for an allogeneic GVT effect against metastatic RCC from single institution case series, a multi-institutional phase II study led by the Cancer and Leukemia Group B (CALGB) cooperative group was designed to evaluate the feasibility and toxicity of this approach. Between 2002 and 2004, 22 patients were treated at 14 institutions with no objective responses observed. The study was closed to further accrual and the results were reported in 2006 [24]. Retrospective critique of this trial noted a very short median progression free survival (3.0 months) and overall patient survival (5.5 months) that may not have permitted sufficient time to observe the development of a GVT effect, which is often delayed in onset by several months from the start of the transplant [26, 36, 40]. In addition, the infrequent use of posttransplant DLI or IFN for management of disease progression (2 of 22 patients) may also have contributed to the lack of beneficial clinical effect observed. The disappointing results of the CALGB trial (and other smaller series that failed to observe tumor responses) called attention to the heterogeneity of response rates between case series for RCC patients and encouraged retrospective analyses of patient-specific clinical factors associated with tumor response or overall survival that might be used prospectively to select RCC patients more likely to benefit from allogeneic HCT.

Barkholt and co-workers, on behalf of the French Immunotherapy and Cancer (ITAC) Group and European Group for Blood and Marrow Transplantation (EBMT) Solid Tumor Working Party, reported the largest retrospective study conducted thus far of 124 RCC patients treated by nonmyeloablative allogeneic HCT performed at 21 European centers. In

multivariate analysis, this study identified factors associated with tumor response or overall patient survival. Factors associated with response included a time period of less than 1 year from diagnosis of RCC to allogeneic HCT, transplantation from an HLA-mismatched donor, and acute GVHD. The factors associated with improved survival following allogeneic HCT included chronic GVHD, use of DLI, a Karnofsky score $\geq 80\%$, and less than three sites of metastases [36]. In a separate analysis of clinical features associated with treatment outcome, Peccatori and co-workers identified 70 RCC patients treated by nonmyeloablative allogeneic HCT at 9 EBMT centers. In multivariate analysis, Karnofsky performance status, C-reactive protein (CRP) level, and lactate dehydrogenase (LDH) level were shown to segregate patients into high-risk and low-risk cohorts with markedly different median survival of 3.5 months versus 23 months respectively [41]. From analysis of the largest single-institution series of 74 RCC patients treated by nonmyeloablative allogeneic HCT, Takahashi and co-workers noted a statistically significant difference in response rate for patients with clear cell RCC versus other histologies (48% versus 0% RR, $P=0.0018$) [26]. Finally, retrospective analyses of smaller case series also reported an association with the number of CD34⁺ transfused cells, disease status at day +90, and hematocrit level with overall patient survival [22, 29].

The retrospectively defined clinical variables associated with tumor regression or patient survival that might be used prospectively to select RCC patients more likely to benefit from allogeneic HCT (a time period of less than 1 year from diagnosis of RCC to treatment, Karnofsky score, less than three sites of metastases, CRP level, LDH level, hematocrit level, and clear cell histology) largely corresponded to previously identified RCC-specific prognostic factors, and were therefore unlikely to represent treatment-specific predictive markers. Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) and other centers used clinical factors that included performance status, serum hemoglobin, calcium, LDH, time from initial diagnosis to systemic treatment, and number of sites of metastases to stratify RCC patients into favorable, intermediate, or poor prognostic groups [42, 43]. Thus, RCC patients corresponding to the previously defined favorable risk group appeared more likely to respond to allogeneic HCT. The sensitivity of clear cell versus other histologic subtypes of RCC to an allogeneic GVT effect was also an association with immunotherapy previously observed for RCC tumors treated with systemic cytokines [44, 45].

2.2 Mechanism of the GVT Effect

Insight into the mechanism of a posttransplant RCC-specific GVT effect might also identify strategies for augmenting the anti-tumor activity. Several lines of evidence suggested a significant role for donor T cells mediating GVT effects following allogeneic HCT for RCC. The conditioning regimens employed for nonmyeloablative HCT lacked anti-tumor activity and the onset of RCC regression following allogeneic HCT was often delayed for several months. For example, the median time to response observed in the two largest case series of RCC patients treated by allogeneic HCT was 150 days and 133 days, respectively [26, 36]. The onset of tumor regression often corresponded to the development of complete donor chimerism of CD3⁺ cells, the withdrawal of immune suppression, or followed posttransplant treatment with DLI or IFN- α and was associated with the development of acute GVHD [18, 36]. In addition, greater numbers of CD8⁺ T cells have been measured in the posttransplant peripheral blood of responding versus nonresponding patients [46]. Infiltration of responding tumors by donor-derived CD8⁺ T cells has also been observed [38, 47].

3. RCC-reactive T cell specificity following allogeneic HCT

Minor histocompatibility (H) antigens are MHC-associated peptides encoded by polymorphic genes that differ between allogeneic transplant donor and recipient resulting in

protein sequence differences that appear “foreign” to donor T lymphocytes and elicit donor T cell responses following HCT. A murine model of allogeneic graft-versus-host effects mediated by CD8⁺ T cells recognizing class I MHC-associated minor H antigens has demonstrated an important role for the presentation of minor H antigens on recipient bone marrow-derived professional antigen presenting cells (APC) [48]. This model for minor H antigen immunogenicity and the clinical observation of RCC tumor regression closely associated with the development of posttransplant GVHD [18, 36] motivated our group to investigate minor H antigen targets shared between hematopoietic and RCC target cells that could be detected in posttransplant peripheral blood samples of RCC patients treated by nonmyeloablative HCT at our institution. Our group demonstrated that tumor-reactive CD8⁺ T cell clones recognizing minor H antigens expressed by RCC tumor cells could be isolated from the peripheral blood of RCC patients treated by nonmyeloablative allogeneic HCT. An RCC-reactive CD8⁺ CTL clone isolated from a patient who experienced a partial regression (PR) of bulky metastatic RCC was specific for the previously characterized HLA-A2-associated HA-1 minor H antigen [23]. Encoded by the *HMHA1* gene located on chromosome 19p13.3, the HA-1 antigen is selectively expressed by hematopoietic cells and some solid tumors including RCC, but not by cells in other normal tissues [49-51].

Our group subsequently identified a novel HLA-A2-associated minor H antigen expressed by RCC tumor that was encoded by an alternative open reading frame in *C19orf48*, a gene of unknown function located on chromosome 19q13. The *C19orf48* reading frame spanning the minor H antigen peptide epitope encoded a predicted polypeptide of only 48 residues. Of interest, the *C19orf48* epitope was recognized by CTL clones isolated from two different patients with metastatic RCC who experienced a PR or prolonged stable disease respectively following nonmyeloablative allogeneic HCT. However, in addition to RCC tumor cells, *C19orf48* transcript was also broadly detected in normal tissues including liver and intestine that are target organs of GVHD [52].

We also evaluated four additional minor H antigens previously identified from studies of leukemic patients and encoded by the Y-chromosome gene *JARID1D* (*SMCY*), or the autosomal genes *KIAA0020* (HA-8), *SP110*, and *AKAP13* (HA-3) for their expression by RCC tumor cells and recognition by CTL clones *in vitro*. Each of these four minor H antigens was a constitutively expressed target for robust CTL-mediated anti-tumor effects measured by *in vitro* assays [S.S. Tykodi and E. H. Warren, unpublished observations]. Along with studies by others demonstrating expression of the minor H antigen encoded by *P2X5* in RCC tumor cells [53], collectively these data identify seven molecularly-defined minor H antigens that have been shown to be expressed by RCC tumor cells measured by *in vitro* assays and that may therefore contribute to posttransplant GVT effects [23, 50-53]. The expression profile of these RCC-associated minor H antigens in nonmalignant tissues are heterogeneous and include minor H antigens broadly expressed in normal tissues (*JARID1D*, HA-8, HA-3, *C19orf48*) [49, 52, 54] as well as minor H antigens with more restricted expression (HA-1, *SP110*, *P2X5*) [49, 53, 55]. CTL targeting RCC-associated minor H antigens broadly expressed in normal tissues may contribute to posttransplant GVT effects [56] but could also account for the observation of tumor regression associated with the development of clinical GVHD [18, 36, 57, 58].

In addition to tumor-associated minor H antigen targets, both murine and human studies have also suggested a contribution of donor-derived CTL specific for nonpolymorphic tumor antigens to posttransplant GVT effects following allogeneic HCT [59, 60]. Childs and co-workers identified a nonpolymorphic RCC antigen encoded by a transcript from human endogenous retrovirus type E (HERV-E) that was recognized by an HLA-A11-restricted CD8⁺ T cell clone isolated from an RCC patient who experienced posttransplant tumor regression. Expression of the HERV-E transcript was highly tumor specific and detected in

~ 50% of cultured RCC tumor cell lines and fresh kidney tumor samples, but not in normal tissues or other non-RCC tumor cell lines [26].

Identified RCC-associated antigens with highly restricted expression in normal tissues such as HA-1 or HERV-E are of substantial interest as potential targets for posttransplant manipulation by vaccination or adoptive cellular therapy designed to augment RCC-specific GVT effects. However, such an approach would be limited to a small percent of the total RCC population due to the low phenotype frequency of the HLA-A11 restricting allele for HERV-E (14% in US Caucasians), heterogeneous expression of HERV-E and HA-1 between RCC tumors, and low probability of disparity rates for individual minor H antigens; even for minor H antigens including HA-1 that are associated with the high-frequency HLA-A2 allele (for example, patient/donor discordance rates for HA-1 are 6.6% for sibling donors or 12.0 % for unrelated donors in Caucasian populations) [23, 26, 50, 61, 62]. Thus, the practical development of posttransplant specific immunotherapy would require a substantially larger panel of RCC-associated antigens.

In vitro studies have demonstrated that mixed lymphocyte / tumor cell (MLTC) cultures using T cells isolated from healthy allogeneic donors HLA-matched to RCC tumors will elicit more vigorous CD8⁺ CTL responses than for fully autologous culture conditions [63, 64]. Forcing RCC tumor cells to serve as the APC for allogeneic CTL in MLTC culture could elicit CTL that recognize novel minor H antigens that are expressed in tumor cells but not expressed in hematopoietic or other normal tissues. Tumor-reactive T cell clones derived in this manner could direct the identification of novel RCC-associated alloantigens [65], although the successful identification of T cell antigens remains a labor intensive and technically challenging endeavor.

The most common sources of genetic variation associated with characterized human minor H antigens are non-synonymous single nucleotide polymorphisms (SNPs) that occur within protein coding sequences [66]. The use of available genetic databases to locate non-synonymous SNPs within characterized genes encoding for tumor-associated antigens with favorable expression patterns also represents a strategy to facilitate the identification of novel minor H antigen peptide sequences [67] that could be targeted therapeutically. As an example applicable to RCC, nonsynonymous SNPs are located in the RCC-associated gene encoding carbonic anhydrase IX [68] including the SNP rs2071617 causing an amino acid substitution within an immunogenic peptide sequence that can be recognized by CTL clones in association with HLA-A2 (amino acid residues 26-35; LLSLLLLMPV vs. LLSLLLLVPV) [69]. However, the presentation of these peptides by HLA-A2-positive and CAIX-expressing RCC tumors has not been established. Further, the application of such a “reverse immunology” approach to minor H antigen identification requiring assays to measure peptide binding to HLA molecules, to expand and isolate peptide-specific CTL, and ultimately to functionally assess tumor cell processing and presentation of candidate epitope sequences also presents significant technical hurdles to minor H antigen discovery.

4. A Paradigm Change for Primary Therapy of Metastatic RCC

In the 10 years since the initial study of nonmyeloablative allogeneic HCT applied to RCC, the treatment options for patients with advanced RCC have substantially evolved. Positive results from phase III clinical trials have led to regulatory approval of six new “targeted” therapeutics for advanced RCC in both the US and Europe since 2005. These include oral tyrosine kinase inhibitors (sorafenib, sunitinib, and pazopanib) [70-72] that disrupt vascular endothelial growth factor (VEGF)-receptor signaling; the intravenous VEGF-binding monoclonal antibody bevacizumab [73, 74]; or inhibitors of the mammalian target of rapamycin (mTOR) signaling pathway (temsirolimus, everolimus) [75, 76]. Therapeutic

agents targeting the VEGF-signaling pathway have been studied primarily in patients with clear cell RCC tumors and prognosis corresponding to good or intermediate risk groups by MSKCC criteria therefore closely corresponding to patients retrospectively identified as more likely to respond to allogeneic HCT. The availability and rapid integration of novel targeted therapies into consensus treatment guidelines as appropriate first- and second-line treatments for metastatic RCC are certain to impact the contemporary study of allogeneic HCT for advanced RCC. A history of prior treatment with one or more targeted agents will undoubtedly supplant the past experience of front-line cytokine therapies for patients referred for treatment by allogeneic HCT.

The use of targeted therapies in combination with allogeneic HCT has also been recognized and described anecdotally [29]. A murine model demonstrating that VEGF-receptor2 blockade enhanced tumor-reactive T cell immunity in a breast carcinoma model system supports the concept of integrating anti-angiogenic therapies with immunotherapies [77]. Our group has also previously commented on the potential for mTOR inhibitors to serve a dual role in nonmyeloablative allogeneic HCT by providing posttransplant immunosuppression as well as direct anti-tumor activity against RCC delaying posttransplant tumor progression and favoring the development of a GVT effect [78]. Clinical activity of mTOR inhibitors against a variety of lymphoma subtypes has been reported, and the retrospective analysis of nonmyeloablative allogeneic HCT treatment protocols for lymphoma patients that included the posttransplant use of the mTOR inhibitor rapamycin observed improved survival for rapamycin-treated patients with a hazard ratio for disease relapse/progression of 0.5 [79]. Such data representing proof-of-concept for the combination of allogeneic immunotherapy with an mTOR inhibitor encourages a similar combinatorial approach to the treatment of metastatic RCC.

5. Expert Opinion

Ten years after Childs and coworkers published the first case series of RCC patients treated by nonmyeloablative allogeneic HCT, advanced RCC is now recognized as a solid tumor that is sensitive to an allogeneic GVT effect. However, in contrast to hematologic malignancies where the success of nonmyeloablative allogeneic HCT is typically judged by rates of sustained complete remissions, complete remissions of RCC following allogeneic HCT have been rare. The paucity of durable complete responders who might justify the exposure of RCC patients to the risks inherent in allogeneic HCT including infections and GVHD that can result in treatment associated deaths, as well as the relatively low aggregate response rate of 22% have diminished interest in the use of nonmyeloablative allogeneic HCT according to currently established treatment protocols applied to hematologic cancers. Nevertheless, the application of nonmyeloablative allogeneic HCT to metastatic RCC may remain a potential treatment option for patients. A search of the ClinicalTrials.gov database identifies five ongoing clinical trials of allogeneic HCT open to patients with metastatic RCC at both US and International transplant centers (Table 2). In addition, a recent consensus practice statement on behalf of the EBMT identifies allogeneic HCT as a “clinical option” for RCC, in contrast to all other solid tumor indications considered [80].

However, the most significant factor to influence contemporary patient accrual to available studies of allogeneic HCT for RCC is likely the development and widespread use of novel targeted therapies for the medical management of metastatic RCC. Oncology providers now have the means to offer multiple lines of therapy to RCC patients in the outpatient clinical setting thereby deferring patient referral to centers that specialize in HCT until later in their treatment course. Treatment associated toxicities can also be more easily managed by dose reduction or treatment interruption than for complications following allogeneic HCT. It is notable that the cumulative experience with allogeneic HCT for metastatic RCC reflects

almost exclusively the treatment of patients following failure of front-line cytokine therapies. Therefore, the consequences of a history of prior VEGF- and/or mTOR-directed therapies on toxicities and outcomes following allogeneic HCT are unknown. Further, patients that have failed one or multiple prior lines of targeted therapies stand at high risk of rapid disease progression and clinical deterioration representing important barriers to the time requirement for patient evaluation and donor identification necessary to coordinate treatment by allogeneic HCT. It has yet to be established that patients can be effectively evaluated and enrolled onto trials of nonmyeloablative allogeneic HCT after the failure of targeted therapy.

Clinical observations and correlative laboratory studies have provided compelling evidence that the anti-tumor effect of allogeneic HCT against RCC is mediated by donor-derived T cells. Despite this insight, the mechanisms of tumor resistance to allogeneic immunotherapy are not understood. The failure of robust posttransplant RCC-reactive T cell responses to develop in some patients or phenotypic heterogeneity within RCC tumors that would predispose to immunoselection for antigen-escape tumor variants represent rational hypotheses [23 and S.S. Tykodi and E. H. Warren, unpublished observations]; however there are insufficient clinical data to draw firm conclusions. T cell responses targeting tumor-associated minor H antigens may represent uniquely potent effector cells and novel treatment strategies designed to augment T cell mediated posttransplant GVT effects without exacerbating GVHD are highly desired. Targeting RCC-associated minor H antigens with a restricted tissue distribution (HA-1, *SP110*, *P2X5*) by posttransplant adoptive T cell therapy or vaccination would be technically possible, but limited to a small fraction of potential RCC patients owing to the low population frequencies for individual minor H antigens. Thus, a sustained commitment to RCC-associated alloantigen discovery would be necessary to identify a sufficiently large panel of suitable target antigens to support pilot clinical studies of posttransplant vaccine or cellular therapies. Augmenting T cell responses against characterized nonpolymorphic and broadly shared T cell antigens with epitopes restricted by common HLA alleles such as 5T4 [81, 82], carbonic anhydrase IX [83], or MUC1 [84] would extend the possibility of delivering posttransplant specific immunotherapies to a much larger fraction of RCC patients, but T cell therapies targeting nonpolymorphic antigens could also be explored outside the context of allogeneic HCT and thereby avoiding associated toxicities.

A practical approach for the development of innovative transplant protocols in the near term would focus on the delivery of posttransplant interventions intended to augment GVT effects that could be applied to all RCC patients who would undergo allogeneic HCT. For example, a recently opened study will test the anti-tumor activity of a novel DLI product (Table 2, NCT00923845). Proof-of-concept studies in patients with hematologic malignancies combining allogeneic HCT with a targeted therapy (mTOR inhibitor) [29, 78] or with immune check point blockade (anti CTLA-4 monoclonal Ab) [85] demonstrating anti-tumor activity without excessive toxicity also represent possible approaches to extend to RCC [86]. Treatment of favorable risk RCC patients on novel clinical trials of allogeneic HCT early on in their disease course may also increase the proportion of patients able to tolerate early posttransplant disease progression allowing sufficient time for the development of posttransplant GVT effects.

In summary, in an era of expanded and competing treatment options for patients with metastatic RCC, the future development of nonmyeloablative allogeneic HCT for RCC will require novel treatment protocols that increase the likelihood for potent and sustained posttransplant GVT effects to generate renewed enthusiasm for this approach amongst patients and referring providers.

7 References

1. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med*. 2005; 353:2477–90. [PubMed: 16339096]
2. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin*. 2010; 60:277–300. [PubMed: 20610543]
3. Amato RJ. Chemotherapy for renal cell carcinoma. *Semin Oncol*. 2000; 27:177–86. [PubMed: 10768596]
4. Collaborators MRCRC. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. *Lancet*. 1999; 353:14–7. [PubMed: 10023944]
5. Pantuck AJ, Belldegrun AS, Figlin RA. Nephrectomy and interleukin-2 for metastatic renal-cell carcinoma. *N Engl J Med*. 2001; 345:1711–2. [PubMed: 11759660]
6. Yang JC, Childs R. Immunotherapy for renal cell cancer. *J Clin Oncol*. 2006; 24:5576–83. [PubMed: 17158543]
7. Klapper JA, Downey SG, Smith FO, et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma: a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. *Cancer*. 2008; 113:293–301. [PubMed: 18457330]
8. Golumbek PT, Lazenby AJ, Levitsky HI, et al. Treatment of established renal cancer by tumor cells engineered to secrete interleukin-4. *Science*. 1991; 254:713–6. [PubMed: 1948050]
9. Seki N, Brooks AD, Carter CR, et al. Tumor-specific CTL kill murine renal cancer cells using both perforin and Fas ligand-mediated lysis in vitro, but cause tumor regression in vivo in the absence of perforin. *J Immunol*. 2002; 168:3484–92. [PubMed: 11907109]
10. Finke JH, Rayman P, Edinger M, et al. Characterization of a human renal cell carcinoma specific cytotoxic CD8+ T cell line. *J Immunother*. 1992; 11:1–11. [PubMed: 1734943]
11. Bernhard H, Jager E, Maeurer MJ, et al. Tumor associated antigens in human renal cell carcinoma: MHC restricted recognition by cytotoxic T lymphocytes. *Tissue Antigens*. 1996; 48:22–31. [PubMed: 8864171]
12. Brouwenstijn N, Gaugler B, Kruse KM, et al. Renal-cell carcinoma-specific lysis by cytotoxic T-lymphocyte clones isolated from peripheral blood lymphocytes and tumor-infiltrating lymphocytes. *Int J Cancer*. 1996; 68:177–82. [PubMed: 8900424]
13. Jantzer P, Schendel DJ. Human renal cell carcinoma antigen-specific CTLs: antigen-driven selection and long-term persistence in vivo. *Cancer Res*. 1998; 58:3078–86. [PubMed: 9679974]
14. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. *Blood*. 1990; 75:555–62. [PubMed: 2297567]
15. Kolb HJ, Schattenberg A, Goldman JM, et al. European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. *Blood*. 1995; 86:2041–50. [PubMed: 7655033]
16. Collins RH Jr, Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol*. 1997; 15:433–44. [PubMed: 9053463]
17. Storb R. Allogeneic hematopoietic stem cell transplantation--yesterday, today, and tomorrow. *Exp Hematol*. 2003; 31:1–10. [PubMed: 12543102]
18. Childs R, Chernoff A, Contentin N, et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. *N Engl J Med*. 2000; 343:750–8. [PubMed: 10984562] •• The seminal case series of RCC patients treated by nonmyeloablative allogeneic HCT that demonstrated an RCC-reactive GVT effect.
19. Rini BI, Zimmerman T, Stadler WM, et al. Allogeneic stem-cell transplantation of renal cell cancer after nonmyeloablative chemotherapy: feasibility, engraftment, and clinical results. *J Clin Oncol*. 2002; 20:2017–24. [PubMed: 11956260]
20. Artz AS, Van Besien K, Zimmerman T, et al. Long-term follow-up of nonmyeloablative allogeneic stem cell transplantation for renal cell carcinoma: The University of Chicago Experience. *Bone Marrow Transplant*. 2005; 35:253–60. [PubMed: 15543195]

21. Ueno NT, Cheng YC, Rondon G, et al. Rapid induction of complete donor chimerism by the use of a reduced-intensity conditioning regimen composed of fludarabine and melphalan in allogeneic stem cell transplantation for metastatic solid tumors. *Blood*. 2003; 102:3829–36. [PubMed: 12881308]
22. Nakayama K, Tannir NM, Liu P, et al. Natural history of metastatic renal cell carcinoma in patients who underwent consultation for allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2007; 13:975–85. [PubMed: 17640602]
23. Tykodi SS, Warren EH, Thompson JA, et al. Allogeneic hematopoietic cell transplantation for metastatic renal cell carcinoma after nonmyeloablative conditioning: toxicity, clinical response, and immunological response to minor histocompatibility antigens. *Clin Cancer Res*. 2004; 10:7799–811. [PubMed: 15585611] •• The first demonstration that RCC-reactive, minor H antigen-specific CTL clones could be isolated from the peripheral blood of an RCC patient responding to nonmyeloablative allogeneic HCT.
24. Rini BI, Halabi S, Barrier R, et al. Adoptive immunotherapy by allogeneic stem cell transplantation for metastatic renal cell carcinoma: a CALGB intergroup phase II study. *Biol Blood Marrow Transplant*. 2006; 12:778–85. [PubMed: 16785067]
25. Peres E, Abidi MH, Mellon-Reppen S, et al. Reduced intensity transplantation for metastatic renal cell cancer with 2-year follow-up. *J Immunother*. 2007; 30:562–6. [PubMed: 17589297]
26. Takahashi Y, Harashima N, Kajigaya S, et al. Regression of human kidney cancer following allogeneic stem cell transplantation is associated with recognition of an HERV-E antigen by T cells. *J Clin Invest*. 2008; 118:1099–109. [PubMed: 18292810] •• The identification of an RCC-associated nonpolymorphic antigen (HERV-E) as a target of CTL isolated from an RCC patient responding to nonmyeloablative allogeneic HCT.
27. Pedrazzoli P, Da Prada GA, Giorgiani G, et al. Allogeneic blood stem cell transplantation after a reduced-intensity, preparative regimen: a pilot study in patients with refractory malignancies. *Cancer*. 2002; 94:2409–15. [PubMed: 12015766]
28. Bregni M, Doderio A, Peccatori J, et al. Nonmyeloablative conditioning followed by hematopoietic cell allografting and donor lymphocyte infusions for patients with metastatic renal and breast cancer. *Blood*. 2002; 99:4234–6. [PubMed: 12010834]
29. Bregni M, Bernardi M, Servida P, et al. Long-term follow-up of metastatic renal cancer patients undergoing reduced-intensity allografting. *Bone Marrow Transplant*. 2009; 44:237–42. [PubMed: 19234510]
30. Hentschke P, Barkholt L, Uzunel M, et al. Low-intensity conditioning and hematopoietic stem cell transplantation in patients with renal and colon carcinoma. *Bone Marrow Transplant*. 2003; 31:253–61. [PubMed: 12621459]
31. Blaise D, Bay JO, Faucher C, et al. Reduced-intensity preparative regimen and allogeneic stem cell transplantation for advanced solid tumors. *Blood*. 2004; 103:435–41. [PubMed: 12946991]
32. Nakagawa T, Kami M, Hori A, et al. Allogeneic hematopoietic stem cell transplantation with a reduced-intensity conditioning regimen for treatment of metastatic renal cell carcinoma: single institution experience with a minimum 1-year follow-up. *Exp Hematol*. 2004; 32:599–606. [PubMed: 15246155]
33. Massenkeil G, Roigas J, Nagy M, et al. Nonmyeloablative stem cell transplantation in metastatic renal cell carcinoma: delayed graft-versus-tumor effect is associated with chimerism conversion but transplantation has high toxicity. *Bone Marrow Transplant*. 2004; 34:309–16. [PubMed: 15220955]
34. Rzepecki P, Zolnierok J, Sarosiek T, et al. Allogeneic non-myeloablative hematopoietic stem cell transplantation for treatment of metastatic renal cell carcinoma -- single center experience. *Neoplasma*. 2005; 52:238–42. [PubMed: 15875086]
35. Busca A, Novarino A, de Fabritiis P, et al. Nonmyeloablative allogeneic blood stem cell transplantation in patients with metastatic solid tumors. *Hematology*. 2006; 11:171–7. [PubMed: 17325957]
36. Barkholt L, Bregni M, Remberger M, et al. Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe. *Ann Oncol*. 2006; 17:1134–40. [PubMed: 16648196]

37. Yun T, Lee KW, Song EG, et al. Non-myeloablative allogeneic stem cell transplantation for metastatic renal cell carcinoma. *Clin Transplant*. 2007; 21:337–43. [PubMed: 17488382]
38. Ishiyama K, Takami A, Suzuki S, et al. Relationship between tumor-infiltrating T lymphocytes and clinical response after reduced-intensity allogeneic hematopoietic stem cell transplantation for advanced renal cell carcinoma: a single center prospective study. *Jpn J Clin Oncol*. 2009; 39:807–12. [PubMed: 19770130] • Postmortem histologic analyses that associated RCC tumor regression with CD8⁺ T lymphocyte infiltration following nonmyeloablative allogeneic HCT
39. Baron F, Storb R. Current roles for allogeneic hematopoietic cell transplantation following nonmyeloablative or reduced-intensity conditioning. *Clin Adv Hematol Oncol*. 2005; 3:799–819. [PubMed: 16258490]
40. Ueno NT, Childs RW. What's past is prologue: lessons learned and the need for further development of allogeneic hematopoietic stem cell transplantation for renal cell carcinoma. *Biol Blood Marrow Transplant*. 2007; 13:31–3. [PubMed: 17222750]
41. Peccatori J, Barkholt L, Demirer T, et al. Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogeneic stem cell transplantation. *Cancer*. 2005; 104:2099–103. [PubMed: 16220555]
42. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. *J Clin Oncol*. 2002; 20:289–96. [PubMed: 11773181]
43. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. *J Clin Oncol*. 2005; 23:832–41. [PubMed: 15681528]
44. Motzer RJ, Bacik J, Mariani T, et al. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. *J Clin Oncol*. 2002; 20:2376–81. [PubMed: 11981011]
45. Upton MP, Parker RA, Youmans A, et al. Histologic predictors of renal cell carcinoma response to interleukin-2-based therapy. *J Immunother*. 2005; 28:488–95. [PubMed: 16113605]
46. Harlin H, Artz AS, Mahowald M, et al. Clinical responses following nonmyeloablative allogeneic stem cell transplantation for renal cell carcinoma are associated with expansion of CD8⁺ IFN- γ -producing T cells. *Bone Marrow Transplant*. 2004; 33:491–497. [PubMed: 14716341]
47. Takami A, Asakura H, Koshida K, et al. Reduced-intensity allogeneic stem cell transplantation for renal cell carcinoma: in vivo evidence of a graft-versus-tumor effect. *Haematologica*. 2004; 89:375–6. [PubMed: 15020287]
48. Shlomchik WD. Graft-versus-host disease. *Nat Rev Immunol*. 2007; 7:340–52. [PubMed: 17438575]
49. de Bueger M, Bakker A, Van Rood JJ, et al. Tissue distribution of human minor histocompatibility antigens. Ubiquitous versus restricted tissue distribution indicates heterogeneity among human cytotoxic T lymphocyte-defined non-MHC antigens. *J Immunol*. 1992; 149:1788–94. [PubMed: 1380540]
50. Klein CA, Wilke M, Pool J, et al. The hematopoietic system-specific minor histocompatibility antigen HA-1 shows aberrant expression in epithelial cancer cells. *J Exp Med*. 2002; 196:359–68. [PubMed: 12163564]
51. Fujii N, Hiraki A, Ikeda K, et al. Expression of minor histocompatibility antigen, HA-1, in solid tumor cells. *Transplantation*. 2002; 73:1137–41. [PubMed: 11965046]
52. Tykodi SS, Fujii N, Vigneron N, et al. C19orf48 encodes a minor histocompatibility antigen recognized by CD8⁺ cytotoxic T cells from renal cell carcinoma patients. *Clin Cancer Res*. 2008; 14:5260–9. [PubMed: 18698046] •• The identification of C19orf48 as the gene encoding a novel minor H antigen recognized by CTL clones isolated from two RCC patients with evidence for a GVT effect following nonmyeloablative allogeneic HCT.
53. Overes IM, Levenga TH, Vos JC, et al. Aberrant expression of the hematopoietic-restricted minor histocompatibility antigen LRH-1 on solid tumors results in efficient cytotoxic T cell-mediated lysis. *Cancer Immunol Immunother*. 2009; 58:429–39. [PubMed: 18719914]

54. Brickner AG, Warren EH, Caldwell JA, et al. The immunogenicity of a new human minor histocompatibility antigen results from differential antigen processing. *J Exp Med.* 2001; 193:195–206. [PubMed: 11148223]
55. Warren EH, Vigneron NJ, Gavin MA, et al. An antigen produced by splicing of noncontiguous peptides in the reverse order. *Science.* 2006; 313:1444–7. [PubMed: 16960008]
56. Meunier MC, Delisle JS, Bergeron J, et al. T cells targeted against a single minor histocompatibility antigen can cure solid tumors. *Nat Med.* 2005; 11:1222–9. [PubMed: 16227989]
57. Dickinson AM, Wang XN, Sviland L, et al. In situ dissection of the graft-versus-host activities of cytotoxic T cells specific for minor histocompatibility antigens. *Nat Med.* 2002; 8:410–4. [PubMed: 11927949]
58. Akatsuka Y, Warren EH, Gooley TA, et al. Disparity for a newly identified minor histocompatibility antigen, HA-8, correlates with acute graft-versus-host disease after haematopoietic stem cell transplantation from an HLA-identical sibling. *Br J Haematol.* 2003; 123:671–5. [PubMed: 14616971]
59. Hess Michelini R, Freschi M, Manzo T, et al. Concomitant tumor and minor histocompatibility antigen-specific immunity initiate rejection and maintain remission from established spontaneous solid tumors. *Cancer Res.* 2010; 70:3505–14. [PubMed: 20388780]
60. Molldrem JJ, Lee PP, Wang C, et al. Evidence that specific T lymphocytes may participate in the elimination of chronic myelogenous leukemia. *Nat Med.* 2000; 6:1018–23. [PubMed: 10973322]
61. Middleton D, Menchaca L, Rood H, Komerofsky R. Tissue Antigens. 2003; 61:403–7. New allele frequency database: <http://www.allelefrequencies.net>. [PubMed: 12753660]
62. Spierings E, Hendriks M, Absi L, et al. Phenotype frequencies of autosomal minor histocompatibility antigens display significant differences among populations. *PLoS Genet.* 2007; 3:e103. [PubMed: 17604453]
63. Kausche S, Wehler T, Schnurer E, et al. Superior antitumor in vitro responses of allogeneic matched sibling compared with autologous patient CD8+ T cells. *Cancer Res.* 2006; 66:11447–54. [PubMed: 17145892]
64. Tykodi SS, Thompson JA, Sandmaier BM, et al. Ex vivo isolation of RCC-reactive CD8+ CTL clones from HLA-identical allogeneic donor T cell lines stimulated by CD80-transfected tumor cells. *J Clin Oncol.* 2007; 25 Abstract #15625.
65. Dorrschuck A, Schmidt A, Schnurer E, et al. CD8+ cytotoxic T lymphocytes isolated from allogeneic healthy donors recognize HLA class Ia/Ib-associated renal carcinoma antigens with ubiquitous or restricted tissue expression. *Blood.* 2004; 104:2591–9. [PubMed: 15231579]
66. Mullally A, Ritz J. Beyond HLA: the significance of genomic variation for allogeneic hematopoietic stem cell transplantation. *Blood.* 2007; 109:1355–62. [PubMed: 17008540]
67. Wenandy L, Kollgaard T, Letsch A, et al. The 1170 A-P single-nucleotide polymorphism (SNP) in the Her-2/neu protein (HER2) as a minor histocompatibility antigen (mHag). *Leukemia.* 2009; 23:1926–9. [PubMed: 19458631] • The demonstration of how a “reverse immunology” approach could take advantage of identified SNPs to guide the discovery of novel minor H antigen epitopes within previously characterized tumor-associated antigens.
68. de Martino M, Klatte T, Seligson DB, et al. CA9 gene: single nucleotide polymorphism predicts metastatic renal cell carcinoma prognosis. *J Urol.* 2009; 182:728–34. [PubMed: 19539328]
69. Vissers JL, De Vries IJ, Schreurs MW, et al. The renal cell carcinoma-associated antigen G250 encodes a human leukocyte antigen (HLA)-A2.1-restricted epitope recognized by cytotoxic T lymphocytes. *Cancer Res.* 1999; 59:5554–9. [PubMed: 10554034]
70. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* 2007; 356:125–34. [PubMed: 17215530]
71. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* 2007; 356:115–24. [PubMed: 17215529]
72. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* 2010; 28:1061–8. [PubMed: 20100962]

73. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet*. 2007; 370:2103–11. [PubMed: 18156031]
74. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. *J Clin Oncol*. 2008; 26:5422–8. [PubMed: 18936475]
75. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med*. 2007; 356:2271–81. [PubMed: 17538086]
76. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008; 372:449–56. [PubMed: 18653228]
77. Manning EA, Ullman JG, Leatherman JM, et al. A vascular endothelial growth factor receptor-2 inhibitor enhances antitumor immunity through an immune-based mechanism. *Clin Cancer Res*. 2007; 13:3951–9. [PubMed: 17606729]
78. Tykodi SS, Voong LN, Warren EH. Combining allogeneic immunotherapy with an mTOR inhibitor for advanced renal cell carcinoma. *Bone Marrow Transplant*. 2010; 45:1360–2. [PubMed: 19966847]
79. Armand P, Gannamaneni S, Kim HT, et al. Improved survival in lymphoma patients receiving sirolimus for graft-versus-host disease prophylaxis after allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning. *J Clin Oncol*. 2008; 26:5767–74. [PubMed: 19001324]
80. Ljungman P, Bregni M, Brune M, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. *Bone Marrow Transplant*. 2010; 45:219–34. [PubMed: 19584824]
81. Tykodi SS, Thompson JA. Development of modified vaccinia Ankara-5T4 as specific immunotherapy for advanced human cancer. *Expert Opin Biol Ther*. 2008; 8:1947–53. [PubMed: 18990081]
82. Tykodi SS, Satoh S, Harrop R, Warren EH. Cytolytic effects of CD8+ CTL clones specific for an HLA-A2 epitope from the 5T4 tumor antigen on tumor cells in vitro. *J Clin Oncol*. 2010; 28(suppl) abstr e13142.
83. Uemura H, Fujimoto K, Tanaka M, et al. A phase I trial of vaccination of CA9-derived peptides for HLA-A24-positive patients with cytokine-refractory metastatic renal cell carcinoma. *Clin Cancer Res*. 2006; 12:1768–75. [PubMed: 16551861]
84. Wiernecky J, Muller MR, Wirths S, et al. Immunologic and clinical responses after vaccinations with peptide-pulsed dendritic cells in metastatic renal cancer patients. *Cancer Res*. 2006; 66:5910–8. [PubMed: 16740731]
85. Bashey A, Medina B, Corringham S, et al. CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. *Blood*. 2009; 113:1581–8. [PubMed: 18974373]
86. Yang JC, Hughes M, Kammula U, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. *J Immunother*. 2007; 30:825–30. [PubMed: 18049334]

6. Article Highlights Box

- The overall response rate calculated for 398 patients with metastatic renal cell carcinoma (RCC) treated by nonmyeloablative allogeneic hematopoietic cell transplantation (HCT) compiled from 21 published reports was 22%.
- Several lines of evidence suggest a significant role for donor T cells mediating graft-versus-tumor (GVT) effects following allogeneic HCT for RCC.
- Donor-derived cytotoxic T lymphocytes specific for RCC-associated minor histocompatibility antigens or a nonpolymorphic tumor antigen have been isolated from posttransplant peripheral blood samples obtained from RCC patients responding to nonmyeloablative allogeneic HCT.
- Novel targeted therapies directed against vascular endothelial growth factor or mammalian target of rapamycin signaling pathways have been rapidly adopted as appropriate first- and second-line treatments for metastatic RCC.
- The future development of nonmyeloablative allogeneic HCT for RCC will require novel treatment protocols that increase the likelihood for sustained posttransplant GVT effects to generate renewed enthusiasm for this approach.

Table 1

Published Series of Allogeneic Hematopoietic Cell Transplantation for RCC[§]

Reference	No. of Patients	Conditioning	GVHD [†] Prophylaxis	% of Patients				Response post DLI / IFN	
				aGVHD (II-IV)	cGVHD	TRM	Response (CR+PR)		
US Centers									
Childs <i>et al.</i> (2000),	19	Flu + Cy	CSP	53	21	11	53	yes	
Takahashi <i>et al.</i> (2008) [¶]	74	Flu + Cy	CSP	55	47	11	39	yes	
Rini <i>et al.</i> (2002), Artz <i>et al.</i> (2005) [¶]	18	Flu + Cy	Tac + MMF	18	58	28	22	no	
Ueno <i>et al.</i> (2003), Nakayama <i>et al.</i> (2007) [¶]	23	Flu + Mel	Tac + MTX	65	no data	39	26	no	
Tykodi <i>et al.</i> (2004)	8	Flu + TBI	CSP + MMF	50	50	13	13	yes	
Rini <i>et al.</i> (2006)	22	Flu + Cy	Tac + MTX	50	23	9	0	N/A	
Peres <i>et al.</i> (2007)	16	Flu + Cy or Flu + TBI	CSP + MMF	44	43	13	31	yes	
International Centers									
Pedrazzoli <i>et al.</i> (2002)	7	Flu + Cy	CSP + MTX	0*	no data	29*	0*	N/A	
Bregni <i>et al.</i> (2002), Bregni <i>et al.</i> (2009) [¶]	25	TT + Flu + Cy	CSP + MTX or sirolimus	48	36	24	20	yes	
Hentschke <i>et al.</i> (2003)	10	Flu + TBI +/- ATG	CSP + MMF	50	43	30	0	N/A	
Blaise <i>et al.</i> (2004)	25	Flu + Bu + ATG	CSP	42	44	9	8*	no	
Nakagawa <i>et al.</i> (2004)	9	Flu/Cla + Bu + ATG	CSP	44	50	0	11	no	
Massenkeil <i>et al.</i> (2004)	7	Flu + Cy + ATG	CSP +/- MMF	29	67	14	29	yes	
Rzepecki <i>et al.</i> (2005)	5	Flu + Cy	CSP + MTX	60	75	0	0	N/A	
Busca <i>et al.</i> (2006)	7	Flu + TBI	CSP + MMF	29*	67*	0*	14*	no	
Barkholt <i>et al.</i> (2006) [¶]	124	Flu + variable	CSP +/- variable	39	40	16	29 [‡]	yes	
Yun <i>et al.</i> (2007)	11	Flu + Cy/Mel/Bu +/- ATG	CSP +/- MTX	30	86	27	9	no	
Ishiyama <i>et al.</i> (2009)	7	Flu + Cy/Bu +/- TBI +/- ATG	CSP or Tac	57	43	43	57	no	

Notes:

[§]Published series with > 3 patients and reported in English are listed.

[†] Abbreviations: GVHD=graft versus host disease; a=acute; c=chronic; TRM=treatment related mortality; CR=complete response; PR=partial response; DLI=donor lymphocyte infusion; IFN=interferon alpha; Flu=fludarabine; Cy=cyclophosphamide; CSP=cyclosporine; Tac=tacrolimus; MMF=mycophenylate mofetil; Mel=melphalan; MTX=methotrexate; TBI=total body irradiation; ATG=anti-thymocyte globulin; Cla=cladribine; N/A=not applicable.

[¶]Reference includes previously reported patients.

^{*} Percentages for RCC subset of patients.

[¥] Response rate calculated for 98/124 patients surviving > 90 days posttransplant.

Table 2Open Studies of Allogeneic HCT for Metastatic RCC[§]

ClinicalTrials.gov Identifier	Start Date	Sponsor	Conditions
NCT00003553	Jan 1999	National Heart, Lung, and Blood Institute (NHLBI), Bethesda, MD	Renal Cell Carcinoma
NCT00058825	Aug 2000	Baylor College of Medicine, Houston, TX	Renal Cell Carcinoma, Hematologic Malignancy
NCT00303719	Mar 2002	Masonic Cancer Center, University of Minnesota, Minneapolis, MN	Renal Cell Carcinoma, Hematologic Malignancy
NCT00056095	Dec 2002	Federation Nationale des Centres de Lutte Contre le Cancer, France	Renal Cell Carcinoma
NCT00923845	Mar 2008	National Cancer Institute (NCI), Bethesda, MD	Renal Cell Carcinoma

[§] search terms for www.ClinicalTrials.gov] - renal cell carcinoma, renal cancer, kidney cancer, transplant, allogeneic, stem cell, open studies. [Last accessed 11 November 2010]