High-Dose Sirolimus and Immune-Selective Pentostatin plus Cyclophosphamide Conditioning Yields Stable Mixed Chimerism and Insufficient Graft-versus-Tumor Responses

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Abstract

Purpose: We hypothesized that lymphoid-selective host conditioning and subsequent adoptive transfer of sirolimus-resistant allogeneic T cells (T-Rapa), when combined with high-dose sirolimus drug therapy in vivo, would safely achieve antitumor effects while avoiding GVHD.

Experimental Design: Patients (n = 10) with metastatic renal cell carcinoma (RCC) were accrued because this disease is relatively refractory to high-dose conditioning yet may respond to high-dose sirolimus therapy, thereby cautioning against use of this intervention in patients with refractory cancer. Clin Cancer Res; 21(19); 4312–20. ©2015 AACR.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is limited by conditioning toxicity, graft rejection, GVHD, and insufficient graft-versus-tumor (GVT) effects. Reduced intensity conditioning decreases toxicity but promotes mixed chimerism (1) and graft rejection or tumor progression (2). Intensiﬁed post-HCT immune suppression or graft-T-cell depletion reduces GVHD but can decrease GVT effects (3); furthermore, donor lymphocyte infusion (DLI) using unmanipulated T cells can mediate GVT effects but also mediate GVHD (4). To address these limitations, we conducted a pilot clinical trial of immune-selective conditioning, in vivo sirolimus GVHD prophylaxis, and multiple infusions of DLI products manufactured ex vivo in sirolimus.

Conditioning varies from myeloablative to reduced intensity to nonmyeloablative (5). However, an ultra–low-intensity platform that avoids any neutropenia has not been fully explored. Stem cell engraftment may not be fully reliant on conditioning-induced “marrow space” (6); we thus reasoned that nonneutropenic conditioning would permit stem cell engraftment if immunologic rejection was prevented. Conditioning also reduces tumor burden, but this rationale is weakened in chemotherapy refractory settings. Finally, because conditioning reduces graft rejection, it should be directed toward host T cells that primarily mediate rejection (7). An immune-selective regimen that avoided
Translational Relevance

Graft rejection, GVHD, and insufficient graft-versus-tumor (GVT) effects each limit the therapeutic application of allogeneic hematopoietic cell transplantation (HCT), particularly for solid tumors such as metastatic renal cell carcinoma. This trial used three interventions to address these limitations: (i) lymphocyte-selective host conditioning using pentostatin plus dose-adjusted cyclophosphamide (PC regimen), (ii) high-dose sirolimus therapy, and (iii) augmentation of T-cell-replete allogeneic HSCT with additional donor lymphocyte infusions (DLI) consisting of CD4+ T cells manufactured ex vivo in sirolimus (T-Rapa cells). The PC regimen represents a new approach to prevent graft rejection, as it selectively modulated host T cells without neutropenia or infection and safely permitted alloengraftment. High-dose sirolimus effectively prevented GVHD but also inhibited multiple T-Rapa DLI, thereby offsetting any potential beneficial direct antitumor effect of sirolimus. These results caution against use of high-dose sirolimus during allogeneic T-cell therapy in patients with refractory cancer.

Materials and Methods

Clinical trial design and implementation

The trial (schema, Fig. 1; ClinicalTrials.gov, NCT00923845) was approved by the National Cancer Institute (NCI) institutional review board and implemented according to an Investigational New Drug Application accepted by FDA. All subjects provided informed consent before participation. On-study dates ranged from June 2008 to June 2010. Subjects were enrolled on the basis of age (18–75 years), presence of metastatic RCC [any histology; active central nervous system (CNS) disease excluded], availability of an eligible 6 of 6 HLA-matched sibling donor, history of nephrectomy, ≥1 prior systemic therapy, life expectancy ≥3 months, Karnofsky score ≥80, and adequate organ function. Patients received a 21-day course of pentostatin (Nipent, Hospira; intravenous infusion on days 1, 8, and 15; 4 mg/m2/dose, adjusted for renal insufficiency) and oral Cy (200 mg flat dose/day). The protocol stated that the goal of PC therapy was to reduce the ALC [<200 cells/μL] while preserving the ANC (>1,000 cells/μL). Cy was reduced or held if ALC reduction goals were met. Specifically, Cy was reduced to 100 mg/d if ALC values on days 8, 11, 15, or 18 were 251–499, 201–399, 151–299, or 101–199, respectively. Cy was held if ALC values on days 8, 11, 15, or 18 were <250, <200, <150, or <100, respectively. Cy was also to be reduced for ANC values <1,000; however, this never occurred. After PC conditioning (‘day −2’), patients started sirolimus (16 mg loading dose; then, 4 mg/d), with further dosing adjusted to achieve 20 to 30 ng/mL trough levels through day 60 post-HCT. On day 0, patients received a mobilized, T-cell-replete allograft (>3 × 106 CD34+cells/kg) and the first infusion of T-Rapa cells (2.5 × 107 cells/kg), which were generated by a 12-day or 6-day culture, as previously described (19,33); furthermore, T-Rapa cells (2.5 × 107 cells/kg) were administered at days 14 and 45 post-HCT.

The primary study objective was to determine whether this transplant approach could safely achieve clinical regression of metastatic RCC [goal of ruling out a 20% overall partial response (PR)/complete response (CR) rate in favor of a 40% PR/CR rate; using a Simon 2-stage design, the occurrence of ≥3 responses in the first 12 evaluable patients would be required to proceed to the second stage of study design. Organ toxicity was evaluated by NCI Common Toxicity Criteria (version 2.0). GVHD was evaluated conditioning (26) or with calcineurin inhibitors (27). However, campath plus high-dose sirolimus (target, 30 ng/mL) after nonmyeloablative conditioning was safe and effective for GVHD prevention (28). We thus reasoned that high-dose, single-agent sirolimus would be safe after immune selective PC conditioning and represent adequate GVHD prophylaxis after T-cell-replete transplant and multiple T-Rapa DLI.

We evaluated this therapy in refractory metastatic renal cell carcinoma (RCC), thereby providing a rationale for lymphocyte-specific conditioning intended for rejection abrogation rather than tumor reduction. Metastatic RCC is susceptible to an allogeneic GVT effect that is generally associated with GVHD, as described by the National Heart Lung and Blood Institute (29) and a summation report from 21 European countries (30). However, GVFT effects were not observed in a separate study (31). Thus, more robust methods of harnessing GVFT effects and modulating GVHD are required in patients with RCC. Finally, metastatic RCC can respond to temsirolimus (32), thus suggesting that high-dose sirolimus might yield an antitumor benefit.
High-dose sirolimus (serum target: 20–30 ng/mL)

Figure 1.
Clinical trial of ex vivo and in vivo sirolimus after immune-selective PC conditioning. Prior to allogeneic HCT, patients received a 21-day course of pentostatin (4 mg/m² given on days 1, 8, and 15) combined with cyclophosphamide [200 mg/d, days 1–21; dose-adjusted for efficacy (reduction in ALC) and toxicity (reduction in ANC)]. After PC conditioning, patients were started on high-dose sirolimus (serum trough levels of 20–30 ng/mL through day 60 posttransplant). The T-cell-replete allograft was augmented with an infusion of ex vivo manufactured donor rapamycin-resistant T cells (T-Rapa), which were also administered at days 14 and 45 posttransplant.

using acute (34) and chronic grading (35); acute GVHD onset within the first 100 days post-HCT was considered classical acute (34), whereas onset after day 100 was considered late acute (35). Disease responses were evaluated by computed tomographic measurements and according to the RECIST Committee criteria. Alloengraftment was monitored using variable N-terminal repeat PCR assays on total peripheral blood mononuclear cell (PBMC), enriched T cells (CD3-selected), or enriched myeloid cells (CD15-selected).

Immune monitoring
Plasma IL7 and IL15 levels were measured by bioplex assay (EMD Millipore). Cytokine assays were performed on cryopreserved peripheral blood samples taken pre- and post-conditioning and at various points post-HCT. As described (19), cells were thawed and stimulated with anti-CD3/28 beads, and resultant supernatants were tested for cytokine content by multiplex assay (EMD Millipore); flow cytometry for transcription factor and differentiation marker expression was also performed as previously described. The statistical significance of the absolute difference or the relative difference from the baseline (or earlier) values was determined using a Wilcoxon signed rank test. Whether the absolute difference or relative difference was selected for evaluation depended on which one was less dependent on the baseline values. All P values are reported without formal adjustment for multiple comparisons. In view of the number of tests performed, only P < 0.01 would be interpretable as being associated with significant differences, whereas P values between 0.01 and 0.05 would suggest strong trends.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age/Sex</th>
<th>Tumor type</th>
<th>Prior therapy</th>
<th>Metastatic sites</th>
</tr>
</thead>
<tbody>
<tr>
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<td>63/M</td>
<td>Clear cell</td>
<td>IFN, sunitinib, temsirolimus</td>
<td>Lung, lymph nodes, brain</td>
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<td>Lung, lymph nodes, renal</td>
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<td>06</td>
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<td>Sunitinib, XRT everolimus</td>
<td>Lung, mediastinum, retroperitoneum</td>
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<td>Clear cell</td>
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</table>
Figure 2.
The PC regimen depletes and suppresses host lymphocytes. A, ALC (left) and ANC (right) are shown for each patient before start of the PC regimen and then at 6 time points performed on a biweekly basis over the 21-day treatment interval. The crossbar at each measurement indicates the median value. B, absolute number of CD4⁺ T-cell subsets (left) and CD8⁺ T-cell subsets (right) was determined before and after the 21-day PC regimen (subsets including naive, central memory, effector memory (EM), and T effector memory expressing CD45RA (TEMRA)). Values shown are mean values ± SEM. C, T cells collected before and after administration of the PC regimen were costimulated for 24 hours; the resultant supernatant was tested for cytokine content (results expressed as pg/mL per 1 x 10⁶ cells/mL per 24 hours). D, plasma was collected before the PC regimen (day –21) and after the PC regimen (day –3) and tested for IL7 and IL15 content by Luminex assay (results in pg/mL).
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(range, 12–131). Absolute numbers of naïve, central memory, and effector memory subsets for CD4+ and CD8+ T cells were all significantly reduced after PC therapy (Fig. 2B). B cells were essentially eliminated [median CD19 cells reduced from 56 (range, 20–176) to 1 (range, 0–7)]. Natural killer cells were relatively resistant [median NK cell reduction from 151 (range, 60–269) to 64 (22–485)].

In murine models, the PC regimen was immunosuppressive, as defined by reduced cytokine secretion in residual, post-therapy T cells (13). Pre-PC T cells responded to co-stimulation with secretion of IFNγ, TNFα, granulocyte macrophage colony-stimulating factor (GM-CSF), IL4, IL5, IL10, and IL13, often at levels greater than 100 pg/ml (n = 17 measurements were above this value; Fig. 2C); in each of these cases (17 of 17), post-PC T cells had a reduction in the cytokine measurement. In clinical trials using Flu/Cy conditioning, the T-cell homeostatic cytokines IL7 and IL15 increased to median values (at the time of transplant) of 37 and 57 pg/ml respectively (36, 37). In contrast, using PC conditioning, there was no statistically significant increase in IL7 and IL15 levels (Fig. 2D).

Stable mixed chimerism despite multiple T-Rapa cell DLI
Median percent donor T-cell chimerism at days 7, 14, 28, 45, and 60 post-HCT were 61 (range, 7–77), 72 (range, 9–91), 74 (range, 21–88), and 77 (range, 26–95), respectively (Fig. 3A). Transplantation of T-cell-replete allografts plus the first infusion of T-Rapa cells thus yielded immediate donor T-cell engraftment; however, chimerism values remained relatively constant during sirolimus therapy despite of multiple T-Rapa DLI. After discontinuation of sirolimus at day 60 post-HCT, donor T-cell chimerism increased to a median value of 92% (range, 21–100). The PC regimen yielded limited donor myeloid engraftment (Fig. 3B): median donor myeloid chimerism at days 7 and 14 post-HCT were each 0% (ranges, 0–1 and 0–27). Median percent donor myeloid chimerism increased modestly during sirolimus therapy, with values at days 28, 45, and 60 post-HCT of 13 (range, 4–50), 18 (range, 11–67), and 26 (range, 13–76). After discontinuation of sirolimus at day 60 post-HCT, donor myeloid chimerism increased to a median of 61% (range, 16–100). The two patients with the lowest T-cell chimerism through day 100 post-HCT also had the lowest myeloid cell chimerism; both of these patients received each of the planned T-Rapa DLI plus additional unmanipulated DLI.

In experimental models, rapamycin therapy increased CD8+ T-cell memory responses (38). Given these data, we measured naïve, central memory, and effector memory CD4+ and CD8+ T cell subsets during and after sirolimus therapy: these subsets did not differ substantially when comparing the days 14, 60, and 100 post-HCT time points (Fig. 3C).

T-cell phenotype post-HCT
Previously, T-Rapa DLI increased T[1]1- and T[1]2-type responses by transcription factor analysis and cytokine secretion assays (19). Similar to this initial trial, we found a preponderance of GATA3+ CD4+ T cells relative to T-bet CD4+ T cells at day 14 post-HCT (T[1]2-type > T[1]1-type); however, these values did not increase with additional T-Rapa DLI and did not increase after sirolimus discontinuation (Fig. 4). In experimental models, rapamycin prevention of acute GVHD increased regulatory T cells (39); in our trial, FoxP3+ CD4+ T cells did not increase during sirolimus therapy (Fig. 4, right). Upon ex vivo co-stimulation, post-HCT T cells secreted both T[1]1 (IFNγ, TNFα, GM-CSF) and T[1]2 (IL4, IL5, IL10, IL13) cytokines, with the magnitude of cytokine secretion being similar at days 14, 60, and 100 post-HCT (not shown).

Clinical outcome
Clinical results are summarized in Table 2. No partial or complete clinical responses were observed by RECIST criteria in the first 10 evaluable patients; because the primary objective was not achieved, further accrual to the protocol was stopped at this point.

Eight of 10 patients received each of the 3 planned T-Rapa DLI; one patient each received either 1 or 2 doses of T-Rapa cells because of poor performance status or inability to tolerate sirolimus. Six of 10 patients received additional, unmanipulated DLI to treat progressive disease (PD; median day of unmanipulated DLI therapy was day 87 post-HCT; range, 76–607 days). In terms of adverse events through day 100 post-HCT, there was no engraftment syndrome or other serious adverse events attributable to T-Rapa cell therapy. High-dose sirolimus was generally well-tolerated; one patient needed to discontinue planned therapy.

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sirolimus therapy (due to exacerbation of renal insufficiency related to hypercalcemia). One patient required red cell transfusion during sirolimus therapy; transplant-associated microangiopathy did not occur. Four patients required topical corticosteroid therapy for sirolimus-related oral ulcers (grade 2 toxicity); there were no other gastrointestinal toxicities. Two patients each had catheter-related thrombosis or catheter-related line infection. One patient each had bacteremia attributable to an intestinal metastasis, bacterial pneumonia, or viral infection (BK cystitis).

Classical acute GVHD of grade II or higher did not occur. Four of 6 patients developed late acute GVHD (at days 115, 124, 163, and 284 post-HCT); 2 cases involved skin only and 2 involved the gut. One of 4 evaluable patients developed chronic GVHD, which was limited to vulvovaginal involvement. By day 60 post-HCT, despite high-dose sirolimus therapy, 4 of 10 patients had PD by RECIST criteria; 5 additional patients developed PD by day 100 posttransplant. One patient continues to have stable disease more than 4 years' posttransplant (collecting duct carcinoma). Each of the 9 protocol deaths were primarily attributable to progressive RCC; one case was additionally attributable to late acute gut GVHD and CMV enteritis that occurred after multiple unmanipulated DLI.

**Discussion**

Pentostatin plus low-dose, dose-adjusted Cy yielded sufficient host T-cell depletion and suppression to permit prompt donor T-cell engraftment. The PC regimen preserved the host myeloid compartment, as evidenced by absence of neutropenia and extremely low initial levels of donor myeloid cell engraftment. Single-agent, high-dose sirolimus was sufficient for acute GVHD prophylaxis despite of T-cell–replete transplantation and multiple T-Rapa DLI. High-dose sirolimus yielded stable mixed T-cell chimerism and a stable posttransplant T-cell cytokine phenotype. However, high-dose sirolimus did not control tumor progression. In sum, these results have identified a novel platform for establishing stable mixed chimerism, yet on the other hand, caution against use of high-dose sirolimus in conjunction with allogeneic T-cell therapy.

The PC regimen is an immune-selective method of nonmyeloablative transplantation that resides at the far range of this discipline (toward nonmyelo suppressive transplantation). The PC regimen was immune-depleting and immunosuppressive, as residual host T cells were not capable of high-level cytokine secretion. This result mirrors our findings in a murine model of graft rejection (13), where pentostatin was more immunosuppressive than fludarabine; it is thus possible that the clinical trial results described here may be relatively unique to pentostatin (i.e., not necessarily interchangeable with other purine analogues). The PC regimen differentially depleted immune subsets, with CD4⁺ T cells and B cells more sensitive than CD8⁺ T cells; the majority of lymphocytes remaining after PC therapy were NK cells. Also, the naïve T-cell subset, which in murine models mediate increased alloreactivity (40), was nearly eliminated. Finally, in contrast to...
previous immune-ablative regimens (36, 37) and other nonmyeloablative conditioning (41), PC therapy did not significantly increase IL7 or IL15 levels. Given that some studies have associated IL7 and IL15 levels with acute GVHD risk (36, 42), this characteristic may have contributed to the nominal GVHD and stable mixed T-cell chimerism.

The mixed chimerism was split in terms of T cell versus myeloid populations. The paucity of donor myeloid engraftment early post-HCT likely represents the lowest values reported to date and demonstrates the relative lack of myeloid toxicity from the PC regimen. Nonetheless, stem cell engraftment was secured, as each patient had a gradual increase in donor myeloid components; this apparent competitive advantage of donor stem cells was likely generated through a GVH reaction that was largely subclinical. Although this pattern of alloengraftment was not conducive to refractory cancer therapy, split mixed chimerism favoring donor T-cell elements may be favorable for therapy of T-cell–based immune deficiencies.

Several factors likely contributed to the low rate and severity of acute GVHD. First, the PC regimen did not increase GVHD-provoking T-cell homeostatic cytokines. Second, the lymphocyte specificity of the PC regimen may have constrained host inflammation, which is known to potentiate GVHD (8). Third, mixed chimerism itself limits clinical acute GVHD (43). Experimental GVHD is restricted by host T cells (44) and promoted by donor antigen-presenting cells (45); because the PC regimen preserved some component of host T cells and severely limited donor myeloid engraftment, the pattern of split mixed chimerism generated may have been particularly protective against GVHD. Fourth, the T-Rapa DLI product expressed a balanced pattern of Tfi1- and Tfi2-type cytokines and previously yielded a low rate of acute GVHD (19). Finally, high-dose sirolimus can protect against acute GVHD (28). In experimental models, rapamycin-anti-GVHD effects occurred by Tfi1 cytokine inhibition (46) and regulatory T-cell promotion (39); because we found low levels of Tfi1- and FoxP3+ CD4+ T cells post-HCT, inhibition of Tfi1 cells may have been largely operational in this trial. Given these collective results, similar to our findings in an experimental model (47), we conclude that ex vivo manufactured T-Rapa cells are not resistant to in vivo rapamycin therapy.

Several factors likely contributed to the lack of GVT effects. First, responses against RCC after allogeneic HCT preferentially occur in patients with less than 3 metastatic sites (48); our study was composed of heavily pretreated patients (median, 3.5 prior regimens) with extensive metastatic burden (median, 3.5 sites). Second, our hypothesis that high-dose sirolimus would limit tumor progression was not confirmed, as 9 of 10 patients had PD during or shortly after sirolimus therapy. Third, high-dose sirolimus was counterproductive due to promotion of stable mixed chimerism (which was seen in a previous study of high-dose sirolimus; ref. 28) and due to inhibition of Tfi1-type cells (which are necessary for murine GVT effects against RCC cells; ref. 49). Fourth, the low donor myeloid engraftment after PC conditioning was likely counterproductive, as donor APC contribute to GVT effects in experimental models (50). Finally, previous clinical trials have indicated that GVT effects against RCC are associated with clinical GVHD (29, 30).

The overall transplant approach we evaluated was not suitable for therapy of refractory cancer but may be advantageous for therapy of nonmalignant disease. These results provide a cautionary note in terms of combining adoptive T-cell therapy with high-dose sirolimus therapy, which did not prevent tumor progression and limited posttransplant T-cell effects. Our future investigations will continue to incorporate ultra–low-intensity conditioning such as the PC regimen as a safe platform for evaluation of novel T-cell therapy products. However, such platforms will incorporate calcineurin inhibitors as GVHD prophylaxis to avoid the in vivo tolerizing effects of sirolimus therapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Writing, review, and/or revision of the manuscript: M.E. Mossoba, D.C. Halverson, R. Kurlander, A. Carpenter, S.M. Steinberg, S.A. Ali, N. Tageja, F.T. Hakim, C. Sportes, S.Z. Pavletic, B.L. Levine, O. Rixe, M.R. Bishop, D.H. Fowler
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Study supervision: B.B. Schuver, A. Carpenter, A.T. Fojo, D.H. Fowler

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References


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