Original Contribution

Development and Implementation of a Computerized System for Collection, Processing, and Administration of Cellular Therapy Products

By Laura C. Gatzos, MT (ASCP), MPH, Susan Barbetti, BS, BA, Suzanne Bas-Davis, DEES, Albert Mailman, SM, Philip Brzezinski, MBA, Paul Ruseau, BS, Holly Barr Vermilya, MHA, Darlys Schott, MT (ASCP), SBB, Edna Marston, RN, MPH, Olive J. Sturtevant, MT (ASCP), MHP, Jerome Ritz, MD, and Lawrence N. Shulman, MD

Partners Healthcare; and Dana-Farber Cancer Institute–Harvard Medical School, Boston, MA

Abstract

Great strides have been made in computerization of ordering processes for general medications and chemotherapy agents. However, systems for ordering, processing, and administration of cellular therapies continue to be largely paper-based, without the safety features of computerized order entry. To address this deficit, Partners Healthcare System Information Services (PHS-IS; Boston, MA) has worked with oncologists and staff in the cell processing laboratory at the Dana-Farber Cancer Institute (Boston, MA) to develop and implement a novel, comprehensive computerized system for physician ordering and management of cellular products. A multidisciplinary team was formed to accomplish the task of developing a cellular product management system. This team identified the unique characteristics of cellular therapies and sought to develop a comprehensive computerized system that addressed these needs. The biotherapy order entry system developed and implemented by PHS-IS includes a suite of three interrelated applications that addresses all requirements of a traditional computerized provider order entry system, as well as features unique to cellular therapies. The biotherapy suite of applications has addressed patient safety concerns, streamlined the ordering of cellular therapy products, and has reduced opportunities for error and delay in product administration.

Case Vignette

A 9-month-old baby is battling leukemia, and a bone marrow transplant derived from the hematopoietic stem cells of a frozen umbilical cord presents her best chance for survival. Laboratory technologists at Dana-Farber Cancer Institute's (DFCI) Cell Manipulation Core Facility (CMCF) will follow a complex procedure to thaw an umbilical cord blood product collected from a healthy baby from a cryopreserved state and prepare it for transplantation.

9:00 AM: Time is a critical factor in this process; the reconstituting stem cells that comprise umbilical cord products do not survive outside the body for long periods of time. They must be infused into the patient within 4 hours of being thawed. In this narrow window of time, all patient and donor demographics and ordering information must be verified to be correct; the product must be thawed and prepared for transplant by laboratory technologists and infused into the patient by her nurse.

The baby's nurse and a technologist schedule an infusion time of 11:00 AM. This should provide ample time for the technologist to prepare the cord blood for transplant into the patient before the product's 1:00 pm expiration time.

At DFCI, all orders for cellular therapies, such as umbilical cord blood products, are on paper. Laboratory supervisors and technologists must rely completely on human vigilance to scan orders for completeness and accuracy; however, they have not noticed that the baby's oncologist has omitted her weight on the order for thawing and processing these cells.

10:30 AM: At 90 minutes after thawing, with the product viability beginning its natural decline, the technologist follows standard procedures and reconstitutes the product with nutritive media. He is unaware that the baby weighs only 10 pounds, and does not tailor the product volume to meet her maximum volume requirement.

11:00 AM: At 2 hours after thawing, the originally planned time of bone marrow infusion, the technologist completes his work and brings the stem cell product to the baby's nurse. The laboratory worker and nursing staff verify all patient and product identifiers. However, action stops when her nurse realizes that, at 150 mL, the volume of the product is too large to be safely infused.

11:30 AM: At 2.5 hours after thawing, the product is quickly returned to the lab. Only 1.5 hours of viable shelf life remain. The lab worker must reduce the volume of the product to a safe level without further compromising product integrity.

12:00 PM: Three hours after thawing, and 1 hour later than originally planned, the baby's cellular product is finally ready to be infused. Her nurse has only 1 hour before the viability of this product will be so compromised that it will not be useful. Once the technologist returns with the cellular product, the baby's nurse works swiftly and efficiently to ensure it is infused within the required timeframe.

Copyright © 2012 by American Society of Clinical Oncology

This baby's transplant was delayed because of an oversight that could have been avoided had a computerized order entry system been used. Despite these obstacles, the technologist and her nurse took the steps required to ensure that the product has remained a viable, safe, and effective treatment.

Introduction

Cellular therapies have long been part of cancer care in the form of stem cells used for myeloablative bone marrow transplants.[1,2] More recently, the array of cellular therapies used in cancer care has increased dramatically, and now includes such products as individualized tumor vaccines,[3-6] autologous ex vivo manufactured immune cell products[7,8] and mesenchymal stromal cells.[9,10] Allogeneic stem cell products are used in many treatments and can be obtained from HLA-matched related donors, volunteer unrelated donors, and umbilical cord blood banks.[2,11,12]

The preparation and administration of cellular therapies is more complex than that of standard medications or chemotherapy, and the consequences of errors in processing or administration carry great risk to the patient.[13] Complexities associated with cellular products, such as variable and heterogeneous cellular content and the demands of specificity of patients and donors emphasize the need for computerized systems and demonstrate the challenges of managing all aspects of cell collection, preparation, ordering, and administration of these products.[14,15]

Although the ordering process for cellular therapies has not been previously automated, considerable progress has been made in the development of computerized order entry systems for standard drugs for physicians, nurses, and other providers. Systems have been developed for ordering of chemotherapy that contain special functionalities, including dose calculations based on body-surface area or area-under-the-curve dosing, multiple checks for maximum and cumulative dosing, and complex dose schedules required for chemotherapy medications. These systems have improved the safety of medication administration both in hospital inpatient units and in the ambulatory setting by using decision support aids that ensure correct drug, dosage and schedule while checking for drug-allergy and drug-drug interactions.[13,16-19]

Most hospitals that use biologic products perform the majority of associated tasks on the basis of written documentation and both oral and written orders, as noted in our case vignette. The record keeping, chance for transcription errors, and the complexity of the process allow multiple opportunities for error. The fact that errors are rare in most centers is a tribute to the expertise and care taken by the staff at all points of the process. But errors do occur, and they can have life-threatening complications.

Creation of a New System for Ordering Cellular Therapies

The CMCF processes and releases hematopoietic stem cells and manufactured cellular products for patients undergoing treatment at Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Children's Hospital Boston (http://www.dfhcc.harvard.edu/core-facilities/cell-manipulation). When needed, complex manufactured cell products are also provided to patients at Massachusetts General Hospital and Beth Israel Deaconess Medical Center. Many of these patients are enrolled on clinical research protocols approved by the US Food and Drug Administration (FDA) and institutional review board of the Dana-Farber Harvard Cancer Center.

The CMCF received paper orders to collect, process, and release cellular products. The CMCF's leadership recognized that this process had the potential to result in errors that could adversely affect patient safety, even though the vast majority of paper-based orders were completed accurately. Partners Healthcare System Information Systems (PHS-IS; Boston, MA) was asked by DFCI leadership to develop and implement an electronic system for ordering the collection, processing, release, and administration of cellular products. A multidisciplinary team was formed to accomplish this task. The team was composed of members of the CMCF; faculty involved in oversight of the CMCF; physicians, nurses, and physician assistants that participate in the care of donors and recipients; and members of the Internet services teams that support oncology order entry systems.

Unique Characteristics of Biotherapy Products

Many aspects of the process to procure, prepare, store and administer cellular products distinguish them from standard medications and present challenges to automating their ordering. These characteristics include:

1. Products are obtained from multiple sources, including a patient's own bone marrow, peripheral blood, tumor biopsy, or other tissues (autologous products), as well as from healthy volunteer donors (allogeneic products). Although some cellular products are provided by large-scale commercial manufacturers, most are provided by relatively small-scale hospital-based laboratories.
2. Products do not come in "standard doses." The number of cells harvested can vary greatly, and the exact number is often not known until laboratory processing has been initiated. Cell loss during product processing can also result in considerable product variability. It is therefore often impossible to determine the exact "dose" of cells administered to patients until all preparation has been completed.[14,15,20]
3. Unlike general pharmacy stock items, cellular products are most often unique, customized, and linked to individual patients; mismatch of patient and donor can be fatal.
4. Many cellular products are experimental and are only provided in the context of clinical research protocols approved by the FDA and local institutional review boards. Experimental protocols are often very complex, using different cell doses and manufacturing procedures.[4,7,20]
5. Cellular products typically have short expiration times. When a decision is made to administer a product, thawing, preparation, transport, and administration of the product

Copyright © 2012 by American Society of Clinical Oncology

must be highly coordinated and performed efficiently and rapidly, with assurances that the product, dose, and other particulars are correct.[14,20]

Unique Requirements of a Computerized Provider Order Entry for Cellular Products

The CMCF and ordering oncologists required that a computerized provider order entry (CPOE) system for cellular products contain standard elements found in many CPOE systems. These elements included patient demographic information such as medical record numbers and dates of birth, clinical information that included patient height and weight, and patient registration to treatment plans or protocols. It was also necessary to incorporate functionality in the electronic process that included electronic signatures, audit trails that recorded order information, order sets templates that standardized complex processes, and confirmation and approval steps that provided an opportunity for double checking of orders for completeness of information such as patient height and weight.

A CPOE for cellular therapies also needed to accommodate elements that were completely unique and typically not required in traditional order entry systems:

1. Discrete order types to accommodate the unique requirements of each step in the manufacturing process: Physician orders were separated into distinct phases of the cellular product life cycle that included product collection, processing or manufacture, and product release.
2. Linking of orders to donor demographic and clinical information, as well as patient information: Orders were required to contain both patient and donor demographic information, when clinically relevant.
3. Ready access by providers to real-time information about the number and content of cellular products: These would be available as view-only access to product inventory in a partnering laboratory system.
4. Mechanism for rapid review and electronic approval of physician orders: This item, which is a critical safety requirement, would prevent errors of omission, as seen in our patient vignette.
5. The ability to create order sets that were specific to both established and novel experimental cellular therapies: This would enable the subsequent development of order sets for new clinical research protocols and approved cellular therapies, as well as modifications of existing protocols.
6. User authorizations that could be assigned by job role, not job title: This would provide a mechanism to designate who could perform specific functions.

CPOE for Biotherapy Products: Final Product

The resulting CPOE that was created by Partners Healthcare Information Services includes a suite of three separate and interrelated applications that addresses all requirements of a traditional CPOE, as well as those unique to cellular therapies. This suite of applications, depicted in Figure 1, includes Biotherapy Tools, the Biotherapy Order Entry (BOE) application, and the Biotherapy Product Availability Application (BPAA).

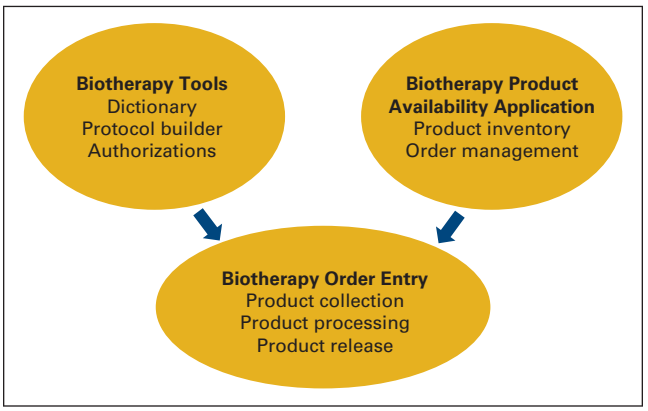

Figure 1. Biotherapy applications.

The functional components included in each of the three applications are summarized below.

Biotherapy Tools was designed to have several functionalities and is composed of the following elements:

- *Dictionary:* This includes all terminology used with the biotherapy applications within a user-friendly database and allows for maintenance and organization of information into meaningful components. Dictionary items include cellular product types (hematopoietic progenitor cells [apheresis or marrow], therapeutic cells); donor types (autologous, allogeneic related or unrelated); cell dose targets; and specific instructions for collection, process, and release of products based on standard laboratory procedures or specific protocol requirements.
- *Protocol and treatment plan builder:* This allows the organization of dictionary terms into protocol and treatment plan templates. These templates, which include items such as a donor type, a cell type to be collected, a location where the product will be collected, and a targeted product collection end point, become the foundation for orders in the BOE. Templates may also include protocol-specific instructions.
- *Authorization system:* This component determines who has access to specific functionality and allows for assignment of user permissions within the BOE, BPAA, and Tools.

Biotherapy Order Entry Application (BOE)

This application is used by providers to place orders for cellular products. All order sets are provided as templates based on product type, standardized treatment plans, or clinical research protocols. Three order types exist in the system and allow providers to designate what should happen to products at each phase of processing. Specific characteristics of collection, process, and release order sets are summarized in Table 1.

The BOE application provides a mechanism for providers to link patients to donors and works in tandem with the BPAA (described below) to allow clinicians to view into the laboratory's application to select specific products for release to a patient. As a safety feature, orders are electronically transmitted from the BOE application to the BPAA application only after all re-

Copyright © 2012 by American Society of Clinical Oncology

Table 1. Essential Characteristics of Biotherapy Orders

Order Type
Collection
Allows for collection of autologous and allogeneic cellular products
Allows for collection of variety of cell types
Links specific donors with recipients
Identifies collection site
Designates specific collection cell dose targets
Process
Allows for designation of type of processing steps required
Processing steps can specify standard procedures or experimental procedures defined by IRB-approved clinical research protocols
After processing is completed, products are placed into an inventory for an individual patient
Processing steps can be added as new procedures incorporating new cells types are required
Allows for entry of patient information critical to the processing of a product, including patient weight, height, or ABO Rh
Release
Allows provider to access product inventory for individual patients
Allows for selection of specific product to be released to a patient
Can specify distribution to different sites, including remanufacture by the laboratory

Abbreviation: IRB, institutional review board.

quired elements are completed and confirmed by a second authorized user.

BPAA

This application is accessed by laboratory users to manage orders and cellular products during all phases of product processing. Real-time, patient-specific customization of products allows the BPAA to act as a pharmacy-like application by creating an inventory of products available for each patient. Each product summary entered into the BPAA contains the date of product collection, product identification, final cell type, and all cell counts that are relevant to each specific product type. Although physicians do not work with the BPAA directly, all product summaries entered by laboratory staff are viewable, and products entered in the BPAA are available for ordering in the BOE.

Three distinct order types for the collection, processing, and release of cellular products were created to meet the specific requirements of each phase of biotherapy product life cycles. The creation of distinct order types allowed the biotherapy application to accommodate many different cellular product types and order templates, while maintaining patient and product specificity and adhering to strict regulatory guidelines. In addition, each order type had required entries that included patient demographics such as height and weight, as well as expected procedure date, and could only be signed electronically when these elements were complete. The features and characteristics of each order type could have prevented the time delays noted in our case vignette and are highlighted in Table 1.

Implementation

In preparation for the May 2010 implementation of the biotherapy suite of applications, PHS-IS provided training in the new system for all clinical users. All users were trained as a functional team. This allowed all professionals and members of clinical teams with various backgrounds to be trained together and fostered discussions about what changes in workflow might be needed to work with electronic orders. PHS-IS performed a phased roll-out of the application that included a pilot phase in which workflows and system bugs could be identified and resolved. Providers retained their old paper system and used it in tandem with the new electronic system for the entire roll-out period.

The clinical group with the smallest number of users and patients started using the new application first. This allowed PHS-IS to have a manageable number of issues and bugs to resolve before the next and larger group of clinical users came online 2 weeks later. Once all user groups were brought online and the pilot was deemed a success, providers stopped writing paper orders and used the biotherapy system exclusively for order management. Since the pilot began in May 2010, more than 3,000 orders have been placed in the BOE ordering application, and the resulting cellular products have been documented in the BPAA.

Future Improvements

As soon as users began utilizing the biotherapy applications on a routine basis, they started looking for ways to expand the functionality of the system. These requests included enhancements to increase ease of use of the application, a mechanism for interfacing with existing PHS-IS applications to create automatic linking of patients and their donors, and a link from an existing PHS-IS ambulatory data repository to autopopulate patient heights and weights on orders.

In addition, the biotherapy applications were put into use by additional groups of providers when the Dendreon (Seattle, WA) product sipuleucel-T received FDA approval for treatment of patients with prostate cancer.[5,6,21] PHS-IS and the CMCF worked to create a new cell type that was based on new terminology in the biotherapy dictionary to accommodate the ordering of this product for patient use. One advantage of this suite of biotherapy applications is that order sets can be easily tailored to accommodate new cellular therapies as they become available as either standard treatments or experimental therapies for patients enrolled onto clinical research protocols.

The biotherapy suite of applications has addressed patient safety concerns and eliminated miscommunications resulting from illegible or duplicate orders. The application has streamlined the ordering of cellular therapy products at DFCI, reduced opportunities for error and delay in product administration, and improved physician documentation of each physician order. Electronic ordering has eliminated the risk that providers will omit any key element at the time of ordering because such entries are now mandatory before an

Copyright © 2012 by American Society of Clinical Oncology

order can be electronically signed, thus fulfilling the business requirements originally outlined by DFCI oncologists.

Accepted for publication on January 31, 2012.

Authors' Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

Author Contributions

Conception and design: Laura C. Gatzos, Susan L. Barbetti, Suzanne Bas-Davis, Albert Mailman, Paul R. Ruseau, Darlys Schott, Edna Marston, Olive J. Sturtevant, Holly Barr Vermilya, Jerome Ritz, Lawrence N. Shulman

Administrative support: Olive J. Sturtevant, Jerome Ritz, Lawrence N. Shulman

Provision of study materials or patients: Jerome Ritz

Collection and assembly of data: Laura C. Gatzos, Albert Mailman, Philip J. Brzezinski, Edna Marston, Olive J. Sturtevant, Jerome Ritz

Data analysis and interpretation: Darlys Schott, Edna Marston, Olive J. Sturtevant, Jerome Ritz

Manuscript writing: Laura C. Gatzos, Edna Marston, Jerome Ritz, Lawrence N. Shulman

Final approval of manuscript: All authors

Corresponding author: Laura C. Gatzos, MT (ASCP), MPH, Partners Healthcare Information Services, One Constitution Center, 284-R, Charlestown, MA 02129-2000; e-mail: lgatzos@partners.org.

DOI: 10.1200/JOP.2011.000499; published online ahead of print at jop.ascopubs.org on May 15, 2012.

References

1. Ezzone SA: History of hematopoietic stem cell transplantation. Semin Oncol Nurs 25:95-99, 2009

2. Gooley TA, Chien JW, Pergam SA, et al: Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 363:2091-2101, 2010

3. Ho VT, Vanneman M, Kim H, et al: Biologic activity of irradiated, autologous, GM-CSF-secreting leukemia cell vaccines early after allogeneic stem cell transplantation. Proceedings of the National Academy of Sciences, U S A 106:15825-15830, 2009

4. Soiffer R, Hodi FS, Haluska F, et al: Vaccination with irradiated, autologous melanoma cells engineered to secrete granulocyte-macrophage colony-stimulating factor by adenoviral-mediated gene transfer augments antitumor immunity in patients with metastatic melanoma. J Clin Oncol 21:3343-3350, 2003

5. Cheever MA, Higano CS: PROVENGE (sipuleucel-T) in prostate cancer: The first FDA-approved therapeutic cancer vaccine. Clin Cancer Res 17:3520-3526, 2011

6. May KF Jr, Gulley JL, Drake CG, et al: Prostate cancer immunotherapy. Clin Cancer Res 17:5233-5238, 2011

7. Rosenberg SA: Cell transfer immunotherapy for metastatic solid cancer–What clinicians need to know. Nat Rev Clin Oncol 8:577-585, 2011

8. Rosenberg SA, Yang JC, Sherry RM, et al: Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res 17:4550-4557, 2011

9. Nombela-Arrieta C, Ritz J, Silberstein LE: The elusive nature and function of mesenchymal stem cells. Nat Rev Mol Cell Biol 12:126-131, 2011

10. Williams AR, Hare JM: Mesenchymal stem cells: Biology, pathophysiology, translational findings, and therapeutic implications for cardiac disease. Circ Res 109:923-940, 2011

11. Cutler C, Stevenson K, Kim HT, et al: Double umbilical cord blood transplantation with reduced intensity conditioning and sirolimus-based GVHD prophylaxis. Bone Marrow Transplant 46:659-667, 2011

12. Ho VT, Kim HT, Aldridge J, et al: Use of matched unrelated donors compared with matched related donors is associated with lower relapse and superior progression-free survival after reduced-intensity conditioning hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 17:1196-1204, 2011

13. Gandhi TK, Bartel SB, Shulman LN, et al: Medication safety in the ambulatory chemotherapy setting. Cancer 104:2477-2483, 2005

14. Kao GS, Kim HT, Daley H, et al: Validation of short-term handling and storage conditions for marrow and peripheral blood stem cell products. Transfusion 51: 137-147, 2011

15. Regan DM, Wofford JD, Wall DA: Comparison of cord blood thawing methods on cell recovery, potency, and infusion. Transfusion 50:2670-2675, 2010

16. Shulman LN, Miller RS, Ambinder EP, et al: Principles of safe practice using an oncology EHR system for chemotherapy ordering, preparation, and administration, Part 2 of 2. J Oncol Pract 4:254-257, 2008

17. Shulman LN, Miller RS, Ambinder EP, Yu PP, Cox JV: Principles of safe practice using an oncology EHR system for chemotherapy ordering, preparation, and administration, Part 1 of 2. J Oncol Pract 4:203-206, 2008

18. Harshberger CA, Harper AJ, Carro GW, et al: Outcomes of computerized physician order entry in an electronic health record after implementation in an outpatient oncology setting. J Oncol Pract 7:233-237, 2011

19. Levy MA, Giuse DA, Eck C, et al: Integrated information systems for electronic chemotherapy medication administration. J Oncol Pract 7:226-230, 2011

20. Majado MJ, Salgado-Cecilia G, Blanquer M, et al: Cryopreservation impact on blood progenitor cells: Influence of diagnoses, mobilization treatments, and cell concentration. Transfusion 51:799-807, 2011

21. Mellman I, Coukos G, Dranoff G: Cancer immunotherapy comes of age. Nature 480:480-489, 2011

Copyright © 2012 by American Society of Clinical Oncology