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REVIEW

Challenges in the harmonization of immune monitoring studies and trial design for cell-based therapies in the context of hematopoietic cell transplantation for pediatric cancer patients

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Abstract

Clinical trials aimed at improving results of hematopoietic cell transplantation (HCT) by adjuvant cell-based interventions in children have been limited by small numbers and pediatric-specific features. The need for a larger number of pediatric HCT centers to participate in trials has resulted in a demand for harmonization of disease-specific clinical trials and immune-monitoring. Thus far, most phase I/II trials select different end points evaluated at disparate time points, making inter-study comparisons difficult and, sometimes, impossible. In this review, we discuss the various aspects that are important to consider for harmonizing clinical trial design as well as the critical elements for standardized (immune)-monitoring protocols in cell-based intervention trials in the context of HCT. Comparison data from trials applying harmonized trial design will lead to optimized immunotherapeutic treatment protocols to maximize clinical efficacy while minimizing toxicity.

Key Words: *cell based therapy, clinical trial design, hematopoietic cell transplantation, immune monitoring, pediatric cancer*

Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative treatment option for a variety of malignant and non-malignant diseases. Treatment-related complications (graft-versus-host disease [GvHD] and viral reactivation) and relapse unfortunately remain unwanted sequelae of the procedure. Multiple studies aim to improve the safety and efficacy of HCT mainly by enhancing engraftment or the use of innovative immunotherapies, including combination cell therapy and antibody approaches.

These trials bring an important set of data to light, but most single-center phase I/II cell therapy trials select different end points evaluated at disparate time points, making inter-study comparisons difficult and, sometimes impossible. The need for a larger number of pediatric HCT centers to participate in trials, applying harmonized end points, has brought out the

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demand for international collaborative groups. Although the goal of many early-phase trials is to identify a maximal tolerated dose, it is also desirable that as much efficacy information as possible is obtained from these trials. In particular, this is true for studies in pediatric patients in whom the relatively small numbers and pediatric-specific variables further complicate side-by-side study comparisons.

Better understanding of the mechanisms and biology of immune reconstitution after HCT and adjuvant cell-based intervention will provide us with clues for the further optimization of immunotherapeutic treatment protocols with the goal of reaching optimal clinical efficacy while minimizing toxicity. In this context, harmonizing designs of disease-specific clinical trials and immune-monitoring for additional immune therapeutic strategies in HCT will facilitate comparisons between early-phase trials enabling optimized dosing regimens and immune monitoring tools for "head-to-head" phase III trials.

Standard protocols in diagnostic immunology laboratories are continuously advancing, but the challenge remains to perform highly sophisticated techniques in a standardized manner and in validated settings for multi-center studies. Direct comparisons are often limited because of confounding factors, such as the immune status of the patient and parameters such as age, genetics and underlying disease. Population-specific traits require further investigation before such a protocol can be applied to a heterogeneous population. For pediatric patients in particular, the immune status, including the presence of immune (effector) cells before and during therapy, is generally undetermined. Hence, the effect size of immune parameters in patients treated with immune-based therapies is often unknown, which may hamper power calculations for the required numbers of patients in future trials. In addition, the acquisition and handling of patient samples requires specific logistics (documented in standard operating procedures [SOPs]) in terms of minimal sample type and volume to acquire sufficient cells for analyses (eg, shortly after HCT) or cell fragility during assay handling. As such, even marginal differences in sample preparation and bio-banking may limit comparison of results generated from different centers.

Harmonizing immune monitoring and clinical trial design

Many diseases, including cancer, are associated with alterations in numbers and function of immune cells within the peripheral circulation and especially at sites of tumor progression [1]. Such immune (response) signatures could serve as biomarkers or as surrogate end points when evaluating treatment responses. Despite the considerable progress in the development of immune-monitoring methodologies, the remaining challenge is how to correlate changes in immune parameters with clinical end points. In malignant disorders, this correlation is further complicated by the complexity of interactions (if known) between the host immune system and the tumor micro-environment. Recent progress in our understanding of the cellular and molecular pathways involved in the immune response has facilitated the selection of relevant immune end points. Also, impressive technological advances in methods that enable multiplex profiling of immune phenotypes, definition of regulatory cell subsets, identification of critical signaling molecules and recognition of biologically important targets have increased our knowledge of potential immune biomarkers that may correlate with patient outcomes [2]. However, for children this information is largely lacking, which hampers the development of optimal immunotherapeutic strategies for this population. Leveraging advances in multiplex technologies (eg, genetics, immune-phenotyping and protein assays) may nevertheless provide us with more insight into the immune status before (in case of reduced intensity condition) and after allo-HCT over time, "mechanisms of action" and immunobiology of post-HCT/adjuvant cell therapies.

In the setting of allo-HCT, critical variables in immune reconstitution are strongly associated with the development of life-threatening complications such as viral reactivation, GvHD and relapse [3] (recently reviewed in de Koning et al. [4]). The failure or success of novel immune approaches to circumvent these complications is also highly affected by the immune status. Hence, the design and the evaluation of studies evaluating the efficacy of novel immune therapies must be standardized for multiple single-center trials. By harmonizing clinical trial design, immune-based therapies can be compared in a more standardized way, enabling us to gain more insights regarding the mechanisms of action as well as the immunobiology of novel therapeutics or combination treatment regimens. Nevertheless, the markers and phenotypes studied in one setting may not be considered relevant in another, supporting the definition of a set of general recommended protocols and a set of add-on trial-specific parameters (Table 1).

To achieve these goals, trial design should include the following consensus end points (Figure 1) described in SOPs:

(i) Disease/complication-specific markers for phase I/II studies: for example, minimal residual disease (MRD), GvHD and viral load after cell therapy assessments at standard time points.
(ii) Standardized sampling and monitoring of immunological markers in accredited quality controlled laboratories.