Demonstrating Scalable Integration of Clinical, Translational, and Manufacturing Data to Explore Role of Manufacturing Approach in Driving Health Outcomes

Ben Smith[1], Trent Peterson[1], Jessica Manzyuk[1]
[1] Principia Health Sciences, Cary, NC

Background

Interest is growing among cell therapy researchers to better understand relationships between manufacturing approaches and patient outcomes.[1] In the past large multi-site research has been difficult to execute due to the significant effort required in linking clinical and manufacturing data sources.

Collaborative observational research has benefitted from growing adoption of the Fast Healthcare Interoperability Resources (FHIR) data standard and the Observational Medical Outcomes Partnership (OMOP) common data model.[2] Efforts to bridge FHIR and OMOP are also simplifying the automation of data acquisition and integration.[3] With the goal of extending similar benefits to research involving cell therapy manufacturing, we decided to explore the feasibility of using OMOP for integrated clinical and manufacturing datasets.

Historically, when researchers seek to integrate new types of data within OMOP CDM, an extension to the model is required to accommodate new concepts. Our approach uses only existing OMOP structure, though custom concepts will need to be added for manufacturing variables not yet used by the OHDSI community.

Methods

Our team consulted with cell therapy manufacturing experts to develop a categorized list of priority variables. We outlined typical manufacturing and logistics steps, identified equipment used, and cataloged expected data outputs. We then created a data dictionary to support generation of synthetic data we could later use in development. We included range and value distribution information to strengthen the data's realism.

Prior to loading the synthetic clinical and manufacturing data in OMOP, we established data links between specimen, patients, therapies, equipment, and process steps using OMOP's FACT_RELATIONSHIP table. This enables analysis of data relevant to target cell therapy patients. We then loaded the data leveraging these links.

To visually demonstrate success, we connected the database to an analysis application developed for use with OMOP data. The application allowed both manufacturing and clinical parameters to be used in defining a research cohort (e.g., multiple myeloma patients receiving CAR-T therapy where the transduction efficiency % during manufacturing was between 60% and 80%), and then supported multiple descriptive and prescriptive analyses.

Manufacturing Parameters (1/3)

Patient vital signs (EMR data to link to rest of manufacturing data)	Post Cell Infusion Parameters	Clinical Validation Parameters	Imaging Parameters
• Heart rate at apheresis • Heart rate at infusion • Heart rate at relapse • Oxygen level at apheresis • Oxygen level at infusion • Patient temperature at apheresis • Patient temperature at infusion • Patient temperature at relapse • Blood pressure at apheresis • Blood pressure at infusion • Blood pressure at relapse • Liver function • Spleen function • Peripheral blood assessment • Cytokine measures • Inflammation makers • Persistence of the CAR product before infusion • Persistence of the CAR product after infusion	• Presence of systemic CRS • Days of CRS onset • Urotoxicity • Days of onset of urotoxicity • Use of immunosuppressive meds • Name, dose, and timing of immunosuppressive meds used • Response at day 14 • Response at day 20 • Response at day 60 • Response at day 90 • Response at month 6 • Response at year 1	• Medical history of disease/condition • Primary disease • Presence and type of any genetic abnormalities • Immunostaining lab results at initial Dx • Disease relapse/ recurrent history • Previous therapies • Previous immunotherapies • Previous radiation therapies • Transplant history	• Imaging procedure • Imaging location/organ • Time of imagining procedure
	Cellular Parameters	**Patient Parameters**	**Progression Parameters**
	• Transduction efficiency • Vector copy number • Dose of cells • Fresh vs. frozen	• Patient ID • Patient age at Dx • Patient's weight at Dx • Disease type • Disease grade at Dx • Disease burden at enrollment • Antigen status of target antigens • Prior Tx • Preparative regimen	• Antigen status at progression • Overall survival • Therapies used after relapse

Manufacturing Parameters (2/3)

Complete blood count at apheresis	Genotyping/Genetic elements	Phenotyping Assays
• Hemoglobin • Platelets • WBC • Blasts • Neutrophil • Monocyte • Lymphocytes • CD3+ lymphocytes • CD3+ • NK • Liters processed • Total blood volume processed • Collection efficiency • % CD4 • % CD8	• Genomic stability • Genotoxicity • Karyotyping/ DNA ploidy • Native MSC molecular markers • In vitro toxicity • Immune suppression • Immunogenicity • Immunopotency • RNA/transcriptomic profile • Genomic sequence/ candidate gene sequences • TCR rearrangement profile (single cell seqng)	• Tumor-induced effector activity • CyTOF panel • T cell central memory (TCM) phenotypes • Stem ell memory (TSCM) phenotypes • Transcription factor expression (TBET, GATA3) • Reagent choice • Panel design • Instrument calibration • Validated antibody cocktail • Antibody titration • Plastic adherent • Spindle or fibroblastic
Immunogenicity parameters	**Critical process parameters (CPP)**	**Purity profile**
• Presence of anti-CAR antibodies • HAMA antibodies detected • Type of collection specimen (e.g., blood)	• Cytokines used • Dose if cytokines • Secretion of cytokines • Duration of expansion/ time-to-patient infusion • Action limits • Process limits • Equipment performance	• Impurities from antibodies • Impurities from raw materials • Content of non-MSC populations • Content of non-viable cells • Sterility • Absence of mycoplasma • Absence of infectious disease

Manufacturing Parameters (3/3)			
End of study parameters	**Critical quality attributes (CQAs)**	**Key process parameters (KPP)**	**Lot release specifications**
• Adverse events (AE) • Date of AEs • Grade/severity of AEs • Connection to CART therapy in trial • Cytokine levels at time of AE • CD4 count at time of AE • CD8 at time of AE • Patient death • Date of patient death • Cytokine levels at patient death • CD$ count at patient death • CD8 count at patient death • CAR levels at patient death • If death, autopsy summary	• Sample purity • Sample potency • Sample release criteria • Acceptance criteria for source material • Acceptance criteria for intermediates • In-process criteria • Final product specifications **Place/point of care vs place/point of manufacturing** • Product stability in the room • Ability to deliver intended dose • Compatibility with the injection device • In-vivo efficacy of cell therapy product	• Equipment/technology used • Minimum volume of bioreactor • Maximum volume of bioreactor • Turndown ratio • Cell doubling times • Feed rates • Aspect ratio • Agitation methods • Format platforms • Media provision regimes • Manual vs automated process/procedures • Dissolved oxygen via aeration of the cell culture media • Dissolved gasses via aeration of the cell culture media • pH of the cell culture media • Temperature of the cell culture media • Enzymes used for cell disaggregation and harvesting • Incubation parameters • Enzyme removal process • Operating pressure • Perfusion flow rate • Processing time at each step of protocol	• Shipping & handling parameters • Vial filling hardware/ filling vessel • Vial filling device • Cryostorage solutions • Days on Cryostorage • Thaw duration • Temperature of thawing • Cryostorage media • %DMSO in Cryostorage media • Cryostorage thawing process • Container closure • Shelf life • Process validation • Product quality • Product comparability

Figure 1. Tables of manufacturing parameters

Conclusion

Through this effort, we were able to validate feasibility of storing manufacturing and logistics data within OMOP for linking with clinical data. OMOP's FACT_RELATIONSHIP table enabled an elegant solution without ambiguity of data type and relationship to the patient. The next step to advance development of this technique is to verify results using live clinical and manufacturing data in a pilot environment.

References

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