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A meta-analysis of biological variation in blood-based therapy as a precursor to bio-manufacturing

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Abstract

Currently cellular therapies, such as hematopoietic stem cell transplantation (HSCT), are produced at a small scale on a case-by-case basis, usually in a clinical or near-clinical setting. Meeting the demand for future cellular therapies will require a robust and scalable manufacturing process that is either designed around or controls the variation associated with biological starting materials. Understanding variation requires both a measure of the allowable variation (that does not negatively affect patient outcome) and the achievable variation (with current technology). The prevalence of HSCT makes it an ideal case study to prepare for more complex biological manufacturing with more challenging regulatory classifications. A systematic meta-analysis of the medical literature surrounding HSCT has been completed of which the key outcomes are the following: (i) the range of transplanted CD34+ cells/kg can be up to six orders of magnitude around the median for allogeneic procedures and four orders of magnitude for autologous procedures, (ii) there is no improvement in variation encountered over a period of 30 years and (iii) as study size increases, the amount of variation encountered also increases. A more detailed, stratified source from a controlled single-site clinical center is required to further define a control strategy for the manufacture of biologics.

Key Words: *Biological variation, Blood, HSCT, Process design, Quality control*

Introduction

Cellular therapies are currently produced in small batches, typically in a clinical setting, under special legislation such as the European Hospital Exemption Clause and the U.S. Food and Drug Administration's Investigational New Drug Exemption. These small batch sizes will struggle to meet future demand, so an appropriate bio-manufacturing process is likely to be required to replace some or all of the manual processing that predominates at present. A quality-by-design approach to process control that is based around or controls the variation inherent to biological starting materials is anticipated to be a key prerequisite to bio-manufacturing at scale and an ongoing challenge for entrepreneurs, manufacturers and regulators alike. Understanding biological variation requires a measure of both:

- the allowable variation that does not impinge on safety or efficacy and
- the achievable variation at our current level of technology and skill.

The allowable variation is based on the specification, set by the prescriber, that details the limits of variation within which a product must remain to avoid negatively affecting patient outcome. The achievable variation is based on the tolerance of the process/machine, set by engineers, which is based on the ability of the process to cope with this variation. Furthermore, understanding of the variation in the starting material, as a result of the patient/donor population; the isolation techniques; and the previous conditioning regimes is required. Together, this knowledge will ultimately inform strategies to account for this

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variation, including how to address the issue of comparability, demonstrating that the process remains the same after a change, which can include distributed manufacture at multiple locations, while remaining cost-effective [1] and within tolerance.

Control of variation will facilitate the production of a consistent, comparable product, with a known efficacy, at scale. This has the potential to increase the quality of the product (therefore maximizing patient longevity and quality of life) or to maintain the quality of a product but at a reduced cost [2].

Exemplar

Hematopoietic stem cell therapy (HSCT) is one of the few cellular therapies currently in routine use [3], with a proven historical track record and is relatively well established worldwide. The therapeutic potential of this therapy originates from hematopoietic progenitor cells, self-renewing precursor cells that have the potential to become a number of specialized cell and tissues. HSCT utilizes the unique properties of these cells, isolated from peripheral blood, bone marrow or cord blood for clinical applications such as the revivification of a patient's bone marrow after potent chemotherapy or radiotherapy.

The prevalence of HSCT is one reason it was chosen as an exemplar to benchmark the variation encountered in cellular therapies. It is a secondary therapeutic (chemotherapy or radiotherapy is the primary therapeutic), but it occupies a unique regulatory niche in that it is "minimally manipulated" and so has the potential as a case study to inform process design for more complex bio-manufacturing of products that are more than minimally manipulated, and fall into more challenging regulatory classifications such as advanced therapy medicinal products [4].

Variation meta-analysis methodology

The objective of this research was to determine the baseline extent of variation encountered for HSCT, under the practice of medicine, because this therapy is manufactured and applied within a clinical setting. This research expands on previous work [5] by adding greater resolution and examining the challenge from a nascent bio-manufacturing perspective.

This analysis was designed to (i) examine the medical literature on HSCT for collected/transplanted cell metrics (such as total nucleated cell count or CD34+ cell count, a cell surface marker present on hematopoietic stem cells), (ii) examine and report the extent of variability in these metrics within and between these studies, and, if sufficient detail was present, (iii) correlate this variation with donor/patient metrics, processing methodology and clinical center, among other variables.

This work is intended to complement a clinical case study by providing a platform for discussion between stakeholders, and a global picture to compare with single-center study data, thus providing a demonstration of the current "state of control." The research presented here focuses on the results of the literature meta-analysis.

Online databases and health resources (PubMed and Web of Knowledge) were used to search the literature for a number of pre-determined keywords, medical search headings (MeSH) and publication dates. Articles were restricted to English language unless a native translation was provided, and only refereed journals were included (conference proceedings, for example, were excluded).

The abstracts of the resultant studies were then screened for the likelihood of containing applicable data, such as clinical trials or outcomes studies. Eligible publications were then obtained in full and stored locally and given a unique identifier that could be linked to the database for future reference. These publications were then manually examined for patient, donor and graft measurements. A predetermined checklist of measurements had been created for this task from mind-mapping and stakeholder discussion (see Table I). A number of primary characteristics, such as the presence of total nucleated cell count (TNC) count or CD34+ cell count, were mandatory for studies to pass to the data collection stage. At this stage, data were transferred and stored next to the identification number within a database. Microsoft Excel and IBM SPSS 22.0 were used for the analysis.

Results

We identified 5,458 peer-reviewed journal articles (previously 3,190) [5] published between 1980 and 2015. This resulted in 269 (previously 126) [5] articles that contained 491 observations included donor, methodological and graft variables.

Variation was measured from reported cell metrics, of which TNC and CD34+ cell count were most prevalent. These were reported as TNC/kilogram and CD34+ cells/kilogram patient bodyweight. Interquartile ranges were often provided in lieu of range data within articles but were not recorded because they are not representative of the true value of biological disparity and avoid up to 50% of possible variation. Cord blood and pediatric data points were removed because of low incidence level, and thus this dataset represents adult bone marrow– and peripheral blood–derived material only. It should be noted that in certain figures, the *x*-axis title refers to the unique identifying number given to each valid study; however, data in each of these figures is

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