

Renal Stem Cell Literatures

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Abstract: The definition of stem cell is “an unspecialized cell that gives rise to a specific specialized cell, such as a blood cell”. Stem Cell is the original of life. All cells come from stem cells. Serving as a repair system for the living body, the stem cells can divide without limit to replenish other cells as long as the living body is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell situation or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, a bone cell, a nerve cell, or a brain cell. Stem cell research is a typical and important topic of life science. This material collects some literatures on renal stem cell.

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Key words: stem cell; life; gene; DNA; protein; renal

Literatures

Akay, O. M., G. Sahin, et al. (2008). "Successful treatment of nephrotic syndrome due to systemic AL amyloidosis after autologous stem cell transplantation: renal response is an important therapeutic end point." *Clin Nephrol* **69**(4): 294-7.

Primary systemic (AL) amyloidosis involves vital organs from the early phase of illness, resulting in poor prognosis. Today, high-dose melphalan followed by autologous peripheral blood stem cell transplantation is an effective treatment for systemic AL amyloidosis. We report a patient with nephrotic syndrome due to systemic AL amyloidosis, who was successfully treated with autologous peripheral blood stem cell transplantation. At follow-up 36 months from ASCT, the patient showed a significant improvement in the signs of peripheral neuropathy and reduction in proteinuria without further organ involvement. Due to poor prognosis with conventional therapy, autologous stem cell transplantation should be considered for treatment in patients with systemic AL amyloidosis, and favorable outcome is ensured with achievement of renal response after ASCT.

Anglani, F., M. Ceol, et al. (2008). "The renal stem cell system in kidney repair and regeneration." *Front Biosci* **13**: 6395-405.

The adult mammalian renal tubular epithelium exists in a relatively quiescent to slowly replicating state, but has great potential for regenerative morphogenesis following severe ischemic or toxic injury. Kidney regeneration and repair occur through three cellular and molecular mechanisms: differentiation of the somatic stem cells, recruitment of circulating stem cells and, more importantly, proliferation/dedifferentiation of mature cells. Dedifferentiation seems to represent a critical

step for the recovery of tubular integrity. Dedifferentiation of tubular cells after injury is characterized by the reactivation of a mesenchymal program that is active during nephrogenesis. Epithelial-to-mesenchymal transition (EMT) of renal tubular cells is an extreme manifestation of epithelial cell plasticity. It is now widely recognized as a fundamental process that marks some physiological, such as morphogenesis, as well as pathological events, such as oncogenesis and fibrogenesis. It might be also considered as a key event in the regenerative process of the kidney. Understanding the molecular mechanisms involved in EMT might be useful for designing therapeutic strategies in order to potentiate the innate capacity of the kidney to regenerate.

Aoyama, Y., H. Nakamae, et al. (2003). "Reduced-intensity stem cell transplantation in two cases of metastatic renal cell carcinoma." *Int J Urol* **10**(11): 610-4; discussion 615.

Allogeneic hematopoietic stem-cell transplantation can induce curative graft-versus-leukemia reactions in patients with hematological malignancies. There is also evidence of such an effect in patients with solid tumors. We report two patients with metastatic renal cell carcinoma who underwent RIST. In both patients, disease progression was observed 6 months after transplantation. However, one patient had transient symptoms of tumor progression after the occurrence of acute graft-versus-host disease, consistent with graft-versus-tumor effects.

Artz, A. S., M. Kocherginsky, et al. (2006). "Order of patient entry influences outcome for metastatic renal cell cancer after non-myeloablative allogeneic stem cell transplantation." *Br J Haematol* **132**(6): 747-54.

Allogeneic transplantation for renal cell carcinoma has shown encouraging preliminary results. We reviewed the published literature to evaluate the impact of patient selection. Most studies did not include information on prognostic factors. We used patient entry rank within individual studies as a novel surrogate for patient selection, motivated by our own experience of an apparent impact of entry rank. One hundred patients were identified from nine studies. Twenty-six per cent of patients demonstrated either a partial or complete response. Median overall survival was 12.3 months. Grade 2-4 acute graft-versus-host disease correlated with an increased likelihood of response (odds ratio: 5.4, 95% confidence interval: 1.6-18.1, $P = 0.006$) but not survival. Earlier patient entry rank on each trial was associated with a higher probability of response ($P = 0.004$) and superior survival ($P = 0.004$). Patient entry rank served as a powerful prognostic factor, suggesting bias in patient selection that evolved over the course of the study. Further studies are warranted to determine the influence of order of patient entry in other early clinical trial settings.

Artz, A. S., K. Van Besien, et al. (2005). "Long-term follow-up of nonmyeloablative allogeneic stem cell transplantation for renal cell carcinoma: The University of Chicago Experience." Bone Marrow Transplant **35**(3): 253-60.

Nonmyeloablative allogeneic stem cell transplantation (NST) has considerable activity in patients with metastatic renal cell carcinoma (RCC), although there are limited long-term follow-up data. Between February 1999 and May 2003, 18 patients with metastatic RCC underwent 19 matched-sibling NSTs after conditioning with fludarabine and cyclophosphamide with tacrolimus and mycophenolate mofetil as post-transplant immunosuppression. Among the four objective responses, all were partial and have relapsed with a median response duration of 609 days (range, 107-926). All responders are alive at a median of 41 months. Median overall survival for the entire cohort was 14 months. There were four early treatment-related deaths and one late treatment-related death. Eight patients died from progressive disease and five (28%) from treatment-related mortality. Stratifying transplant outcome as early death, intermediate (no response, no early death), or response, the combination of pre-treatment anemia and decreased performance status, was associated with adverse outcome ($P = 0.015$) and reduced survival (HR 5.4, 95% confidence interval of 1.4 to 21, $P = 0.007$). Responders demonstrated prolonged survival compared to nonresponders ($P = 0.002$). NST leads to durable responses in a minority of metastatic RCC

patients. Appropriate patient selection is paramount. Anemia and decreased performance status may enable risk stratification.

Arya, M., D. Chao, et al. (2004). "Allogeneic hematopoietic stem-cell transplantation: the next generation of therapy for metastatic renal cell cancer." Nat Clin Pract Oncol **1**(1): 32-8.

The management of metastatic renal cell carcinoma (mRCC) remains a therapeutic challenge; less than 10% of patients survive for longer than 5 years. The resistance of renal cancer to chemotherapy may be explained by high levels of the multidrug resistance gene, MDR1. Immune-based treatments for renal cancer have been explored because of their unusual susceptibility to immunological assault. However, response rates to cytokines such as interleukin-2 and interferon-alpha have ranged from only 10% to 20%, prompting other immunotherapy approaches, such as allogeneic stem-cell transplantation, to be investigated. Several clinical trials have provided evidence of partial or complete disease regression in refractory mRCC following nonmyeloablative stem-cell transplantation. This effect is because of a donor antimalignancy effect mediated by immunocompetent donor T cells, called graft-versus-tumor effect. Unfortunately, less than 30% of patients who could have this procedure will have a human-leukocyte-antigen-compatible sibling, and attention is focusing on alternative donors such as matched unrelated donors and partially mismatched related donors. Despite the improved safety of nonmyeloablative conditioning regimens, transplant-related toxic effects (particularly graft-versus-host disease) remain obstacles to the safe and effective use of this treatment. Regardless of these limitations, innovative approaches have attempted to harness the potential of the graft-versus-tumor effect in mRCC and other solid tumors.

Ballester, O. F., R. Tummala, et al. (1997). "High-dose chemotherapy and autologous peripheral blood stem cell transplantation in patients with multiple myeloma and renal insufficiency." Bone Marrow Transplant **20**(8): 653-6.

Six patients with multiple myeloma and chronic renal insufficiency (serum creatinine >3.0 mg/dl), including four on dialysis, received high-dose busulfan and cyclophosphamide (BUCY) followed by autologous peripheral stem cell transplantation. Peripheral blood stem cells were collected after priming with cyclophosphamide, etoposide and G-CSF. Patterns of engraftment and toxicities were not apparently different from those seen in myeloma patients with normal renal function. There was one toxicity-related death, resulting from a massive

spontaneous subdural hematoma. One patient died of disease progression 6 months after transplant, while the remaining four patients are alive and free of myeloma progression 6 to 39 months after high-dose therapy. Two of these patients have remained in complete remission for 28 and 39 months. Our experience suggests that high-dose therapy with BUCY and autologous peripheral blood stem cell rescue is feasible in patients with multiple myeloma and renal failure.

Barkholt, L., M. Bregni, et al. (2006). "Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe." *Ann Oncol* **17**(7): 1134-40.

BACKGROUND: An allogeneic antitumour effect has been reported for various cancers. We evaluated the experience of allogeneic haematopoietic stem cell transplantation (HSCT) for renal cell carcinoma (RCC) in 124 patients from 21 European centres. **PATIENTS AND METHODS:** Reduced intensity conditioning and peripheral blood stem cells from an HLA-identical sibling (n = 106), a mismatched related (n = 5), or an unrelated (n = 13) donor were used. Immunosuppression was cyclosporine alone, or combined with methotrexate or mycophenolate mofetil. Donor lymphocyte infusions (DLI) were given to 42 patients. The median follow-up was 15 (range 3-41) months. **RESULTS:** All but three patients engrafted. The cumulative incidence of moderate to severe, grades II-IV acute GVHD was 40% and for chronic GVHD it was 33%. Transplant-related mortality was 16% at one year. Complete (n = 4) or partial (n = 24) responses, median 150 (range 42-600) days post-transplant, were associated with time from diagnosis to HSCT, mismatched donor and acute GVHD II-IV. Factors associated with survival included chronic GVHD (hazards ratio, HR 4.12, P < 0.001), DLI (HR 3.39, P < 0.001), <3 metastatic sites (HR 2.61, P = 0.002) and a Karnofsky score >70 (HR 2.33, P = 0.03). Patients (n = 17) with chronic GVHD and given DLI had a 2-year survival of 70%. **CONCLUSION:** Patients with metastatic RCC, less than three metastatic locations and a Karnofsky score >70% can be considered for HSCT. Posttransplant DLI and limited chronic GVHD improved the patient survival.

Barkholt, L., R. Danielsson, et al. (2004). "Indium-111-labelled donor-lymphocyte infusion by way of hepatic artery and radio-frequency ablation against liver metastases of renal and colon carcinoma after allogeneic hematopoietic stem-cell transplantation." *Transplantation* **78**(5): 697-703.

BACKGROUND: In patients with metastatic solid cancer, antitumor effects occur after allogeneic

stem-cell transplantation (SCT). However, this treatment is not as effective in the liver as against pulmonary and lymph-node metastases. To intensify the effect of donor-lymphocyte infusions (DLI) against liver metastases, intra-arterial (IA) cell injection by way of the hepatic artery (HA) can be used. **METHODS:** To trace infused cells, three patients with colorectal, three with renal, and one with breast carcinoma were treated with Indium-111 (111-In)-oxinate-labeled lymphocytes. Four patients received the DLI IA, all after radio-frequency ablation (RFA) of liver metastases. Three patients with other metastases received 111-In DLI intravenously (IV). One of them had RFA before SCT. **RESULTS:** Localization of the IA 111-In DLI activity on scintigrams homed to the liver. After IA injection, the liver to sternum ratio of radioactivity was higher compared with IV injection. Cells (CD3+, 19+, and 56+) of donor origin in biopsies of liver metastasis in two patients treated with IA injection increased to 80% to 100%. Two of four patients treated using the IA DLI showed stable size and number of liver metastases for 5 and 21 months, respectively. Both are alive 18 and 34 months after SCT. Two of three patients receiving DLI IV are doing well, with a stable metastatic disease or still without metastases 21 and 20 months after cell infusions (26 and 34 months after SCT), respectively. Three patients died because of progressive disease. **CONCLUSION:** When infused by way of the HA, 111-In-labeled lymphocytes home to the liver and its metastases. The liver metastasis infiltrating cells of donor origin increased. DLI by way of the HA combined with RFA may be used to treat liver metastases after SCT.

Battiwalla, M., P. Paplham, et al. (2007). "Leflunomide failure to control recurrent cytomegalovirus infection in the setting of renal failure after allogeneic stem cell transplantation." *Transpl Infect Dis* **9**(1): 28-32.

Cytomegalovirus (CMV) reactivation is common in the allogeneic stem cell transplant setting but the incidence of CMV organ disease and mortality has been dramatically reduced by prophylactic or preemptive antiviral therapy. We report the case of a CMV-seropositive 46-year-old man with non-Hodgkin's lymphoma who underwent an unrelated allogeneic stem cell transplant from a CMV-seronegative HLA-matched unrelated donor. CMV encephalitis and colitis developed that was refractory to single-agent therapy. The CMV isolate demonstrated genotypic resistance to both ganciclovir and foscarnet. CMV disease was controlled by prolonged combination ganciclovir and cidofovir therapy, but severe renal dysfunction developed. Leflunomide was selected as a last resort to avoid the

nephrotoxicity of cidofovir. CMV antigenemia rapidly increased following leflunomide administration, necessitating discontinuing this agent and resuming prior antiviral therapy. The pharmacokinetics of leflunomide in the setting of renal insufficiency is presented. Options for salvage therapy in refractory CMV disease in allogeneic stem cell transplant recipients are briefly reviewed.

Beyzadeoglu, M., F. Arpacı, et al. (2008). "Acute renal toxicity of 2 conditioning regimens in patients undergoing autologous peripheral blood stem-cell transplantation. Total body irradiation-cyclophosphamide versus ifosfamide, carboplatin, etoposide." *Saudi Med J* **29**(6): 832-6.

OBJECTIVE: To compare acute renal toxicity of 2 conditioning regimens of total body irradiation/cyclophosphamide (TBI-Cy) and Ifosfamide, Carboplatin, and Etoposide (ICE). **METHODS:** Between August 1996 and February 2004, patients treated with autologous peripheral stem cell transplantation in the Department of Medical and Radiation Oncology, Gulhane Military Medical School, Ankara, Turkey with 2 different conditioning regimens was comparatively analyzed for acute renal toxicity in the early post-transplant period. Forty-seven patients received ICE regimen with 12 g/m²; 1.2 g/m²; and 1.2 g/m² divided to 6 consecutive days, whereas 21 patients received 12 Gy TBI (6 fractions twice daily in 3 consecutive days) and 60 mg/m²/day cyclophosphamide for 2 days. **RESULTS:** Sixty-eight patients were evaluated in this study. There was no significant difference in baseline renal function between patients in the ICE and TBI-Cy groups. Eleven patients developed nephrotoxicity (23.4%) in the ICE group while one patient (4.8%) in the TBI-Cy group developed nephrotoxicity (p=0.06). Five out of 11 patients developing nephrotoxicity in ICE group required hemodialysis and subsequently 4 (8.5%) of them died. In contrast, one patient (4.8%) died due to nephrotoxicity despite hemodialysis in the TBI-Cy arm. **CONCLUSION:** This study reveals that the TBI-Cy conditioning regimen seems no more nephrotoxic than an ICE regimen particularly in patients who had used cisplatin prior to transplantation.

Bird, J. M., R. Fuge, et al. (2006). "The clinical outcome and toxicity of high-dose chemotherapy and autologous stem cell transplantation in patients with myeloma or amyloid and severe renal impairment: a British Society of Blood and Marrow Transplantation study." *Br J Haematol* **134**(4): 385-90.

The outcome of high-dose chemotherapy (HDT) was evaluated retrospectively in 27 patients with myeloma and four patients with AL amyloidosis with severe renal impairment. Twenty-three patients

were receiving dialysis and the rest had a creatinine clearance of <20 ml/min. The median melphalan dose was 140 mg/m² (range: 60-200 mg/m²), but 10 patients (37%) received 200 mg/m². Myeloid and platelet engraftment were similar to that seen in patients without renal failure. Five of 27 patients died of transplant-related toxicity before the day 100. Twenty of 27 patients had a response (70%). The median time to disease progression was 32 months (range: 6-54 months) and the median time to best response was 6.5 months. Four of 17 evaluable patients (24%) became dialysis-independent at a median of 5 months post-HDT/stem cell transplantation. At a median follow-up of 70 months, 7/23 patients with myeloma were alive but three of these seven patients had progressive disease. Two of the four patients with amyloidosis have survived. HDT is feasible in these patients and results in 5-year survival in about one-third of patients.

Bobey, N. A., D. A. Stewart, et al. (2002). "Successful treatment of posttransplant lymphoproliferative disorder in a renal transplant patient by autologous peripheral blood stem cell transplantation." *Leuk Lymphoma* **43**(12): 2421-3.

Posttransplant lymphoproliferative disorder (PTLD), a well recognized complication of organ transplantation, comprises a wide spectrum of heterogeneous lymphoid proliferations ranging from self-limiting mononucleosis through aggressive monoclonal non-Hodgkin's lymphoma (NHL). There has been marginal success in treating PTLD using a number of treatment modalities, including combination chemotherapy. There have been few reports of the use of high dose chemotherapy with stem cell rescue as a treatment for PTLD. We report a renal allograft recipient who developed PTLD of the diffuse large cleaved B cell, NHL type. Reduction of immunosuppression was initially effective, however the patient relapsed, and was treated successfully with CHOP chemotherapy. Two years later he again relapsed and was treated with high dose melphalan followed by autologous peripheral blood stem cell transplantation (PSCT). The patient has remained in complete remission for 4 years with no major organ toxicities and a functioning renal allograft on minimal immunosuppression. This case illustrates a potential role for high dose chemotherapy with stem cell transplantation for the treatment of PTLD.

Brodie, J. C. and H. D. Humes (2005). "Stem cell approaches for the treatment of renal failure." *Pharmacol Rev* **57**(3): 299-313.

The inadequacy of current treatment modalities and insufficiency of donor organs for cadaveric transplantation have driven a search for

improved methods of dealing with renal failure. The rising concept of cell-based therapeutics has provided a framework around which new approaches are being generated, and its combination with advances in stem cell research stands to bring both fields to clinical fruition. This budding partnership is presently in its very early stages, but an examination of the cell-based therapies currently under development clearly shows the magnitude of the role that stem cells will ultimately play. The issue over reports of unexpected plasticity in adult stem cell differentiation remains a focus of debate, and evidence for bone marrow-derived stem cell contributions to renal repair has been challenged. The search for adult renal stem cells, which could have a considerable impact on much of the work discussed here, appears to be narrowing. The use of embryonic tissue in research continues to provide valuable insights but will be the subject of intense societal scrutiny and debate before it reaches the stage of clinical application. Embryonic stem (ES) cells, with their ability to generate all, or nearly all, of the cell types in the adult body and a possible source of cells genetically identical to the donor, hold great promise but face ethical and political hurdles for human use. Immunoisolation of heterologous cells by encapsulation creates opportunities for their safe use as a component of implanted or ex vivo devices.

Bussolati, B., S. Bruno, et al. (2008). "Identification of a tumor-initiating stem cell population in human renal carcinomas." *Faseb J* **22**(10): 3696-705.

The purpose of the present study was to search for the presence of a tumor-initiating stem cell population in renal carcinomas. Based on the recent identification of mesenchymal stem cells in normal kidneys, we sorted cells expressing the mesenchymal stem cell marker CD105 from 5 human renal carcinomas. Because the CD105(+) but not the CD105(-) population showed enhanced tumorigenicity when injected in severely compromised immunodeficient (SCID) mice, we cloned and characterized CD105(+) cells and evaluated their stemness, differentiative ability, and serial tumor generation. Characterization of the phenotype of CD105(+) clones revealed several stem cell properties: 1) clonogenic ability, 2) expression of nestin, Nanog, Oct4 stem cell markers, and lack of differentiative epithelial markers, 3) ability to grow in nonadhesive spheroids, 4) in vitro differentiation into epithelial and endothelial cell types, and 5) generation in vivo of serially transplantable carcinomas containing an undifferentiated CD105(+) tumorigenic and a differentiated CD105(-) nontumorigenic population. In addition, some vessels present in carcinomas generated from CD105(+) clones were of human origin, suggesting the capability of tumor-

initiating stem cells to in vivo differentiate also in endothelial cells. In conclusion, we demonstrate that CD105(+) cells and clones derived from renal carcinomas were enriched in tumor-initiating cells with stem characteristics.

Butani, L., D. C. West, et al. (2003). "End-stage renal disease after high-dose carboplatinum in preparation of autologous stem cell transplantation." *Pediatr Transplant* **7**(5): 408-12.

Stem cell transplantation is one therapy employed in the management of children with high-risk solid tumors. However, this therapy is not without risk, having been associated with multiple end-organ toxicities. Both acute renal failure and chronic renal insufficiency have been reported in marrow transplant recipients, primarily in the context of the use of calcineurin inhibitors and radiation therapy. This report reviews our experience in managing an adolescent with metastatic Ewing's sarcoma who developed rapid progression to end-stage renal disease following a pretransplant conditioning regimen with high-dose carboplatinum. She had not received radiation or prior cisplatin therapy. The possible reasons for the patient's highly unusual course and recommendations on ways to prevent this complication are discussed.

Cassery, L. F., A. Fadia, et al. (2003). "High-dose intravenous melphalan with autologous stem cell transplantation in AL amyloidosis-associated end-stage renal disease." *Kidney Int* **63**(3): 1051-7.

BACKGROUND: The development of end-stage renal disease (ESRD) is common among patients with amyloid light-chain AL amyloidosis-associated renal disease and survival of these patients is poor. High-dose intravenous melphalan and autologous stem cell transplantation induce remission of the plasma cell dyscrasia in a significant proportion of patients with AL amyloidosis. The efficacy and tolerability of such treatment for patients with AL amyloidosis-associated ESRD are unknown. **METHODS:** Between June 1994 and June 2000, 15 patients with AL amyloidosis-associated ESRD were treated with intravenous melphalan (70 to 200 mg/m²) and autologous peripheral blood stem cell transplantation. Clinical and laboratory data were prospectively collected prior to treatment, during the peritransplant period, and at 3 months, 12 months, and annually thereafter. Treatment outcomes and toxicities were compared with 180 non-ESRD patients treated during the study period. **RESULTS:** Eight of 15 patients (53%) had a hematologic complete response following treatment. Two patients (13%) died during the peritransplant period. Transfusion requirements were greater and there was a trend toward increased

severity of mucositis in the ESRD patients compared with the non-ESRD patients. Median survival for the ESRD patients with a hematologic complete response was 4.5 years. Five patients with hematologic complete response have either undergone or are awaiting renal transplantation. **CONCLUSION:** High-dose intravenous melphalan with stem cell transplantation is an effective treatment in selected patients with AL amyloidosis-associated ESRD. Although the toxicity profile is greater in ESRD patients, the treatment offers the possibility of successful renal transplantation if hematologic remission is achieved. This treatment should be considered for patients with AL amyloidosis-associated ESRD.

Chan, G. S., M. F. Lam, et al. (2008). "Clinicopathologic analysis of renal biopsies after haematopoietic stem cell transplantation." *Nephrology (Carlton)* **13**(4): 322-30.

AIM: The ever-growing number and increasing survival of haematopoietic stem cell transplantation (HSCT) allow better recognition of its associated renal injuries. We aimed to study the clinicopathologic features of renal biopsies after HSCT by reviewing 13 percutaneous renal biopsies in our institute (Queen Mary Hospital). **METHODS:** A retrospective clinicopathologic study of all renal biopsies archived to the Department of Pathology, Queen Mary Hospital during the period January 1999 to December 2006 was performed. Biopsies from patients with HSCT were selected. Clinical data on presentation and follow up were retrieved from hospital records and physicians. **RESULTS:** In the 8-year period, a total of 2233 native renal biopsies were archived. Thirteen renal biopsies were selected from 12 patients with HSCT (11 allogeneic, one autologous). All but one patient were male. The age at renal biopsy ranged from 7 to 63 years (median: 32 years). The median interval of renal biopsy after HSCT was 24 months (range 1-134 months). Evidence of graft-versus-host disease was found in nine patients. The most common presentation was significant proteinuria (10 cases) and renal impairment (eight cases). The predominant histological changes were membranous glomerulonephritis (n = 4) and thrombotic microangiopathy (n = 4). One case of focal segmental glomerulosclerosis, IgA nephropathy, minimal change disease, acute tubular necrosis and hypertensive nephrosclerosis were also recorded. Four of our patients died at 0-11 months after renal biopsy. Of the remaining eight patients with a mean follow up of 43.6 months (range, 10-98 months), chronic renal impairment were found in three (37.5%) patients and significant proteinuria also persisted in three. One patient had cytogenetic evidence of relapse of

underlying haematological malignancy after HSCT. **CONCLUSION:** Among the various renal lesions after HSCT, membranous glomerulonephritis and thrombotic microangiopathy were the most common. Mechanisms of renal injury varied from graft-versus-host disease-associated immune complex deposition to non-immune complex injury on endothelial cells, glomerular epithelial cells and tubular epithelium. Pathologists and clinicians should attend to the histological and temporal heterogeneity of renal injury when managing patients after HSCT.

Childs, R., A. Chernoff, et al. (2000). "Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation." *N Engl J Med* **343**(11): 750-8.

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.

Childs, R. and D. Drachenberg (2001). "Allogeneic stem cell transplantation for renal cell carcinoma." Curr Opin Urol **11**(5): 495-502.

Although the prognosis for patients with metastatic kidney cancer remains poor, a number of promising immunotherapeutic approaches for the treatment of metastatic disease have been developed over the past decade. The response of some patients to cytokines such as interleukin-2 and interferon-alpha, and more recently, vaccination with dendritic cell/tumor fusions has laid the ground work for ongoing immune-based investigational approaches. Allogeneic stem cell transplantation is a potent form of immunotherapy capable of delivering potentially curative immune-mediated anti-tumor effects against a number of different hematological malignancies. Knowledge of renal cell carcinoma's unusual susceptibility to immune attack has led to the hypothesis that tumor rejection, mediated through immunocompetent donor T-cells, might be generated against this solid tumor following the transplantation of an allogeneic immune system. Although clinical trials are early and ongoing, the recent observation of metastatic disease regression following non-myeloablative stem cell transplantation has identified renal cell carcinoma as being susceptible to a graft-versus-tumor effect. Disease responses following such therapy have ranged from partial to complete and have been observed even in patients who have failed conventional cytokine based strategies. This article reviews the design, methodology and early clinical results of studies investigating the use of allogeneic stem cell transplantation in metastatic renal cell carcinoma.

Childs, R. W. (2001). "Nonmyeloablative blood stem cell transplantation as adoptive allogeneic immunotherapy for metastatic renal cell carcinoma." Crit Rev Immunol **21**(1-3): 191-203.

Allogeneic stem cell transplantation has emerged as a potentially curative form of immunotherapy for patients with hematological malignancies that are resistant to conventional chemo/radiotherapy. Donor T cell populations targeting allogeneic minor histocompatibility antigens expressed on the patient's malignant cells are felt to be the driving force of the graft-versus-leukemia reaction, although to date only a handful of these antigens have been fully characterized. Recent data from experimental animal models and limited clinical data in humans suggest that graft-versus-tumor effects, analogous to the graft-versus-leukemia reaction, may be generated against malignancies of epithelial origin. This article reviews the results of a pilot trial demonstrating graft-versus-renal cell carcinoma effects following nonmyeloablative stem

cell transplantation, highlighting the potential of allogeneic immunotherapy for treating cancer.

Cohen, E. P., A. A. Irving, et al. (2008). "Captopril to mitigate chronic renal failure after hematopoietic stem cell transplantation: a randomized controlled trial." Int J Radiat Oncol Biol Phys **70**(5): 1546-51.

PURPOSE: To test whether the angiotensin-converting enzyme inhibitor captopril was effective in mitigating chronic renal failure after hematopoietic stem cell transplantation (HSCT). **METHODS AND MATERIALS:** A total of 55 subjects undergoing total body irradiation (TBI)-HSCT were enrolled in this randomized controlled trial. Captopril or identical placebo was started at engraftment and continued as tolerated until 1 year after HSCT. **RESULTS:** The baseline serum creatinine and calculated glomerular filtration rate (GFR) did not differ between groups. The 1-year serum creatinine level was lower and the GFR higher in the captopril compared with the placebo group ($p = 0.07$ for GFR). Patient survival was higher in the captopril compared with the placebo group, but this was also not statistically significant ($p = 0.09$). In study subjects who received the study drug for more than 2 months, the 1-year calculated GFRs were 92 mL/min and 80 mL/min, for the captopril and placebo groups, respectively ($p = 0.1$). There was no adverse effect on hematologic outcome. **CONCLUSIONS:** There is a trend in favor of captopril in mitigation of chronic renal failure after radiation-based HSCT.

Cooper, B. W., R. J. Creger, et al. (1993). "Renal dysfunction during high-dose cisplatin therapy and autologous hematopoietic stem cell transplantation: effect of aminoglycoside therapy." Am J Med **94**(5): 497-504.

PURPOSE: Renal dysfunction is a common cause of morbidity after cancer therapy and bone marrow transplantation. In this study, we evaluated the effects of aminoglycosides and other nephrotoxic antibiotics on the occurrence of renal dysfunction in patients who received high-dose cisplatin-containing chemotherapy regimens. **PATIENTS AND METHODS:** The subjects of this analysis were 102 consecutive patients, studied from September 1985 to February 1991, who received high-dose cisplatin, administered as 40 mg/m² for 5 consecutive days in 3% saline with saline hydration and mannitol diuresis, followed by autologous stem cell transplantation. Renal dysfunction was defined as an increase in serum creatinine greater than or equal to 44.2 $\mu\text{mol/L}$ above baseline. **RESULTS:** Characteristics of the 43 patients who were given aminoglycosides were similar to those in patients who did not receive aminoglycosides with respect to initial renal function,

age, cancer type, and previous exposure to cisplatin. Patients who experienced serious treatment-related toxicities such as hemorrhage or septicemia were more likely to have received aminoglycoside antibiotics ($p = 0.005$). A multivariate analysis showed that increased duration of neutropenia, advanced patient age, and amphotericin B use were predictors of renal failure. Aminoglycoside therapy did not significantly increase the risk of renal dysfunction. **CONCLUSIONS:** Our data suggest that with appropriate supportive care measures, aminoglycosides can safely be administered to febrile, neutropenic patients who recently have received high-dose cisplatin therapy.

Couillard, M. and M. Trudel (2009). "C-myc as a modulator of renal stem/progenitor cell population." *Dev Dyn* **238**(2): 405-14.

The role of c-myc has been well-studied in gene regulation and oncogenesis but remains elusive in murine development from midgestation. We determined c-myc function during kidney development, organogenesis, and homeostasis by conditional loss of c-myc induced at two distinct phases of nephrogenesis, embryonic day (e) 11.5 and e17.5. Deletion of c-myc in early metanephric mesenchyme (e11.5) led to renal hypoplasia from e15.5 to e17.5 that was sustained until adulthood (range, 20-25%) and, hence, reproduced the human pathologic condition of renal hypoplasia. This phenotype resulted from depletion of c-myc-positive cells in cap mesenchyme, causing a approximately 35% marked decrease of Six2- and Cited1-stem/progenitor population and of proliferation that likely impaired self-renewal. By contrast, c-myc loss from e17.5 onward had no impact on late renal differentiation/maturation and/or homeostasis, providing evidence that c-myc is dispensable during these phases. This study identified c-myc as a modulator of renal organogenesis through regulation of stem/progenitor cell population.

de Souza, J. A., R. M. Saliba, et al. (2009). "Moderate renal function impairment does not affect outcomes of reduced-intensity conditioning with fludarabine and melphalan for allogeneic hematopoietic stem cell transplantation." *Biol Blood Marrow Transplant* **15**(9): 1094-9.

Nonrelapse mortality (NRM) after reduced-intensity allogeneic transplants is likely to be influenced by abnormalities in renal function. We studied 141 patients diagnosed with acute myelogenous leukemia (AML) ($n = 131$) or high-risk myelodysplastic syndrome (MDS) ($n = 10$) who underwent allogeneic transplantation with fludarabine (Flu)/melphalan (Mel)-based regimens and

hypothesized that moderate to mild renal function impairment increases NRM in this setting. Flu dose consisted of 25-30 mg/m² for 4 days and Mel dose was 100-180 mg/m². Donors were HLA-compatible siblings ($n = 69$) and matched unrelated donors ($n = 72$). Disease status at transplantation was complete remission ($n = 56$, 40%) or active disease ($n = 85$, 60%). The influence of the estimated glomerular filtration rate (GFR) measured before transplantation on outcomes was analyzed. GFR was estimated by both the Cockcroft-Gault (CG) and the modified diet in renal disease (MDRD) equations, using the creatinine value obtained prior to starting chemotherapy. Evaluated outcomes were overall survival (OS), NRM, and treatment-related mortality (TRM) at day 100 and 1-year posttransplantation. Median age was 55 years (range: 21-74 years); 59% of the patients were male. Estimated GFR by CG was $>$ or $=90$ for 45 (32%), 60-89 for 78 (55%), and <60 for 18 (13%) patients. When estimated by MDRD, GFR was $>$ or $=90$ for 65 (46%), 60-89 from 66 (47%), and <60 for 10 (7%) patients. The majority of patients by both estimations had a GFR between 60 and 89 ($n = 78$ by CG and $n = 66$ by MDRD) with no difference in the evaluated outcomes between this group and the subgroup of patients with a GFR <60 ($P > .05$). There were no differences in OS and NRM at day 100 and 1-year posttransplantation in the 3 groups by any GFR estimation method. In conclusion, a mild to moderate decrease in GFR was not associated with an increase in NRM.

Dember, L. M., V. Sanchowala, et al. (2001). "Effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on al amyloidosis-associated renal disease." *Ann Intern Med* **134**(9 Pt 1): 746-53.

BACKGROUND: Dose-intensive intravenous melphalan with autologous blood stem-cell transplantation induces remission of the plasma cell dyscrasia in a substantial proportion of patients with AL amyloidosis. The impact of this treatment on associated renal disease is not known. **OBJECTIVE:** To determine the effect of dose-intensive intravenous melphalan and autologous blood stem-cell transplantation on AL amyloidosis-associated renal disease. **DESIGN:** Prospective cohort study. **SETTING:** Academic medical center. **PATIENTS:** 65 patients with AL amyloidosis and urinary protein excretion greater than 1 g/24 h who received dose-intensive intravenous melphalan and autologous blood stem-cell transplantation between 1 July 1994 and 30 June 1998. **MEASUREMENTS:** 24-hour urinary protein excretion, serum cholesterol level, serum albumin level, creatinine clearance, urine and serum immunoelectrophoresis, and bone marrow biopsy.

Renal response was defined as a greater than 50% reduction in urinary protein excretion in the absence of a 25% or greater reduction in creatinine clearance. Complete hematologic response was defined as absence of detectable monoclonal protein in serum and urine and a bone marrow specimen containing less than 5% plasma cells without clonal dominance of kappa or lambda isotype. RESULTS: Among the 50 patients who survived for at least 12 months, proteinuria, hypoalbuminemia, and hypercholesterolemia improved during follow-up; 36% met criteria for a renal response. Median 24-hour urinary protein excretion decreased from a baseline value of 9.6 g/24 h to 1.6 g/24 h at 12 months among patients with complete hematologic response, and 71% met criteria for a renal response. Twenty-hour urinary protein excretion did not decrease during follow-up among patients with persistent plasma cell disease, and only 11% had a renal response at 12 months ($P < 0.001$ for hematologic responders vs. nonresponders). CONCLUSION: Dose-intensive intravenous melphalan with autologous blood stem-cell transplantation improves the nephrotic syndrome in patients with AL amyloidosis-associated renal disease. The benefit is largely limited to patients achieving eradication of the underlying plasma cell dyscrasia.

Drachenberg, D. and R. W. Childs (2003). "Allogeneic stem cell transplantation as immunotherapy for renal cell carcinoma: from immune enhancement to immune replacement." *Urol Clin North Am* **30**(3): 611-22.

The lack of efficacy of chemotherapeutics, radiotherapy, and cytokine-based immunotherapy has catalyzed the preliminary enthusiasm for nonmyeloablative stem cell transplants as a novel investigational tool for treating metastatic RCC. The observation that cytokine-refractory metastatic RCC may regress following allogeneic transplantation attests to the powerful nature of the graft-versus-tumor effect that results from this treatment modality. Pilot trials and recent in vitro data provide the first clear evidence that the graft-versus-tumor effect mounted against RCC can produce clinically meaningful regression of a metastatic solid tumor. Given this observation, the authors have begun to expand the investigational use of nonmyeloablative stem cell transplants to other treatment-refractory genitourinary tumors, including metastatic bladder and prostate cancer. It is hoped that future demonstrations of graft-versus-tumor effects in other solid malignancies will lay the groundwork for the development of tumor-targeted strategies that use allogeneic transplantation of donor lymphocytes as an immunotherapeutic platform. Further advances in systemic and selective

immunosuppressive agents that limit acute GVHD hold the potential to decrease the toxicity associated with nonmyeloablative stem cell transplants and may ultimately broaden the clinical applicability of this approach.

Elsamman, E. M., T. Fukumori, et al. (2006). "The expression of prostate stem cell antigen in human clear cell renal cell carcinoma: a quantitative reverse transcriptase-polymerase chain reaction analysis." *BJU Int* **98**(3): 668-73.

OBJECTIVES: To analyse the gene expression level of prostate stem cell antigen (PSCA) in human clear cell renal cell carcinoma (CC-RCC) and its relationship with conventional clinicopathological manifestations, to evaluate its prognostic value for patient outcome, and to determine the effect of PSCA on the progression of CC-RCC. PATIENTS AND METHODS: We quantified PSCA mRNA level in human RCC cell lines (ACHN, A704, KPK-1, Caki-1, and Caki-2) and in 154 surgical tissue samples (81 from CC-RCC, 73 from normal kidney) using real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The findings were analysed in relation to clinicopathological factors. Immunohistochemical expression was examined using confocal laser scanning light-microscopy. RESULTS: PSCA was overexpressed in all RCC cell lines. PSCA mRNA levels were significantly higher in CC-RCC than in normal kidney tissue samples ($P < 0.001$), in G2-G3 than in G1 tumours ($P = 0.028$), and in advanced disease (T3-T4) than in organ-confined (T1-T2) tumours ($P = 0.016$). There was significantly higher PSCA mRNA expression in patients with M1 than in those with M0 disease ($P = 0.029$). Patients in whom the lesions had high PSCA expression levels had a significantly worse prognosis than those with low PSCA expression levels ($P = 0.044$). Using immunohistochemical analysis there was markedly greater PSCA expression in CC-RCC than in normal kidney, and in advanced-disease high-grade tumours than in organ-confined low-grade tumours. CONCLUSIONS: A significant correlation was detected in the gene expression level of PSCA with histological grade, clinicopathological stage and prognosis in CC-RCC. Our data indicate that PSCA is associated with carcinogenesis and progression of CC-RCC.

El-Seisi, S., R. Gupta, et al. (2003). "Renal pathology at autopsy in patients who died after hematopoietic stem cell transplantation." *Biol Blood Marrow Transplant* **9**(11): 683-8.

Acute and chronic renal dysfunction are common after hematopoietic stem cell transplantation (HSCT). Although the pathology of chronic HSCT

nephropathy is well described, the histologic changes that accompany acute renal dysfunction after HSCT are less well known because renal biopsies are rarely undertaken in the peritransplantation period. Archival renal tissue from consecutive HSCT recipients who died and underwent autopsy at a single center during an 8-year period was studied. Abnormalities of renal pathology were described, and associations of histologic abnormalities with clinical events were systemically studied. Abnormalities of renal histology were common among the 26 patients in this study. The 3 most common histologic abnormalities were glomerular sclerosis (19/26; 73%), tubular epithelial atypia (19/26; 73%), and tubular calcification (18/26; 69%). Tubulitis (16/24; 67%) and interstitial fibrosis (16/26; 62%) were also frequently observed. Clinical veno-occlusive disease was not associated with histologic evidence of thrombotic microangiopathy in the kidney at autopsy. Also, clinical graft-versus-host disease was not associated with renal tubulitis. Unexpectedly, the proportion of patients with tubular atrophy (54%) or interstitial fibrosis (62%) was high, considering the young age of the patients at transplantation and their normal pretransplantation creatinine clearance. Well-recognized histologic abnormalities are common in the kidneys of patients who die after HSCT. Although we did not demonstrate associations of these histologic changes with clinical variables before death, larger studies with prospectively collected renal tissue are warranted.

Erotocritou, P., H. Ahmed, et al. (2006). "Nonmyeloablative allogeneic stem-cell transplantation for metastatic renal cell cancer: a review and update." *ScientificWorldJournal* 6: 2519-28.

Metastatic renal cell carcinoma (RCC) is resistant to conventional chemotherapy and radiotherapy. However, immunotherapy appears to be effective in 15-20% of cases, with interleukin-2 becoming the standard therapy for this disease. As a consequence of the immune susceptibility of RCC, other avenues of immunotherapy are being explored, such as nonmyeloablative allogeneic stem cell transplantation (NST). A number of trials have shown NST to be effective in varying degrees, causing partial or complete regression. Although nonmyeloablative conditioning is safer than myeloablative conditioning, its role has yet to be clearly proven as many studies have shown variable effect. Alongside this limitation, transplant-related toxicity also forms obstacles. Regardless of the limitation of NST, further refinement of the technique, with appropriate patient selection, may lead to this being an effective therapeutic choice for a significant number of individuals.

Fadia, A., L. F. Casserly, et al. (2003). "Incidence and outcome of acute renal failure complicating autologous stem cell transplantation for AL amyloidosis." *Kidney Int* 63(5): 1868-73.

BACKGROUND: High-dose intravenous melphalan and autologous peripheral blood stem cell transplantation (HDM/SCT) is an effective treatment for AL amyloidosis but is associated with significant toxicity, including the development of acute renal failure (ARF). The incidence and outcome of ARF as a complication of such treatment is not known. **METHODS:** All AL amyloidosis patients treated with HDM/SCT at a single institution between July 1, 1994 and May 31, 2000 were included in the analysis unless they were dialysis-dependent prior to treatment. Baseline data were collected prospectively. Treatment-related data were obtained from a prospectively maintained database and medical record review. ARF was defined as either a ≥ 1 mg/dL increase in serum creatinine or a doubling of serum creatinine to ≥ 1.5 mg/dL for at least 2 days. Recovery of renal function was defined as a return of serum creatinine to less than or within 0.5 mg/dL of the pretreatment value or the ability to discontinue dialysis initiated as a result of ARF. **RESULTS:** ARF occurred in 37 of 173 patients (21%). Initiation of dialysis was required in nine patients (5%). Forty-six percent of patients with ARF, including four of nine who required dialysis, had recovery of renal function. Baseline clinical variables that were independent predictors of transplant-associated ARF included creatinine clearance, proteinuria, and cardiac amyloidosis. Treatment-related variables associated with ARF included melphalan dose and bacteremia. ARF was associated with reduced survival at 90 days but did not have an impact on overall survival at a median follow-up of 2.9 years. **CONCLUSION:** ARF is a frequent but often reversible complication of HDM/SCT for AL amyloidosis. Specific clinical and treatment-related factors are associated with the development of this complication.

Flores, F. X., P. D. Brophy, et al. (2008). "Continuous renal replacement therapy (CRRT) after stem cell transplantation. A report from the prospective pediatric CRRT Registry Group." *Pediatr Nephrol* 23(4): 625-30.

Pediatric stem cell transplant (SCT) recipients commonly develop acute renal failure (ARF). We report the demographic and survival data of pediatric SCT patients enrolled in the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry. Since 1 January 2001, 51/370 (13.8%) patients entered in the ppCRRT Registry had received a SCT. Median age was 13.63 (0.53-23.52)

years. The primary reasons for the initiation of continuous renal replacement therapy (CRRT) were treatment of fluid overload (FO) and electrolyte imbalance (49%), FO only (39%), electrolyte imbalance only (8%) and other reasons (4%). The CRRT modalities included continuous veno-veno hemodialysis (CVVHD), 43%, continuous veno-veno hemofiltration (CVVH), 37% and continuous veno-veno hemodiafiltration (CVVHDF), 20%. Seventy-six percent had multi-organ dysfunction syndrome (MODS), 72% received ventilatory support and the mean FO was 12.41 +/- 3.70%. Forty-five percent of patients survived. Patients receiving convective therapies had better survival rates (59% vs 27%, $P < 0.05$). Patients requiring ventilatory support had worse survival (35% vs 71%, $P < 0.05$). Mean airway pressure (Paw) at the end of CRRT was lower in survivors (8.7 +/- 2.94 vs 25.76 +/- 2.03 mmH(2)O, $P < 0.05$). Development of high mean airway pressure in non-survivors is likely related to non-fluid injury, as it was not prevented by early and aggressive fluid management by CRRT therapy.

Francois, C., C. Decaestecker, et al. (1998). "Prognostic value of stem cell line identification for renal cell carcinomas." *Anal Quant Cytol Histol* **20**(3): 207-14.

OBJECTIVE: To investigate the prognostic value of nuclear DNA content (DNA ploidy level) in a series of 95 renal cell carcinomas (RCCs). **STUDY DESIGN:** Eight variables were used to characterize DNA ploidy levels. They included DNA index and seven others characterizing the presence of specific stem cell lines in each of the 95 RCCs under study. All these variables were determined by means of computer-assisted microscopy applied to Feulgen-stained nuclei. The actual information contributed by each of the eight variables was determined by means of univariate statistical analyses. **RESULTS:** The results showed that in the DNA ploidy-related eight variables, the presence of at least 4% aneuploid nuclei with $> 5C$ DNA content was associated with the most significant prognostic value in RCCs with intermediate (T2, T3) invasion levels. **CONCLUSION:** The present study clearly showed that stem cell line characterization, and particularly the presence of highly aneuploid cells (with $> 5C$ DNA content), is associated in RCCs with significant prognostic value. This kind of marker may help the identification of patients who will develop metastases after surgery and for whom adjuvant therapy might thus be indicated.

Gerstein, J., A. Meyer, et al. (2009). "Long-term renal toxicity in children following fractionated total-body irradiation (TBI) before allogeneic stem cell

transplantation (SCT)." *Strahlenther Onkol* **185**(11): 751-5.

PURPOSE: To retrospectively assess the incidence and time course of renal dysfunction in children ($< \text{ or } = 16$ years) following total-body irradiation (TBI) before allogeneic stem cell transplantation (SCT). **PATIENTS AND METHODS:** Between 1986 and 2003, 92 children (median age, 11 years; range, 3-16 years) underwent TBI before allogeneic SCT. 43 of them had a minimum follow-up of 12 months (median, 51 months; range, 12-186 months) and were included into this analysis. Conditioning regimen included chemotherapy and fractionated TBI with 12 Gy ($n = 26$) or 11.1 Gy ($n = 17$). In one patient, renal dose was limited to 10 Gy by customized renal shielding due to known nephropathy prior to SCT. Renal dysfunction was defined as an increase of serum creatinine > 1.25 times the upper limit of age-dependent normal. **RESULTS:** Twelve children (28%) experienced an episode of renal dysfunction after a median of 2 months (range, 1-10 months) following SCT. In all but one patient renal dysfunction was transient and resolved after a median of 8 months (range, 3-16 months). One single patient developed persistent renal dysfunction with onset at 10 months after SCT. None of these patients required dialysis. The actuarial 3-year freedom from persistent renal toxicity for children surviving > 12 months after SCT was 97.3%. **CONCLUSION:** The incidence of persistent renal dysfunction after fractionated TBI with total doses $< \text{ or } = 12$ Gy was very low in this analysis.

Gommersall, L., D. Hayne, et al. (2004). "Allogeneic stem-cell transplantation for renal-cell cancer." *Lancet Oncol* **5**(9): 561-7.

Metastatic renal-cell carcinoma (RCC) is resistant to chemotherapy, and patients with this disease have a poor outlook. Immunotherapy by use of cytokines and vaccines against tumour antigens has shown encouraging results in a small group of patients. Advances in the understanding of the graft-versus-tumour effect in haematological malignant disorders have led to the use of stem-cell transplantation for treatment of solid-organ malignant diseases such as RCC. Techniques of bone-marrow ablation have been superseded by safer conditioning regimens, with occasional complete remission and partial remission in some patients. Graft-versus-host disease, engraftment failure, and disease progression remain important obstacles to the widespread use of new techniques for metastatic RCC. Here, we summarise important issues surrounding immunotherapy for RCC, the problems encountered with use of immunotherapy, and the present use of

non-myeloablative techniques for treatment of this disease.

Hamaki, T., H. Katori, et al. (2002). "Successful allogeneic blood stem cell transplantation for aplastic anemia in a patient with renal insufficiency requiring dialysis." *Bone Marrow Transplant* **30**(3): 195-8.

A 27-year-old man with aplastic anemia and renal insufficiency requiring dialysis underwent allogeneic PBSCT. The preparative regimen consisted of melphalan, ATG and TLI. GVHD prophylaxis consisted of cyclosporine and prednisolone. He was dialyzed prior to administration of melphalan and at 24 and 72 h after it. Otherwise, the dialysis schedule was unchanged, at three times a week. Engraftment was rapid. Regimen-related toxicity was minimal. Pharmacokinetic parameters of melphalan were not significantly altered with its plasma half-life 1.5 h. Patients with renal failure can receive allogeneic HSCT, and a combination of melphalan, ATG and TLI may serve as an alternative to CY and ATG.

Harlin, H., A. S. Artz, et al. (2004). "Clinical responses following nonmyeloablative allogeneic stem cell transplantation for renal cell carcinoma are associated with expansion of CD8+ IFN-gamma-producing T cells." *Bone Marrow Transplant* **33**(5): 491-7.

Nonmyeloablative allogeneic stem cell transplantation (NST) is thought to be an immunologic therapy in which donor T cells mediate a graft-versus-tumor effect. We recently reported the clinical outcome of a phase II trial of NST in metastatic renal cell carcinoma (RCC). However, the immune response correlates of clinical activity remain unknown. We now describe the analysis of T-cell subsets and T-cell cytokine-producing potential for those patients evaluable for immune monitoring. The incidence of graft-versus-host disease (GVHD) correlated with clinical outcome, with all responders exhibiting chronic GVHD. Following initial tapering of immunosuppression, an increase in the total numbers of CD8+ T cells but not CD4+ T cells was observed among responders compared to nonresponders. In addition, a greater ratio of CD8+ to CD4+ T cells producing IFN-gamma and IL-2 was seen in clinical responders at the time when clinical responses were first detected (day 180 after transplantation). Our results support the hypothesis that the antitumor effects of NST may be mediated by IFN-gamma-producing CD8+ T cells, and indicate that isolation of putative tumor antigen-specific T cells, ideally, should be pursued around day +180.

Hashino, S., M. Imamura, et al. (1996). "Renal Salmonella enteritidis abscess in a patient with severe

aplastic anemia after allogeneic stem cell transplantation." *Bone Marrow Transplant* **18**(4): 807-8.

We describe an unusual case of a renal abscess by Salmonella enteritidis in a 32-year-old man with severe aplastic anemia undergoing allogeneic stem cell transplantation. He was receiving immunosuppressive therapy with CsA and corticosteroids for chronic GVHD. He was not neutropenic and had no history of enterocolitis or cholelithiasis before the onset. Four months after the transplantation, he developed an abscess in the upper pole of his right kidney from which Salmonella enteritidis was isolated in culture. He was successfully treated with a combination of percutaneous drainage and washing the cyst through the catheter using piperacillin sodium-containing solution. The possibility of salmonellosis should be considered in the differential diagnosis of such patients.

Hayes-Lattin, B. M., R. T. Maziarz, et al. (2001). "Allogeneic stem-cell transplantation in renal-cell carcinoma." *Curr Oncol Rep* **3**(5): 433-7.

Metastatic renal-cell carcinoma (RCC) remains resistant to nearly all standard cytotoxic therapies, but immune-based cytokine therapies benefit a small minority of patients with advanced RCC. Nonmyeloablative allogeneic stem-cell transplantation is a novel approach to harnessing the immune system to combat this cancer. The strategy relies on a T-cell graft-versus-malignancy effect mediated by donor T cells. Preliminary work in using nonmyeloablative allogeneic stem-cell transplant in RCC has identified a graft-versus-RCC effect and yielded encouraging clinical responses.

Hazar, V., O. Gungor, et al. (2009). "Renal function after hematopoietic stem cell transplantation in children." *Pediatr Blood Cancer* **53**(2): 197-202.

OBJECTIVES: The aim of this study was to assess glomerular and tubular renal function after HSCT in children in a prospective trial. **METHODS:** Renal function was assessed prospectively before HSCT (on day -10), on days +30, +100, and at least 6 months after transplantation in 34 patients (21 females/13 males) with a mean age of 8.2 years. The following parameters were investigated: glomerular filtration rate (GFR) by creatinine clearance (CrCl), cystatin C (CysC)-based formula and plasma clearance of radiolabeled diethylenetriaminepentaacetic acid ((99m)Tc-DTPA), urinary excretion of beta(2)-microglobulin (beta(2)M), beta-N-acetylglucosaminidase (beta-NAG), fractional excretion of sodium (FE(Na)) and fractional tubular phosphate reabsorption (TP/CrCl). **RESULTS:** Nine patients (26.4%) suffered from acute renal

insufficiency within the first 100 days after transplantation. All patients who developed acute renal insufficiency were treated successfully without renal replacement therapy. Age, sex, primary diagnosis, sepsis, veno-occlusive disease, acute graft versus host disease, and use of vancomycin were not significant risk factors for the development of acute renal insufficiency. The medians (99m)Tc-DTPA-based GFR of patients after HSCT showed a statistically significant decrease when compared with pre-transplant values. beta-NAG excretion was significantly elevated in the first 30 days after HSCT. CONCLUSION: Acute and chronic renal impairment can be developed in patients who undergo HSCT even though the pre-transplant renal function is in normal limits and the conditioning regimen does not include TBI. Both glomerular and tubular renal function evaluation should be part of a long-term follow-up in children following HSCT.

Hentschke, P., L. Barkholt, et al. (2003). "Low-intensity conditioning and hematopoietic stem cell transplantation in patients with renal and colon carcinoma." *Bone Marrow Transplant* **31**(4): 253-61.

We have evaluated whether allogeneic hematopoietic stem cell transplantation (HSCT) could induce an antitumor effect in patients with metastatic solid tumors. A total of 12 HLA-identical siblings and 6 HLA-A-, -B- and -DR beta 1-compatible unrelated grafts were used. Diagnoses were adenocarcinoma of kidney (n=10), colon (n=6), breast (n=1) and cholangiocarcinoma (n=1). Conditioning was fludarabine 30 mg/m²/day for 3 days and 2 Gy of total body irradiation. Recipients of unrelated HSCT were also given thymoglobuline and two additional days of fludarabine. The median CD34+ cell dose was 7.5 x 10⁶/kg. Immunosuppression was mycophenolate mofetil and cyclosporin. Among all, 12 patients became complete donor chimeras within a median of 28, 29 and 65 days for B, myeloid and T cells, respectively. Two patients rejected the grafts, one developed marrow aplasia and three were mixed chimeras. The probability of grades II-IV acute graft-versus-host-disease (GVHD) was 57%. Regression of all tumor metastases was seen in one patient with colon carcinoma. Another patient with colon and two with renal carcinoma had regression of lung metastases, but progression of metastases in the liver and/or bone. Necrosis of lung metastasis was found in one further patient with renal carcinoma who died of graft-versus-host-disease (GVHD). In all, 10 patients died; four of transplant-related complications, one of trauma and five of progressive disease. Thus, progression was common after allogeneic HSCT in unselected patients with advanced solid tumors. However, the regression of some metastases

associated with GVHD provides suggestive evidence that the GVHD effect may occur in renal and colon adenocarcinoma using reduced intensity conditioning.

Herget-Rosenthal, S., M. Uppenkamp, et al. (2000). "Renal complications of high-dose chemotherapy and peripheral blood stem cell transplantation." *Nephron* **84**(2): 136-41.

Following bone marrow transplantation, acute renal failure and proteinuria are common complications with a high mortality, particularly in patients requiring hemodialysis. Incidence, potential predisposing factors, and outcome of acute renal complications in patients with hematological malignancies receiving autologous peripheral blood stem cell transplantation were prospectively studied in 53 patients. Eight patients developed acute renal failure. Three of them required hemodialysis. Of all patients with acute renal failure, only those requiring hemodialysis died, due to nonrenal causes. Only 1 of the 45 patients without renal failure died. Mild proteinuria of predominantly tubular origin occurred in 16 patients, in 3 with and in 13 without acute renal failure. As predisposing factors for acute renal failure were identified: renal hypoperfusion due to systemic inflammatory response syndrome, sepsis or septic shock, and combined administration of nephrotoxic drugs. Especially those patients receiving high numbers of nephrotoxic drugs in combination with renal hypoperfusion were likely to develop acute renal failure. These results suggest that patients receiving high-dose chemotherapy and autologous peripheral blood stem cell transplantation have a low risk of developing acute renal failure and proteinuria.

Horwitz, M. E., I. Spasojevic, et al. (2007). "Fludarabine-based nonmyeloablative stem cell transplantation for sickle cell disease with and without renal failure: clinical outcome and pharmacokinetics." *Biol Blood Marrow Transplant* **13**(12): 1422-6.

End-organ damage is common in patients with sickle cell disease (SCD) thereby limiting the use of allogeneic stem cell transplantation (SCT). We report the outcome of 2 adult SCD patients, 1 with end-stage renal disease (ESRD), who underwent fludarabine-based nonmyeloablative SCT from HLA-identical matched siblings. To prevent fludarabine toxicity, the patient with ESRD underwent aggressive dialysis following adjusted fludarabine dosing. Pharmacokinetics of the fludarabine metabolite F-Ara-A was studied on the patient with ESRD and 2 additional patients with normal renal function. Both patients with SCD achieved full donor erythroid chimerism, have normal blood counts, and are on no immunosuppressive medications. With a 20% dose reduction followed by daily dialysis, we achieved

fludarabine drug exposure that is nearly identical to that achieved in patients with normal renal function. We conclude that fludarabine-based nonmyeloablative allogeneic SCT for adult patients with SCD is feasible, even in the setting of ESRD.

Huck, K., H. J. Laws, et al. (2006). "Three cases of renal relapse after allogeneic hematopoietic stem cell transplantation for childhood acute lymphoblastic leukemia." *Haematologica* **91**(5 Suppl): ECR07.

Isolated renal relapse after allogeneic hematopoietic stem cell transplantation (alloHSCT) in children with acute lymphoblastic leukemia (ALL) is a rare condition. Generally, in ALL, the sites most frequently affected by extramedullary relapse are the central nervous system (CNS) and the testicles. Here we report on three young boys with relapsed B-precursor ALL, who underwent alloHSCT from HLA-identical siblings and suffered a histopathologically proven isolated unilateral renal relapse (two patients) or a combined renal and testicular relapse (one patient) 6, 10 and 12 months post alloHSCT. In all patients at the time of relapse bone marrow showed complete remission with complete donor hematopoiesis. They all received total body irradiation with partial shielding of the kidneys as part of their conditioning therapy, such that renal shielding could be an explanation for the observed accumulation of renal relapses. Moreover, during the past few years so called immune privilege has been postulated for frequent relapse sites such as the CNS, the testicles and the anterior chamber of the eye. Impaired accessibility of these organs by cytotoxic T-cells (CTLs) with a reduced graft-versus-leukemia (GvL) effect after alloHSCT is based on a number of different molecular and cellular mechanisms. Similar mechanisms have been shown to be effective in the tubulointerstitial space of the kidney, rendering the kidney a potentially immune privileged site. Due to these observations we advocate sufficient treatment of the kidneys during conditioning therapy.

Imberti, B., M. Morigi, et al. (2007). "Insulin-like growth factor-1 sustains stem cell mediated renal repair." *J Am Soc Nephrol* **18**(11): 2921-8.

In mice with cisplatin-induced acute kidney injury, administration of bone marrow-derived mesenchymal stem cells (MSC) restores renal tubular structure and improves renal function, but the underlying mechanism is unclear. Here, we examined the process of kidney cell repair in co-culture experiments with MSC and cisplatin-injured proximal tubular epithelial cells (PTEC). Exposure of PTEC to cisplatin markedly reduced cell viability at 4 days, but co-culture with MSC provided a protective effect by promoting tubular cell proliferation. This effect was

mediated by insulin-like growth factor-1 (IGF-1), highly expressed by MSC as mRNA and protein, since blocking the growth factor's function with a specific antibody attenuated cell proliferation of PTEC. Confirming this, knocking down IGF-1 expression in MSC by small interfering-RNA also resulted in a significant decrease in PTEC proliferation and increased apoptosis. Furthermore, in the murine model of cisplatin-induced kidney injury, administering IGF-1 gene-silenced MSC limited their protective effect on renal function and tubular structure. These findings indicate that MSC exert beneficial effects on tubular cell repair in acute kidney injury by producing the mitogenic and pro-survival factor IGF-1.

Ishiyama, K., A. Takami, et al. (2009). "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* **39**(12): 807-12.

OBJECTIVE: Renal cell carcinoma (RCC) is refractory to conventional therapy, including chemotherapy and radiation. However, because RCC is sensitive to cytokine therapy, an immunotherapeutic approach such as hematopoietic stem cell transplantation (HSCT) might lead to a cure. We performed an institutional clinical study of HSCT for refractory RCC patients. **METHODS:** RCC patients aged 50 years or over, refractory to therapy, were eligible for the study. HSCT was performed after reduced-intensity conditioning. Primary endpoint was defined as the survival at day 100 after HSCT with complete donor chimerism, and secondary endpoint was the effectiveness of HSCT. **RESULTS:** Seven patients, provided with written informed consent, were enrolled in the study. Six of the seven patients achieved complete donor chimera at day 30 after HSCT, but one patient received second HSCT because of graft rejection. Four patients achieved a partial response (PR) and stable disease was observed in another patient, but these responses were temporary. The disease of the other two patients became progressive. Autopsy findings revealed an accumulation of CD8(+) lymphocytes and degenerative changes in the local RCC lesion in three of six patients who responded clinically. An autopsy of a patient who had obtained a PR revealed lymphocyte involvement with a cytotoxic T cell (CTL) phenotype in the metastasis of RCC. **CONCLUSIONS:** Our results demonstrate the efficacy of HSCT for RCC and suggest that the graft-versus-tumor effect elicited by CTLs is induced in vivo. HSCT should be further explored as a potential curative treatment for RCC.

Kersting, S., S. V. Dorp, et al. (2008). "Acute renal failure after nonmyeloablative stem cell transplantation in adults." Biol Blood Marrow Transplant **14**(1): 125-31.

Acute renal failure (ARF) after myeloablative stem cell transplantation (SCT) is a well-established problem. Little is known about ARF after nonmyeloablative SCT. The aim of the present study was to assess the incidence of ARF and to analyze risk factors for ARF. Moreover, we wanted to study whether ARF influenced survival. We performed a retrospective cohort study of 150 adults who received nonmyeloablative SCT (fludarabine 30 mg/m²/day for 3 days and/or total-body irradiation (TBI) 200 cGy). ARF was categorized into grade 0 (no ARF), grade 1 (decrease in glomerular filtration rate $\geq 25\%$ and \leq doubling in serum creatinine), grade 2 ($>$ doubling in serum creatinine), and grade 2 plus ($>$ tripling in serum creatinine). ARF grade 2-2 plus developed in 49 of 150 patients (33%) after a median of 37 days, 14 patients (9%) had ARF grade 2 plus. No patient required dialysis. Risk factors at baseline for ARF grade 2-2 plus were a history of autologous transplantation ($P = .008$), the absence of vascular disease ($P = .012$) lower serum creatinine ($P < .001$), and higher glomerular filtration rate ($P < .001$). Acute graft-versus-host disease (aGVHD) grade III-IV was the only complication that was associated with ARF ($P = .035$). Overall mortality at 1 year was 23%. Patients with ARF grade 2-2 plus had significantly higher mortality compared to ARF grade 0-1 ($P = .006$). This was largely attributable to a diminished survival in patients with ARF grade 2 plus, who had a mortality rate of 71% caused by, among others, progression of malignancy and GVHD. This makes severe ARF an indicator for decreased survival.

Kersting, S., H. A. Koomans, et al. (2007). "Acute renal failure after allogeneic myeloablative stem cell transplantation: retrospective analysis of incidence, risk factors and survival." Bone Marrow Transplant **39**(6): 359-65.

Acute renal failure (ARF) is an important complication after stem cell transplantation (SCT). We retrospectively analysed ARF in 363 recipients of allogeneic myeloablative SCT to identify incidence, risk factors, associated post-transplantation complications and mortality of ARF. ARF was graded as grade 0 (no ARF) to grade 3 (need for dialysis) according to creatinine, estimated glomerular filtration rate and need for dialysis. The incidence of severe renal failure (grades 2 and 3 combined) was 49.6% (180 of 363 patients). Hypertension present at SCT was identified as a risk factor for ARF ($P=0.003$). Despite this, survival of these patients was not different compared to patients without hypertension.

Admission to the intensive care unit (ICU) was a post-transplantation complication significantly associated with ARF ($P<0.001$). Survival rate was highest in patients with ARF grade 0-1 and lowest in patients with grade 3 ($P<0.001$). However, after correction for complications associated with high mortality (admission to the ICU, thrombotic thrombocytopenic purpura, sinusoidal occlusion syndrome (SOS) and acute graft-versus-host disease) the significant difference in survival disappeared, showing that ARF without co-morbid conditions has a good prognosis, and ARF with co-morbid conditions has a poor prognosis. This poor prognosis is due to the presence of co-morbid conditions rather than development of ARF itself.

Kersting, S. and L. F. Verdonck (2008). "Successful outcome after nonmyeloablative allogeneic hematopoietic stem cell transplantation in patients with renal dysfunction." Biol Blood Marrow Transplant **14**(11): 1312-6.

Nonmyeloablative allogeneic hematopoietic stem cell transplantation (HSCT) is a transplantation approach that enables patients with comorbid conditions to undergo allogeneic HSCT. We investigated the outcome of patients with reduced renal function as a single comorbidity before HSCT. Thirteen patients with a glomerular filtration rate (GFR) of <60 mL/min/1.73 m² were matched on sex, age, and type of transplant to 26 controls with normal renal function. All patients received a nonmyeloablative HSCT with fludarabine and/or total body irradiation conditioning (TBI). Graft-versus-host disease (GVHD) prophylaxis consisted of mycophenolate mofetil and cyclosporine. Data on renal function, cyclosporine dose, cyclosporine trough levels, hypertension, and GVHD were collected. Of the 13 patients with impaired renal function, 7 patients (54%) improved or stabilized to a $GFR \geq 60$ mL/min/1.73 m² at last follow-up. Four patients (31%) developed chronic kidney disease stage 3 ($GFR < 60$ mL/min/1.73 m²) compared to 3 patients (12%) in the control group ($P=.039$). There was no difference in survival between cases and controls. Furthermore, there were no differences in complications after HSCT, and cyclosporine dose and trough levels were similar between cases and controls. Nonmyeloablative HSCT can be safely offered to patients with mildly reduced renal function. Cyclosporine can be administered at the same dose as patients without renal dysfunction, as long as cyclosporine trough levels and creatinine are monitored and dose adjustments are made if necessary.

Kida, Y., T. Ishii, et al. (2007). "A case report of thrombotic thrombocytopenic purpura and severe

acute renal failure post non-myeloablative allogeneic peripheral blood stem cell transplantation treated with plasma exchange and hemodialysis." Ther Apher Dial **11**(5): 402-6.

A 59-year-old-woman received related non-myeloablative allogeneic peripheral blood stem cell transplantation (PBSCT) subsequent to autologous PBSCT in our hospital five years after she was diagnosed as oligo-secretory myeloma. She was admitted to our hospital because of vomiting and grayish diarrhea 4 months after non-myeloablative allogeneic PBSCT (mini-alloPBSCT). Although her initial symptoms improved after admission, she gradually showed thrombocytopenia, anemia, and oliguria during the 2 weeks after admission. Our diagnosis was thrombotic thrombocytopenic purpura (TTP) and acute renal failure (ARF) secondary to mini-alloPBSCT. After cessation of cyclosporine administration, we began to treat her with plasma exchange (PE) and hemodialysis. During the three and a half months after we started PE, the TTP gradually improved. Although PE had been reported to be ineffective for TTP post bone marrow transplantation, we could finally discontinue PE. In contrast, since her anuria continued, she was managed with hemodialysis. One month after PE was started, her activity of von Willebrand factor-cleaving protease was 41% (normal range, >50%) and the ultrasonographic investigation of both kidneys was normal. She could be discharged after four and a half months hospitalization and lived well as an outpatient for a further two months. She died shortly after readmission from multiple organ failure without the relapse of TTP. The patient's clinical course would suggest that TTP post mini-alloPBSCT could be treated with PE in some cases, despite the development of dialysis-requiring severe ARF being a poor prognostic factor.

Kist-van Holthe, J. E., D. Bresters, et al. (2005). "Long-term renal function after hemopoietic stem cell transplantation in children." Bone Marrow Transplant **36**(7): 605-10.

Glomerular function of all long-term survivors who underwent hemopoietic stem cell transplantation (HSCT) from 1991 to 1998 (study I, n=121) was studied retrospectively. In addition, we prospectively analyzed glomerular and tubular function of all long-term surviving children who received an HSCT between 1998 and 2000 (study II, n=41). We found a lower prevalence of children with chronic renal failure (CRF) post-HSCT in our more recent cohort (study II: 10%) as compared to the older cohort (study I: 24%) 5.0 (0.7 s.d.) and 7.6 (2.4 s.d.) year's post-HSCT, respectively. Furthermore, it seems that renal function may stabilize after 1-year post-

HSCT. None of the patients required dialysis or antihypertensive medication at long-term follow-up. The sole predictor of CRF in our study was high serum creatinine pre-HSCT (P=0.007), while acute renal failure within 3 months after HSCT (P=0.08) only showed a trend towards predicting CRF. We could not confirm a relation of conditioning with irradiation with CRF post-HSCT, as was shown in several other pediatric and adult studies. Proximal and distal tubular dysfunction only occurred in a minority of long-time survivors of HSCT (3-12 and 9-13%, respectively) and had no clinical consequences.

Kiykim, A. A., G. Genctoy, et al. (2009). "Serum stem cell factor level in renal transplant recipients with posttransplant erythrocytosis." Artif Organs **33**(12): 1086-90.

The etiology of posttransplant erythrocytosis (PTE) remains unclear, and the most frequently suggested causative factors are still a matter of controversy. We aimed to investigate serum-soluble stem cell factor (sSCF) along with serum erythropoietin (EPO) levels in renal transplant recipients (RTRs) with PTE. Thirteen RTRs with PTE, 42 RTRs without PTE, and 42 healthy controls were included. Serum sSCF and EPO levels were determined using an enzyme-linked immunosorbent assay kit. Expected and observed/expected EPO levels were calculated. Serum sSCF levels and observed/expected EPO were significantly higher in RTRs with PTE than both RTRs without PTE and controls. In RTRs with PTE, sSCF level was significantly correlated with hematocrit and observed/expected EPO, respectively. Significant correlation was also observed between hematocrit level and observed/expected EPO in RTRs with PTE. Increased sSCF level and inadequate suppression of EPO production seem to have a role in the pathogenesis of PTE.

Kletzel, M., L. Pirich, et al. (2005). "Comparison of Tc-99 measurement of glomerular filtration rate vs. calculated creatinine clearance to assess renal function pretransplant in pediatric patients undergoing hematopoietic stem cell transplantation." Pediatr Transplant **9**(5): 584-8.

We compared the results of Tc-99 evaluation of glomerular filtration rate (GFR) vs. the calculation of the creatinine clearance (CCrC) as a predictor for the development of renal insufficiency in pediatric patients following hematopoietic stem cell transplantation (HSCT). We reviewed 95 consecutive patients receiving autologous (n = 37) or allogeneic (n = 58) HSCT at Children's Memorial Hospital between January, 1995 and February, 1998. Diagnoses included leukemia (n = 43), solid tumor (n = 27), bone

marrow failure syndrome (n = 12), non-malignant disease (n = 8), CNS tumors (n = 5) and immunodeficiency (n = 3). Tc-99 GFR was compared with a calculated creatinine clearance derived from the Schwartz formula (CCrC) prior to HSCT. These measures of renal function were compared with the patient's subsequent clinical course to determine if patients who developed renal insufficiency of sufficient magnitude as to require continuous venovenous hemofiltration (CVVH) or dialysis, could have been identified. Overall comparison of the two methods of evaluation of renal function showed low correlation with values obtained by CCrC, which were consistently higher in most patients (r-value 0.01 in the regression analysis and a p = 0.08 95% CI -24.15 to 1.48). When stratified for age, correlation between the two methods was excellent only in children younger than 5 yr of age p = 0.02 95% CI 0.032-0.49). Eleven patients required therapy with CVVH or dialysis but neither CCrC nor Tc-99 GFR prior to transplant predicted this event. Patients who received TBI were statistically more prone to develop renal insufficiency than those without TBI (p < 0.0001, 95% CI 0.25-0.008). Neither the Tc-99 GFR nor the CCrC was predictive of the development of renal insufficiency in HSCT patients as the majority of patients who required dialysis had normal Tc-99 GFR prior to transplant. The characteristics found in the patients who developed renal insufficiency and required dialysis include: the use of total body irradiation as part of the transplant-conditioning regimen (p < 0.0001) and the use of continuous infusion CSA (p = 0.04).

Knudsen, L. M., B. Nielsen, et al. (2005). "Autologous stem cell transplantation in multiple myeloma: outcome in patients with renal failure." *Eur J Haematol* **75**(1): 27-33.

The impact of renal failure on prognosis of multiple myeloma patients treated with high-dose chemotherapy and stem cell support is incompletely studied. A total of 137 patients received high-dose chemotherapy with autologous transplantation at our centre. The patient population was divided into three groups based on their estimated creatinine clearance (Ccr); renal failure defined as Ccr < 60 mL/min: Group A: normal renal function both at diagnosis and at transplant (n = 78), Group B: renal failure at diagnosis but normal renal function at transplant (n = 30), Group C: renal failure both at diagnosis and at transplant (n = 29). There were no differences in the number of stem cells harvested, time to engraftment or response to transplantation between the groups. Ten of the patients in Group C had a normalisation of renal function post-transplant. Significantly longer hospitalisation, increased use of blood products and

increased number of infections were seen in Group C compared to Groups A and B. The transplant-related mortality was 17% in Group C compared to 0% and 1% in Groups B and A respectively. Eight patients were on dialysis during transplant and four of these died within the first 100 d post-transplant. Disease response was similar in the three groups. Overall survival was significantly longer in Group A than in Groups B and C. High-dose chemotherapy with autologous transplantation is feasible in MM with renal failure. Whereas patients with moderate renal insufficiency seem to benefit from this treatment, patients in need for dialysis at the time of transplant must be carefully evaluated before proceeding to high-dose chemotherapy.

Kodama, M., F. Takeshita, et al. (2008). "Pancreatic endocrine and exocrine cell ontogeny from renal capsule transplanted embryonic stem cells in streptozocin-injured mice." *J Histochem Cytochem* **56**(1): 33-44.

In this study, we describe pancreatic cell ontogeny in renal capsule-transplanted embryonic stem cells (ES) after injury by streptozocin (STZ), showing pancreatogenesis in situ. Seven-week-old female BALB/c nude mice were treated with either a single 175- or 200-mg/kg STZ dose, a regimen that induces substantial beta-cell damage without overt hyperglycemia, and transplanted 24 hr later with 1 x 10⁵ ES. Immunohistochemistry was performed on ES tissue at 15, 21, and 28 days after transplantation using antibodies against stage- and lineage-specific pancreatic markers. After 21 days, PDX-1+ pancreatic foci first appeared in the renal capsule and expressed both amylase and endocrine hormones (insulin, glucagon, and somatostatin). These foci increased in size by day 28 because of acinar and duct cell proliferation, whereas endocrine cells remained non-dividing, and made up 2-4% of ES tumor volume. PDX-1, Nkx6.1, Ngn3, and ISL-1 protein localization patterns in pancreatic foci were comparable with embryonic pancreatogenesis. A prevalence of multihormonal endocrine cells, a characteristic of adult beta-cell regeneration, indicated a possible divergence from embryonic islet cell development. The results indicate that beta-cell damage, without overt hyperglycemia, induces a process of fetal-like pancreatogenesis in renal capsule-transplanted ES, leading to beta-cell neogenesis.

Leung, N., A. Dispenzieri, et al. (2005). "Renal response after high-dose melphalan and stem cell transplantation is a favorable marker in patients with primary systemic amyloidosis." *Am J Kidney Dis* **46**(2): 270-7.

BACKGROUND: Primary systemic (AL) amyloidosis is a rare plasma cell disorder characterized by soft-tissue deposition of monoclonal light chain fragments. High-dose melphalan followed by autologous stem cell transplantation currently has become the treatment of choice. Favorable outcome is ensured with achievement of hematologic response, but little is known about organ response. This study was undertaken to determine the prognostic importance of renal response after high-dose melphalan and stem cell transplantation. **METHODS:** All patients with AL amyloidosis who underwent autologous stem cell transplantation between 1996 and December 2002 were selected for study. Renal response is defined as a 50% or greater reduction in proteinuria with less than 25% decline in renal function. Exclusion criteria included pretransplantation dialysis therapy or dialysis dependence posttransplantation, treatment mortality, lack of proteinuria assessment posttransplantation, and baseline proteinuria with protein less than 1 g/d. **RESULTS:** Of 105 patients, 47 were excluded for stated reasons. Renal response was achieved in 60.3% of evaluated patients. Proteinuria was reduced by greater than 90% in 37.9% and returned to normal in 15.5%. Median response time was 12 months. Renal response was associated with a greater increase in serum albumin level ($P = 0.001$), maintenance of renal function ($P < 0.001$), and better survival ($P = 0.0003$). Renal responders had better survival regardless of hematologic response ($P = 0.01$ to 0.05). **CONCLUSION:** Currently, high-dose melphalan followed by stem cell transplantation is the most effective treatment for AL amyloidosis for those who are eligible. Our data show that renal response after high-dose melphalan followed by stem cell transplantation is associated with improved survival. Renal response is an independent marker of treatment success and can be used in cases in which determination of hematologic response is difficult.

Leung, N., A. Dispenzieri, et al. (2007). "Severity of baseline proteinuria predicts renal response in immunoglobulin light chain-associated amyloidosis after autologous stem cell transplantation." *Clin J Am Soc Nephrol* **2**(3): 440-4.

Ig light chain-associated amyloidosis is a fatal plasma cell proliferative disorder that is characterized by fibril deposition in various organs. High-dose melphalan followed by autologous stem cell transplantation has been shown to improve organ dysfunction and survival. This study was undertaken to investigate factors that influence renal response. Patients who had AL amyloidosis with $>$ or $=$ 1 g/d proteinuria and a minimum follow-up of 12 mo were recruited. Renal response was defined by $>$ 50%

reduction in proteinuria with $<$ 25% decline in renal function. Hematologic response was defined as a 50% reduction in serum monoclonal protein or free light chains. Baseline characteristics were examined for relationship to renal response. Thirteen of the 135 patients were excluded for various reasons. Median follow-up was 45.4 mo. Hematologic and renal response was noted in 73 and 43.4% of the patients, respectively. Median response time for the kidney was 10 mo (1 to 40 mo). In univariate analysis, low cardiac troponin T (cTnT), higher albumin, lower proteinuria, and hematologic response were associated with renal response. In multivariate analysis, cTnT and proteinuria were predictive of renal response. Renal response was associated with a longer survival than hematologic response alone. This study showed that severe proteinuria and high cTnT negatively affected renal response after autologous stem cell transplantation. Achievement of renal response was associated with improved survival. These results suggest that early intervention with aggressive therapy is not only justified but recommended to achieve optimal response.

Leung, N., M. D. Griffin, et al. (2005). "Living donor kidney and autologous stem cell transplantation for primary systemic amyloidosis (AL) with predominant renal involvement." *Am J Transplant* **5**(7): 1660-70.

Primary systemic amyloidosis (AL) is characterized by multiorgan deposition of monoclonal immunoglobulin light chain. Renal involvement is common and impaired kidney function is associated with reduced median survival. Autologous stem cell transplantation (SCT) for AL achieves superior response rates compared to chemotherapy alone but patients with end-stage renal disease (ESRD) may be excluded from consideration. A treatment approach consisting of living donor kidney transplantation (LDKTx) followed by autologous SCT was developed for AL with ESRD. Eight patients underwent LDKTx with immediate graft function. Two suffered unanticipated complications post-KTx and died 10 and 3 months later. Two cases of subclinical acute cellular rejection (ACR) and one case of clinical ACR occurred--all reversible with corticosteroid. Six patients had successful stem cell harvests performed and five of these underwent SCT with satisfactory trilineage engraftment. Renal function remained stable following SCT in four and was reduced in one due to infectious and bleeding complications. One patient, who has thus far elected not to undergo SCT, has proteinuria and histologic evidence of recurrent renal amyloidosis. This experience supports the feasibility of sequential living donor KTx and autologous SCT for carefully selected patients with ESRD due to AL.

Leung, N., J. M. Slezak, et al. (2005). "Acute renal insufficiency after high-dose melphalan in patients with primary systemic amyloidosis during stem cell transplantation." *Am J Kidney Dis* **45**(1): 102-11.

BACKGROUND: Patients with primary systemic amyloidosis (AL) have a poor prognosis. Median survival time from standard treatments is only 17 months. High-dose intravenous melphalan followed by peripheral blood stem cell transplant (PBSCT) appears to be the most promising therapy, but treatment mortality can be high. The authors have noted the development of acute renal insufficiency immediately after melphalan conditioning. This study was undertaken to further examine its risk factors and impact on posttransplant mortality. **METHODS:** Consecutive AL patients who underwent PBSCT were studied retrospectively. Acute renal insufficiency (ARI) after high-dose melphalan was defined by a minimum increase of 0.5 mg/dL (44 micromol/L) in the serum creatinine level that is greater than 50% of baseline immediately after conditioning. Urine sediment score was the sum of the individual types of sediment identified on urine microscopy. **RESULTS:** Of the 80 patients studied, ARI developed in 18.8% of the patients after high-dose melphalan. Univariate analysis identified age, hypoalbuminemia, heavy proteinuria, diuretic use, and urine sediment score (>3) as risk factors. Age and urine sediment score remained independently significant risk factors in the multivariate analysis. Patients who had ARI after high-dose melphalan underwent dialysis more often ($P = 0.007$), and had a worse 1-year survival ($P = 0.03$). **CONCLUSION:** The timing of renal injury strongly suggests melphalan as the causative agent. Ongoing tubular injury may be a prerequisite for renal injury by melphalan as evidenced by the active urinary sediment. Development of ARI adversely affected the outcome after PBSCT. Effective preventive measures may help decrease the treatment mortality of PBSCT in AL patients.

Lipkin, A. C. and P. Lenssen (2008). "Hypervitaminosis A in pediatric hematopoietic stem cell patients requiring renal replacement therapy." *Nutr Clin Pract* **23**(6): 621-9.

BACKGROUND: Chronic renal failure patients have been known to develop vitamin A toxicity, but a descriptive study of hypervitaminosis A in patients with acute renal failure (ARF) has not yet been published. The authors observed hypervitaminosis A in pediatric hematopoietic stem cell transplant (HSCT) patients. **METHODS:** All HSCT patients admitted between January 2001 and May 2006 who experienced ARF, received renal replacement therapy (RRT), and had a vitamin A level drawn were included in this retrospective, descriptive

study. Molar ratios of vitamin A and retinol-binding protein (RBP) were calculated to more accurately assess vitamin A status. Nineteen patients met the criteria for this study. **RESULTS:** At initial testing (generally between days 6 and 10 after initiation of RRT), 17 of the 19 patients had abnormally elevated vitamin A levels for their age. Molar ratios of vitamin A to RBP were elevated in 6 patients at initial testing. Prescribed vitamin A intake information (parenteral and enteral) was available for most patients; all but 3 had an average daily intake greater than 2000 IU/kg over the 30 days prior to RRT initiation. Many patients had symptoms possibly related to vitamin A toxicity, although interpretation of hair, skin, and liver abnormalities are difficult to ascertain in HSCT patients. Seven patients had other findings that may have been associated with vitamin A toxicity. **CONCLUSION:** Children undergoing HSCT who receive nutrition support (predominantly parenteral nutrition), experience ARF, and require RRT are at risk for hypervitaminosis A and toxicity.

Little, M. H. and J. F. Bertram (2009). "Is there such a thing as a renal stem cell?" *J Am Soc Nephrol* **20**(10): 2112-7.

Increasing interest in the potential of adult stem cells in regenerative medicine has led to numerous studies focused on the identification of endogenous renal stem cells within the mature mammalian kidney. A variety of approaches have been taken to identify such cells, including physical location, cell surface marker expression, and functional properties. Proof of clonogenicity or renal potential remains questionable, and few such populations have been characterized in humans; however, recent evidence that even podocytes, a cell type with limited proliferative capacity under normal conditions, are constantly regenerated from a population within the Bowman's capsule has breathed new life into the quest for a renal stem cell. Here we examine whether current evidence is sufficient to conclude such a population does indeed exist or whether the jury is still out. We also ask which properties we would wish such a cell to possess to allow for repair of the diseased kidney.

Liu, H., J. H. Ding, et al. (2007). "Early renal injury after nonmyeloablative allogeneic peripheral blood stem cell transplantation in patients with chronic myelocytic leukemia." *Am J Nephrol* **27**(4): 336-41.

BACKGROUND: Renal insufficiency is a common complication early after hematopoietic stem cell transplantation (HSCT). Over the past several years, significant advancement has been achieved in HSCT, especially in nonmyeloablative stem cell transplantation. Compared with traditional HSCT,

nonmyeloablative HSCT employs significantly lower doses of chemoradiotherapy and lower toxicity. The current study evaluated renal insufficiency during the first 100 days in patients with chronic myelocytic leukemia (CML) who underwent nonmyeloablative allogeneic peripheral blood stem cell transplantation (allo-PBSCT) in a single center. **METHODS:** A total of 26 consecutive patients with CML received nonmyeloablative allo-PBSCT from 2002 to 2005 in Zhong Da Hospital. The average age of the patients was 40.2 +/- 8.2 years. Renal function was measured by serum creatinine concentration and estimated glomerular filtration rate (GFR) during the first 100 days after nonmyeloablative allo-PBSCT. Renal dysfunction was classified as follows: grade 0 (<25% decline in GFR), grade 1 (> or =25% decrease in GFR but <twofold rising in serum creatinine), grade 2 (> or =twofold increase in serum creatinine but no need for dialysis) and grade 3 (> or =twofold increase in serum creatinine and need for dialysis). Acute renal failure (ARF) was defined as a doubling of baseline serum creatinine, grade 2 and grade 3. **RESULTS:** All the patients were successfully engrafted. Of the 26 patients, 10 (38%) patients had some degree of renal dysfunction (grade 1, 5 patients; grade 2, 4 patients; grade 3, 1 patient). They developed ARF at an average of 32.8 +/- 4.0 days after transplantation. No significant difference was observed in terms of age, baseline serum creatinine, albumin and hemoglobin between the patients with ARF and without ARF. Renal dysfunction was associated with significantly higher frequencies of sepsis and hepatic veno-occlusive disease (VOD, $p < 0.01$, respectively). The overall mortality rate at the end of 100 days was 19% (5/26). The mortality rate for patients with ARF was significantly higher than those without ARF ($p < 0.001$). **CONCLUSION:** During the first 100 days following nonmyeloablative allo-PBSCT in patients with CML, a 38% incidence of renal dysfunction and a 19% of ARF were found, which were much less than previous studies. Sepsis and VOD were significantly correlated with the development of renal dysfunction. Severe nephrotoxicity was associated with the increase in mortality.

Massenkeil, G., J. Roigas, et al. (2004). "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 **34**(4): 309-16.

Seven out of 29 patients with metastatic renal cell carcinoma (RCC) considered eligible for allogeneic stem cell transplantation underwent nonmyeloablative stem cell transplantation (NST) from HLA-identical donors. Conditioning comprised

cyclophosphamide, fludarabine and antithymocyte globulin. Prolonged mixed chimerism (MC) after engraftment converted to complete donor chimerism (CC) after infusion of donor lymphocytes and/or graft-versus-host disease (GvHD) in six patients. Five patients developed severe GvHD. Two of seven patients had a delayed tumor response after conversion to CC. After a median follow-up of 10 months (4-24 months), 5/7 patients are alive, one in very good partial remission (PR), one with stable and three with progressive disease. One of the seven patients died from sepsis in PR and 1/7 died from rapid tumor progression after sustained MC. None of the 22 nontransplanted patients responded to further therapies. Survival after 1 year was 59% in transplanted and 66% in nontransplanted patients (n.s.). A pooled data analysis from the literature suggests a graft-versus-tumor effect after transplant in patients with metastatic RCC, which becomes effective after chimerism conversion. Available data demonstrate high nonrelapse mortality in these patients. NST in RCC still has to be regarded as an investigational approach requiring careful patients' selection and longer follow-up within clinical studies.

Michael, M., I. Kuehnle, et al. (2004). "Fluid overload and acute renal failure in pediatric stem cell transplant patients." Pediatr Nephrol **19**(1): 91-5.

Acute renal failure (ARF) with fluid overload (FO) occurs often in stem cell transplant (SCT) recipients. We have previously demonstrated that an increased percentage of FO prior to the initiation of continuous renal replacement therapy (CRRT) is associated with mortality in children with ARF. Based on these data, we devised a protocol for the prevention of FO in SCT patients with ARF. SCT patients with ARF and 5% FO were started on furosemide and low-dose dopamine. To allow for nutrition, medication, and blood product administration, RRT was initiated for patients with > or =10% FO. There were 272 patients who received allogeneic SCT from 1999 to 2002. Of these, medical records of 26 SCT patients with a first episode of oliguric ARF were reviewed. The mean patient age was 13 +/- 5 years (range 2-23.5 years). Mean days to ARF after SCT were 28 +/- 29 days (range 2-90 days). Of the 26 patients, 11 (42%) survived an initial ARF episode. All 11 survivors either maintained <10% FO during their course or re-attained <10% FO with RRT treatment. Of the 15 non-survivors, 6 had <10% FO at the time of death. Of 14 patients who received RRT, 4 (29%) survived. Mechanical ventilation and pediatric risk of mortality score > or =10 at the time of admission to the intensive care unit were associated with lower survival ($P < 0.05$). The use of one or more pressors, the presence of graft-versus-host disease, and septic shock

were not correlated with survival. Our data demonstrate that maintenance of euolemia (<10% FO) is critical but not sufficient for survival in SCT patients with ARF, as all non-euvolemic patients died. We suggest that aggressive use of diuretics and early initiation of RRT to prevent worsening of FO may improve the survival of SCT patients.

Mollura, D. J., J. M. Hare, et al. (2003). "Stem-cell therapy for renal diseases." *Am J Kidney Dis* **42**(5): 891-905.

Significant attention is currently directed to the biological and therapeutic capabilities of stem cells for developing novel treatments for acute and chronic kidney diseases. To date, viable sources of stem cells for renal therapies include adult bone marrow and embryonic tissues, including the metanephric mesenchyme and mesonephros. Native adult kidney stem cells have yet to be identified. Systemically introduced stem cells can engraft in sites of renal disease and injury to show donor phenotypes. Stem cells can differentiate into cells similar to glomeruli, mesangium, and tubules in the kidneys. The impact of stem-cell engraftment and differentiation on renal function presently is unknown. Identification of renal diseases treatable with stem-cell therapies is expected to evolve as stem-cell technologies advance. Methods of modifying stem cells to improve homing, differentiation, and integration into host tissues need further characterization. Ethical and legal controversies about embryonic research and cloning are shaping the regulation and funding of stem-cell research for kidney diseases. Scientific and clinical understanding of stem cells and their potential for renal treatments are in the early stage of development. This field offers great promise, and there are significant opportunities for future investigation in clinical, biological, and ethical aspects of stem-cell therapy for kidney diseases.

Nakagawa, T., M. Kami, et al. (2004). "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* **32**(7): 599-606.

OBJECTIVE: The aim of this study was to evaluate the safety and efficacy of allogeneic hematopoietic stem cell transplantation with a reduced-intensity conditioning regimen (RIST) for interferon-alpha-refractory metastatic renal cell carcinoma (RCC). **PATIENTS AND METHODS:** Of 26 patients referred to the National Cancer Center Hospital for possible RIST between June 2000 and April 2002, an HLA-identical relative was identified

for 12 patients. Nine patients underwent RIST. The conditioning regimen consisted of fludarabine 180 mg/m² or cladribine 0.66 mg/kg, plus busulfan 8 mg/kg and rabbit antithymocyte globulin 5 mg/kg. Graft-vs-host disease (GVHD) prophylaxis was cyclosporine alone. **RESULTS:** All patients achieved engraftment without grade III to IV nonhematologic regimen-related toxicity. All patients achieved complete donor-type chimerism without donor lymphocyte infusion by day 60. Four patients developed acute GVHD, and four developed chronic GVHD. One patient (11%) achieved partial response. As of July 2003, six patients were alive at median follow-up of 681 days. The actuarial overall survival rate was 89% at 1 year and 74% at 2 years. The overall survival rate tended to be higher in the 12 patients with a matched donor than in the other 14 patients without a matched donor ($p = 0.088$). **CONCLUSION:** Our RIST procedure is feasible without severe toxicity. The efficacy of RIST for RCC should be confirmed in phase II/III clinical trials.

Nakayama, K., N. M. Tannir, et al. (2007). "Natural history of metastatic renal cell carcinoma in patients who underwent consultation for allogeneic hematopoietic stem cell transplantation." *Biol Blood Marrow Transplant* **13**(8): 975-85.

We characterized the natural history of metastatic renal cell carcinoma (RCC) and identified prognostic factors among patients who did or did not undergo allogeneic hematopoietic stem cell transplantation (HSCT). A total of 99 patients (23 who underwent HSCT and 76 who did not) were included in the study. Overall survival rates were comparable between the HSCT and no-HSCT groups (excluding patients with poor performance status or brain metastasis from the latter group) at a median 17.4 months of follow-up ($P=.92$). In univariate analyses, Fuhrman's nuclear grade 4 ($P=.05$), high serum calcium ($P=.002$), or low hemoglobin levels ($P=.02$), 3 or more metastatic sites ($P=.02$), and <12 months from diagnosis to initial recurrence ($P=.04$) were identified as poor prognostic factors. In multivariate analyses, 3 or more metastatic sites ($P=.005$) and low hemoglobin levels ($P=.02$) were poor prognostic factors. In the HSCT group, median survival times from consultation and from transplant were 25 and 19 months for those with 0 prognostic factors ($n=7$) and 11 and 7 months for those with 1 or more prognostic factors ($n=16$). In conclusion, previous concerns that HSCT would negatively affect long-term outcome of patients with metastatic RCC were not confirmed. Patients with any of these poor prognostic factors should not consider HSCT for metastatic RCC. The role of allogeneic HSCT for patients with no prognostic factors should

be explored in clinical trials for patients with targeted therapy-resistant metastatic RCC.

O'Donnell, P. H., K. Swanson, et al. (2009). "BK virus infection is associated with hematuria and renal impairment in recipients of allogeneic hematopoietic stem cell transplants." *Biol Blood Marrow Transplant* **15**(9): 1038-1048 e1.

BK virus (BKV) is an important pathogen and cause of nephropathy in renal transplant recipients, but its significance following hematopoietic stem cell transplantation (HSCT) is less well described. We measured blood and urine BKV in 124 allogeneic HSCT patients (67 had undergone prior HSCT [surveillance cohort]; 57 were monitored from transplant day 0 [prospective cohort]). BK viremia was manifest in 64.8% of the patients; 16.9% developed viremia. In the prospective cohort, the median time from transplantation to BK viremia development (128 days) was longer than for viruria (24 days; $P < .0001$). Among clinical factors (sex, disease, transplant type, alemtuzumab use, cytomegalovirus [CMV] viremia, graft-versus-host disease [GVHD], donor HLA C7 allele), only CMV viremia was more common in patients with BKV infection ($P < \text{or} = .04$). There was a direct relationship between blood and urine BKV levels and the occurrence, and degree, of hematuria ($P < \text{or} = .03$). Finally, BKV infection was analyzed along with other clinical factors in relation to the development of post-HSCT renal impairment. On multivariate analysis, only BK viremia ($P = .000002$) and alternative-donor transplantation ($P = .002$) were independent predictors of development of post-HSCT renal impairment, with BK viremia associated with a median 1.62mg/dL rise in creatinine from the pretransplant baseline. Among 8 patients in the surveillance cohort with BK viremia, 2 developed biopsy-proven BKV nephropathy requiring hemodialysis. Investigation of whether prophylaxis against, or treatment of, BKV in the post-HSCT setting mitigates the associated morbidities, especially kidney injury, warrants prospective evaluation.

Ogita, M., J. Hoshino, et al. (2007). "Multicentric Castleman disease with secondary AA renal amyloidosis, nephrotic syndrome and chronic renal failure, remission after high-dose melphalan and autologous stem cell transplantation." *Clin Nephrol* **68**(3): 171-6.

Multicentric Castleman disease is a systemic lymphoproliferative disease with incomplete understood etiology. The various renal complications of this disease may include minimal change disease, mesangial proliferative glomerulonephritis, membranous glomerulonephritis and nephrotic syndrome, caused by secondary amyloidosis. In

several reported cases of localized Castleman disease associated with renal amyloidosis and nephrotic syndrome, resection of organs involved by lymphoid proliferation resulted in complete remission. However, therapy of multicentric Castleman disease with renal amyloidosis is not well-established. We treated a case of a 39-year-old woman with multicentric Castleman disease complicated by nephrotic syndrome caused by secondary AA amyloidosis. The patient underwent autologous peripheral blood stem cell transplantation (auto-PBSCT), achieving complete remission. Autologous stem cell transplantation may be an attractive choice in therapy for refractory multicentric Castleman disease.

Parikh, G. C., A. I. Amjad, et al. (2009). "Autologous hematopoietic stem cell transplantation may reverse renal failure in patients with multiple myeloma." *Biol Blood Marrow Transplant* **15**(7): 812-6.

Approximately 20% of patients with multiple myeloma (MM) have renal failure at diagnosis, and about 5% are dialysis-dependent. Many of these patients are considered ineligible for autologous hematopoietic stem cell transplantation (auto-HSCT) because of a high risk of treatment-related toxicity. We evaluated the outcome of 46 patient with MM and renal failure, defined as serum creatinine >2 mg/dL sustained for >1 month before the start of preparative regimen. Patients received auto-HSCT at our institution between September 1997 and September 2006. Median serum creatinine and creatinine clearance (CrCl) at auto-HSCT were 2.9 mg/dL (range: 2.0-12.5) and 33 mL/min (range: 8.7-63), respectively. Ten patients (21%) were dialysis-dependent. Median follow-up in surviving patients was 34 months (range: 5-81). Complete (CR) and partial responses (PR) after auto-HSCT were seen in 9 (22%) and 22 (53%) of the 41 evaluable patients, with an overall response rate of 75%. Two patients (4%) died within 100 days of auto-HSCT. Grade 2-4 nonhematologic adverse events were seen in 18 patients (39%) and included cardiac arrhythmias, pulmonary edema, and hyperbilirubinemia. Significant improvement in renal function, defined as an increase in glomerular filtration rate (GFR) by 25% above baseline, was seen in 15 patients (32%). Kaplan-Meier estimates of 3-year progression-free survival (PFS) and overall survival (OS) were 36% and 64%, respectively. In conclusion, auto HSCT can be offered to patients with MM and renal failure with acceptable toxicity and with a significant improvement in renal function in approximately one-third of the transplanted patients. In this analysis, a melphalan (Mel) dose of 200 mg/m² was not associated with an increase in toxicity or nonrelapse (Mel) mortality (NRM).

Patzer, L., K. Kentouche, et al. (2003). "Renal function following hematological stem cell transplantation in childhood." *Pediatr Nephrol* **18**(7): 623-35.

Renal function greatly influences mortality rates in the early phase following hematological stem cell transplantation (HSCT) in childhood, as well as the quality of life in long-term survivors. Nevertheless, the number of studies in pediatric populations is limited and some important aspects of kidney function after HSCT have only been elucidated in adults. The incidence of acute renal failure (ARF) immediately after HSCT in pediatric patients is between 25% and 50%, with 5%-10% of children requiring renal replacement therapy. Doubling of serum creatinine is associated with a twofold increase in mortality. However, the need for dialysis leads to a further increase in mortality rates to 80%-90%. Specific renal syndromes appear at different times following HSCT, revealing a similar pattern in children and adult patients. In both children and adults, impaired renal function associated with liver impairment (hepatorenal syndrome) is the most important cause for ARF. Therapeutic approaches have not been able to reduce the frequency or to improve outcome so far. In adults surviving long term, bone marrow transplant (BMT) nephropathy is the most frequent renal complication, although a considerable variation in incidence (up to 70%) has been published, partly due to various definitions and manifestations. Little is known about the long-term outcome of renal function in patients treated with HSCT in childhood. However, chronic renal failure has been reported in 0%-28%, but no end-stage renal failure has been published so far. Tubular function following HSCT is rarely investigated, although its impact on long-term survivors of BMT in childhood might be of some importance, especially for growth and bone metabolism.

Patzer, L., F. Ringelmann, et al. (2001). "Renal function in long-term survivors of stem cell transplantation in childhood. A prospective trial." *Bone Marrow Transplant* **27**(3): 319-27.

The aim of this prospective study was to assess glomerular and tubular renal function before, and 1 and 2 years after hematological stem cell therapy (HSCT) in children and adolescents. 137 consecutive patients undergoing HSCT, for malignant diseases, were included in a prospective trial. Forty-four patients were followed for up to 1 year after HSCT and 36 for up to 2 years, without relapse. Ninety healthy school children were used as a control group. The following parameters were investigated: inulin clearance (GFR), urinary excretion of albumin,

alpha1-microglobulin (alpha1-MG), calcium, beta-N-acetylglucosaminidase (beta-NAG) and Tamm-Horsfall protein (THP), tubular phosphate reabsorption (TP/Cl(cr)) and percent reabsorption of amino acids (TAA). Significantly lower GFR was found 1 and 2 years after HSCT but within the normal range in the period before HSCT. There was no correlation between GFR within the first month after HSCT and long-term outcome of GFR. Tubular dysfunction was found in 14-45% of patients 1 and 2 years after HSCT depending on the parameter investigated. Pathological values 1 and 2 years after HSCT were found for alpha1-MG excretion in 40% and 39%, respectively, for TP/Cl(cr) in 44% and 45%, for beta-NAG in 26% and 19%. Median TP/Cl(cr) was significantly lower 2 years after HSCT than before. TAA was mildly impaired in 7/14 patients before, in 5/29 one and in 9/29 2 years after HSCT, but median TAA was within normal range at all times. The median excretion of albumin, THP and calcium was within the normal range at all investigations. No influence of ifosfamide pre-treatment on the severity of tubulopathy was found. The investigation of tubular renal function should be part of a long-term follow-up in children after HSCT.

Peccatori, J., L. Barkholt, et al. (2005). "Prognostic factors for survival in patients with advanced renal cell carcinoma undergoing nonmyeloablative allogeneic stem cell transplantation." *Cancer* **104**(10): 2099-103.

BACKGROUND: The objective of this study was to identify prognostic factors for predicting survival in patients with advanced renal cell carcinoma (RCC) who had undergone an allogeneic stem cell transplantation after failure on immunotherapy. **METHODS:** The authors studied 70 patients with advanced RCC who underwent allogeneic transplantation with a fludarabine-based, reduced-intensity regimen. Ten parameters were analyzed at the time of transplantation for their power to predict survival. Clinical features were examined first univariately; then, variables that were correlated significantly with survival in the univariate analysis were included in a multivariate Cox regression model. **RESULTS:** Factors that were found to be associated significantly with limited survival were performance status, the number of metastatic sites, the presence of mediastinal metastasis, hemoglobin level, C-reactive protein (CRP) level, lactate dehydrogenase (LDH) level, and neutrophil counts. All these variables were included in a multivariate Cox regression model, and three were retained in the final model. Patients were classified according to the score estimated by the final Cox model in two groups (above or below the median value): The median survival was 3.5 months for

patients who had a poor prognosis patients versus 23 months for patients who had a good prognosis. CONCLUSIONS: The current findings suggested that three easily available parameters (performance status, CRP level, and LDH level) could be used to stratify patients with advanced RCC who are candidates for allografting and to assist clinicians in decision-making and selection of an appropriate treatment program.

Perin, L., S. Giuliani, et al. (2008). "Stem cell and regenerative science applications in the development of bioengineering of renal tissue." *Pediatr Res* **63**(5): 467-71.

A rising number of patients with acute and chronic renal failure worldwide have created urgency for clinicians and investigators to search out alternative therapies other than chronic renal dialysis and/or organ transplantation. This review focuses on the recent achievements in this area, and discusses the various approaches in the development of bioengineering of renal tissue including recent discoveries in the field of regenerative medicine research and stem cells. A variety of stem cells, ranging from embryonic, bone marrow, endogenous, and amniotic fluid, have been investigated and may prove useful as novel alternatives for organ regeneration both in vitro and in vivo. Tissue engineering, developmental biology, and therapeutic cloning techniques have significantly contributed to our understanding of some of the molecular mechanisms involved in renal regeneration and have demonstrated that renal tissue can be generated de novo with similar physiologic functions as native tissue. Ultimately all of these emerging technologies may provide viable therapeutic options for regenerative medicine applications focused on the bioengineering of renal tissue for the future.

Pode-Shakked, N., S. Metsuyanin, et al. (2009). "Developmental tumorigenesis: NCAM as a putative marker for the malignant renal stem/progenitor cell population." *J Cell Mol Med* **13**(8B): 1792-808.

During development, renal stem cells reside in the nephrogenic blastema. Wilms' tumour (WT), a common childhood malignancy, is suggested to arise from the nephrogenic blastema that undergoes partial differentiation and as such is an attractive model to study renal stem cells leading to cancer initiation and maintenance. Previously we have made use of blastema-enriched WT stem-like xenografts propagated in vivo to define a 'WT-stem' signature set, which includes cell surface markers convenient for cell isolation (frizzled homolog 2 [Drosophila] - FZD2, FZD7, G-protein coupled receptor 39, activin receptor type 2B, neural cell adhesion molecule - NCAM). We show by fluorescenceactivated cell

sorting analysis of sphere-forming heterogeneous primary WT cultures that most of these markers and other stem cell surface antigens (haematopoietic, CD133, CD34, c-Kit; mesenchymal, CD105, CD90, CD44; cancer, CD133, MDR1; hESC, CD24 and putative renal, cadherin 11), are expressed in WT cell sub-populations in varying levels. Of all markers, NCAM, CD133 and FZD7 were constantly detected in low-to-moderate portions likely to contain the stem cell fraction. Sorting according to FZD7 resulted in extensive cell death, while sorted NCAM and CD133 cell fractions were subjected to clonogenicity assays and quantitative RT-PCR analysis, exclusively demonstrating the NCAM fraction as highly clonogenic, overexpressing the WT 'stemness' genes and topoisomerase2A (TOP2A), a bad prognostic marker for WT. Moreover, treatment of WT cells with the topoisomerase inhibitors, Etoposide and Irinotecan resulted in down-regulation of TOP2A along with NCAM and WT1. Thus, we suggest NCAM as a marker for the WT progenitor cell population. These findings provide novel insights into the cellular hierarchy of WT, having possible implications for future therapeutic options.

Raman, J. D., N. P. Mongan, et al. (2006). "Decreased expression of the human stem cell marker, Rex-1 (zfp-42), in renal cell carcinoma." *Carcinogenesis* **27**(3): 499-507.

The Rex-1 (Zfp-42) gene encodes a zinc finger family transcription factor which is highly expressed in mouse and human embryonic stem cells. It is one of several gene markers used to identify human stem cells. While several organs are known to harbor adult human stem cells, the presence and distribution of stem cells in both the normal and neoplastic adult kidney remains largely unknown. In this study we evaluated Rex-1 mRNA and protein expression in normal and malignant kidney tissue specimens from human patients. Rex-1 mRNA expression was determined using both reverse transcription and real-time PCR. REX1 protein expression was assessed by western analysis and immunohistochemistry, using an affinity-purified, polyclonal antibody to the REX1 protein. We found that 14 of 15 (93%) non-tumor renal parenchymal specimens demonstrated Rex-1 mRNA, compared with 5 of 14 (36%) renal tumors ($P < 0.005$). REX1 protein expression was detected in 21 of 23 (91%) non-tumor and in 7 of 19 (37%) tumor specimens ($P < 0.001$). Furthermore, in six of these seven renal tumor specimens where REX1 protein expression was detected, the levels were at least 3-fold lower than those in adjacent, normal kidney tissue. There were no differences in Rex-1 mRNA or protein expression among the various histologic subtypes of renal tumors

(clear cell carcinoma, papillary carcinoma, chromophobe carcinoma and oncocytoma). Immunohistochemical staining confirmed the absence of REX1 in three renal tumor specimens (two clear cell and one papillary carcinoma), while the REX1 protein was detected in a small percentage of proximal tubular cells in normal renal tissue. Immunohistochemical staining of another stem cell marker, OCT4, demonstrated a similar pattern of protein expression in a small percentage of normal renal proximal tubular cells. In summary, we were able to detect Rex-1 mRNA and protein expression in over 90% of normal renal parenchymal specimens and we observed a significant reduction in REX1 expression in renal tumor specimens of all histologic subtypes.

Rini, B. I., S. Halabi, et al. (2006). "Adoptive immunotherapy by allogeneic stem cell transplantation for metastatic renal cell carcinoma: a CALGB intergroup phase II study." *Biol Blood Marrow Transplant* **12**(7): 778-85.

A graft-versus-tumor effect through nonmyeloablative allogeneic stem cell transplantation (N-SCT) in metastatic renal cell carcinoma (RCC) has been reported. An Intergroup phase II trial was undertaken to define further the feasibility, toxicity and efficacy of this approach in a multi-institutional setting. Patients with cytokine-refractory, metastatic RCC were treated with N-SCT. The conditioning regimen was fludarabine 30 mg . m(-2) . d(-1) on day (d) -7 through d -3 and cyclophosphamide 60 mg . kg(-1) . d(-1) on d -4 and d -3. Patients received 2-8 x 10(6) CD34+ cells/kg of granulocyte colony-stimulating factor mobilized stem cells from a 6/6 HLA-matched sibling donor. Immunosuppression after transplantation included tacrolimus and methotrexate. Twenty-two patients were enrolled at 14 institutions. Greater than 90% donor T-cell chimerism was observed in 17 of 19 evaluable patients (89%) by d +120. No objective response was observed. Acute graft-versus-host disease (GVHD) was observed in 11 patients (50%). Chronic GVHD was reported in 5 patients (23%). There was 1 patient death from liver failure secondary to chronic GVHD. Regimen-related mortality was 2 of 22 (9%; liver failure, sepsis). Median survival time was 5.5 months (95% confidence interval, 3.9-12.0 months) and the median time to progression was 3.0 months (95% confidence interval, 2.3-4.2 months). N-SCT for metastatic RCC is feasible in a multi-institutional setting. Adequate donor T-cell engraftment was achieved in most patients before disease progression. A graft-versus-tumor effect was not observed in this study despite acute and chronic GVHD, thus highlighting the need

for further understanding of this approach. Allogeneic SCT remains investigational in RCC.

Rini, B. I., T. Zimmerman, et al. (2002). "Allogeneic stem-cell transplantation of renal cell cancer after nonmyeloablative chemotherapy: feasibility, engraftment, and clinical results." *J Clin Oncol* **20**(8): 2017-24.

PURPOSE: To evaluate the feasibility and safety of nonmyeloablative allogeneic stem-cell transplantation in patients with metastatic renal cell cancer (RCC) and to evaluate efficacy with respect to engraftment and tumor regression. **PATIENTS AND METHODS:** Between February 1999 and June 2001, patients with refractory, metastatic RCC were screened for enrollment. A fludarabine and cyclophosphamide-based conditioning regimen was used. Patients received granulocyte-macrophage colony-stimulating factor-mobilized, unmanipulated stem cells from a 6/6 HLA-matched sibling donor. Prophylaxis against graft rejection and graft-versus-host disease (GVHD) included tacrolimus and mycophenolate mofetil. **RESULTS:** A total of 284 patients with metastatic RCC were seen during this time period. Eighty-four patients who had siblings available for HLA typing were actively screened for enrollment, and 15 patients have undergone treatment. Durable donor engraftment was achieved in one of the first four patients treated. Patients no. 5 through 15 received a more immunosuppressive conditioning regimen, and all have achieved sustained donor engraftment. In the 12 patients with at least 180 days of follow-up, acute GVHD has occurred in two patients and chronic GVHD in six patients, with four transplant-related mortalities. Four partial responses have been observed (response rate, 33% in all patients; 44% in the nine patients with sustained donor engraftment). **CONCLUSION:** Nonmyeloablative allogeneic stem-cell transplantation is feasible for a minority of patients with metastatic RCC. Adequately immunosuppressive conditioning is required for sustained donor engraftment, which is required for an antitumor response. Acute and chronic GVHD are the major causes of substantial morbidity and mortality. Metastatic RCC is susceptible to a graft-versus-tumor effect promoted by allogeneic stem-cell transplantation.

Roessger, A., L. Denk, et al. (2009). "Potential of stem/progenitor cell cultures within polyester fleeces to regenerate renal tubules." *Biomaterials* **30**(22): 3723-32.

The cell biological mechanism controlling the regeneration of renal tubules in renal failure after application of stem/progenitor cells is subject of actual research. Unsolved issues are the integration of

stem/progenitor cells in a diseased organ environment, the differentiation into epithelial tissue and the formation of tubules in a spatial environment. Following this therapeutic strategy new biomaterials have to be found promoting spatial development of tubules. To obtain new information about the growth of tubules renal stem/progenitor cells from neonatal rabbit kidney were isolated and mounted in a tissue carrier between a selection of commercially available polyester fleeces. This procedure replaces coating by extracellular matrix proteins and creates an artificial interstitium supporting development of tubules. Perfusion culture was performed with chemically defined IMDM containing aldosterone as tubulogenic factor. Polyester fleeces were investigated by scanning electron microscopy. The spatial development of tubules was registered on whole-mount specimens and on cryosections labeled with SBA and antibodies indicating tubule differentiation. It is found that some polyester fleeces promote the spatial development of tubules between the fibers, whereat each of them produces its individual growth pattern.

Roigas, J., M. Johannsen, et al. (2006). "Allogeneic stem cell transplantation for patients with metastatic renal cell carcinoma." *Expert Rev Anticancer Ther* **6**(10): 1449-58.

Allogeneic stem cell transplantation and donor lymphocyte infusions are currently under clinical investigation as an innovative therapeutic option for patients with metastatic renal cell carcinoma. A variety of trials have proven the clinical efficacy of allogeneic stem cell transplantation using reduced-intensity conditioning protocols and donor lymphocyte infusions, as demonstrated by the induction of objective remissions in metastatic renal cell carcinoma patients. However, despite clinical remissions, reduced-intensity conditioning protocols and donor lymphocyte infusions were associated with a high treatment-related mortality rate of approximately 17%. The disproportion between clinical efficacy and treatment-related mortality may mainly be caused by the selection of patients that had often been heavily pretreated, with a large tumor burden and rapidly progressing tumors. The improvement of efficacy with the preservation of a powerful graft-versus-tumor effect while reducing the toxicity, is the major experimental and clinical challenge of allogeneic stem cell transplantation in the treatment of metastatic renal cancer and other solid tumors. Recently, there has been a revolutionary development of molecular-targeted agents in metastatic renal cancer. These inhibitors of angiogenesis and signal-transduction pathways have demonstrated clinical efficacy and significant survival prolongation in the first- and second-line settings,

while causing moderate toxicity. Some of these agents have already been approved by the US FDA and will probably replace standard cytokines, such as interferon-alpha2 and interleukin-2, in metastatic renal cancer. In the context of these innovative clinical developments, allogeneic stem cell transplantation clearly has to be regarded an investigational clinical treatment approach. Therefore, patients should only be treated at centers that are experienced in clinical trials, and patient selection remains a critical factor for a successful transplant procedure.

Roigas, J. and G. Massenkeil (2005). "Nonmyeloablative allogeneic stem cell transplantation in metastatic renal cell carcinoma: a new therapeutic option or just a clinical experiment?" *World J Urol* **23**(3): 213-20.

Nonmyeloablative stem cell transplantation (NST) and donor lymphocyte infusions (DLI) are currently under clinical investigation as an innovative therapeutic option for patients with metastatic renal cell carcinoma (RCC). The underlying concept, adopted from patients with hematologic malignancies, aims at a reduction of conditioning toxicity and exploits the graft versus malignancy effect of donor T-lymphocytes after transplantation. Clinical data from more than 100 patients treated worldwide have been published so far. The data provide evidence that NST is feasible with a very low rate of engraftment failure. Objective remissions in these heterogeneous studies were observed in 23% of the patients overall. Remissions after NST developed only after complete engraftment of donor lymphoid cells had occurred. Objective responses were almost always accompanied by graft versus host disease (GvHD) after withdrawal of immunosuppression and/or DLI. GvHD and infections were the main contributors to a substantial transplant related morbidity and mortality, the major drawback of allogeneic stem cell transplantation. Therefore, clinical studies are necessary to further investigate and improve the selection of patients with metastatic RCC or other solid tumors for NST and to reduce post-transplant complications. This article reviews the results, side effects and potential future developments of NST in the treatment of solid tumors.

Romagnani, P., E. Lazzeri, et al. (2005). "Nephrotic syndrome and renal failure after allogeneic stem cell transplantation: novel molecular diagnostic tools for a challenging differential diagnosis." *Am J Kidney Dis* **46**(3): 550-6.

BACKGROUND: Sudden onset of nephrotic syndrome after allogeneic stem cell transplantation is rare and has been associated mostly with membranous glomerulonephritis related to chronic graft-versus-host disease (cGVHD). We report a case of nephrotic

syndrome and rapidly progressive renal failure occurring in a young woman 3 years after allogeneic stem cell transplantation from her HLA-identical brother. In the renal biopsy, a diffuse mononuclear cell infiltrate was observed. Furthermore, histological analysis, immunofluorescence, and electron microscopy of the kidney specimen defined the diagnosis as minimal change disease, a T-cell-mediated glomerulopathy associated with lymphoproliferative disorders, but that has never been described as an isolated manifestation of cGVHD. METHODS: The differential diagnosis was performed by using immunohistochemistry and laser capture microdissection combined with Taq-Man quantitative polymerase chain reaction. RESULTS: Infiltrating mononuclear cells in renal tissue consisted of T cells expressing DNA levels of a Y chromosome-specific gene quantitatively similar to those observed in a male subject, showing that these cells derived from the transplant donor and definitely excluding leukemia relapse. However, the large number of infiltrating T cells allowed the possibility that in this patient, minimal change disease could be related to an atypical form of GVHD. CONCLUSION: This is the first study to use molecular techniques to show the differential diagnosis of nephrotic syndrome after allogeneic stem cell transplantation. This novel method approach might represent a key tool to characterize kidney infiltrate after allogeneic stem cell transplantation.

Rzepecki, P., J. Zolnierek, et al. (2005). "Allogeneic non-myeloablative hematopoietic stem cell transplantation for treatment of metastatic renal cell carcinoma -- single center experience." *Neoplasma* 52(3): 238-42.

We evaluated the efficacy of allogeneic non-myeloablative stem cell transplantation (NST) in patients with metastatic renal cell carcinoma (RCC). A total of 5 patients received blood stem cells from HLA identical siblings. Conditioning consisted of: cyclophosphamide 60 mg/kg/d, days -7 to -6 and fludarabine 25 mg/m²/d for consecutive days [days -5, -4, -3, -2, -1]. The median CD34+ cell dose was 3.34 million/kg. Immunosuppression consisted of cyclosporine A and methotrexate. Among all, four patients achieved full donor chimerism with a median of 89 days. One patient rejected the graft and received the second transplantation. Grade II-III acute GVHD occurred in 3 patients. None of patients achieved complete or partial response and there were only two mixed responses. All patients died due to cancer progression. There were no transplant-related deaths. Summarising, NST regimen allows allogeneic engraftment with low treatment related mortality in this high-risk population of patients. Acute and

chronic GVHD are the major morbidities. Progression is common after NST in unselected patients with advanced RCC. However, regression of some metastases suggests that the graft versus tumor effect may occur after this type of treatment. At present such a procedure should be considered as an experimental approach.

Saarinen-Pihkala, U. M., S. Wikstrom, et al. (1998). "Maximal preservation of renal function in patients with bilateral Wilms' tumor: therapeutic strategy of late kidney-sparing surgery and replacement of radiotherapy by high-dose melphalan and stem cell rescue." *Bone Marrow Transplant* 22(1): 53-9.

In children with bilateral Wilms' tumor, the therapy should aim at maximal preservation of renal parenchyma and function. Local radiotherapy may give rise to second malignant neoplasms and may impair renal function. We present a therapeutic strategy without any irradiation. Three children were diagnosed with bilateral Wilms' tumor at ages from 6 months to 5 years. Each patient had a massive tumor with local stage III on one side; one had pulmonary metastases. The therapeutic strategy was first to obtain tissue for histology by percutaneous needle biopsy, to administer pre-operative chemotherapy until desired tumor shrinkage, and then to perform kidney-sparing resective surgery. After a period of conventional chemotherapy, the patients were consolidated with high-dose (HD) melphalan and ABMT. Renal parenchyma spared post-surgery (right/left) was 0%/70%, 60%/40% and 40%/60% of the original kidney volumes. The toxicity of the ABMT procedure was mild, the patients engrafted promptly, and were discharged on days +14 to +27. All patients survive disease-free, 3 years 4 months to 4 years 5 months post-transplant. Our program resulted in good preservation of renal parenchyma and normal function, and we consider the risk of this ABMT program smaller than the late consequences of local radiotherapy for children with bilateral Wilms' tumor. The therapeutic strategy described merits further evaluation.

San Miguel, J. F., J. J. Lahuerta, et al. (2000). "Are myeloma patients with renal failure candidates for autologous stem cell transplantation?" *Hematol J* 1(1): 28-36.

INTRODUCTION: Renal function is one of the most important prognostic factors in multiple myeloma (MM). Patients with renal failure are generally excluded from high dose therapy even though they display a poor prognosis with conventional chemotherapy schemes. The aim of this study was to analyze the outcome of MM patients with renal insufficiency undergoing autologous stem

cell transplantation (ASCT), including the evaluation of the quality of PB stem cell collections, kinetics of engraftment, transplant-related mortality, response to high dose chemotherapy and survival. **MATERIALS AND METHODS:** From a total of 566 valuable patients included in the MM Spanish ASCT registry, three groups of patients were defined: group BA, patients with abnormal renal function at diagnosis but normal at transplant (73 cases); group BB, patients with abnormal function both at diagnosis and at transplant (14 cases); and group AA (control group, 479 cases), patients who constantly had normal renal function. **RESULTS AND CONCLUSION:** Patients from groups BA and BB presented with a significantly higher number of adverse prognostic factors, reflecting that we were dealing with high tumor MM cases, as compared with patients from group AA. The number of mononuclear cells, CD34+ cells and CFU-GM cells collected in patients with non-reversible renal insufficiency was similar to those harvested in MM patients with normal renal function. Moreover, neutrophil and platelet engraftments were identical in patients with and without renal failure (days +11 and +12, respectively). By contrast, transplant-related mortality (TRM) was significantly higher in group BB patients (29%) than in groups BA (4.1%) and AA (3.3%). In multivariate analysis only three variables showed independent influence on TRM: poor performance status (ECOG 3), hemoglobin <9.5 g/dl and serum creatinine > or =5 mg/dl. The response to high dose therapy was independent of renal function. Interestingly, 43% of patients from group BB showed an improvement in renal function (creatinine < 2 mg/dl) after transplant. The three-year overall survival from transplantation was 56, 49 and 61% for the BB, BA and AA groups, respectively, with a statistically significant difference favoring group AA ($P < 0.01$). PFS did not differ significantly between the three groups of patients. In multivariate analysis the only unfavorable independent prognostic factors for overall survival were poor performance status either at diagnosis or at transplant, high beta(2)-microglobulin levels, and no response to transplant. According to these results, ASCT is an attractive alternative for MM patients with renal insufficiency, and it should not constitute a criterion for exclusion from transplant unless patients display poor performance status and very high creatinine levels (>5 mg/dl).

Schaer, J. C. and J. C. Reubi (1999). "High gastrin and cholecystokinin (CCK) gene expression in human neuronal, renal, and myogenic stem cell tumors: comparison with CCK-A and CCK-B receptor contents." *J Clin Endocrinol Metab* **84**(1): 233-9.

Gastrin and cholecystokinin (CCK) are two major regulatory peptides synthesized by human gut

and brain tissues as well as by selected tumors, in particular gastrin-producing neuroendocrine tumors. In the present study we have evaluated gastrin and CCK gene expression in a group of primary human tumors, including neuronal, renal, and myogenic stem cell tumors, using in situ hybridization techniques. In addition, CCK-A and CCK-B receptors were evaluated in the same group of tumors with receptor autoradiography. Most tumors had gastrin messenger ribonucleic acid (mRNA): 10 of 11 medulloblastomas, 5 of 5 central primitive neuroectodermal tumors, 11 of 11 Ewing sarcomas, 8 of 10 neuroblastomas, 4 of 4 Wilms' tumors, 5 of 5 rhabdomyosarcomas, and 10 of 10 leiomyosarcomas. CCK mRNA was restricted predominantly to Ewing sarcomas (9 of 11) and leiomyosarcomas (5 of 10). CCK-A and CCK-B receptors were not frequently found in these tumors, except for leiomyosarcomas. These data suggest that gastrin and CCK may play a previously unrecognized role in this group of human stem cell tumors. If the increased gastrin mRNA indeed translates into increased gastrin production, measurement of gastrinemia may have a diagnostic significance in the early detection of these tumors. As these two hormones have been reported to act as potent growth factors, they may be of pathophysiological relevance for patients with such stem cell tumors.

Shaughnessy, P., W. Alexander, et al. (2006). "Phase I and pharmacokinetic study of once-daily dosing of intravenously administered busulfan in the setting of a reduced-intensity preparative regimen and allogeneic hematopoietic stem cell transplantation as immunotherapy for renal cell carcinoma." *Mil Med* **171**(2): 161-5.

We performed a Phase I and pharmacokinetic study of once-daily, intravenously administered busulfan in the setting of a reduced-intensity preparative regimen and matched sibling donor allogeneic stem cell transplantation for treatment of metastatic renal cell carcinoma. Seven male patients with metastatic renal cell carcinoma received intravenously administered busulfan at 3.2 mg/kg once daily on day -10 and day -9, fludarabine at 30 mg/m² on day -7 through day -2, and equine antithymocyte globulin at 15 mg/kg per day on day -5 through day -2. The mean area under the plasma concentration-time curve (AUC) and the half-life of the first dose of intravenously administered busulfan were 6,253 microM x minute (range, 5,036-7,482 microM x minute) and 3.37 hours (range, 2.54-4.00 hours), respectively. The AUC was higher than predicted from extrapolation of AUC data for the same total dose of intravenously administered busulfan divided into four doses daily. Patients experienced greater than expected regimen-related

toxicity for a reduced-intensity preparative regimen, and the study was stopped. In conclusion, this preparative regimen was associated with unacceptable regimen-related toxicity among patients with metastatic renal cell carcinoma.

Shimony, N., I. Avrahami, et al. (2008). "A 3D rotary renal and mesenchymal stem cell culture model unveils cell death mechanisms induced by matrix deficiency and low shear stress." Nephrol Dial Transplant **23**(6): 2071-80.

BACKGROUND: In epithelial and endothelial cells, detachment from the matrix results in anoikis, a form of apoptosis, whereas stromal and cancer cells are often anchorage independent. The classical anoikis model is based on static 3D epithelial cell culture conditions (STCK). **METHODS:** We characterized a new model of renal, stromal and mesenchymal stem cell (MSC) matrix deprivation, based on slow rotation cell culture conditions (ROCK). This model induces anoikis using a low shear stress, laminar flow. The mechanism of cell death was determined via FACS (fluorescence-activated cell sorting) analysis for annexin V and propidium iodide uptake and via DNA laddering. **RESULTS:** While only renal epithelial cells progressively died in STCK, the ROCK model could induce apoptosis in stromal and transformed cells; cell survival decreased in ROCK versus STCK to 40%, 52%, 62% and 7% in human fibroblast, rat MSC, renal cell carcinoma (RCC) and human melanoma cell lines, respectively. Furthermore, while ROCK induced primarily apoptosis in renal epithelial cells, necrosis was more prevalent in transformed and cancer cells [necrosis/apoptosis ratio of 72.7% in CaKi-1 RCC cells versus 4.3% in MDCK (Madin-Darby canine kidney) cells]. The ROCK-mediated shift to necrosis in RCC cells was further accentuated 3.4-fold by H₂O₂-mediated oxidative stress while in adherent HK-2 renal epithelial cells, oxidative stress enhanced apoptosis. ROCK conditions could also unveil a similar pattern in the LZ100 rat MSC line where in ROCK 44% less apoptosis was observed versus STCK and 45% less apoptosis versus monolayer conditions. Apoptosis in response to oxidative stress was also attenuated in the rat MSC line in ROCK, thereby highlighting rat MSC transformation. **CONCLUSIONS:** The ROCK matrix-deficiency cell culture model may provide a valuable insight into the mechanism of renal and MSC cell death in response to matrix deprivation.

Stephens, E., I. Bolderson, et al. (2006). "The measurement of whole blood pre-treatment cyclosporine A: metabolite ratios predicts the onset of

renal dysfunction in recipients of allogeneic stem cell transplantation." Ann Clin Biochem **43**(Pt 5): 382-8.

BACKGROUND: In the context of post-transplant immunosuppression, cyclosporine A (CSA) is dose adjusted in accordance with whole blood drug monitoring. While currently available immunoassay systems primarily target the parent drug, cross-reactivity results in the detection of the major circulating CSA metabolites, though their contribution to both immunosuppression and toxicity remain unclear. This study examines the relationship of CSA metabolites to hepatic and renal dysfunction and the incidence of graft-versus-host disease (GvHD) through parallel assaying of parent drug and drug/metabolites expressed as a metabolite ratio (Cp:mR). **METHOD:** Sequential pre-treatment (trough) whole blood samples (n=527) were collected from 31 allo-stem cell transplantation (SCT) recipients. Both parent drug and drug/metabolite levels were determined using the Abbott fluorescence polarization immunoassay. **RESULTS:** The average mean Cp:mR was significantly higher in patients with hepatic (P=0.004) and renal dysfunction (P=0.004) than in those without. Significantly higher Cp:mR were also found in patients with grades II-IV GvHD (P=0.001) than were observed in patients who did not experience significant GvHD. When measured prospectively, an increasing Cp:mR predated the rise in serum creatinine concentration by a median of two weeks. **CONCLUSIONS:** This study demonstrates a clinically useful CSA metabolite ratio that shows association with hepatic and renal dysfunction and with GvHD. The measure can be used to predict those patients on CSA therapy who are likely to develop renal dysfunction.

Stokman, G., J. C. Leemans, et al. (2005). "Hematopoietic stem cell mobilization therapy accelerates recovery of renal function independent of stem cell contribution." J Am Soc Nephrol **16**(6): 1684-92.

Acute renal failure and tubular cell loss as a result of ischemia constitute major challenges in renal pathophysiology. Increasing evidence suggests important roles for bone marrow stem cells in the regeneration of renal tissue after injury. This study investigated whether the enhanced availability of hematopoietic stem cells, induced by stem cell factor and granulocyte colony-stimulating factor, to the injured kidney provides an adequate strategy for stem cell-based therapy to counteract renal ischemia/reperfusion injury. It is interesting that cytokine treatment before injury resulted in significant enhancement of function recovery of the kidney. This, however, was not due to increased incorporation of tubular epithelial cells from bone marrow origin.

Importantly, cytokine treatment resulted in impaired influx of granulocytes into the injured kidney. Although cytokine treatment improved renal function rapidly after ischemic injury, the results show that the underlying mechanism likely is not based on stem cell transdifferentiation but rather on altered inflammatory kinetics.

Sumboonnanonda, A., K. Sanpakit, et al. (2009). "Renal tubule function in beta-thalassemia after hematopoietic stem cell transplantation." *Pediatr Nephrol* **24**(1): 183-7.

Advances in hematopoietic stem cell transplantation (HSCT) for beta-thalassemia major make the long-term outcome of these patients very important. Few data on long-term renal function of thalassemia patients are available. We evaluated the renal function in children after successful allogeneic HSCT for beta-thalassemia. Twenty-nine patients were included; the mean age at HSCT was 4.9 years. Mean follow-up time was 7.6 years. After HSCT, two patients developed acute renal failure and two had graft versus host disease. At last follow up, height standard deviation score (SDS) remained the same, but weight SDS had improved. Mean hemoglobin was 12.5 g/dl, and serum ferritin level was 545 ng/ml. All children had normal estimated glomerular filtration rate (GFR). One patient had hypertension and proteinuria, 10 years after HSCT. When comparing 39 children of the same age with beta-thalassemia of similar disease severity but who had not experienced HSCT, we found that the parameters of renal tubule function were better in patients that had undergone HSCT, as demonstrated by urine protein level (0.36 mg/mg creatinine vs 3.03 mg/mg creatinine, $P < 0.001$), osmolality (712 mosmol/kg vs 573 mosmol/kg, $P = 0.006$), N-acetyl-beta-D: -glucosaminidase (17.7 U/g creatinine vs 42.9 U/g creatinine, $P = 0.045$), and beta 2 microglobulin (0.09 microg/mg creatinine vs 0.13 microg/mg creatinine, $P = 0.029$). This study showed a low incidence of long-term renal impairment after HSCT and indicated that renal tubule function may be better in beta-thalassemia patients after HSCT.

Tichelli, A., A. Roivo, et al. (2008). "Late pulmonary, cardiovascular, and renal complications after hematopoietic stem cell transplantation and recommended screening practices." *Hematology Am Soc Hematol Educ Program*: 125-33.

Non-malignant late effects after hematopoietic stem cell transplantation (HSCT) are heterogeneous in nature and intensity. The type and severity of the late complications depend on the type of transplantation and the conditioning regimen applied. Based on the most recent knowledge, we

discuss three typical non-malignant complications in long-term survivors after HSCT, namely pulmonary, cardiovascular and renal complications. These complications illustrate perfectly the great diversity in respect of frequency, time of appearance, risk factors, and outcome. Respiratory tract complications are frequent, appear usually within the first two years, are closely related to chronic graft-versus-host disease (GVHD) and are often of poor prognosis. Cardiac and cardiovascular complications are mainly related to cardiotoxic chemotherapy and total body irradiation, and to the increase of cardiovascular risk factors. They appear very late after HSCT, with a low magnitude of risk during the first decade. However, their incidence might increase significantly with longer follow-up. The chronic kidney diseases are usually asymptomatic until end stage disease, occur within the first decade after HSCT, and are mainly related with the use of nephrotoxic drugs such as calcineurin inhibitors. We will discuss the practical screening recommendations that could assist practitioner in the follow-up of long-term survivors after HSCT.

Togel, F., J. Isaac, et al. (2004). "Hematopoietic stem cell mobilization-associated granulocytosis severely worsens acute renal failure." *J Am Soc Nephrol* **15**(5): 1261-7.

Acute renal failure (ARF), resulting from ischemic or toxic insults, remains a major health care problem because of its grave prognosis and the limited effectiveness of available treatment modalities. On the basis of the recent demonstration that hematopoietic stem cells can differentiate into renal cells and the authors' observation here that ARF results in a rise in peripheral CD34+ cells, the authors tested whether a further increase in circulating stem cell numbers, induced by their mobilization from the bone marrow, would improve renal function and outcome in mice with ischemic ARF. Unexpectedly, it was found that the boosting of peripheral stem cell numbers failed to exert any renoprotective effects but rather was associated both with greatly increased severity of renal failure and mortality. Because identical ischemic injury in neutropenic mice resulted in milder renal insufficiency and significantly reduced mortality, it was deduced that the adverse effects of pharmacologic stem cell mobilization are primarily mediated by the concomitant induction of marked granulocytosis. In this manner, high numbers of activated granulocytes seem to obscure the potential renoprotective and positive survival effects of pluripotent hematopoietic stem cells, mediated by both their injurious renal and systemic actions. The data strongly argue against the clinical use of granulocytosis-inducing hematopoietic stem cell mobilization protocols for the prevention or treatment of ischemic ARF. Additional caution with

this regimen may be warranted in patients with underlying renal insufficiency and those who develop renal insufficiency while undergoing stem cell mobilization in preparation for an autologous bone marrow transplant.

Tosi, P., E. Zamagni, et al. (2000). "Safety of autologous hematopoietic stem cell transplantation in patients with multiple myeloma and chronic renal failure." *Leukemia* **14**(7): 1310-3.

Patients with multiple myeloma (MM) and chronic renal failure have generally been excluded from myeloablative therapy programs followed by hematopoietic stem cell support because of the potential increase in transplant-related morbidity and mortality. We here report our experience treating six MM patients with moderate to severe renal insufficiency, with autologous stem cell transplantation. One of these patients required chronic hemodialysis since the diagnosis of MM was made. Peripheral blood stem cell collection was performed with either cyclophosphamide 5.5-7 g/m² + G-CSF, 5 microg/kg/day (patients 1-3, 5 and 6) or G-CSF, 15 microg/kg/day alone (patient No. 4). Four patients (Nos 1-4) received autotransplant as front-line therapy, while the last two patients were treated in relapse, which occurred following prior autologous stem cell transplantation in support of melphalan, 200 mg/m² (No. 5) or maintenance therapy with alpha-interferon (No. 6). High-dose chemotherapy administered as preparation to transplant included busulfan 12 mg/kg + melphalan 80 mg/m² (patients 1-3 and 6) or melphalan 80 mg/m² alone (patients 4 and 5) in order to reduce mucosal damage. Following transplant, prompt and sustained recovery of hematopoiesis was documented in all the patients; 500 PMN/microI and 20000 platelets/microI were reached after a median of 13 and 14 days, respectively. None of the patients suffered from WHO grade 3-4 infectious complications. Transplant-related toxicity included grade 3-4 oral mucositis (patients 1, 4 and 5) and veno-occlusive disease (patient No. 3). Renal function either improved or remained stable throughout the transplant period. All the patients but one responded to therapy, three of them are progression free after 2, 15 and 26 months; two relapsed after 16 and 4 months and one died from cholangiocarcinoma 7 months after transplant, while still in remission. Although our experience is limited so far, these results appear promising and support the investigational use of myeloablative therapy in MM patients with chronic renal failure.

Trivedi, H. L., V. V. Mishra, et al. (2006). "Embryonic stem cell derived and adult hematopoietic stem cell transplantation for tolerance induction in a

renal allograft recipient:--a case report." *Transplant Proc* **38**(9): 3103-8.

We generated a human embryonic stem cell (hESC) line to augment chimerism-associated tolerance. A 40-year-old African with chronic glomerulonephritis-chronic renal failure with 100% G6PD enzyme deficiency presented for renal transplantation with a 27-year-old, 6/6 HLA-matched sister as a willing donor. METHOD: We generated an hESC line from the donor's oocytes using long ovarian stimulation protocol simultaneously with tolerance induction protocol. A nuclear transfer (NT)-hESC line was derived by transferring a donor cumulus cell into an enucleated oocyte, subjected to electrical fusion, and cultured for 5 days. ESCs hatched from the blastocyst on day 6 were cocultured with her unmodified bone marrow for 2 days and suspended in Ringer's lactate. Five milliliters of suspension were collected for cell counting, viability, pluripotency, flow cytometry, and karyotyping. The remaining suspension was infused into the periphery of the recipient. Transplantation was performed 1 week later following a negative lymphocytotoxicity cross-match test using no immunosuppression. Peripheral blood chimerism (PBC) was studied using fluorescent in situ hybridization technique. Allograft biopsy was performed on day 7. RESULTS: NT-hESC CD34+ count was 7.6%, viability 100%, karyotyping normal, pluripotency markers: SSEA-1, SSEA-4, OCT-3/4, TRA-1/60:positive; 12% PBC was noted at 1 week after transplantation. Serum creatinine was 1.2 mg%, graft biopsy was unremarkable, and G6PD enzyme deficiency was corrected to 0% at 100 days posttransplant. Liver function tests and hematology profile were unremarkable for graft-versus-host disease. CONCLUSION: This is the first report of tolerance induction using NT-hESC-induced hematopoietic chimerism with synergistic use of adult bone marrow. It was safe and effective.

Trivedi, H. L., V. R. Shah, et al. (2002). "High-dose peripheral blood stem cell infusion: a strategy to induce donor-specific hyporesponsiveness to allografts in pediatric renal transplant recipients." *Pediatr Transplant* **6**(1): 63-8.

We designed and implemented a clinical trial to achieve zero-rejection status in pediatric renal allograft recipients, using granulocyte-macrophage colony-stimulating factor (GM-CSF)-stimulated peripheral blood stem cell (PBSC) infusion. We studied 44 consecutive patients: 24 volunteers in a treated group (Tn) and 20 in a control group (Cn). Both groups were comparable with respect to clinical and laboratory parameters. The Tn group had 70.8% one haplo-match donors and the Cn group had 80% one haplo-match donors. Patients in the Tn group

received cyclosporin A (CsA) and 0.4 mg/kg body weight prednisolone as immunosuppressants; azathioprine was added for patients of the Cn group, who received 1 mg/kg body weight prednisolone together with CsA. Living-related donors (LRD) of patients in the Tn group received GM-CSF 450 microg on four consecutive days followed by leucopheresis and immediate transfusion of unmodified PBSC into the recipient. This procedure was repeated once/twice, with one portal and one/two systemic infusions. Our aim was to maximize the dose of PBSC. The total average dose was 22×10^8 cells/kg body weight. Lymphocyte cross-match (LCM) was performed before GM-CSF injection and after the last PBSC infusion. Follow-up over an 18-month period revealed 100% graft survival with sustained low serum creatinine (SCr) values in patients of the Tn group as compared with 80% graft survival in patients of the control group who had marginally higher SCr levels. Absence of graft vs. host disease (GvHD), acute rejection episodes, and low incidence of cytomegalovirus (CMV) disease were the principal benefits of this protocol.

Trivedi, H. L., A. V. Vanikar, et al. (2005). "Allogeneic hematopoietic stem-cell transplantation, mixed chimerism, and tolerance in living related donor renal allograft recipients." *Transplant Proc* 37(2): 737-42.

OBJECTIVE: We designed a prospective, randomized, and controlled clinical trial to evaluate the efficacy and safety of achieving a mixed chimerism-associated tolerance protocol for recipients of living related donor (LRD) renal allografts. **PATIENTS AND METHODS:** Sixty-six consecutive patients were divided into two equal groups of 33 patients with end-stage renal disease. They were enrolled for transplantation after negative lymphocytotoxicity cross-matching (LCM). Both groups (treated [Tn] and control [Cn]) showed similar clinical and laboratory parameters and donor HLA match profiles. The Tn group underwent thymic transplantation of donor renal tissue, two donor-specific transfusions, low-intensity conditioning, and high-dose hematopoietic stem-cell transplantation (HSCT) before renal transplantation. The conditioning regimen included low-dose, target-specific irradiation (to abdominal and inguinal lymph nodes, bone marrow [BM] from thoracolumbar vertebrae and part of the pelvis on alternate days, 100 rad x 4), anti-T-cell antibodies (1.5 mg/kg body weight [BW]), cyclophosphamide (10 mg/kg BW x 2 consecutive days), and cyclosporine (CyA; >3 mg/kg BW/d). Unfractionated HSCT procured from the donor marrow was administered into the BM, portal and peripheral circulations, within 24 hours of achieving

CD 4+/CD 8+ T-cell count less than 10% of normal. This infusion was supplemented with a dose of peripherally mobilized stem cells (mean total dose of 20×10^8 cells/kg recipient BW) administered peripherally. Renal transplantation was performed after negative LCM. Donor-specific cytotoxic antibodies were eliminated with intravenous immunoglobulins and plasmapheresis before renal transplantation. Mixed chimerism was evaluated before and after transplantation at monthly intervals in patients with donors of opposite gender by the FISH technique. Both groups received CyA and prednisolone for immunosuppression; Cn subjects also received mycophenolate mofetil/azathioprine. Rejection was treated with standard treatment. Immunosuppression was withdrawn 6 months after renal transplantation for patients with consistently positive chimerism. Clinical tolerance was defined as stable allograft function for more than 100 days without immunosuppression and confirmed by allograft biopsy. **RESULTS:** Over a mean follow-up of 210 days, all Tn patients showed stable allograft function with mean serum creatinines (SCr) of 1.20 mg/dL, no rejection/CMV infections/graft or patient loss. A low-level donor-specific cytotoxic antibody was observed in all Tn patients. The CyA toxicity was noted in 10 (30.3%) patients. Persistent mixed hematopoietic chimerism was seen in all 21 patients irrespective of donor-recipient HLA matching (mean 0.5% before and $1 \pm 0.3\%$ after transplantation). All four patients on drug withdrawal have shown donor-specific tolerance at a mean follow-up of 129.8 days. Other Tn patients are in the process of being weaned off immunosuppression. Mean SCr of controls was 1.45 mg/dL over a mean follow-up of 216 days. Acute rejection was observed in 17 (51.5%) patients; no CMV infection/patient loss was noted and one (3.03%) graft was lost in controls. No patient was lost in controls. No graft-versus-host disease was observed in Tn patients. **CONCLUSION:** We have achieved mixed hematopoietic chimerism-associated tolerance with high-dose HSCT, intrathymic donor renal tissue transplantation, and minimal conditioning without any adverse effects.

Trivedi, H. L., A. V. Vanikar, et al. (2004). "A strategy to achieve donor-specific hyporesponsiveness in cadaver renal allograft recipients by donor haematopoietic stem cell transplantation into the thymus and periphery." *Nephrol Dial Transplant* 19(9): 2374-7.

INTRODUCTION: We designed a prospective, randomized clinical trial to evaluate the immune response to thymic and peripheral infusions of donor haematopoietic stem cells (HSCs) to create tolerance in recipients of cadaver renal allografts.

METHOD: We divided 24 patients into two equal groups. For group A, 350 ml of unfractionated bone marrow (BM) was aspirated from the anterior iliac crests of donor cadavers. A 2 ml aliquot of concentrated marrow was infused into the thymus of the subject and 100 ml into the BM before surgery; the remaining 250 ml was infused peripherally post-transplantation. The mean nucleated cell count inoculated into the thymus was 3.3×10^4 cells/cm³ and into the periphery 8.6×10^7 cells/kg body weight. Group B (controls) underwent renal transplantation directly. Recipients were lymphocytotoxicity cross-match negative in both groups. Group A received low dose prednisolone and cyclosporin; controls also received azathioprine. **RESULTS:** Over a mean follow-up of 703 days for both groups, group A had significantly better graft function with minimum acute rejection episodes or cytomegalovirus (CMV) infections, a mean serum creatinine (SCr) of 1.23 mg/dl and no graft or patient loss. Group B, with a mean SCr of 2.19 mg/dl had three patients with single acute rejection episodes, two of whom died following uncontrolled rejection-associated infections. The third patient maintained an SCr of 2.5 mg%. Actuarial graft survival was 87.5% in controls at the end of 2 years compared with group A with 100% graft survival at the end of 2 years. **CONCLUSION:** This novel approach of introducing unfractionated HSCs into the thymus and periphery to create tolerance is safe and efficacious and gives significantly better graft function, minimum acute rejection and no CMV disease with monotherapy.

Vigneau, C., K. Polgar, et al. (2007). "Mouse embryonic stem cell-derived embryoid bodies generate progenitors that integrate long term into renal proximal tubules in vivo." *J Am Soc Nephrol* **18**(6): 1709-20.

The metanephric kidney is a mesodermal organ that develops as a result of reciprocal interactions between the ureteric bud and the blastema. The generation of embryonic stem (ES) cell-derived progenitors offers potential for regenerative therapies but is often limited by development of tumor formation. Because brachyury (T) denotes mesoderm specification, a mouse ES cell line with green fluorescence protein (GFP) knocked into the functional T locus as well as lacZ in the ROSA26 locus (LacZ/T/GFP) was used in cell selection and lineage tracing. In the absence of leukemia inhibitory factor, mouse ES cells give rise to embryoid bodies that can differentiate into mesoderm. Culture conditions were optimized (4 d, 10 ng/ml Activin-A) to generate maximal numbers of renal progenitor populations identified by expression of the specific combination of renal markers cadherin-11, WT-1,

Pax-2, and Wnt-4. LacZ/T/GFP+ cells were further enriched by FACS selection. Five days after injection of LacZ/T/GFP+ cells into embryonic kidney explants in organ culture, beta-galactosidase immunohistochemistry showed incorporation into blastemal cells of the nephrogenic zone. After a single injection into developing live newborn mouse kidneys, co-localization studies showed that the LacZ/T/GFP+ cells were stably integrated into proximal tubules with normal morphology and normal polarization of alkaline phosphatase and aquaporin-1 for 7 mo, without teratoma formation. It is concluded that defined differentiation of ES cells into embryoid bodies with Activin-A and selection for T expression provides a means to isolate and purify renal proximal tubular progenitor cells with the potential for safe use in regenerative therapies.

Yokoo, T., K. Sakurai, et al. (2003). "Stem cell gene therapy for chronic renal failure." *Curr Gene Ther* **3**(5): 387-94.

Recently, stem cell research has attracted considerable attention because it could be used for the regeneration of damaged organs that are untreatable by conventional techniques, and several stem cells (or progenitor cells), such as endothelial stem cells and neural stem cells have been discovered. Following the progression of this field of research, the potential for stem cell gene therapy has increased and several therapeutic benefits have already been reported. Although this approach was originally investigated for fatal or hereditary diseases, chronic renal failure is also a candidate for stem cell gene therapy. We have proposed two different therapeutic strategies for chronic renal failure depending on whether the bone marrow stem cells differentiate and commit into mesenchymal or hematopoietic stem cells. In the case of diseases, which need reconstitution of residential renal cells, such as congenital enzyme deficiency diseases, mesenchymal stem cells should be transplanted, and in contrast, hematopoietic stem cells may be used for gene delivery for diseases, which need foreign cytokines and growth factors, such as glomerulonephritis. This article reviews the recent investigation on this tailor-made stem cell gene therapy for chronic renal failure and discusses the potential of this novel strategy and the major practical challenges of its clinical application.

Yun, T., K. W. Lee, et al. (2007). "Non-myeloablative allogeneic stem cell transplantation for metastatic renal cell carcinoma." *Clin Transplant* **21**(3): 337-43.

Between 1999 and 2004, 11 patients with metastatic renal cell carcinoma (RCC) underwent non-myeloablative stem cell transplantation (NST) with conditioning using fludarabine-based regimens in two

institutions of Korea. Among 11 patients, only one patient showed partial response (response rate: 9%), three showed stable disease, and six progressive disease. Three patients developed acute graft-versus-host disease (GVHD), and among them, one developed grade III acute GVHD which caused early death at day 60 after transplantation, and this patient showed partial response at day 30. Six patients developed chronic GVHD, three limited, and three extensive GVHD, respectively. Survival after one yr was 18% in transplanted patients. Median overall survival for entire cohort was 4.3 months. Eight patients died from progressive disease and three (27%) from treatment-related mortality. Only one patient survived 51.2 months after NST with slowly progressive disease. This patient received donor lymphocyte infusion three times after NST and achieved complete donor chimerism. NST does not lead to durable response and prolonged overall survival in the majority of patients with RCC in our series.

Zeier, M., J. Perz, et al. (2003). "No regression of renal AL amyloid in monoclonal gammopathy after successful autologous blood stem cell transplantation and significant clinical improvement." Nephrol Dial Transplant **18**(12): 2644-7.

BACKGROUND: High-dose chemotherapy followed by autologous blood stem cell transplantation induces remission of plasma cell dyscrasia in patients with AL amyloidosis. The impact of this treatment on the glomerular amyloid mass is still unknown. **METHODS:** In the present study, the quantity of the renal amyloid mass before and more than 3 years after high-dose melphalan treatment and autologous blood stem cell transplantation was assessed in two patients. At the time of the second renal biopsy, both patients were in complete remission without detectable serum and urinary monoclonal IgA-lambda and a normal percentage of plasma cells in the bone marrow. **RESULTS:** In both patients with biopsy-proven AL amyloidosis, urinary protein excretion decreased from 7 g/24 h to <2 g/24 h more than 3 years after autologous blood stem cell transplantation. In contrast, glomerular amyloid deposits persisted, as shown in the second biopsy. **CONCLUSION:** Despite complete remission of the plasma cell dyscrasia and improvement of glomerular permeability, the amount of glomerular amyloid mass did not regress.

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