general health care access. This may address racial disparities in incidence of ESRD, as well as risk factors such as hypertension and diabetes that rely on adequate health care management and control to prevent disease progression.18

Finally, future research should consider other minority populations as well. Recent data show the Hispanic population in the United States experiences higher incidence rates of ESRD and a faster progression from chronic kidney disease to ESRD compared with non-Hispanic white individuals.19 Most studies on racial disparities, however, do not include Hispanic participants. This signifies a growing need to include the Hispanic population in future studies on racial or ethnic disparities in kidney disease.

DISCLOSURES
None.

REFERENCES


See related article, “Racial Composition of Residential Areas Associates with Access to Pre-ESRD Nephrology Care,” on pages 1192–1199.

Stem Cell Therapy for the Kidney: A Cautionary Tale

Andras Nagy† and Susan E. Quaggin‡§
†Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada; and Departments of ‡Molecular Genetics and §Medicine, and Division of Nephrology, St. Michael’s Hospital, University of Toronto, Toronto, Ontario, Canada


Over the past few years, tremendous advances have occurred in stem cell biology. With the development of induced pluripotent stem cell technology, it is now possible to reprogram adult cells to differentiate into multiple cell types, including renal cells.1 Although induced pluripotent stem cells hold great promise for treatment of chronic diseases such as kidney failure in the future, current therapies are limited to readily available endogenous progenitor cell populations that can be isolated or mobilized from the bone marrow. These include hematopoietic stem cells (HSCs), mesenchymal stem cells, and endothelial progenitor cells, collectively known as bone marrow–derived cells (BMDCs).

Therapies to enhance mobilization of endogenous BMDCs or infusions of BMDCs have been used in preclinical models of renal disease that include ischemia-reperfusion injury, the
Thy1.1 model of mesangial proliferative glomerulonephritis, renovascular disease, and Alport syndrome, to name a few. Improved renal outcomes were reported in a number of these studies, although it is debated whether this is the result of cytokines or secreted factors produced by the BMDCs or the consequence of transdifferentiation of BMDCs into specific renal cell types. In regard to the latter, studies suggested variable abilities of these cells to transdifferentiate into renal endothelial, tubular, and glomerular epithelial cell lineages. Although it is not uniformly accepted that true transdifferentiation from BMDCs occurs, most agree that if it does occur, then it contributes only a small proportion of cells to the kidney. In the renal clinical setting, the majority of stem cell–based therapies to date have been limited to autologous hematopoietic peripheral stem cell transplantation to treat lupus nephritis.

In this issue of JASN, Thirabanjasak et al. report the development of angiomyloloproliferative lesions after direct injection of autologous stem cells into the renal parenchyma of a patient with lupus nephritis. The time course, multifocal nature of the lesions, and the identification of both myeloproliferative and angioproliferative components provide strong circumstantial evidence that the tumor lesion arose from injected stem cells.

Autologous or allogeneic stem cell transplants have been used since the 1990s for treatment of severe, disabling autoimmune diseases, including lupus. The goal of therapy is to deplete autoreactive T lymphocytes using immunosuppressive therapy and provide nonreactive T lymphocyte progenitors from infused HSCs. The procedure involves mobilization and collection of CD34+ HSCs (CD34+ identifies multipotential HSCs with the ability to differentiate into myeloid, endothelial, and hematopoietic cell lineages) through the use of combined cyclophosphamide and G-CSF. The patient is then conditioned with high-dose immunosuppressive therapy followed by infusion of the collected CD34+ autologous HSCs. Bone marrow reconstitution occurs from the HSCs. Small case series and studies offer promising results, with long-term remission of active lupus nephritis in some cases and loss of antiphospholipid antibodies in others.

A larger, retrospective study reported by the European Group for Blood and Marrow Transplantation and the European League against Rheumatism confirmed benefit in lupus nephritis but reported a treatment-associated 1-year mortality of 12% and a relapse rate of 32%. Thus, the risks associated with autologous transplantation in patients with lupus are similar to that for patients with cancer, and performance of this therapy is restricted to refractory cases in centers with expertise.

In the case reported here, CD34+ cells were mobilized, expanded, and collected after administration of G-CSF to the patient, but instead of peripheral infusion of the cells, they were injected directly into the renal parenchyma in multiple blind passes. One of the hurdles in developing stem cell–based therapies for patients with renal disease is the structural complexity of the mature kidney and that renal development does not occur postnataally. It is not clear why the CD34+ cells were injected locally in this case, because there are no experimental data or clinical experience to support this mode of delivery, and it is inconceivable that they would integrate into a kidney with end-stage disease.

After the injection, the course of the patient’s renal failure was not altered, and within 3 months, the patient required initiation of dialysis. Shortly thereafter, a mass was identified in the kidney into which the cells had been injected, and nephrectomy was performed for suspected transitional cell carcinoma. Pathologic analysis revealed angiomyloloproliferative lesions composed of cells from both myeloid and hematopoietic lineages. Cells were actively cycling and expressed increased levels of vascular endothelial growth factor, a known mitogen for development of similar lesions in other circumstances. The malignant potential of this lesion is not known, although the presence of an adrenal and a liver mass is suggestive of metastasis.

What can we learn from this case report? Although the mode of stem cell–based treatment in this patient is not an established therapy, it underscores a growing risk associated with the proliferation of private clinics that offer stem cell therapies to patients with little or no oversight from the scientific stem cell community. Internationally, hundreds of free-standing stem cell clinics are offering stem cell transplantation to patients without providing any guidance from safety or efficacy studies. The International Society of Stem Cell Research set up a professional guideline for clinics providing unproven stem cell–based therapies. This guideline requests a written plan for the procedure that includes the scientific rationale and any preclinical evidence of proof of principle for efficacy and safety, a full characterization of the types of cells being transplanted and how they will be administered, clinical and administrative leadership support for the clinical experiment, voluntary informed consent for patients, an action plan for adverse events, insurance coverage or other financial resources to cover complications, submission of systematic and objective tracking of outcomes to the scientific community for critical review, and a timely move to a formal clinical trial after experience with a very small number of patients.

Unfortunately, this request is not without foundation. There are a few other documented case reports of tumors after injection of a variety of other stem cells. For example, a 9-year-old boy with ataxia telangiectasia underwent fetal neural stem cell injection into the brain in Russia. Four years later, the boy received a diagnosis of a slow-growing form of cancer called glioneural neoplasm in a medical center outside Tel Aviv. Similar to the tumor described in the article by Thirabanjasak et al., multiple cell types were identified, suggesting that it arose from a stem cell or multipotent progenitor. Genetic analysis confirmed that the tumor arose from transplanted cells that carried the wild-type allele for ataxia telangiectasia.

Despite the incredible advances that have been made in stem cell biology, this report in JASN provides a cautionary note. Premature enthusiasm and protocols that are not fully vetted are dangerous and result in negative publicity for the field of stem cell research and, more important, may result in disastrous outcomes with no benefit to the patient. As Thirabanjasak et al.,
did, it is important for physicians who take care of patients who have developed complications to alert the public and clinical community by reporting these cases. Although there is promise, a large gap still exists between scientific knowledge and clinical translation for safe and effective stem cell–based therapies.

DISCLOSURES
None.

REFERENCES