Cell Stem Cell
Forum

Hematopoietic Stem Cell Transplantation and Implications for Cell Therapy Reimbursement

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As costly stem cell treatments progress from experimental concepts toward licensed products and routine procedures, governmental and private payers grapple with shrinking budgets to cover more lives. We describe efforts underway in the US to create mechanisms for reimbursement of cell therapies and discuss other reimbursement-related issues for the stem cell community.

Cell therapy, previously the exclusive domain of hematopoietic stem cell transplantation (HSCT), is rapidly extending into newer cardiovascular, neurodegenerative, cerebrovascular, and endocrine applications, as well as tissue and organ replacement. However, despite the fast pace of the science and medicine, the availability of reimbursement for these applications is progressing slowly, for a number of reasons; most importantly, to date there are few marketed cell therapies in the US, much less marketed *stem* cell therapy products. Therefore, payers, both governmental and private, have not had to make major coverage decisions in the stem-cells-as-products arena. In order to ensure that future commercial and clinical applications of stem cell products will be reimbursable, researchers should consider lessons learned by the HSCT field. While a US-centric perspective is highlighted here, analogous insight can be extrapolated to international efforts in this regard. Without establishing a development strategy that allows for the reimbursement of providers for an applied clinical product, even the most effective therapy may not make it off the shelves.

Lessons from the Past: HSCT as a Model

Today's emerging cellular therapy field is firmly rooted in the development of HSCT, which stems from multiple preclinical investigations, early attempts at adoptive therapeutic marrow transfer to terminal patients, and the first successful allogeneic transplantation procedure performed in 1968. Multiple refinements and expanded attempts to use cellular therapy followed, and by ~1980, marrow allografting was no longer viewed as "experimental," but rather was recognized as acceptable therapy for patients with a variety of hematologic disorders. As such, reimbursement became available from governmental and private payers and was soon thereafter extended to autologous transplantation. New patient-specific initiatives, including ex vivo purging of bone marrow of T cells as a means to reduce the risk of GVHD and for purging minimal residual disease, expanded the potential applications of HSCT. During this decade, coverage was in the form of indemnity insurance, also known as "fee-for-service" and, consequently, there was significant financial incentive for clinical performance and expansion of transplant procedures. Perhaps in response to the predicted financial impact of transplantation, in 1987 the state of Oregon opted to no longer provide Medicaid support for transplant procedures (bone marrow, liver, kidney, heart) to avoid favoring the expensive needs of a few over the resulting financial restrictions placed on the many (Welch and Larson, 1988). Seven years later, the creation of the Oregon Health Plan reversed this decision, and reimbursement decisions for specific cases were based on rankings of evidence-based efficacy of therapies, not costs (Bodenheimer, 1997a, 1997b).

During the 1990s, cell therapy was primarily used to treat hematologic malignancies. However, while individual blood cancers remain classified as orphan diseases (defined as less than 200,000 individuals in the US), the potential application of HSCT to solid tumor malignancies such as breast, ovarian, and lung cancer dramatically expanded the numbers of transplant candidates, magnifying the potential financial impact on healthcare budgets. Consequently, previously collaborative relationships between payers and cell therapists were strained, and therapeutic decisions were sometimes made in court rooms rather than in well-designed clinical trials. As a consequence, the national Blue Cross' Demonstration Project was initiated to provide support for autologous transplantation in indications such as multiple myeloma and high risk or metastatic breast cancer, but only (1) in the setting of well-designed, phase 3 clinical trials, and (2) within boundaries of a predetermined target financial case rate. Evidence-based medicine in conjunction with managed care was the focus, and many payers followed suit, effectively contributing to the development of transplant access networks.

Another landmark in the evolution of reimbursement for cell therapy was the FDA's decision to equate the administration of cells with the utilization of a "drug" (Fink, 2009; Halme and Kessler, 2006). As of May 2005, the FDA must rule whether any human application of cells or tissues requires regulation for a given context. In effect, cells and cell therapy moved out of the realm of medical practice and into the pharmacological drug sphere. In the HSCT arena, most standard current practices still remain exempt, but any nonminimal manipulation will require FDA oversight, including the current utilization of cord blood units

processed in unlicensed facilities. While the classification of cells as drugs provides some clarity as to the applicable regulations, it also inherently drives up the cost of the final product and, therefore, the overall costs to the health care system. Further, it adds a new level of complexity to the questions of how clinicians claim reimbursement for varying forms of cell therapy and how much reimbursement payers will provide. Any researcher, clinician, or commercial enterprise desiring to provide a patient population with cell therapy must learn to navigate their local reimbursement system, and it is wise to be aware of these workings before a potential therapy is ready for entry into any market.

Reimbursement and Reimbursement Codes

The pathway to reimbursement for both products and services can be extremely complex, as it varies with national and local government, as well as with private payers. (For detailed descriptions of reimbursement pathways in multiple countries, see http://www.ispor.org/HTAspecialissue/index.asp/.)

Payments to providers for those reimbursed products and services are even more complex and are based upon whether a patient is funded by a governmental plan (generally, The Centers for Medicare & Medicaid Services [CMS] in the US) or has payer support from a range of private insurer options. However, most plans follow the governmental CMS payer approach, which is based on the diagnosis-related group (DRG) reimbursement strategy for inpatient services. DRGs bundle the labor and nonlabor resources that are used to treat patients in a hospital with a particular disease or disorder. These payments are designed to cover routine costs attributable to patient care, and payment is based on the average costs of a particular diagnosis. Standard rates can be increased if the patient has complicating conditions, but not if more expensive agents are substituted for less expensive ones in the absence of complicating conditions. Similarly, ambulatory payment classifications (APCs) are used for determination of reimbursement for outpatient services. Thus, both DRGs and APCs have upper limits of reimbursement, and if the provider exceeds those limits due to the use of a more expensive therapy such as a pricey stem cell treatment, then the excess expense is not reimbursed. Therefore, developers of stem cell products should be aware of the DRGs and APCs applicable to their cell therapy that define the upper limit of reimbursement a provider can currently expect.

Establishing reimbursement to a provider has two major components: the unique alphanumeric code designated for the candidate product or service and the financial amount assigned to that code. Since review of clinical intervention is retrospective, payers must have clear and highly specific definitions of the products, procedures, and services performed for a patient in order to provide the assigned amount of financial compensation to the provider. These descriptions are captured in the codes.

Of import in the context of the stem cell field: if a code doesn't exist, then for all intents and purposes there is no routine method for a health care provider or a company selling the stem cell product to be paid by an insurer for that product or service. For example, the original bone marrow transplant cell processing code was a single blood bank code that was subsequently divided into several independent codes, covering various processing technologies including T cell, platelet or RBC depletion, or tumor cell purging (Gajewski et al., 2005). Unfortunately, the refinement of the coding lagged behind the evolution of the technology, and it took years for CMS and payers to accept the subdivided codes as standard. As a consequence, some investigators feel that the adaptation and further exploration of T cell depletion was delayed due to fear of lack of reimbursement, despite FDA approval of devices that could provide a T cell depleted allogeneic product.

Despite these caveats, progress has been made to define more specific codes that will be the basis of reimbursement for the developing fields of cell therapy and regenerative medicine. Table 1 lists some of the relevant codes and their corresponding current reimbursement rates. The rates are continually adjusted and can either increase or decrease over time. Notably, within the current CPT codes, the actual administration of cells is limited to intravenous infusion of allogeneic or autologous hematopoietic stem cell products or to the intravenous administration of unmanipulated allogeneic donor lymphocytes with the purpose of providing the graft versus malignancy effect.

Considering the vast number of potential indications, not to mention alternative sources of emerging cell therapies, it is clear that additional codes will be required. Many new therapies will require novel procurement protocols, GMP processing, storing of cell products, and, possibly, novel delivery systems. Using a still-experimental protocol as an example, if autologous bone marrow mononuclear cells are harvested and then directly injected intramuscularly into a lower extremity to treat critical limb ischemia, one can string together a list of codes that might be provided to gain reimbursement. However, based on the track record observed in HSCT, any rapid adjustment to existing codes seems unlikely. Thus, if current and future trials confirm a therapeutic benefit in critical limb ischemia, advocates must also pursue adoption of the appropriate reimbursement codes, bundling the procedure codes with diagnosis. For a commercial effort, planning ahead for such an eventuality could make the difference between success and failure, irrespective of the effectiveness of the treatment itself.

Reimbursement Rate

Despite today's widespread reimbursement coverage of stem cell transplants in the hematology/oncology setting, it is frequently inadequate and difficult to navigate for complicated cases due to the case rate structure of reimbursement that has evolved. New stem cell therapy products will likewise be faced with several difficult years, during which time the sponsors will need not only to obtain appropriate codes, but negotiate the reimbursement rate for that code, potentially in the setting of the elderly patient with other comorbid conditions.

For both autologous and allogeneic cell therapies, new pricing and reimbursement models may include DRG-like codes that encompass the multiple clinic, lab, and GMP manufacturing activities, as well as the products and services necessary to deliver them. Thus, when setting a price for their cell product, sponsors will need to consider not only their costs of goods sold (COGS) plus their desired

Table 1. Reimbursement Codes and Rates for Selected Transfusion, Apheresis, and Stem Cell Collection or Processing Procedures

CPT/ HCPCS	Description	2011 Payment Rate	%Change since 2010
36511	Apheresis wbc	$853.18	5.99%
36515	Apheresis, adsorp/reinfuse	$2,166.33	-3.55%
36516	Apheresis, selective	$2,166.33	-3.55%
36522	Photopheresis	$2,166.33	-3.55%
38206	Harvest auto stem cells	$853.18	5.99%
38207	Cryopreserve stem cells	$233.61	2.51%
38208	Thaw preserved stem cells	$233.61	2.51%
38209	Wash harvest stem cells	$233.61	2.51%
38210	T-cell depletion of harvest	$418.39	7.25%
38211	Tumor cell deplete of harvest	$418.39	7.25%
38212	Rbc depletion of harvest	$418.39	7.25%
38213	Platelet deplete of harvest	$418.39	7.25%
38214	Volume deplete of harvest	$418.39	7.25%
38215	Harvest stem cell concentrate	$418.39	7.25%
38220	Bone marrow aspiration	$257.53	23.25%
38221	Bone marrow biopsy	$257.53	23.25%
38230	Bone marrow collection	$2,166.33	-3.55%
38240	Bone marrow/stem transplant (allogeneic)	$2,166.33	-3.55%
38241	Bone marrow/stem transplant (autologous)	$2,166.33	-3.55%
38242	Lymphocyte infuse transplant	$853.18	5.99%

mark up, they will need to consider the impact of all ancillary products and services needed to deliver the cell product. Sponsors are encouraged to collect costs data throughout their product development in order to substantiate their desired price and to support appropriate reimbursement for the DRG. Costs include all expenditures for the development phases of the product, as well as for the commercial production. Of course, costs data alone are not sufficient to justify a price and future reimbursement rates, and permanent codes will be based upon a payer's review of the data supporting a product or service's clinical effectiveness, its comparative effectiveness, and long-term economic outcomes.

That said, it is important to note that issuance of permanent codes and a reimbursement rate do not guarantee usage. Some reimbursed drugs are not widely utilized, often because the single drug's cost alone could consume significant amounts of the DRG payment. For example, plerixafor is a small molecule inhibitor of the SDF1 receptor CXCR3 and has been FDA approved for hematopoietic stem cell mobilization in conjunction with G-CSF. The $6000+ cost/vial of the agent may be offset by avoiding additional apheresis and stem cell cryopreservation, but most institutions have developed restrictive algorithms for its utilization based on pre-existing fixed case rates in order to protect against financial losses (Shaughnessy et al., 2011).

Product costs can also affect medical practice due to the lag between rapid changes in clinical methods versus slower changes in reimbursement rates; for example, adult recipients of umbilical cord blood transplantation are increasingly receiving dual cord transplants based on improved clinical outcomes in advanced clinical trials. However, centers that pursue this therapy often receive a fixed bundled payment based on the acquisition cost of a single cord blood product. Consequently, the hospital or other provider generally absorbs the $30,000–$50,000 additional cost of the second cord. This expense is accepted with the expectation that long-term complications (and corresponding costs) may be minimized for dual cord transplant patients.

Thus, in a world with cells-as-drugs and evolving health care reform, health systems will be motivated to consider fiscal austerity, payer systems will measure both quality measures and cost of care, and commercial entities will need to be careful not to price themselves out of the market, all activities which could contribute to slowing the expansion of regenerative medicine (Nugent, 2011). Finally, and unfortunately, much attention in health care remains on tangible, short-term cost containment, as opposed to assessing the longer term economic and human impact of failing to pursue therapies for an aging population.

Reimbursement for Cell Therapies

In the US, there are a handful of FDA-approved cell therapies that are generally covered by payers. These include products such as Dermagraft and Carticel and the latest entrant, Provenge (Chambers and Neumann, 2011; Goozner, 2011). The latter is an autologous dendritic cell therapy for use in advanced prostate cancer and costs approximately $93,000 for a three dose course of therapy. In response to the price tag and potentially large number of patients, CMS conducted its own review of the safety and efficacy of the product before announcing, almost a year later, that it would provide national coverage, strictly in line with the approved FDA indication. Provenge is currently using a temporary code often assigned to new drugs, and codes applied for the clinical and lab services necessary for its use are taken from existing procedures. While this approach is adequate for Provenge, the same may not be true for more complex stem cell products.

An older example of a reimbursed cell therapy is Carticel (autologous cultured chondrocytes). Carticel is generally used in a young patient population and is covered at different rates depending on the patient's health insurance policy. CMS is not tremendously affected by Carticel due to the age of the patients and the relatively infrequent use of the product; however, a number of new cell-based cartilage repair products are in development and many are likely to be used in seniors, CMS's largest covered population. Thus, reimbursement for these products is likely to attract substantial review. While Carticel does have a unique and permanent code, its application to newer cartilage cell therapies is

unlikely to be adequate both in terms of the description of the new cartilage-replacement products and cell processing services as well as in the dollar amount covered.

For emerging cell therapies, depending on how the cells are sourced, processed, stored, and administered, as well as on the product's indication, reimbursement codes may not yet exist. Developers of such therapies need to determine very early what the existing relevant codes and rates may be. Existing codes may apply in terms of the procedural description, but may fall far short of covering the product's costs, much less its price.

Current Advocacy Efforts

As outlined above, the first hurdle to achieving reimbursement for stem cell products is to create codes where there are none. Ultimately, community advocacy is required, along with a significant commitment of time and personnel to support the evolution of the coding system. Many professional organizations contribute to these efforts, but the process can be costly and often hinges on a few interested and committed individuals. In the case of cell therapy, organizations such as the National Marrow Donor Program (NMDP), the American Association of Blood Banks, and American Society for Bone Marrow Transplant do contribute to these efforts; however, future advocacy will likely stem from tissue-specific societies such as the American Vascular Association's efforts in support of cell therapy for critical limb ischemia as well by focused stem cell societies. For example, the Alliance for Regenerative Medicine combines commercial, academic, and not-for-profit institutional members in its mission to educate policymakers and to advocate for favorable public policies for funding, reimbursement, and regulatory issues. Additionally, ongoing education of hospital billing systems is critical to ensure the accurate collection of data and submission of appropriate documentation to CMS and other payers. In a recent NMDP evaluation of transplant centers, widespread failure to report accurate individual donor or cellular acquisition costs was observed (M. Boo, personal communication). This incomplete cost reporting ultimately contributes to the underfunding of procedures.

Looking Ahead

In many countries, exciting stem cell therapies are in early stages of clinical development; however, if the billing codes are not legally in place to describe the procedures and products, and if adequate coverage is not provided by payers, patients will gain nothing from these medical advances.

Sponsors wishing to bring new stem cell therapies to market cannot only focus on regulators' requirements for approval, but must also consider payers' requirements. Recently, CMS and FDA sought public commentary on a proposal to conduct parallel review of new device and new drug applications. At this point, a pilot program for parallel review of devices appears likely and, pending the results, the FDA and CMS will consider expanding the program to include new drug applications. Simultaneous evaluation of endpoints for therapies by these two US agencies might streamline the path to market. Indeed, a parallel review approach is already in place in many countries with nationalized health services.

As seen during the long history of HSCT and the recent experience with Provenge, reimbursement for expensive, intricate, personalized medicines is possible. Sufficient reimbursement, however, is not guaranteed, nor even necessarily tied to clinical effectiveness. In order to help themselves help patients, all sponsors who ultimately hope to register their product in the US will do well to participate in the requests from CMS and FDA to provide feedback on the proposed parallel review process and to participate in the ongoing advocacy efforts to create proper billing codes with adequate reimbursement values. The involvement of international societies that advocate for responsible translation of stem cell-mediated therapies might also allow different regulatory bodies to learn from one another.

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