Cytotherapy, 2012; 14: 775–790

informa
healthcare

REVIEW ARTICLE

Current translational and clinical practices in hematopoietic cell and gene therapy

DAVID L. DIGIUSTO[1] & HANS-PETER KIEM[2]

[1]*Department of Virology and Laboratory for Cellular Medicine, Beckman Research Institute of the City of Hope, Duarte, California, USA, and* [2]*Clinical Research Division, Fred Hutchinson Cancer Research Center, Departments of Medicine and Pathology, University of Washington, Seattle, Washington, USA*

Abstract

Clinical trials over the last 15 years have demonstrated that cell and gene therapies for cancer, monogenic and infectious disease are feasible and can lead to long-term benefit for patients. However, these trials have been limited to proof-of-principle and were conducted on modest numbers of patients or over long periods of time. In order for these studies to move towards standard practice and commercialization, scalable technologies for the isolation, *ex vivo* manipulation and delivery of these cells to patients must be developed. Additionally, regulatory strategies and clinical protocols for the collection, creation and delivery of cell products must be generated. In this article we review recent progress in hematopoietic cell and gene therapy, describe some of the current issues facing the field and discuss clinical, technical and regulatory approaches used to navigate the road to product development.

Key Words: *adoptive immunotherapy, cell therapy, clinical trials, gene therapy, stem cells*

Introduction

The transition from the laboratory to the clinic (bench to bedside) is well charted for small molecules but less so for cellular therapeutics. Moving a cell product from the basic research laboratory, through process development and on to manufacturing and clinical trials, is known as translational research (1) and has become the focus of both federal and private investment. Passage through this proverbial 'valley of death' is typically where most candidate therapeutics are stalled, many never to see the clinic. The funding of more than 49 clinical and translational science award centers across the USA reflects the National Institutes of Health's (NIH) view that translational sciences are a high priority in the NIH roadmap for medical research (2). The stages of developing (translating) new therapeutics have been broken down into distinct phases (often termed T1–T3 activities) to describe the translation from basic science to clinical trials (T1), clinical trials to clinical practice (T2) and broad dissemination to the population (T3) (3). We often only think of the T1 component of this process, but all of the steps are necessary to justify the investment in research made by the Federal Government and private industry.

Like any new medical treatment, the initial years of clinical investigation define both the utility and limitations of cellular therapy but also lead to significant innovation and development of infrastructure in support of subsequent, more advanced studies. For example, bone marrow transplantation was one of the first and still most widely used forms of cell therapy and has helped define both the therapeutic potential of and significant hurdles in developing stem cell products. An important (enabling) development in cellular therapy was the discovery of a subpopulation of white blood cells expressing the CD34 antigen that contains virtually all of the long-term hematopoietic reconstituting (stem cell) activity in a bone marrow graft (4). The correlation between the number of $CD34^+$ cells transplanted and successful engraftment has helped establish the first stem cell therapy dosing specification to be used in standard clinical practice: a minimum of 2×10^6 $CD34^+$ cells/kg for complete hematopoietic recovery (5). Moreover, $CD34^+$ cells have become the substrate of choice

Correspondence: Dr **David L. DiGiusto**, Department of Virology, Beckman Research Institute of the City of Hope, 1500 E. Duarte Rd, Duarte, CA 91010, USA. E-mail: ddigiusto@coh.org

(Received 12 April 2012; accepted 14 May 2012)

ISSN 1465-3249 print/ISSN 1477-2566 online
DOI: 10.3109/14653249.2012.694420

for genetic modification to treat a number of disease indications with an autologous product (6). In a similar fashion, allogeneic transplantation of bone marrow has led to an understanding of the benefits of the transfer of T cells, with anti-tumor as well as the potentially devastating consequences of T-cell-mediated graft-versus-host disease (GvHD) (8). These latter observations have played a major role in the development of adoptive immunotherapy (AI) strategies for cancer and infectious disease and will be used as examples of how subsequent cell therapies may be developed.

Proof-of-concept: Adoptive Immunotherapy

A prominent example of the power of AI is the provision of anti-viral immunity following hematopoietic stem cell transplantation where cytomegalovirus (CMV), Epstein–Barr virus (EBV) and adenoviral infections are the primary cause of morbidity and mortality (9–11). Since the demonstration of transfer of anti-viral immunity with isolated clones of T cells (12–14), numerous approaches have emerged to enrich, isolate or otherwise engineer immunity to viruses (14–22). An example is the use of EBV-transformed lymphoid cells lines (LCL) as antigen-presenting cells that can be infected with adenoviral vectors expressing both adenoviral and CMV peptides. The LCL then act as antigen-specific feeders during T-cell expansion and result in a population of T cells with enriched specificity for all three (EBV, adeno- and CMV) viral antigens (23,24). These approaches have met with reasonable clinical success in controlling CMV and adenoviral infections as well as EBV-associated lymphoproliferative disease (18,25,26), although for CMV immunity the number and identity of CMV epitopes required to confer broad protective immunity is still of significant debate (24,27). A recent safety report on more than 180 recipients receiving more than 380 infusions of a range of antigen-specific and/or engineered T cells indicates that the treatments are safe, without evidence of severe adverse events related to infusion, and that close monitoring can be limited to a short period following infusion (28). These studies demonstrate the safety and efficacy of AI for a variety of viral pathogens and have resulted in the development of methodologies to prepare and release T cells for clinical use that have driven the field forward towards current good manufacturing practice (cGMP)-compliant production platforms (24,29). Additionally, regulatory policy and practice at the Food and Drug Administration (FDA) has been shaped (in part) by the progression of these trials from the laboratory to the clinic and back, in an iterative process that helps fine tune the translational infrastructure.

Another compelling and well-tested application of AI is the use of tumor-infiltrating T lymphocytes (TIL) to treat melanoma (30–33). A recent report by Rosenberg *et al*. (34) summarizes the results from three separate clinical trials in which 93 patients with recurrent, refractory stage IV melanoma were treated with *ex vivo*-expanded TI. Patients were infused with TIL following a lymphodepleting preparative regimen (cyclophosphamide and fludarabine; CyFlu) ± total body irradiation (TBI) (0, 2, 12 Gy TBI). (Note: when TBI was administered, patients also received an autologous stem cell transplant; ASCT.) All patients received high-dose interleukin (IL)-2 (720 000 IU/kg) following infusion of TIL to support their proliferation and *in vivo* activity. Overall Response Evaluation Criteria In Solid Tumors (RECIST) response rates were as high as 72%, with (durable) complete responses in up to 40% of patients who received the CyFlu + 12 Gy TBI. Interestingly, the highest rate of survival at 5 years was among those patients who had undergone prior immunotherapy with anti-CTLA-4 Cytotoxic T-Lymphocyte Antigen-4 antibody (Ipilumimab). Ipilumimab blocks CTLA-4-mediated down-regulation of T-cell activity and presumably allows for a more sustained anti-tumor response by the infused cells. This series of trials confirms the utility of TIL in treating metastatic tumors but also supports previous evidence that multiple factors work to limit the activity of tumor-associated T cells *in vivo* (35,36). *Ex vivo* expansion of tumor-infiltrating T cells can overcome some of the *in vivo* anergy induced by the tumor microenvironment, but the conditioning of the patient with CyFlu and irradiation creates an *in vivo* environment favoring homeostatic proliferation and (unsuppressed) expansion of adoptively transferred T cells, and results in more durable complete responses. While this is currently the most promising therapy for melanoma, concerns still exist about the quality of T cells from patients with large tumor burdens or 'high antigen loads' (37). Recent evidence demonstrates that T cells isolated from tumor-infiltrating lymph nodes express higher levels of markers associated with cellular 'exhaustion' (apoptosis genes, CTLA-4), which may partly explain the limited ability to generate TIL from some patients and efficacy in less than half the patients treated (38). Nonetheless, similar attempts to isolate TIL from other solid tumors are currently under investigation (39–44).

In a similar fashion, T cells from the peripheral blood of allogeneic donors have been expanded *ex vivo* in an attempt to generate allogeneic anti-tumor T cells for a number of hematologic malignancies (45). These studies have demonstrated the therapeutic potential of the approach but GvHD was observed