Biol Blood Marrow Transplant 23 (2017) 1463–1472

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Manufacture of Autologous CD34+ Selected Grafts in the NIAID-Sponsored HALT-MS and SCOT Multicenter Clinical Trials for Autoimmune Diseases

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Article history:
Received 27 April 2017
Accepted 15 May 2017

Key Words:
Autologous hematopoietic cell transplantation
CD34 selection
Graft processing
Drug master file
Clinical trial
Multiple sclerosis
Systemic sclerosis (scleroderma)

A B S T R A C T

To ensure comparable grafts for autologous hematopoietic cell transplantation (HCT) in the National Institute of Allergy and Infectious Diseases–sponsored Investigational New Drug protocols for multiple sclerosis (HALT-MS) and systemic sclerosis (SCOT), a Drug Master File approach to control manufacture was implemented, including a common Master Production Batch Record and site-specific standard operating procedures with "Critical Elements." We assessed comparability of flow cytometry and controlled rate cryopreservation among sites and stability of cryopreserved grafts using hematopoietic progenitor cells (HPCs) from healthy donors. Hematopoietic Progenitor Cells, Apheresis-CD34+ Enriched, for Autologous Use (Auto-CD34+HPC) graft specifications included ≥70% viable CD34+ cells before cryopreservation. For the 2 protocols, 110 apheresis collections were performed; 121 lots of Auto-CD34+HPC were cryopreserved, and 107 of these (88.4%) met release criteria. Grafts were infused at a median of 25 days (range, 17 to 68) post-apheresis for HALT-MS (n = 24), and 25 days (range, 14 to 78) for SCOT (n = 33). Subjects received precryopreservation doses of a median 5.1 × 10^6 viable CD34+ cells/kg (range, 3.9 to 12.8) for HALT-MS and 5.6 × 10^6 viable CD34+ cells/kg (range, 2.6 to 10.2) for SCOT. Recovery of granulocytes occurred at a median of 11 days (range, 9 to 15) post-HCT for HALT-MS and 10 days (range, 8 to 12) for SCOT, independent of CD34+ cell dose. Subjects received their last platelet transfusion at a median of 9 days (range, 6 to 16) for HALT-MS and 8 days (range, 6 to 23) for SCOT; higher CD34+/kg doses were associated with faster platelet recovery. Stability testing of cryopreserved healthy donor CD34+ HPCs over 6 months of vapor phase liquid nitrogen storage demonstrated consistent 69% to 73% recovery of viable CD34+ cells. Manufacturing of Auto-CD34+HPC for the HALT-MS and SCOT protocols was comparable across all sites and supportive for timely recovery of granulocytes and platelets.

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INTRODUCTION

Clinical trials of autologous hematopoietic cell transplantation (HCT) for 2 autoimmune diseases, multiple sclerosis (MS) and scleroderma, opened during 2005, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID). Clinical outcomes for the Phase II study in MS (HALT-MS) [1,2] and the prospective randomized study versus standard care for scleroderma (SCOT) [3] are available.

Even though processing for autologous CD34+ cell enrichment was regarded as minimal manipulation, the US Food and Drug Administration (FDA) determined use of this product for therapy of autoimmune diseases was nonhomologous and therefore subject to regulation under Section 351 of the Public Health Service Act. The protocols were conducted as 2 Investigational New Drug (IND) applications, and the manufacturing process for the autologous CD34+ selected graft was described in a Drug Master File (DMF), with the NIAID

Financial disclosure: See Acknowledgments on page 1471.

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http://dx.doi.org/10.1016/j.bbmt.2017.05.018
1083-8791/Published by Elsevier Inc. on behalf of the American Society for Blood and Marrow Transplantation.

serving as sponsor for the applications. The NIAID collaborated with experts in cell processing from the participating centers to develop the DMF for CD34 enrichment and cryopreservation. The objective was to ensure better control and standard methods of graft production, common to both clinical protocols at all clinical sites (Supplementary Appendix S2, Attachment I).

Here we describe our specifications for potency and purity for the cellular product, Auto-CD34$^+$HPC, and our proposals to the FDA for demonstration of comparability of manufacturing and analytical processes between the participating centers as well as for short-term stability of the final cryopreserved product. We correlated manufacturing data with engraftment outcomes to further assess our ability to meet the prespecified targets for safety, identity, purity, and potency of Auto-CD34$^+$HPC and the clinical efficacy of the grafts.

METHODS

Drug Master File

Specifications for potency and purity for Auto-CD34$^+$HPC

We specified viable CD34$^+$ HPC concentration measured after CD34$^+$ selection but before cryopreservation as our potency assay. Purity was defined as ≥70% total nucleated cell (TNC) viability and ≥70% of nucleated cells being viable CD34$^+$ cells in our type II DMF submission to the FDA for Auto-CD34$^+$HPC (BB-IND 11821; July 14, 2004; Supplementary Appendix S2, SOP 3000). To substantiate this choice, we provided data from the published literature in autologous HCT for malignancy, demonstrating faster neutrophil and platelet engraftment kinetics with higher CD34$^+$ cell content of bone marrow, mobilized peripheral blood, and CD34$^+$ selected products. CD34$^+$ cells/kg recipient body weight (RBW) ("dose") related to time to engraftment, with a threshold of 2 to 5×10^6/kg needed for recovery of granulocyte and platelet counts within about 14 days post-transplant (Supplementary Appendix S2, Attachment II). We also provided data from earlier Phase I/II studies in autoimmune diseases conducted at our participating sites. At CD34$^+$ cell doses ≥ 2×10^6/kg [4] for patients with MS, or ≥3.5×10^6/kg [5,6] for patients with MS or scleroderma, granulocyte counts recovered within about 10 days (data not shown).

Comparability of manufacturing processes at sites

Per the DMF, before participation manufacturing sites were qualified (Supplementary Appendix S2, Attachment III) by providing data for 3 batches of CD34-enriched cells produced using Baxter Isolex technology and performance of the Auto-CD34$^+$HPC potency assay. Facilities were required to be Current Good Manufacturing Practice compliant as confirmed by site inspection by a Good Manufacturing Practice expert.

Centers used site-specific standard operating procedures (SOPs) after NIAID review verified inclusion of "Critical Elements" of production described in common study-specific SOPs (Supplementary Appendix S2, Attachment IV). Comparability of product and process manufacture was ensured by implementation of the "Critical Elements" and by use of common Master Production (Supplementary Appendix S2, SOP 3001) and Master Postproduction (Supplementary Appendix S2, SOP 3002) Batch Records.

We conducted site-to-site comparability studies of flow cytometry techniques and controlled rate cryopreservation procedures. The usually discarded CD34$^+$ cell-depleted fraction remaining after CD34$^+$ selection, produced from mobilized peripheral blood of healthy volunteers at 1 site, the Fred Hutchinson Cancer Research Center (FHCRC), was used. To investigate comparability of flow cytometry techniques, samples of freshly processed CD34$^+$ cell-depleted fractions were shipped from FHCRC to the sites for measurement of TNC and flow cytometry analysis. Results from the sites were compared with a reference sample at FHCRC. To determine comparability of cryopreservation methods, each manufacturing site initiated controlled rate cryopreservation in Cryocyte bags with storage in the vapor phase of liquid nitrogen for ≥1 week; cryopreserved bags were then shipped back to FHCRC where after thaw and washing of samples to remove dimethyl sulfoxide (DMSO), measurement of TNC and analysis by flow cytometry was done, and results from other sites were compared with FHCRC.

Stability of Auto-CD34$^+$HPC with storage

We proposed Auto-CD34$^+$HPC would be infused within 3 months of the date of manufacture. Product was stored in the vapor phase of liquid nitrogen after controlled rate cryopreservation. We provided data to the FDA from published literature indicating grafts stored in this way supported engraftment after >10 years (Supplementary Appendix S2, Attachment V). Further, we provided data from prior Phase I/II studies in autoimmune diseases conducted at our participating sites [4-6] indicating products stored ≤ 1015 days supported robust engraftment (data not shown).

We conducted a 6-month stability study of controlled rate cryopreserved Auto-CD34$^+$HPC manufactured per the Master Production Batch Record using mobilized peripheral blood of a healthy volunteer at 1 site, FHCRC. A granulocyte colony-stimulating factor (G-CSF) mobilized healthy donor underwent 2 apheresis collections. These 2 collections were combined, and after CD34$^+$ selection enriched cells were aliquoted and cryopreserved with DMSO in 4 Cryocyte bags. One bag was thawed at 1 week and at 1, 3, and 6 months; after washing to remove DMSO, cell counts and flow cytometry were performed. Test parameters included potency (viable CD34$^+$ cells/mL), purity (proportions of viable TNC; viable CD34$^+$ cells), impurities (CD3$^+$ cells; other cells), appearance, and sterility. Product assessed before cryopreservation served as baseline for comparison of cell recovery and other assays at 1 week and later time points.

Manufacturing process control

Specifications for method(s) of apheresis collection of G-CSF mobilized peripheral blood stem cells (PBSCs) were per site-specific practice and were not regulated by our DMF. We defined the start of the manufacturing process for Auto-CD34$^+$HPC at the cell processing facility upon receipt of the apheresis product, which was considered the raw material. Process flow per the Master Production Batch Record (Supplementary Appendix S2, SOP 3001) provided for purification and characterization before cryopreservation and storage.

For CD34$^+$ enrichment, we used the Baxter Isolex (Baxter Healthcare Corporation, One Baxter Parkway, Deerfield, IL) 300i Magnetic Cell Selection System per the manufacturer's instructions, which specified a device load of ≤1000 mL containing ≤8×10^{10} TNC [7]. When production of Isolex was discontinued in 2010, we amended our DMF and the SCOT protocol, which had not yet completed enrollment, for substitution with the Miltenyi CliniMACS Instrument. Additional process flow specifications were per NIAID SOPs.

We defined a manufacturing "lot" as the product from 1 run of Isolex or CliniMACS CD34$^+$ cell selection, containing ≥3.5×10^6 viable cells. Depending on variables of the apheresis collection, processing of an individual subject's graft required manufacture of 1 or more lots of Auto-CD34$^+$HPC.

Product specifications and certificate of analysis

Auto-CD34$^+$HPC specifications included viable cells ≥ 70% TNC, viable CD34$^+$ ≥ 70% TNC, and impurities (including viable CD3$^+$ cells) ≤ 30% TNC (Supplementary Appendix S2, SOP 3000). Assessment by flow cytometry for CD34$^+$ and CD3$^+$ cells was performed before and after CD34$^+$ cell enrichment. Additional testing for CD56, CD19 or CD20, and CD14 was performed for further research characterization. Flow cytometry panels included 7-aminoactinomycin-D to assess overall viability. TNC and flow cytometry were used to determine absolute viable subset values (dual platform method) in the final CD34$^+$ cell enriched fraction. Sterility testing was performed after CD34$^+$ cell enrichment, on aliquots of each lot as described in 21CFR610.12. The Endotoxin assay (Endosafe, Charles River Laboratories, Wilmington, MA) was validated by each testing laboratory.

Clinical Protocols and Patients

Protocol ITN033AI (HALT-MS; BB-IND 12164; December 17, 2004; Clinicaltrials.gov NCT00288626) and Protocol SCSSc-01 (SCOT; BB-IND 11839; July 21, 2004; Clinicaltrials.gov NCT00114530) were approved by the institutional review boards at participating sites, and participants provided written informed consent. Participants self-identified race and ethnicity at screening. No financial compensation was provided. A total of 59 patients, 25 for HALT-MS and 34 for SCOT, were enrolled at 9 participating centers, 3 for HALT-MS and 8 for SCOT, from April 2006 to July 2011. Two subjects, 1 on each study, underwent graft manufacture and are included with the manufacturing data but did not proceed to transplant.

Mobilization of PBSCs

Subjects were mobilized for PBSC collection using G-CSF and prednisone, for the HALT-MS and SCOT studies, as described [1,2,6].

Graft Target Doses

The protocol-specified target dose of Auto-CD34$^+$HPC was ≥2×10^6/kg RBW for HALT-MS and ≥2.5×10^6/kg RBW for SCOT.

Engraftment Criteria

For HALT-MS, neutrophil engraftment was defined as an absolute neutrophil count > 500/μL for 2 consecutive measurements on different days. Platelet engraftment was defined as a platelet count > 20,000/μL for 2 consecutive measurements on different days, with no platelet transfusions in the preceding 7 days. For SCOT, engraftment was defined as achieving an absolute neutrophil count > 500 cells/μL and an unsupported platelet count > 20,000 cells/μL (unsupported defined as 7 days between last platelet transfusion and first of 3 consecutive daily platelet counts meeting this criterion).

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